Clinical trial results:
IMPRESS-AF: IMproved exercise tolerance in patients with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation

Summary

EudraCT number	2014-003702-33
Trial protocol	GB
Global end of trial date	27 September 2019

Results information

Result version number	v1 (current)
This version publication date	05 March 2021
First version publication date	05 March 2021

Trial information

Trial identification

Sponsor protocol code	RG_14-150

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	University of Birmingham, Birmingham, United Kingdom,
Public contact	Eduard Shantsila, University of Birmingham, +44 01215075086, eduard.shantsila1@nhs.net
Scientific contact	Eduard Shantsila, University of Birmingham, +44 01215075086, eduard.shantsila1@nhs.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2019
Global end of trial reached?	Yes
Global end of trial date	27 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The IMPRESS-AF trial addressed whether two years of treatment with spironolactone as compared to placebo improves exercise tolerance, quality of life and diastolic function in patients with permanent AF and preserved left ventricular ejection fraction (LVEF).

Protection of trial subjects:

*The trial will be managed by the Primary Care Clinical Trials Unit (PCCRTU), an NIHR accredited CTU that is experienced in the management of clinical trials. The unit has developed the infrastructure, processes and systems to eliminate potential risks and burdens wherever possible and manage where this is not the case.
* Spironolactone is a widely used drug and has a large evidence base for the effective treatment in heart failure. Side effects and safety data are therefore well established.
* Cardiopulmonary exercise test and 6minute walk test: there is a small risk of complications, such as myocardial infarction,left ventricular rupture, ventricular fibrillation or ventricular tachycardia The study involves low risk patients. Any participant presenting with factors associated with higher risk of complications (eg, symptomatic coronary disease, recent acute coronary events, severe valvular disease, impaired left ventricular systolic function) will be excluded from the study. Protocol specific training will be given to the personnel who will be performing the tests and taking the bloods. The tests will be done on a hospital site and facilities and staff for emergency help will be available at all times.
* Blood tests may cause minimal discomfort and bruising at the site of the needle going through the skin. All blood sampling will be done by experienced clinical research fellow.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 250
Worldwide total number of subjects	250
EEA total number of subjects	250

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	41
From 65 to 84 years	199
85 years and over	10

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients ≥ 50 years old, no spironolactone treatment with permanent AF according to ESC criteria as a cardiac arrhythmia with surface ECG 'absolutely' irregular RR intervals, no distinct P waves on surface ECG, atrial cycle length usually variable and <300 bpm, duration of the AF >12 months & no plans for pharmacological/electrical cardioversion

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	spironolactone

Arm description: -

Arm type	Experimental
Investigational medicinal product name	spironolactone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

single 25 milligram tablet taken orally once per day (typically to be taken during the morning, but can be taken regularly at other time of day if preferable) for a 24 month period

Arm title	placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

a single 25 milligram tablet taken orally once per day (typically to be taken during the morning, but can be taken regularly at other time of day if preferable) for a 24 month period

Number of subjects in period 1	spironolactone	placebo
Started	125	125
Completed	125	125

Period 2	
Period 2 title	12 month time point
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	spironolactone

Arm description: -

Arm type	Experimental
Investigational medicinal product name	spironolactone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

single 25 milligram tablet taken orally once per day (typically to be taken during the morning, but can be taken regularly at other time of day if preferable) for a 24 month period

Arm title	placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

a single 25 milligram tablet taken orally once per day (typically to be taken during the morning, but can be taken regularly at other time of day if preferable) for a 24 month period

Number of subjects in period 2	spironolactone	placebo
Started	125	125
Completed	111	117
Not completed	14	8
Consent withdrawn by subject	11	7
death	3	1

Period 3	
Period 3 title	24 month time point
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	spironolactone

Arm description: -

Arm type	Experimental
Investigational medicinal product name	spironolactone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

single 25 milligram tablet taken orally once per day (typically to be taken during the morning, but can be taken regularly at other time of day if preferable) for a 24 month period

Arm title	placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

a single 25 milligram tablet taken orally once per day (typically to be taken during the morning, but can be taken regularly at other time of day if preferable) for a 24 month period

Number of subjects in period 3	spironolactone	placebo
Started	111	117
Completed	101	106
Not completed	10	11
Consent withdrawn by subject	8	9
death	2	2

Baseline characteristics

Reporting groups	
Reporting group title	spironolactone
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Reporting group values	spironolactone	placebo	Total
Number of subjects	125	125	250
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	72.4	72.3	
standard deviation	± 7.1	± 7.9	-
Gender categorical Units: Subjects			
Female	28	31	59
Male	97	94	191
Peak VO2			
The dichotomised peak VO2 score (ml O2/kg/min) was used as the stratification variable			
Units: Subjects			
≤ 16 mL	77	78	155
> 16 mL	48	47	95
Not recorded	0	0	0
Current medication			
1 patients data missing (reporting group 2)			
Units: Subjects			
Yes	123	124	247
No	2	0	2
Not recorded	0	1	1
Smoking status Units: Subjects			
Current smoker	6	8	14
Ex-smoker	66	68	134
Non-smoker	53	49	102
Not recorded	0	0	0

Ethnicity Units: Subjects			
White	118	118	236
Mixed	1	0	1
Black	3	3	6
Asian	3	2	5
Other ethnic group	0	2	2
Not recorded	0	0	0
Peak VO2 Units: ml O2/kg/min			
arithmetic mean	14.5	14.6	
standard deviation	± 4.6	± 5.1	-
BMI			
2 patients data missing (reporting group 2)			
Units: kg/m2			
arithmetic mean	30.4	30.5	
standard deviation	± 5.2	± 5.6	-
Alcohol use Units: Units per week			
arithmetic mean	7.2	8.8	
standard deviation	± 9.9	± 10.8	-
6 minute walk test Units: meters			
arithmetic mean	256.7	270.4	
standard deviation	± 83.4	± 89.5	-
Resting heart rate Units: bpm			
arithmetic mean	87.3	86.7	
standard deviation	± 19.4	± 18.7	-
Peak heart rate during CPET Units: bpm			
arithmetic mean	128.4	129.9	
standard deviation	± 26.1	± 25.4	-
BNP			
One patient data not recorded (Reporting group 2)			
Units: pg/ml			
arithmetic mean	163.5	183.3	
standard deviation	± 125.4	± 168.5	-
Systolic blood pressure			
One patient data not recorded (Reporting group 2)			
Units: mmHg			
arithmetic mean	129.2	130.1	
standard deviation	± 15.5	± 15.0	-
Diastolic blood pressure			
One patient data not recorded (Reporting group 2)			
Units: mmHg			
arithmetic mean	75.7	75.6	
standard deviation	± 10.9	± 13.9	-
Waist circumference			
Two patients data not recorded (Reporting group 2)			
Units: cm			
arithmetic mean	99.5	100.3	

standard deviation	± 12.5	± 14.4	-
Hip circumference			
Two patients data not recorded (Hip circumference) reporting group 2			
Units: cm			
arithmetic mean	107.4	108.0	
standard deviation	± 10.0	± 13.2	-
Left ventricular ejection fraction			
Units: percent			
arithmetic mean	60.4	60.5	
standard deviation	± 5.4	± 5.7	-
Mitral valve measurement			
Units: E/E’ ratio			
arithmetic mean	10.7	10.6	
standard deviation	± 4.4	± 4.2	-
EQ-5D-5L			
9 patient's data not recorded (4 reporting group 1, 5 reporting group 2)			
Units: Score			
arithmetic mean	0.81	0.83	
standard deviation	± 0.19	± 0.16	-
ML WHF			
To score MLWHF (Minnesota Living with Heart Failure) questionnaire, it was allowed that at most 20% of 21 responses missing which was equivalent to 4 data items. If there were less than or equal to 4 data items missing then we used mean substitution to impute the missing responses and then scored the questionnaire by summating the responses to all 21 questions; otherwise, the persons score was left missing. 12 patients data was not recorded (8 reporting arm 1, 4 reporting arm 2)			
Units: Score			
arithmetic mean	22.9	21.9	
standard deviation	± 20.4	± 22.9	-

End points

End points reporting groups

Reporting group title	spironolactone
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	
Reporting group title	spironolactone
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	
Reporting group title	spironolactone
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Primary: peak VO2 on cardiopulmonary exercise testing (Primary analysis adjusted for stratification variable)

End point title	peak VO2 on cardiopulmonary exercise testing (Primary analysis adjusted for stratification variable)

End point description:

The primary analysis followed intention to treat principles including participants regardless of their compliance with the medication. Participants with missing data for the final assessment were excluded except for those who died before the 24 month follow-up assessment. For these participants, their peak VO2 scores at 24 months were imputed as zero values regardless of cause. Whilst the value of 0 was not actually measured, it allowed inclusion of the patient in the study and it should be a suitable reflection of the health state of the patient. The imputation rules were defined prior to any data analysis and reported in the Statistical Analysis Plan.
A value of 0 was assigned to peak VO2 score for those who died before the 24 month follow-up assessment

End point type	Primary

End point timeframe:

24 months

End point values	spironolactone	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	106		
Units: ml O2/kg/min				
arithmetic mean (standard deviation)	14.03 (± 5.38)	14.45 (± 5.14)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	placebo v spironolactone

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Regression, Linear

Secondary: Exercise tolerance measured by 6-minute walking test (a simple test of exercise performance) at 2 years- Primary analysis (adjusted for stratification variable)

End point title	Exercise tolerance measured by 6-minute walking test (a simple test of exercise performance) at 2 years- Primary analysis (adjusted for stratification variable)

End point description:

Analyses of secondary outcomes were performed on the intention to treat basis as for the primary outcome. For the 6 minute walking test, the analysis substituted a zero value for those participants who had died before the 24 month follow-up assessment regardless of causes. Placebo group is the reference group.

End point type	Secondary

End point timeframe:

24 months

End point values	spironolactone	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	107		
Units: meter				
arithmetic mean (standard deviation)	312.90 (± 108.12)	330.43 (± 112.16)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	spironolactone v placebo
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Regression, Linear

Secondary: left ventricular diastolic function (E/E’ ratio on echocardiography) assessed at 2 years (Primary analysis (adjusted for stratification variable)

End point title	left ventricular diastolic function (E/E’ ratio on echocardiography) assessed at 2 years (Primary analysis (adjusted for stratification variable)

End point description:

if patients who died before the 24 month follow-up assessment, no imputation was done for these missing values and so analysis for those was done on all available data only, i.e. complete case analysis.

End point type	Secondary

End point timeframe:

24 months

End point values	spironolactone	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	106		
Units: E/E' ratio				
arithmetic mean (standard deviation)	9.00 (± 3.05)	9.72 (± 3.57)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	spironolactone v placebo
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Regression, Linear

Secondary: Brain natriuretic peptide level (BNP) at 2 years Primary analysis (adjusted for stratification variable)

End point title	Brain natriuretic peptide level (BNP) at 2 years Primary analysis (adjusted for stratification variable)

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	spironolactone	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	105		
Units: pg/mL				
arithmetic mean (standard deviation)	179.43 (± 170.55)	185.61 (± 109.65)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	spironolactone v placebo
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Regression, Linear

Secondary: Quality of life (EQ-5D-5L questionnaire) over the two year duration Primary analysis (adjusted for stratification variable)

End point title	Quality of life (EQ-5D-5L questionnaire) over the two year duration Primary analysis (adjusted for stratification variable)

End point description:

Analyses of secondary outcomes were performed on the intention to treat basis as for the primary outcome. EQ-5D-5L score, the lowest value across the whole participants was assigned to those who died before the 12 month follow-up assessment (Placebo group is the reference group)

End point type	Secondary

End point timeframe:

12 months

End point values	spironolactone	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	111		
Units: EuroQol score				
arithmetic mean (standard deviation)	0.83 (± 0.21)	0.84 (± 0.18)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	spironolactone v placebo

Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	Regression, Linear

Secondary: Quality of life (EQ-5D-5L questionnaire) over the 24 month duration Primary analysis (adjusted for stratification variable)

End point title	Quality of life (EQ-5D-5L questionnaire) over the 24 month duration Primary analysis (adjusted for stratification variable)

End point description:

Analyses of secondary outcomes were performed on the intention to treat basis as for the primary outcome. EQ-5D-5L score, the lowest value across the whole participants was assigned to those who died before the 24 month follow-up assessment (Placebo group is the reference group)

End point type	Secondary

End point timeframe:

24 months

End point values	spironolactone	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	104		
Units: EuroQol score				
arithmetic mean (standard deviation)	0.82 (± 0.24)	0.84 (± 0.20)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	spironolactone v placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Regression, Linear

Secondary: Quality of life (MLWHF questionnaire) over the two year duration Primary analysis (adjusted for stratification variable)

End point title	Quality of life (MLWHF questionnaire) over the two year duration Primary analysis (adjusted for stratification variable)

End point description:

Analyses of secondary outcomes were performed on the intention to treat basis as for the primary outcome. Minnesota Living with Heart Failure questionnaire, the highest value across the whole participants was assigned to those who died before the 12 month follow-up assessment. Minnesota Living with Heart Failure questionnaire; score ranges from 0 to 105 with a higher score reflecting poorer quality of life

End point type	Secondary
End point timeframe: 12 months	

End point values	spironolactone	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	110		
Units: MLWHF score				
arithmetic mean (standard deviation)	18.44 (± 20.89)	16.90 (± 17.76)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	spironolactone v placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Regression, Linear

Secondary: Quality of life (MLWHF questionnaire) over the two year duration Primary analysis (adjusted for stratification variable)

End point title	Quality of life (MLWHF questionnaire) over the two year duration Primary analysis (adjusted for stratification variable)
End point description: Analyses of secondary outcomes were performed on the intention to treat basis as for the primary outcome. Minnesota Living with Heart Failure questionnaire, the highest value across the whole participants was assigned to those who died before the 24 month follow-up assessment. Minnesota Living with Heart Failure questionnaire; score ranges from 0 to 105 with a higher score reflecting poorer quality of life	
End point type	Secondary
End point timeframe: 24 months	

End point values	spironolactone	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: MLWHF score				
arithmetic mean (standard deviation)	17.39 (± 22.72)	15.34 (± 20.35)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	spironolactone v placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Regression, Linear

Secondary: spontaneous return to sinus rhythm (ECG) at 2 years- Primary analysis (adjusted for stratification variable)

End point title	spontaneous return to sinus rhythm (ECG) at 2 years- Primary analysis (adjusted for stratification variable)

End point description:

Analysis undertaken on complete cases only. "Yes" means spontaneous return to sinus rhythm (ECG) after 2 years of treatment (Placebo group is the reference group)

End point type	Secondary

End point timeframe:

24 months

End point values	spironolactone	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	106		
Units: number				
Yes	8	4		
No	93	102		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	spironolactone v placebo

Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Regression, Logistic

Secondary: rates of all-cause hospitalisations during 2 year follow-up Participants with at least one event- Primary analysis (adjusted for stratification variable)

End point title	rates of all-cause hospitalisations during 2 year follow-up Participants with at least one event- Primary analysis (adjusted for stratification variable)

End point description:

End point type	Secondary

End point timeframe:

during 24 month follow up

End point values	spironolactone	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: number	18	28		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: The SAE reporting period was from the date of consent (screening) until 7 days after the last dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	spironolactone
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Serious adverse events	spironolactone	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 125 (18.40%)	32 / 125 (25.60%)	
number of deaths (all causes)	5	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 125 (0.00%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile cancer			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal cancer metastatic			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung cancer			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pulmonary emboli			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
sacrohysteropexy			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
total hip replacement			
subjects affected / exposed	1 / 125 (0.80%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Total knee replacement			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Facial swelling			

subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
shortness of breath			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
fracture neck of femur			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			

subjects affected / exposed	1 / 125 (0.80%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 125 (0.80%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
symptomatic bradycardia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dilated right ventricle			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
complications of Bypass surgery			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina episode			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope Asystole Pacemaker insertion			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 125 (0.80%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Stroke			

subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
transient ischaemic attack			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
intra cranial bleed			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Iron deficiency anaemia	Additional description: Chest infection with symptomatic iron deficiency anaemia.		
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
unilateral loss of vision			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
gut emboli			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 125 (1.60%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper GI bleeding			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

duodenal bleeding ulcer			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary clot			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
cellulitis sepsis			
subjects affected / exposed	1 / 125 (0.80%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Diarrhoea			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea and vomiting			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
infected left leg ulcers			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 125 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	3 / 125 (2.40%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest infection			
subjects affected / exposed	2 / 125 (1.60%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
septic arthritis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septicaemia			
subjects affected / exposed	0 / 125 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
infective endocarditis			
subjects affected / exposed	0 / 125 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
clostridium difficile bacterial sepsis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	spironolactone	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 125 (69.60%)	65 / 125 (52.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignancy			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	

General disorders and administration site conditions			
Constitutional Symptoms			
subjects affected / exposed	15 / 125 (12.00%)	22 / 125 (17.60%)	
occurrences (all)	20	30	
Haemorrhage/Bleeding			
subjects affected / exposed	2 / 125 (1.60%)	3 / 125 (2.40%)	
occurrences (all)	2	3	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 125 (1.60%)	0 / 125 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	17 / 125 (13.60%)	5 / 125 (4.00%)	
occurrences (all)	40	9	
Breast swelling			
subjects affected / exposed	11 / 125 (8.80%)	4 / 125 (3.20%)	
occurrences (all)	26	10	
Sexual/Reproductive Function			
subjects affected / exposed	1 / 125 (0.80%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Cardiac disorders			
Cardiac Arrhythmia/ Cardiac General			
subjects affected / exposed	21 / 125 (16.80%)	33 / 125 (26.40%)	
occurrences (all)	34	65	
Nervous system disorders			
Neurology			
subjects affected / exposed	7 / 125 (5.60%)	5 / 125 (4.00%)	
occurrences (all)	9	6	
Eye disorders			
Ocular/Visual			
subjects affected / exposed	2 / 125 (1.60%)	3 / 125 (2.40%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	13 / 125 (10.40%)	19 / 125 (15.20%)	
occurrences (all)	18	24	

Skin and subcutaneous tissue disorders			
Dermatology/Skin			
subjects affected / exposed	6 / 125 (4.80%)	5 / 125 (4.00%)	
occurrences (all)	9	7	
Renal and urinary disorders			
Estimated glomerular filtration < 30 mL/min/1.73m2			
subjects affected / exposed	8 / 125 (6.40%)	2 / 125 (1.60%)	
occurrences (all)	8	2	
Renal			
subjects affected / exposed	0 / 125 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Genitourinary			
subjects affected / exposed	3 / 125 (2.40%)	1 / 125 (0.80%)	
occurrences (all)	4	1	
Endocrine disorders			
Endocrine			
subjects affected / exposed	1 / 125 (0.80%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal/Soft Tissue			
subjects affected / exposed	16 / 125 (12.80%)	23 / 125 (18.40%)	
occurrences (all)	20	26	
Infections and infestations			
Infection			
subjects affected / exposed	12 / 125 (9.60%)	10 / 125 (8.00%)	
occurrences (all)	13	11	
Metabolism and nutrition disorders			
Hyperkalaemia (≥5.1 mmol/L)			
subjects affected / exposed	46 / 125 (36.80%)	17 / 125 (13.60%)	
occurrences (all)	72	30	
Hyperkalaemia (≥6.0 mmol/L)			
subjects affected / exposed	3 / 125 (2.40%)	0 / 125 (0.00%)	
occurrences (all)	3	0	
Serum creatinine ever >220 µmol/L			
subjects affected / exposed	1 / 125 (0.80%)	0 / 125 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2015	Change in blood tests Change in drug manufacturer. Removal of GP checklist. Addition of rebooking tests. Clarification of randomisation and blinding.
01 May 2015	Inclusion in the trial is no longer conditional on the patient having normal BNP levels (<100pg/mL). Clarification of personnel designated as CI and PI. Trial Management Group to meet regularly rather than weekly (section 14.3). Amendment of section 6.3 (Blinding) to clarify that individual sealed code break envelopes will be used, rather than a master list. Change of trial statistician due to retirement of original person. Pharmacy to audit drug storage facility annually, rather than six monthly, in line with internal NHS policy (section 7.1.4). Non-responders to invitation from Primary Care to be sent a reminder letter (Section 4.1 and 8.1). Minor corrections to grammar and spelling.
12 October 2015	A mechanistic sub-analysis of impact of biomarkers of fibrosis and haemostasis in the study population (Appendix 1) To include a timeline for visit windows. The Ability to understand questionnaires being removed as an inclusion criteria and added as an exclusion criteria.(section 4.1)
10 March 2016	IMP dispensing schedule amended to reflect that Drug will be dispensed at different clinic visits for a small number of patients. GP invitation letter amended to reflect that The University of Birmingham will keep the information provided on reply slips on a secure database until they are no longer needed, and they will then be destroyed. Telephone pre-screening added to the protocol. Participants that have expressed an interest will be prescreened by telephone and asked the medical questions outlined in section 3.1. Minor corrections to grammar and spelling.
05 January 2017	Threshold for withdrawal due to hyperkalaemia increased to K+>6.0 mmol/L, up from >5.5 mmol/L. Reduced follow-up focussed on trial outcomes permitted for patients that have withdrawn from trial treatment only. Increased flexibility for dispensing of trial medication to ensure continuous supply. Changes to reflect merger of trials units at University of Birmingham. Clarifications to required trial assessments, time window frame permitted for follow up visits at month 6, 12 and 18 changed and to monitoring of concomitant medications. Minor corrections and clarifications.
13 April 2017	Section 6.3: Additional spare bottles of trial medication will be ordered as required as part of the scheduled order has been added. Section 7.2: to ensure consistency of wording throughout the protocol nonlife threatening side effects such as gynaecomastia has been changed to "significant" gynaecomastia. IMP re-up-titration clarification added: "the patient is likely to maintain potassium levels ≤5.0 mmol/L after returning to a full dose" Section 8.4: Participant incentive detailed in the protocol in line with approved PIS v5 dated 30th March 2015. Section 8.5: Definitions of Patient discontinuation in the trial have been added. Section 8.6: The process of informing patients of their treatment allocation after data analysis has been completed stipulated. Section 9: Reference Safety Information (RSI) is specified as undesirable effects of Summary of Medicinal Product Characteristics (SmPC) for spironolactone 25mg (updated 13/04/2016). Assessment of all Adverse Events changed from CI & PI to PI & medically qualified delegate. PI signature page added. Data manager name added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported