Clinical trial results:
Effects of Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction (HF-PEF): Cardiac MRI, Echocardiography, Exercise Physiology & Quality of Life Assessment

Summary

EudraCT number	2013-000867-10
Trial protocol	GB
Global end of trial date	27 July 2017

Results information

Result version number	v1 (current)
This version publication date	05 September 2019
First version publication date	05 September 2019
Summary attachment (see zip file)	HF-PEF JAHA final (HF-PEF JAHA final.pdf) HF-PEF tables final (Tables HF-PEF JAHA final.pdf)

Trial information

Trial identification

Sponsor protocol code	CD13/10671

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1145-4102

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Leeds, Leeds, United Kingdom, LS2 9JT
Public contact	A K McDiarmid, University of Leeds, a.k.mcdiarmid@leeds.ac.uk
Scientific contact	A K McDiarmid, University of Leeds, a.k.mcdiarmid@leeds.ac.uk

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	01 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 July 2017
Global end of trial reached?	Yes
Global end of trial date	27 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To define mechanisms for effect of Aldosterone antagonism in the treatment of heart failure with preserved ejection fraction (HF-PEF) using cardiac magnetic resonance imaging.

Protection of trial subjects:

An independent Trial Steering Committee assisted the CI and the research team to ensure trial participants were protected from harm.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 51
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	3
From 65 to 84 years	45
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Adults aged 18-90 with a clinical diagnosis of HF-PEF according to 2012 European Society of Cardiology (ESC)(1) criteria under the care of the local heart failure service (Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom) were eligible to participate in the study. Recruitment took place between 04/06/2014 and 06/12/2016.

Pre-assignment

Screening details:

Inclusion criteria: NYHA class II-IV, physical signs consistent with heart failure, LVEF on clinical echocardiography >50% and NT-proBNP >400pg/L at routine clinic attendance.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	spironolactone

Arm description: -

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

Dosage and administration details:

25 mg od.

Arm title	no treatment

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	spironolactone	no treatment
Started	27	24
Completed	19	21
Not completed	8	3
Physician decision	3	-
Consent withdrawn by subject	1	3
inability to tolerate CMR	1	-
Protocol deviation	3	-

Baseline characteristics

Reporting groups	
Reporting group title	spironolactone
Reporting group description: -	
Reporting group title	no treatment
Reporting group description: -	

Reporting group values	spironolactone	no treatment	Total
Number of subjects	27	24	51
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	76.4	74.0	
standard deviation	± 5.4	± 8.8	-
Gender categorical Units: Subjects			
Female	14	13	27
Male	13	11	24

End points

End points reporting groups

Reporting group title	spironolactone
Reporting group description: -	
Reporting group title	no treatment
Reporting group description: -	

Primary: Change in myocardial extracellular volume (ECV) fraction by cardiovascular magnetic resonance (CMR) as a surrogate of diffuse fibrosis.

End point title	Change in myocardial extracellular volume (ECV) fraction by cardiovascular magnetic resonance (CMR) as a surrogate of diffuse fibrosis.[1]

End point description:

End point type	Primary

End point timeframe:

after 6 months of treatment/no intervention

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see the results paper which has been uploaded and contains details of the statistical analysis.

End point values	spironolactone	no treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: percent volume/volume				
number (not applicable)	-1.0	0.8		

Attachments (see zip file)	HF-PEF tables final/Tables HF-PEF JAHA final.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: overall study	
Assessment type	Systematic

Dictionary used	
Dictionary name	per study protocol
Dictionary version	2.5

Reporting groups	
Reporting group title	spironolactone
Reporting group description: -	
Reporting group title	no treatment
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no non-serious adverse events in this study.

Serious adverse events	spironolactone	no treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 27 (11.11%)	0 / 24 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Renal failure	Additional description: Impairment of renal function		
subjects affected / exposed	3 / 27 (11.11%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	spironolactone	no treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2014	Substantial Amendment 1: Changes were made to the protocol and patient documentation to provide greater clarity around the prescription of the IMP and around additional visits for the participants. These changes were suggested following an early internal monitoring visit and after discussion with the Chief Investigator.
25 February 2016	Substantial Amendment 2: A notification of serious breach of GCP or the trial protocol was submitted to the competent authority. The sponsor and the research team were of the opinion that no further patients should be approached and recruited until appropriate changes have been made to the study protocol. These are changes surrounding the management of study visits.
06 April 2016	The changes were made to provide greater clarity around the blood tests and around additional visits for the participants. Time windows were added to the visit schedule. We implemented these changes due to repeated problems with getting the blood tests performed in a timely manner in the community. We requested to restart the trial which had been temporarily halted on 25/02/2016.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 February 2016	As described in amendment 2, the trial was halted whilst new safety measures surrounding blood testing were put in place.	23 March 2016

Notes:

Limitations and caveats

None reported