Clinical trial results:
Impact of Eplerenone on Asymptomatic Left Ventricular Diastolic Dysfunction in Diabetic Patients

Summary

EudraCT number	2011-006123-37
Trial protocol	IE
Global end of trial date	23 November 2015

Results information

Result version number	v1 (current)
This version publication date	08 December 2016
First version publication date	08 December 2016
Summary attachment (see zip file)	Study Synopsis (Eplerenone_EOS Synopsis_23Nov2016.pdf)

Trial information

Trial identification

Sponsor protocol code	SI-C-019

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Solvotrin Innovations Ltd
Sponsor organisation address	Hoffmann Park, Inchera, Little Island, Cork, Ireland, T45 YX04
Public contact	Clinical Trials Project Manager, Solvotrin Innovations Ltd, +353 21 4205339, fionaryan@solvotrin.com
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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	23 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 November 2015
Global end of trial reached?	Yes
Global end of trial date	23 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the change in Left Atrial Volume Index (LAVI), measured by magnetic resonance imaging (MRI) in the treated group vs. the untreated group

Protection of trial subjects:

This study was carried out in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Before initiating the study, all relevant documentation including the study protocol and patient information and informed consent form were reviewed and approved by the relevant competent authority and the St Vincent's University Hospital Ethics Committee. Each participant was provided with an information and consent form in clear, simple language and was given ample time to inquire about details of the study and to decide whether of not to participate in the study. Participants anonymity was maintained at all times throughout the study.

Background therapy:

Usual medical care

Evidence for comparator:

The comparator group was usual medical care. There was no placebo.

Actual start date of recruitment	03 September 2012
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	Ireland: 52
Worldwide total number of subjects	52
EEA total number of subjects	52

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)	36
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial participants were recruited from the Blood Pressure Unit of St Michael's Hospital, Dun Laoghaire, Co Dublin. Male and female patients >18 years of age were eligible to participate once eligibility criteria were met.

Pre-assignment

Screening details:

The STOP-HF database was screened to identify patients that met the inclusion criteria (age, diabetes, diastolic dysfunction). Potentially eligible patients were invited to a 'Screening visit' at which eligibility was further assessed/confirmed.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Unblinded study

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention (eplerenone)

Arm description:

Usual medical therapy and additional treatment with eplerenone. Eplerenone was administered at an initial dose of 25 mg once daily and increased to 50 mg once daily after one month (providing the increase in creatinine from baseline was no greater than 25% and the potassium level within one week of commencing eplerenone was <5.5 mmol/L)

Arm type	Experimental
Investigational medicinal product name	Eplerenone
Investigational medicinal product code	
Other name	Inspra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Eplerenone 25mg once daily orally for one month. Dose increased to 50mg once daily orally for the remainder of the study (11 months) providing the increase in creatinine from baseline is no greater than 25% and the potassium level within one week of commencing eplerenone is <5.5 mmol/L.

Arm title	Control

Arm description:

Usual medical care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Intervention (eplerenone)	Control
Started	28	24
Completed	28	24

Period 2	
Period 2 title	12 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Intervention (eplerenone)

Arm description:

Usual medical therapy and additional treatment with eplerenone. Eplerenone was administered at an initial dose of 25 mg once daily and increased to 50 mg once daily after one month (providing the increase in creatinine from baseline was no greater than 25% and the potassium level within one week of commencing eplerenone was <5.5 mmol/L)

Arm type	Experimental
Investigational medicinal product name	Eplerenone
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Arm title	Control

Arm description:

Usual medical care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Intervention (eplerenone)	Control
Started	28	24
Completed	24	24
Not completed	4	0
Consent withdrawn by subject	3	-
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Intervention (eplerenone)
Reporting group description:	
Usual medical therapy and additional treatment with eplerenone. Eplerenone was administered at an initial dose of 25 mg once daily and increased to 50 mg once daily after one month (providing the increase in creatinine from baseline was no greater than 25% and the potassium level within one week of commencing eplerenone was <5.5 mmol/L)	
Reporting group title	Control
Reporting group description:	
Usual medical care	

Reporting group values	Intervention (eplerenone)	Control	Total
Number of subjects	28	24	52
Age categorical Units: Subjects			
Adults (18-64 years)	7	9	16
From 65-84 years	21	15	36
85 years and over	0	0	0
Age continuous Units: years			
median	72	67	
inter-quartile range (Q1-Q3)	65 to 76	63 to 72	-
Gender categorical Units: Subjects			
Female	6	8	14
Male	22	16	38
Diabetes			
The demographics and comorbidity profile of the population are typical of patients with asymptomatic left ventricular diastolic dysfunction (ALVDD). In this diabetic population, subject had diabetes for over 10 years. At baseline, the majority of the study population had hypertension (over 85%) and over two thirds had dyslipidaemia. There was no statistical significance of the variables (clinical assessment, medical history, lifestyle factors, and medication) between the intervention and control groups.			
Units: Subjects			
Diabetes	28	24	52
No diabetes	0	0	0
Hypertension Units: Subjects			
Hypertension	25	21	46
No hypertension	3	3	6
Dyslipidemia Units: Subjects			
Dyslipidemia	19	16	35
No dyslipidemia	9	8	17
Atrial fibrillation Units: Subjects			
Atrial fibrillation	0	0	0
No atrial fibrillation	28	24	52
Ischemic heart disease			

Units: Subjects			
Ischemic heart disease	9	2	11
No ischemic heart disease	19	22	41
Percutaneous coronary intervention Units: Subjects			
Percutaneous coronary intervention	1	0	1
No Percutaneous coronary intervention	27	24	51
Coronary artery bypass graft Units: Subjects			
Coronary artery bypass graft	5	0	5
No coronary artery bypass graft	23	24	47
Stroke Units: Subjects			
Stroke	1	0	1
No stroke	27	24	51
Smoking history Units: Subjects			
Current smoker	1	1	2
Former smoker	15	13	28
Never smoked	11	9	20
Not reported	1	1	2
Alcohol habit Units: Subjects			
Drinks alcohol	22	17	39
Does not drink alcohol	6	7	13
Medication history. Angiotensin converting enzyme (ACE) inhibitor Units: Subjects			
ACE inhibitor	15	16	31
No ACE inhibitor	13	8	21
Medication history: Angiotensin receptor blocker (ARB) Units: Subjects			
ARB	10	4	14
No ARB	18	20	38
Medication history: Diuretic Units: Subjects			
Diuretic	13	12	25
No diuretic	15	12	27
Medication history: Beta-blocker Units: Subjects			
Beta-blocker	18	14	32
No beta-blocker	10	10	20
Medication history: Alpha-blocker Units: Subjects			
Alpha-blocker	10	9	19
No alpha-blocker	18	15	33
Medication history: Calcium channel blocker (CCB) Units: Subjects			
CCB	15	8	23

No CCB	13	16	29
Medication history: Statin Units: Subjects			
Statin	21	15	36
No statin	7	9	16
Medication history: Antiplatelet Units: Subjects			
Antiplatelet	21	22	43
No antiplatelet	7	2	9
Medication history: Biguanide Units: Subjects			
Biguanide	20	18	38
No biguanide	8	6	14
Medication history: Sulphonylurea Units: Subjects			
Sulphonylurea	7	4	11
No sulphonylurea	21	20	41
Medication history: Thiazolidinedione Units: Subjects			
Thiazolidinedione	2	1	3
No thiazolidinedione	26	23	49
Medication history: Gliptin Units: Subjects			
Gliptin	5	5	10
No gliptin	23	19	42
Medication history: GLP-1 agonist Units: Subjects			
GLP-1 agonist	1	0	1
No GLP-1 agonist	27	24	51
Medication history: Insulin Units: Subjects			
Insulin	5	4	9
No insulin	23	20	43
Body Mass Index (BMI) Units: kg/m2			
median	30.2	30	
inter-quartile range (Q1-Q3)	27.02 to 32.92	27.9 to 33.12	-
Height Units: cm			
median	175	171.5	
inter-quartile range (Q1-Q3)	163.25 to 180.23	161.88 to 179	-
Weight Units: kilogram(s)			
median	89.6	86.3	
inter-quartile range (Q1-Q3)	81.43 to 99.28	83 to 98.33	-
Waist Units: cm			
median	106.75	107.5	
inter-quartile range (Q1-Q3)	99.5 to 114.75	103.75 to 112	-
Heart rate Units: Beats per minute			

median	62.5	63	
inter-quartile range (Q1-Q3)	57.5 to 72	57.5 to 67.5	-
Systolic Blood Pressure (SBP)			
Units: mmHg			
median	136	134	
inter-quartile range (Q1-Q3)	123.5 to 144	122.25 to 146.25	-
Diastolic Blood Pressure (DBP)			
Units: mmHg			
median	75	74.5	
inter-quartile range (Q1-Q3)	69.25 to 85.75	66.75 to 82	-

End points

End points reporting groups

Reporting group title	Intervention (eplerenone)
Reporting group description:	
Usual medical therapy and additional treatment with eplerenone. Eplerenone was administered at an initial dose of 25 mg once daily and increased to 50 mg once daily after one month (providing the increase in creatinine from baseline was no greater than 25% and the potassium level within one week of commencing eplerenone was <5.5 mmol/L)	
Reporting group title	Control
Reporting group description:	
Usual medical care	
Reporting group title	Intervention (eplerenone)
Reporting group description:	
Usual medical therapy and additional treatment with eplerenone. Eplerenone was administered at an initial dose of 25 mg once daily and increased to 50 mg once daily after one month (providing the increase in creatinine from baseline was no greater than 25% and the potassium level within one week of commencing eplerenone was <5.5 mmol/L)	
Reporting group title	Control
Reporting group description:	
Usual medical care	

Primary: Change of left atrial volume index (LAVI) (measured by MRI)

End point title	Change of left atrial volume index (LAVI) (measured by MRI)
End point description:	
The primary endpoint of this study was the change in LAVI measured by cardiac MRI between the study groups. Accordingly, the efficacy evaluations for primary and secondary endpoints were carried out on subjects with paired baseline and 12 month analyses. The endpoint analysis, therefore, excludes the four subjects who were withdrawn from the study. Treatment with eplerenone for 12 months did not result in a significant impact on LAVI measured by MRI.	
End point type	Primary
End point timeframe:	
Baseline to 12 months	

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: ml/m2				
median (inter-quartile range (Q1-Q3))	0.32 (-3.47 to 3.01)	0.77 (-3.13 to 4.97)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Control v Intervention (eplerenone)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7817
Method	t-test, 2-sided

Secondary: b-type natriuretic peptide (BNP) (Change)

End point title	b-type natriuretic peptide (BNP) (Change)

End point description:

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	0 (-10.85 to 20.58)	-1.45 (-28.95 to 15.65)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5416
Method	Wilcoxon (Mann-Whitney)

Secondary: Carboxy-terminal propeptide of procollagen type I (PICP) (Change)

End point title	Carboxy-terminal propeptide of procollagen type I (PICP) (Change)

End point description:

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	-44.04 (-191.72 to 64.74)	-7.69 (-63.46 to 51.23)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3219
Method	Wilcoxon (Mann-Whitney)

Secondary: Matrix metalloproteinase-1 (MMP-1) (Change)

End point title	Matrix metalloproteinase-1 (MMP-1) (Change)

End point description:

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	7752.02 (1710.01 to 15248.07)	7801.07 (2474.48 to 22017.26)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9422
Method	t-test, 2-sided

Secondary: Matrix metalloproteinase-9 (MMP-9) (Change)

End point title	Matrix metalloproteinase-9 (MMP-9) (Change)

End point description:

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	20556.64 (3509.67 to 48564.5)	39190.54 (-15653.1 to 75745.61)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7539
Method	t-test, 2-sided

Secondary: Left ventricular mass index (LVMI) (Change)

End point title	Left ventricular mass index (LVMI) (Change)

End point description:

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: g/m2				
median (inter-quartile range (Q1-Q3))	0.95 (-8.51 to 11.17)	-2.71 (-20.45 to 3.45)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0806
Method	t-test, 2-sided

Secondary: Left ventricular ejection fraction (LVEF) (Change)

End point title	Left ventricular ejection fraction (LVEF) (Change)

End point description:

For the doppler-echocardiographic markers of diastolic function, there were no between-group changes in the study groups. Eplerenone did not manifest significant changes in measurements of diastolic function.

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	0.5 (-5.25 to 4.75)	-2 (-5 to 2)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4262
Method	Wilcoxon (Mann-Whitney)

Secondary: Left atrial volume index (LAVI) (measured by Doppler Echo) (Change)

End point title	Left atrial volume index (LAVI) (measured by Doppler Echo) (Change)

End point description:

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: mL/m2				
median (inter-quartile range (Q1-Q3))	0.3 (-1 to 5.8)	1.3 (-4 to 2.8)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6918
Method	Wilcoxon (Mann-Whitney)

Secondary: E/E' average (ratio) (Change)

End point title	E/E' average (ratio) (Change)

End point description:

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Ratio				
median (inter-quartile range (Q1-Q3))	-0.15 (-1.92 to 0.48)	1.15 (-1.08 to 2.05)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2446
Method	t-test, 2-sided

Post-hoc: Systolic blood pressure (SBP) (Change)

End point title	Systolic blood pressure (SBP) (Change)

End point description:

Eplerenone is a blood pressure lowering agent. As an exploratory endpoint, a post-hoc analysis of the effects of eplerenone on blood pressure was carried out. Eplerenone did not have any significant effect on blood pressure in this study cohort.

End point type	Post-hoc

End point timeframe:

Baseline to 12 months

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: mmHg				
median (inter-quartile range (Q1-Q3))	-0.5 (-8.5 to 5)	-3.5 (-8 to 1.25)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5388
Method	t-test, 2-sided

Post-hoc: Diastolic blood pressure (DBP) (Change)

End point title	Diastolic blood pressure (DBP) (Change)

End point description:

End point type	Post-hoc

End point timeframe:

Baseline to 12 months

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: mmHg				
median (inter-quartile range (Q1-Q3))	-1 (-4.25 to 2.25)	-1.5 (-5.25 to 2)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9025
Method	t-test, 2-sided

Post-hoc: Pulse pressure (Change)

End point title	Pulse pressure (Change)

End point description:

There is a progressive increase in pulse pressure in the control group, which is significant. The pulse pressure in the intervention group is maintained with eplerenone. High pulse pressure is a strong predictor for evolving heart dysfunction, especially for older adults. Pulse pressure beyond 60 is considered as a risk factor of cardiovascular disease. Thus, while the blood pressure parameters did not improve with eplerenone, the pulse pressure is maintained, which suggests a potential effect of eplerenone.

End point type	Post-hoc
End point timeframe: Baseline to 12 months	

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: mmHg				
median (inter-quartile range (Q1-Q3))	0 (-3 to 4.25)	-1.5 (-5.5 to 1)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.0402
Method	t-test, 2-sided

Post-hoc: Heart rate (Change)	
End point title	Heart rate (Change)
End point description:	

End point type	Post-hoc
End point timeframe: Baseline to 12 months	

End point values	Intervention (eplerenone)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: beats per minute				
median (inter-quartile range (Q1-Q3))	-2 (-4.5 to 1)	0.5 (-4.5 to 3)		

Statistical analyses

Statistical analysis title	Comparison of change between groups
Comparison groups	Intervention (eplerenone) v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4201
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of the informed consent form through 30 days after the last dose of investigational product.

Adverse event reporting additional description:

Information was collected at each visit based on information provided spontaneously by the subject and/or through questioning. If any changes to medication suggested a new illness or worsening of a pre-existing condition, the subject was questioned further. Abnormal laboratory/test results if deemed medically significant, were considered AEs

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Intervention (eplerenone)

Reporting group description:

Usual medical therapy and additional treatment with eplerenone. Eplerenone was administered at an initial dose of 25 mg once daily and increased to 50 mg once daily after one month (providing the increase in creatinine from baseline was no greater than 25% and the potassium level within one week of commencing eplerenone was <5.5 mmol/L)

Reporting group title	Control

Reporting group description:

Usual medical care

Serious adverse events	Intervention (eplerenone)	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 28 (17.86%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Syncope			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 28 (7.14%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension	Additional description: Postural hypotension		

subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Angioedema			
subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Intervention (eplerenone)	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 28 (78.57%)	13 / 24 (54.17%)	
Vascular disorders			
Dizziness			
subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Syncope			
subjects affected / exposed	1 / 28 (3.57%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 28 (3.57%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	7 / 28 (25.00%)	1 / 24 (4.17%)	
occurrences (all)	7	1	
General body pains			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Angioedema			
subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Psychiatric disorders			

Abnormal dreams			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nightmare			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	4 / 28 (14.29%)	1 / 24 (4.17%)	
occurrences (all)	4	1	
Blood iron decreased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Prostatic specific antigen increased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dizziness postural			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	4 / 28 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Dyspnoea exertional			
subjects affected / exposed	2 / 28 (7.14%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Hypertension			

subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 28 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Nervous system disorders			
Tension headache			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Hypochromic anaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 28 (7.14%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 28 (7.14%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			

Diuresis excessive			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Renal impairment			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Diabetic neuropathy			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Muscular weakness			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Gastroenteritis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	2 / 28 (7.14%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Lower respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	4 / 28 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Paronychia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Wound infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Hyponatraemia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 24 (4.17%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2014	Inclusion Criteria No 2 amended: Diastolic dysfunction on Doppler-echocardiogram as evidenced by either LAVI >32ml/m2 and/or e' <10 cm/s. Previously, only patients with diastolic dysfunction as evidenced by LAVI >32ml/m2 were eligible for inclusion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported