Clinical trial results:
A Randomised Multicentre Open Label Blinded End Point Trial to Compare the Effects of Spironolactone to Chlortalidone on Left Ventricular Mass and Arterial Stiffness in Stage 3 Chronic Kidney Disease

Summary

EudraCT number	2013-002636-25
Trial protocol	GB
Global end of trial date	09 April 2019

Results information

Result version number	v1 (current)
This version publication date	25 June 2020
First version publication date	25 June 2020

Trial information

Trial identification

Sponsor protocol code	RG_13-013NS

Additional study identifiers

ISRCTN number	ISRCTN94696478
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Aston Webb Building, Birmingham, United Kingdom, B15 2TT
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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	09 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 December 2017
Global end of trial reached?	Yes
Global end of trial date	09 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does giving Spironolactone to patients with early stage chronic kidney disease reduce arterial stiffness and left ventricular mass to a greater degree than the standard blood pressure lowering drug treatment, Chlortalidone?

Updated April 2016
Does giving Spironolactone to patients with early stage chronic kidney disease reduce left ventricular mass to a greater degree than the standard blood pressure lowering drug treatment, Chlortalidone?

Protection of trial subjects:

All sites were provided with the SPIRO-CKD protocol that provided specific instruction relating to inclusion/exclusion criteria and trial patient safety.
There was clear instruction relating to trial intervention safety and considerations detailed within the protocol.
SPIRO-CKD had two Data Monitoring Committees to monitor patient safety throughout the trial.

Background therapy:

Chronic Kidney Disease (CKD) is a major but poorly recognised and under-treated risk factor for cardiovascular disease. Stages 2 and 3 CKD are defined by a GFR of 30-89 ml/min/1.73m2 were investigated in this study. There is a graded inverse relationship between cardiovascular risk and GFR which is independent of age, sex and other risk factors such as hypertension and diabetes. While the cardiovascular risk of end-stage CKD is extreme, in public health terms the burden resides in early stage disease (CKD stages 1-3), which is more prevalent, affecting almost 1 in 7 of the entire population, including approximately 4% of those aged 40-59, and more than 40% of those aged over 70 years. Thus, CKD is a potentially important risk factor for cardiovascular disease in the general population. The main pathological features of cardiovascular disease in CKD are:
a) Myocardial disease characterised by LVH and fibrosis accompanied by systolic and diastolic dysfunction.
b) Arterial wall thickening, stiffening and calcification (arteriosclerosis).
c) Coronary and peripheral artery atherosclerosis.

Previous research suggested that compared with placebo, the use of spironolactone resulted in large reductions in left ventricular mass and arterial stiffness (pulse wave velocity, augmentation index and aortic distensibility). This trial has given rise to considerable optimism that MRB therapy might help to prevent cardiovascular disease in patients with CKD.
Chlortalidone (until recently known by its US adopted name, chlorthalidone) is a thiazide-like diuretic and an effective anti-hypertensive drug proven to reduce blood pressure, adverse cardiovascular events and adverse renal outcomes as effectively as calcium channel blockers or ACE inhibitors.
Therefore SPIRO-CKD compared the effects of spironolactone versus chlortalidone on LV mass in patients with stage 2 and stage 3.

Evidence for comparator:

A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.
All recruited patients will receive either spironolactone (25mg) or Chlortalidone (½ of a 50mg tablet) daily for 40 weeks.
Patients were followed-up for the duration of treatment and for 6 weeks after discontinuation of trial medication (wash-out period).

Actual start date of recruitment	02 September 2013
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: 154
Worldwide total number of subjects	154
EEA total number of subjects	154

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)	96
From 65 to 84 years	56
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The trial opened for recruitment on the 3rd June 2014 and the first patient was randomised on the 26th June 2014 and the last patient was randomised on the 21st December 2016. A total of 154 patients were randomised into the SPIRO-CKD Trial with 4 centres recruiting patients into the trial with equal numbers in both arms.

Pre-assignment

Screening details:

A total of 9325 were screened for the trial, of these screened 154 were randomised.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

A Randomised Multicentre Open Label Blinded End Point Trial to Compare the Effects of Spironolactone to Chlortalidone on Left Ventricular Mass in Stage 2 and Stage 3 Chronic Kidney Disease.
A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

Arms

Are arms mutually exclusive?	Yes
Arm title	Spironolactone

Arm description:

Baseline

Arm type	Experimental
Investigational medicinal product name	Spironolactone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

One 25mg tablet OD for 40 weeks orally

Arm title	Chlortalidone

Arm description:

Baseline

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

Dosage and administration details:

Chlortalidone at a dose of ½ a 50 mg tablet od. The duration of treatment will be 40 weeks in total.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: SPIRO-CKD was an assessor blind trial.

Number of subjects in period 1	Spironolactone	Chlortalidone
Started	77	77
Completed	77	77

Period 2	
Period 2 title	Week 40
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[2]

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	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

One 25mg tablet OD for 40 weeks orally

Arm title	Chlortalidone

Arm description: -

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

Dosage and administration details:

Chlortalidone at a dose of ½ a 50 mg tablet od. The duration of treatment will be 40 weeks in total.

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: SPIRO-CKD was an assessor blind trial.

Number of subjects in period 2	Spironolactone	Chlortalidone
Started	77	77
Completed	69	69
Not completed	8	8
Consent withdrawn by subject	4	3
Adverse event, non-fatal	3	3
Pregnancy	-	1
Lost to follow-up	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Spironolactone
Reporting group description: Baseline	
Reporting group title	Chlortalidone
Reporting group description: Baseline	

Reporting group values	Spironolactone	Chlortalidone	Total
Number of subjects	77	77	154
Age categorical Units: Subjects			
Less than 55 years	35	35	70
55 and over	42	42	84
Age continuous Units: years			
arithmetic mean	56.5	56.3	
standard deviation	± 13.8	± 15.1	-
Gender categorical Units: Subjects			
Female	24	24	48
Male	53	53	106
Smoking Status Units: Subjects			
Never smoked	37	37	74
Ex-smoker	35	29	64
Current smoker	5	11	16
Systolic Blood Pressure Units: Subjects			
<130mmHg	32	32	64
≥130mmHg	45	45	90
Is the cause of Chronic Kidney Disease known?			
Is the cause known?			
Units: Subjects			
Yes	60	59	119
No	17	18	35
Patient with previous Myocardial Infarction (MI) Units: Subjects			
Yes	1	4	5
No	76	73	149
Patients with a history of Hypertension			
Patients with a history of hypertension			
Units: Subjects			
Yes	67	64	131
No	10	13	23

Patients with a history of Hypercholesterolemia			
Patients with a history of hypercholesterolemia			
Units: Subjects			
Yes	30	34	64
No	47	43	90
Patients previously had a CVA or TIA			
Patients previously had a CVA or TIA			
Units: Subjects			
Yes	1	1	2
No	76	76	152
Patients with Asthma			
Patients with Asthma			
Units: Subjects			
Yes	8	11	19
No	69	66	135
Patients with COPD			
Patients with COPD			
Units: Subjects			
Yes	1	1	2
No	76	76	152
Patients with Liver Disease Units: Subjects			
Yes	3	1	4
No	74	76	150
Malignancy			
Patients with previous malignancy			
Units: Subjects			
Yes	5	6	11
No	72	71	143
ACE Inhibitor Medication Units: Subjects			
Yes	40	41	81
No	35	36	71
Missing	2	0	2
ARB Medication Units: Subjects			
Yes	33	32	65
No	42	45	87
Missing	2	0	2
CCB Medication Units: Subjects			
Yes	33	23	56
No	42	54	96
Missing	2	0	2
Alpha Blocker Medication Units: Subjects			
Yes	13	6	19
No	62	71	133
Missing	2	0	2
Beta Blocker Medication			

Units: Subjects			
Yes	13	13	26
No	62	64	126
Missing	2	0	2
Cause of Chronic Kidney Disease Units: Subjects			
Primary glomerulonephritis	29	20	49
Interstitial nephropathies	5	10	15
Hereditary Nephropathy	15	16	31
Renal vascular disease	2	4	6
Hypertensive nephropathy	4	3	7
Secondary Glomerulonephritis	0	3	3
Other multisystem disease	2	2	4
Other	3	1	4
No cause known	17	18	35
Height Units: Metres			
arithmetic mean	1.7	1.7	
standard deviation	± 0.1	± 0.1	-
Weight Units: Kilograms			
arithmetic mean	85.5	80.1	
standard deviation	± 15.7	± 13.7	-
BMI Units: BMI			
arithmetic mean	29.5	27.6	
standard deviation	± 5.0	± 3.8	-
Systolic Blood Pressure Units: mmHg			
arithmetic mean	133.9	135.3	
standard deviation	± 13.8	± 14.4	-
Diastolic Blood Pressure Units: mmHg			
arithmetic mean	80.3	80.5	
standard deviation	± 10.3	± 9.3	-
Pulse Rate Units: BPM			
arithmetic mean	71.8	70.8	
standard deviation	± 13.6	± 12.4	-
Creatinine Units: umol/L			
arithmetic mean	128.4	117.2	
standard deviation	± 40.5	± 31.2	-
eGFR Units: (4v-MDRD) (mL/min/1.73)			
arithmetic mean	52.2	56.9	
standard deviation	± 16.1	± 15.3	-
Potassium Units: mmol/L			
arithmetic mean	4.4	4.5	
standard deviation	± 0.4	± 0.3	-

End points

End points reporting groups	
Reporting group title	Spironolactone
Reporting group description: Baseline	
Reporting group title	Chlortalidone
Reporting group description: Baseline	
Reporting group title	Spironolactone
Reporting group description: -	
Reporting group title	Chlortalidone
Reporting group description: -	

Primary: Left Ventricular Mass (LV)	
End point title	Left Ventricular Mass (LV)
End point description:	
End point type	Primary
End point timeframe: Baseline to week 40	

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	68	60	59
Units: gram(s)/gram				
arithmetic mean (standard deviation)	130.6 (± 27.7)	123.9 (± 33.1)	124 (± 24.3)	122.2 (± 37.3)

Statistical analyses

Statistical analysis title	Linear Regression Model

Statistical analysis description:

A linear regression model was fitted with LV mass at week 40 as the outcome variable, and treatment group (with Chlortalidone as the reference category), baseline LV mass and all the minimisation variables (age, systolic blood pressure and gender) included as covariates in the model.

Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-3.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.13
upper limit	0.47
Variability estimate	Standard error of the mean

Primary: LV mass indexed to Body Surface Area (g/m2)

End point title	LV mass indexed to Body Surface Area (g/m2)

End point description:

As an additional sensitivity analysis, LV mass data was also analysed accounting for any missing data at week 40 using multiple imputation methods to impute missing data

End point type	Primary

End point timeframe:

Baseline to week 40

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	68	60	59
Units: g/m2				
arithmetic mean (standard deviation)	65.6 (± 11.9)	64.1 (± 13.9)	62.2 (± 11.4)	63.1 (± 14.9)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.185
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.79
upper limit	0.74
Variability estimate	Standard error of the mean

Secondary: Changes in arterial stiffness

End point title	Changes in arterial stiffness

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	75	65	68
Units: m/s				
arithmetic mean (standard deviation)	7.37 (± 1.78)	7.6 (± 2.17)	7.34 (± 1.90)	7.5 (± 1.97)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.384
upper limit	0.459
Variability estimate	Standard error of the mean

Secondary: Systolic Blood Pressure

End point title	Systolic Blood Pressure

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	77	77	69	69
Units: mmHg				
arithmetic mean (standard deviation)	133.6 (± 10.7)	135.9 (± 14.2)	123.8 (± 15.3)	127.2 (± 14.2)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.284
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.209
upper limit	2.129
Variability estimate	Standard error of the mean

Secondary: Diastolic Blood Pressure

End point title	Diastolic Blood Pressure
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 40	

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	77	77	69	69
Units: mmHg				
arithmetic mean (standard deviation)	81.7 (± 8.1)	81.2 (± 9.6)	75.8 (± 11.1)	77.6 (± 8.2)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.398
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.239
upper limit	0.442
Variability estimate	Standard error of the mean

Secondary: Mean 24 hour peripheral systolic blood pressure

End point title	Mean 24 hour peripheral systolic blood pressure
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 40	

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	70	62	64
Units: mmHg				
arithmetic mean (standard deviation)	126.5 (± 11.1)	127.6 (± 13.4)	121.8 (± 12.5)	121.4 (± 14)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.279
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	2.035

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.667
upper limit	5.738
Variability estimate	Standard error of the mean

Secondary: Mean 24 hour peripheral diastolic blood pressure

End point title	Mean 24 hour peripheral diastolic blood pressure
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 40	

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	70	62	64
Units: mmHg				
arithmetic mean (standard deviation)	78.8 (± 8.4)	79.5 (± 9.3)	75.4 (± 9)	74.6 (± 7.9)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.257
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.951
upper limit	3.523
Variability estimate	Standard error of the mean

Secondary: Mean 24 hour central systolic blood pressure

End point title	Mean 24 hour central systolic blood pressure

End point description:

End point type	Secondary

End point timeframe:
Baseline to week 40

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	68	58	64
Units: mmHg				
arithmetic mean (standard deviation)	115.6 (± 9)	117.4 (± 12.6)	111.3 (± 10.6)	110.4 (± 11.5)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.263
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.974
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.503
upper limit	5.452
Variability estimate	Standard error of the mean

Secondary: Mean 24 hour central diastolic blood pressure

End point title	Mean 24 hour central diastolic blood pressure

End point description:

End point type	Secondary

End point timeframe:
Baseline to week 40

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	68	58	64
Units: mmHg				
arithmetic mean (standard deviation)	80 (± 8.1)	81 (± 9.7)	76.9 (± 9.2)	75.6 (± 8.6)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.334
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.187
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.237
upper limit	3.612
Variability estimate	Standard error of the mean

Secondary: Left ventricular-end systolic volume

End point title	Left ventricular-end systolic volume
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 40	

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	68	60	59
Units: mL				
arithmetic mean (standard deviation)	30.6 (± 11.3)	32 (± 13.1)	30.8 (± 12.1)	30.7 (± 12.6)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.393
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.408
upper limit	3.554
Variability estimate	Standard error of the mean

Secondary: Left ventricular end-systolic volume indexed to Body Surface Area

End point title	Left ventricular end-systolic volume indexed to Body Surface Area
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 40	

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	68	60	59
Units: mL/m^				
arithmetic mean (standard deviation)	15.4 (± 5.5)	16.6 (± 6.3)	15.5 (± 6.1)	15.9 (± 6.0)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.466
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.472

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.807
upper limit	1.751
Variability estimate	Standard error of the mean

Secondary: Left ventricular end-diastolic volume

End point title	Left ventricular end-diastolic volume
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 40	

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	68	60	59
Units: mL				
arithmetic mean (standard deviation)	116 (± 26.1)	114.1 (± 27.4)	114.2 (± 26.7)	108.2 (± 26.5)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.149
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	4.205
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.526
upper limit	9.936
Variability estimate	Standard error of the mean

Secondary: Left ventricular end-diastolic volume indexed to Body Surface Area

End point title	Left ventricular end-diastolic volume indexed to Body Surface

	Area

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	68	60	59
Units: mL/m^				
arithmetic mean (standard deviation)	58.4 (± 12.3)	59.3 (± 12.7)	57.4 (± 13.4)	56.3 (± 12.3)

Statistical analyses

Statistical analysis title	Linear Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.205
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.813
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.006
upper limit	4.632
Variability estimate	Standard error of the mean

Secondary: Incidence of Hyperkalaemia

End point title	Incidence of Hyperkalaemia

End point description:

15 patients were excluded from this analysis (7 in Spironolactone group and 8 in Chlortalidone group) because these patients withdrew, were lost to follow up or died prior to incidence of hyperkalaemia and did not complete the 40 weeks of trial follow up.

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Spironolactone	Chlortalidone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	69		
Units: Total Hyperkalaemia Events				
0 incidences	58	67		
1 incidence	7	2		
2 incidences	2	0		
3 incidences	2	0		
4 incidences	1	0		

Statistical analyses

Statistical analysis title	Poisson Regression Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Poisson Regression Model
Parameter estimate	Incidence Rate Ratio
Point estimate	10.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.38
upper limit	43.66
Variability estimate	Standard error of the mean

Secondary: Changes in UACR ratio

End point title	Changes in UACR ratio
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 40	

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	75	69	69
Units: mg/mmol				
median (inter-quartile range (Q1-Q3))	5.5 (1.2 to 38.6)	5 (1.5 to 49)	4.8 (1.8 to 18)	2.1 (0.6 to 16.6)

Statistical analyses

Statistical analysis title	Ratio of Geometric Mean
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046
Method	Regression, Linear
Parameter estimate	Ratio of geometric means
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.75
Variability estimate	Standard error of the mean

Secondary: NT proBNP	
End point title	NT proBNP
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and week 40	

End point values	Spironolactone	Chlortalidone	Spironolactone	Chlortalidone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	70	63	56
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	74 (41 to 161)	113.5 (39 to 189)	78 (38 to 171)	65.5 (31 to 162)

Statistical analyses

Statistical analysis title	Ratio of Geometric Means
Comparison groups	Spironolactone v Chlortalidone

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.198
Method	Regression, Linear
Parameter estimate	Ratio of geometric means
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.41
Variability estimate	Standard error of the mean

Secondary: Decline in Renal Function

End point title	Decline in Renal Function
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 40	

End point values	Spironolactone	Chlortalidone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	70		
Units: Yes/No				
Yes	2	8		
No	67	62		

Statistical analyses

Statistical analysis title	Log Binomial Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.069
Method	Log Binomial
Parameter estimate	Risk ratio (RR)
Point estimate	0.246

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.054
upper limit	1.118
Variability estimate	Standard error of the mean

Secondary: Symptomatic Hypotension

End point title	Symptomatic Hypotension
End point description:	
Requiring discontinuation of trial treatment	
End point type	Secondary
End point timeframe:	
Baseline to week 40	

End point values	Spironolactone	Chlortalidone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	69		
Units: Yes/No				
Yes	0	0		
No	69	69		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Side Effects

End point title	Incidence of Side Effects
End point description:	
Requiring discontinuation of trial treatment	
End point type	Secondary
End point timeframe:	
Baseline to week 40	

End point values	Spironolactone	Chlortalidone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	70		
Units: Yes/No				
Yes	11	19		
No	60	51		

Statistical analyses

Statistical analysis title	Log Binomial Model
Comparison groups	Spironolactone v Chlortalidone
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.074
Method	Log Binomial
Parameter estimate	Risk ratio (RR)
Point estimate	0.556
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.292
upper limit	1.058
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were reportable to the SPIRO-CKD Trial Office up to 6 weeks post last IMP administration.
Any SUSAR related to the IMP was expected to be reported irrespective of how long after IMP administration the reaction has occurred.

Adverse event reporting additional description:

Adverse events were recorded in the medical records and case report forms. Most adverse events/reactions that occurred in this trial, whether they were serious or not, were 'expected' treatment-related toxicities due to the drugs used in this trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Spironolactone
Reporting group description: -	
Reporting group title	Chlortalidone
Reporting group description: -	

Serious adverse events	Spironolactone	Chlortalidone	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 77 (6.49%)	6 / 77 (7.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall	Additional description: Subject tripped and fell onto left side and was admitted into AE and thoracic surgery with a rib fracture and small pneumothorax on left side		
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Elective surgery, right ankle reconstruction			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Elective surgery	Additional description: Elective knee replacement		

subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Chest pain	Additional description: Chest pain		
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness	Additional description: Collapsed with loss of consciousness which has resulted in a fractured left ankle. In the emergency room was found to have a prolonged QTC on ECG, possibly due to hypotension.		
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Shortness of breath, muscle cramps, Anaemia, tiredness			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Perforated diverticulum			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain	Additional description: Admitted to hospital with a four day history of upper and lower abdominal pain, diarrhoea, nausea and vomiting, Imaging revealed duodenitis.		
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Shortness of breath			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Kidney Pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash	Additional description: Developed a rash on chest.		
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Spironolactone	Chlortalidone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 77 (77.92%)	65 / 77 (84.42%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 77 (16.88%)	22 / 77 (28.57%)	
occurrences (all)	21	32	
Headache			

subjects affected / exposed	11 / 77 (14.29%)	9 / 77 (11.69%)	
occurrences (all)	14	13	
General disorders and administration site conditions			
Drowsiness			
subjects affected / exposed	4 / 77 (5.19%)	5 / 77 (6.49%)	
occurrences (all)	7	5	
Symptomatic hypotension			
subjects affected / exposed	7 / 77 (9.09%)	9 / 77 (11.69%)	
occurrences (all)	12	12	
Immune system disorders			
Hypersensitivity reactions			
subjects affected / exposed	2 / 77 (2.60%)	0 / 77 (0.00%)	
occurrences (all)	3	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Breast tenderness/enlargement			
subjects affected / exposed	4 / 77 (5.19%)	0 / 77 (0.00%)	
occurrences (all)	4	0	
Gynecomastia			
subjects affected / exposed	3 / 77 (3.90%)	0 / 77 (0.00%)	
occurrences (all)	6	0	
Sexual dysfunction			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 77 (1.30%)	4 / 77 (5.19%)	
occurrences (all)	1	4	
Diarrhoea			
subjects affected / exposed	8 / 77 (10.39%)	5 / 77 (6.49%)	
occurrences (all)	10	5	
GI cramping			

subjects affected / exposed	1 / 77 (1.30%)	4 / 77 (5.19%)	
occurrences (all)	1	4	
Gastric irritation			
subjects affected / exposed	6 / 77 (7.79%)	5 / 77 (6.49%)	
occurrences (all)	6	5	
Nausea			
subjects affected / exposed	7 / 77 (9.09%)	5 / 77 (6.49%)	
occurrences (all)	7	5	
Vomiting			
subjects affected / exposed	3 / 77 (3.90%)	1 / 77 (1.30%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	10 / 77 (12.99%)	3 / 77 (3.90%)	
occurrences (all)	13	5	
Psychiatric disorders			
Anorexia			
subjects affected / exposed	2 / 77 (2.60%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Hyperkalaemia			
subjects affected / exposed	3 / 77 (3.90%)	0 / 77 (0.00%)	
occurrences (all)	5	0	
Hypokalaemia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	8 / 77 (10.39%)	6 / 77 (7.79%)	
occurrences (all)	8	7	
Parasthesia			
subjects affected / exposed	3 / 77 (3.90%)	3 / 77 (3.90%)	
occurrences (all)	5	4	
Restlessness			
subjects affected / exposed	1 / 77 (1.30%)	2 / 77 (2.60%)	
occurrences (all)	11	4	

Weakness subjects affected / exposed occurrences (all)	7 / 77 (9.09%) 7	5 / 77 (6.49%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2015	* Changes made to the Protocol * Changes made to the Participant Information Leaflets/Consent Forms * Documents to be submitted: Poster Patient information sheets Consent forms Invitation letter (secondary and primary care)
23 April 2015	Changes made to the Participant Postal Invitation Letter
11 August 2015	* Changes to the protocol * Changes to the patient information sheet * Changes made to GP letter
28 November 2016	* Changes to the protocol * Administrative updates to the patient facing documents SPIRO-CKD Diet sheets SPIRO-CKD GP Letter SPIRO-CKD Participant Postal Invitation to Take Part Letter SPIRO-CKD Letter SPIRO-CKD Screening Information Sheet SPIRO-CKD Participant Information Sheet SPIRO-CKD Sub-studies Information Sheet SPIRO-CKD Screening Consent Form SPIRO-CKD Informed Consent Form SPIRO-CKD Sub-studies Consent Form SPIRO-CKD OPD Poster SPIRO-CKD Patient End of Study Letter SPIRO-CKD GP End of Study Lette
19 June 2018	Amendment to the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported