



Clinical trial results: Mineralocorticoid Receptor antagonists in End stage reNal DiseAse Summary

EudraCT number	2011-003179-12
Trial protocol	DE
Global end of trial date	14 February 2017

Results information

Result version number	v1 (current)
This version publication date	09 September 2022
First version publication date	09 September 2022

Trial information

Trial identification

Sponsor protocol code	MN0511_1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01691053
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Wuerzburg
Sponsor organisation address	Josef-Schneider-Str. 2, Wuerzburg, Germany, 97080
Public contact	Clinical Trial Information Desk, University Hospital of Wuerzburg, +49 93120143311, hammer_f@klinik.uni-wuerzburg.de
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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	28 March 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of the mineralocorticoid receptor antagonist spironolactone on left ventricular mass index in end stage renal disease patients on hemodialysis.

Protection of trial subjects:

Patient attend regular study visits as part of routine dialysis sessions three times a week for monitoring pre-dialysis potassium and -sodium levels (if pre-dialysis potassium levels are ≥ 6.5 mmol/l study medication will be stopped) and safety monitoring (adverse Events, serious adverse Events, adverse drug reactions).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2012
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	Germany: 97
Worldwide total number of subjects	97
EEA total number of subjects	97

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)	58
From 65 to 84 years	38
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients will be screened and recruited by the participating dialysis centers. Eligible patients fulfilling the inclusion but not exclusion criteria will be enrolled in the study after written informed consent has been obtained. Date of first patient: 12/2012 (FPFV), Date of last patient: 11/2016 (LPLV)

Pre-assignment

Screening details:

Dialysis patients will be screened by their renal physician according to inclusion and exclusion criteria. Eligible patients will be handed out a patient information sheet. Once written informed consent has been obtained, the patient will be enrolled in the study and the screening visit will be scheduled within the next 4 weeks after enrollment.

Period 1

Period 1 title	Double-blind treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Following baseline investigations the patient will be randomized. Following dispense of study medication the patient will attend regular study visits (as part of routine dialysis sessions). The trial medication is blind. Parameters will be assessed and documented as part of routine dialysis sessions.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Spironolactone
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Spironolactone
Investigational medicinal product code	PR1
Other name	Spironolacton Hexal
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets administered once daily by oral intake in the evening (after dialysis sessions), 50 mg per day

Arm title	Placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PL1
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets administered once daily by oral intake in the evening (after dialysis sessions). Tablets provided by Winthrop Arzneimittel GmbH.

Number of subjects in period 1	Spironolactone	Placebo
Started	50	47
Completed	50	47

Period 2

Period 2 title	Post-Treatment follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Once the study medication is stopped, the trial will be continued for another 4 weeks during which parameters will be assessed and documented as part of routine dialysis sessions.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control Follow-up

Arm description: -

Arm type	Placebo
Investigational medicinal product name	P-Tabletten weiß 7 mm Lichtenstein
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet per day

Arm title	Spironolactone follow-up
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Arm description: -

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

Dosage and administration details:

50 mg tablet

Number of subjects in period 2	Control Follow-up	Spironolactone follow-up
Started	47	50
Completed	47	50

Baseline characteristics

Reporting groups

Reporting group title	Double-blind treatment
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Reporting group description: -

Reporting group values	Double-blind treatment	Total	
Number of subjects	97	97	
Age categorical			
Ten years age categories			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	58	58	
From 65-84 years	38	38	
85 years and over	1	1	
Age continuous			
Summarizing age statistics			
Units: years			
arithmetic mean	60.3		
standard deviation	± 13.2	-	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	75	75	
Kind of dialysis			
Units: Subjects			
haemodialysis	90	90	
haemodiafiltration	7	7	
Kind of dialysis			
Units: Subjects			
haemodialysis	90	90	
haemodiafiltration	7	7	

Subject analysis sets

Subject analysis set title	Intention to treat analysis set
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All randomized patients

Subject analysis set title	Per protocol analyse set
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Subject analysis set type	Per protocol
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Subject analysis set description:

Patients from the ITT analysis set who completed the study per protocol

Reporting group values	Intention to treat analysis set	Per protocol analyse set	
Number of subjects	97	82	
Age categorical			
Ten years age categories			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	58	48	
From 65-84 years	38	33	
85 years and over	1	1	
Age continuous			
Summarizing age statistics			
Units: years			
arithmetic mean	60.3	60.3	
standard deviation	± 13.2	± 13.3	
Gender categorical			
Units: Subjects			
Female	22	18	
Male	75	64	
Kind of dialysis			
Units: Subjects			
haemodialysis	90	76	
haemodiafiltration	7	6	
Kind of dialysis			
Units: Subjects			
haemodialysis	90	76	
haemodiafiltration	7	6	

End points

End points reporting groups

Reporting group title	Spironolactone
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Control Follow-up
Reporting group description: -	
Reporting group title	Spironolactone follow-up
Reporting group description: -	
Subject analysis set title	Intention to treat analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients	
Subject analysis set title	Per protocol analyse set
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients from the ITT analysis set who completed the study per protocol	

Primary: Change in left ventricular mass index (LVMI) measured by CMR

End point title	Change in left ventricular mass index (LVMI) measured by CMR
End point description:	
Change in left ventricular mass index (LVMI) measured by CMR	
The primary analysis consists of a mean value comparison of the primary endpoint variable between end-stage renal disease patients treated with the experimental treatment spironolactone + standard medical care and patients under placebo + standard medical care. We used as statistical method a baseline adjusted comparison of the mean change by ANCOVA with the change score Diff_LVMI as response, treatment group as factor and baseline LVMI0 as covariate. Within a secondary analysis, we excluded from this collective patients with adverse events and/or with pathological laboratory values and noncompliance patients (per-protocol population)	
Model-based estimation for the effect size, the mean difference in the change scores between patients under the experimental treatment and patients under the control treatment,	
ITT analysis set: -2.27 (-6.94 , 2.41)	
PP analysis set: -2.01 (-6.91 , 2.89)	
End point type	Primary
End point timeframe:	
CMR week 0 (baseline) and week 40 (FU)	
Change from Baseline to week 40	

End point values	Spironolactone	Placebo	Intention to treat analysis set	Per protocol analyse set
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	47	97	82
Units: g/m2				
number (not applicable)	44	41	85	80

Statistical analyses

Statistical analysis title	Primary objective and primary response variable
Statistical analysis description:	
The primary endpoint is the difference score of the left ventricular mass index from baseline to week 40:	
The primary analysis consists of a mean value comparison of the primary endpoint variable between end-stage renal disease patients treated with the treatment spironolactone and patients under the control intervention. We used a baseline adjusted comparison of the mean change by ANCOVA with the treatment group as factor and baseline LVMI0 as covariate	
Analysis in the ITT ANALYSIS SET	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.337
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.94
upper limit	2.41
Variability estimate	Standard error of the mean
Dispersion value	2.35

Statistical analysis title	Secondary analysis of the primary endpoint
Statistical analysis description:	
The primary endpoint is the difference score of the left ventricular mass index from baseline to week 40:	
The secondary analysis consists of a mean value comparison of the primary endpoint variable between end-stage renal disease patients treated with the treatment spironolactone and patients under the control intervention. We used a baseline adjusted comparison of the mean change by ANCOVA with the treatment group as factor and baseline LVMI0 as covariate	
Analysis in the PP ANALYSIS SET	
Comparison groups	Placebo v Spironolactone v Per protocol analyse set
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.418
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.91
upper limit	2.89
Variability estimate	Standard error of the mean
Dispersion value	2.46

Secondary: End-systolic volume (ESV)

End point title	End-systolic volume (ESV)
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End point description:

Secondary objectives and secondary response variables

endpoints of ventricular geometry and function: end-systolic volume, ESV in ml. Global functional analysis of the left ventricle based on SSFP Cine-MRI
no statistical significant difference was detected between the two treatments spironolactone and placebo (+ standard medical care) regarding the mean change from baseline to 40 weeks under treatment analyzed by ANCOVA, that means adjusted by the corresponding baseline variables.
we present the results of the inferential statistics:
- The model-based estimation for the effect size, the mean difference in the change scores between patients under spironolactone and patients under placebo with corresponding 95% CI.
- The p-value for the Type III F-test within the ANCOVA analysis

Function resp. volume parameter	Model-based estimation of effect size	p-value
ESV, absolute	7.52 (-1.24 , 16.27)	0.266

End point type	Secondary
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End point timeframe:

change from baseline (visit 2) to visit 4, after 40 weeks

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	44	41	85	
Units: ml				
arithmetic mean (standard deviation)	6.23 (± 22.47)	-0.71 (± 17.79)	2.88 (± 20.52)	

Statistical analyses

No statistical analyses for this end point

Secondary: End-diastolic volume (EDV)

End point title	End-diastolic volume (EDV)
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End point description:

Global functional analysis of the left ventricle based on SSFP Cine-MRI
no statistical significant difference was detected between the two treatments spironolactone and placebo (+ standard medical care) regarding the mean change from baseline to 40 weeks under treatment analyzed by ANCOVA, that means adjusted by the corresponding baseline variables.
we present the results of the inferential statistics:
- The model-based estimation for the effect size, the mean difference in the change scores between patients under spironolactone and patients under placebo with corresponding 95% CI.
- The p-value for the Type III F-test within the ANCOVA analysis

Function resp. volume parameter	Model-based estimation of effect size	p-value
EDV, absolute	10.21 (-2.57 , 22.98)	0.116

End point type	Secondary
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End point timeframe:
change from baseline (visit 2) to visit 4 after 4 weeks of treatment

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	44	41	85	
Units: ml				
arithmetic mean (standard deviation)	7.45 (\pm 33.85)	0.10 (\pm 27.10)	3.91 (\pm 30.82)	

Statistical analyses

No statistical analyses for this end point

Secondary: Left ventricular ejection fraction (LVEF)

End point title	Left ventricular ejection fraction (LVEF)
End point description: LVEF is a further cardiac function parameter. No statistical significant difference was detected between the two treatments spironolactone and placebo regarding the mean change from baseline to 40 weeks under treatment analyzed by ANCOVA. Function resp. volume parameter Model-based estimation of effect size p-value LVEF, % 0.84 (-1.91 , 3.58) 0.545	
End point type	Secondary
End point timeframe: change from baseline (week 0) to week 40	

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	46	41	87	
Units: percent volume/volume				
arithmetic mean (standard deviation)	1.46 (\pm 6.51)	-0.71 (\pm 7.32)	0.44 (\pm 6.95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Stroke volume

End point title	Stroke volume
End point description: Stroke volume (absolute value) is a further left ventricular functional parameter based on SSFP Cine-MRI. No statistical significant difference was detected between the two treatments spironolactone and	

placebo regarding the mean change from baseline to 40 weeks under treatment analyzed by ANCOVA
 Function resp. volume parameter Model-based estimation of effect size p-value
 Stroke volume 0.49 (-8.30 , 9.27) 0.913

End point type	Secondary
End point timeframe:	
change from baseline (week 0) to week 40	

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	44	41	85	
Units: ml				
arithmetic mean (standard deviation)	1.07 (± 23.61)	0.85 (± 21.19)	0.96 (± 22.34)	

Statistical analyses

No statistical analyses for this end point

Secondary: 24-h systolic Blood pressure in mmHg

End point title	24-h systolic Blood pressure in mmHg
End point description:	
Baseline adjusted analysis of mean changes. Comparison of patients treated with Spironolactone and patients under placebo by ANCOVA	
Blood pressure in mmHg Model-based estimation of effect size p-value	
24h systolic ABP -2.24 (-7.91 , 3.42) 0.433	
24h diastolic ABP -1.16 (-4.61 , 2.29) 0.505	
Office systolic -1.25 (-9.51 , 7.01) 0.764	
Office diastolic 1.51 (-4.43 , 7.45) 0.614	
There are no trends for a significant effect of spironolactone on blood pressure change from baseline to weeks 40 under treatment.	
End point type	Secondary
End point timeframe:	
change from baseline (week 0) to week 40	

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	39	38	77	
Units: mmHg				
arithmetic mean (standard deviation)	0.03 (± 11.58)	2.08 (± 15.36)	1.04 (± 13.53)	

Statistical analyses

No statistical analyses for this end point

Secondary: Patients functional capacity: 6-minute walk distance

End point title	Patients functional capacity: 6-minute walk distance
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End point description:

There are no indications for an effect of spironolactone on the performance in the 6-minute walk distance test (measured in meters) at all. The model-based estimation for the effect size with corresponding 95% CI and p-value for the Type III F-test within the ANCOVA analysis are -0.36 meter (-52.13 , 51.40) and 0.989.

A considerable skewness in the observed values within the spironolactone group makes modelling by ANCOVA questionable. Therefore, we analyzed the 6-minute walk distance test data alternatively by nonparametric methods. Precisely we compared the distributions of the change score (from baseline to week 40) between patients under spironolactone and patients under placebo by the Mann-Whitney U test and estimated the location shift for the change score between spironolactone and placebo by the Hodges-Lehmann estimator.

Again we can't detect a hint to a possible effect-. The estimated location shift with corresponding 95% CI is 3.50 meter (-34.0, 50.0), p-value = 0.771.

End point type	Secondary
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End point timeframe:

week 0, week 40

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	25	51	
Units: meter				
arithmetic mean (standard deviation)	17.50 (± 86.99)	25.44 (± 113.91)	21.39 (± 100.14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of prescribed antihypertensives

End point title	Number of prescribed antihypertensives
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End point description:

To analyse the effect of the treatment (Spironolactone versus placebo) on the change in the distribution of the number of prescribed antihypertensives from baseline to week 40, we again used the Wald-test for an interaction effect within generalized linear modelling. Specifically we applied ordinal logistic regression with treatment as between- and the week (0, 40) as within subject factor. By reason of limited sample size we categorized the number of prescribed antihypertensives (none, one, more than one).

No significant interaction effect could be detected. That means there was no significant difference between patients under spironolactone and patients under placebo regarding the change in the distribution of the number of prescribed antihypertensives. The p-value belonging to the effect was 0.298, the corresponding cumulative odds ratio with 95% CI was 0.74 (0.43 , 1.30).

End point type	Secondary
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End point timeframe:

change from baseline (week 0) to week 40

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	50	47	97	
Units: 0 1 2 3 4 5 6 7				
non antihypertensives	8	9	17	
one antihypertensive	19	14	33	
more than one antihypersensitive	23	24	47	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety endpoint: Hyperkalemia events

End point title	Safety endpoint: Hyperkalemia events
End point description:	
<p>The main safety endpoint was the development of hyperkalemia.</p> <p>To compare the counts of hyperkalemia events between patients treated with Spironolactone and patients under placebo, we fitted generalized linear models and applied a Wald-χ^2-test within a negative binomial model (NB) for count data.</p> <p>During the double-blind treatment phase mild hyperkalemia ($6.0 \leq$ pre-dialysis potassium <6.5 mmol/l) occurred significantly more frequent in spironolactone compared to placebo treated patients (155 vs. 80 events; $p=0.034$), whereas severe hyperkalemia (pre-dialysis potassium ≥ 6.5mmol/l) events were not significantly different between the two groups patients (14 vs. 24 events, $p=0.225$).</p> <p>Precisely: During the double-blind treatment phase 104 pre-potassium values ≥ 6.0, which means all hyperkalemia events together, were observed for 29 patients within the control group and 169 pre-potassium values ≥ 6.0, which means all hyperkalemia events together, were observed for 34 patients within the s</p>	
End point type	Secondary
End point timeframe:	
40 week double-blind treatment phase	

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	50	47	97	
Units: events	14	24	38	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety-endpoint: Pre-dialysis potassium levels

End point title	Safety-endpoint: Pre-dialysis potassium levels
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End point description:

Analysis of run-in phase data: 989 pre-potassium values from 109 patients

Analysis of double-blind treatment phase data (week 0 - week 40): 10050 pre-potassium values from 97 patients

Analysis of Follow-up phase data (week 40 – week 44): 679 pre-potassium values from 83 patients

Analysis of double-blind phase and follow-up phase by a Mixed Model approach

Conclusion:

There is a borderline treatment effect of spironolactone on the pre-dialysis potassium levels during the double-blind treatment phase: in the mean, for fixed visit within this study phase, the pre-potassium value is 0.167 (95% confidence interval (0 , 0.334) higher for a patient under spironolactone compared to a patient not under spironolactone, p-value 0.05 (exactly 0.0498). This effect disappeared during the follow-up phase.

End point type	Secondary
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End point timeframe:

Analysis of run-in phase data

Analysis of double-blind treatment phase data (week 0 - week 40)

Analysis of Follow-up phase data (week 40 – week 44)

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	50	47	97	
Units: mEq/L				
arithmetic mean (standard deviation)	5.02 (± 0.52)	4.88 (± 0.54)	4.95 (± 0.52)	

Statistical analyses

No statistical analyses for this end point

Secondary: Residual renal function by globular filtration rate (GFR)

End point title	Residual renal function by globular filtration rate (GFR)
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End point description:

Because of sparse data and a high variability, summary statistics were presented as median, minima and maxima. Analysis of changes from baseline to week 39 within study groups was done by the Wilcoxon signed rank test. Comparisons of the distributions of the changes in urine volume and GFR from baseline to week 39 between patients treated with Spironolactone and patients under placebo were done by the Mann-Whitney U-test.

There was no significant difference between spironolactone and placebo treatment in the urine volume change, p-value = 0.169.

The median change in GFR from baseline to 39 weeks under treatment was -0.408 ml/min in the placebo group and -0.247 ml/min in the spironolactone group. The maximum patient-specific decrease from baseline to week 39 was 1.96 ml/min in the placebo group and 6.65 ml/min in the spironolactone group. The maximum patient-specific increase from baseline to week 39 was 0.09 ml/min in the placebo group and 3.39 m

End point type	Secondary
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End point timeframe:

change from baseline (week 0) to week 39

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	8	21	
Units: ml/min				
median (full range (min-max))	-0.25 (-6.65 to 3.39)	-0.41 (-1.96 to 0.09)	-0.32 (-6.65 to 3.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: 24-h diastolic Blood pressure in mmHg

End point title	24-h diastolic Blood pressure in mmHg
End point description:	
End point type	Secondary
End point timeframe:	
change from week 0 to week 40	

End point values	Spironolactone	Placebo	Intention to treat analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	50	47	97	
Units: mmHg				
arithmetic mean (standard deviation)	-1.26 (± 7.91)	0.05 (± 8.97)	-0.61 (± 8.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean count of tablets

End point title	Mean count of tablets
End point description:	
Mean count of tablets per visite	
End point type	Secondary
End point timeframe:	
week 0 to week 40	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	47		
Units: half tablets				
arithmetic mean (standard deviation)	0.828 (\pm 0.197)	0.906 (\pm 0.126)		

Statistical analyses

Statistical analysis title	Multilevel modelling
Statistical analysis description: hierarchical ordinal logistic regression	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	97
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.014
Method	type III F-test
Parameter estimate	cumulative odds ratio
Point estimate	3.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.31
upper limit	10.61

Adverse events

Adverse events information

Timeframe for reporting adverse events:

run-in, double-blind (week 0 - week 40) and follow-up (week 41 - week 44) phase

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	5.0
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Reporting groups

Reporting group title	Spironolactone group
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Reporting group description: -

Reporting group title	Placebo group
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Reporting group description: -

Serious adverse events	Spironolactone group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 50 (56.00%)	23 / 47 (48.94%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
General disorders and administration site conditions			
All serious adverse events	Additional description: Summary for AE / SAE analyses: considering all adverse events together across the double-blind treatment phase and the follow-up phase there are no significant differences between the two treatment groups.		
subjects affected / exposed	28 / 50 (56.00%)	23 / 47 (48.94%)	
occurrences causally related to treatment / all	0 / 81	4 / 85	
deaths causally related to treatment / all	0 / 0	0 / 2	

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

Non-serious adverse events	Spironolactone group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 50 (42.00%)	17 / 47 (36.17%)	
General disorders and administration site conditions			
All adverse events	Additional description: Summary for AE / SAE analyses: considering all adverse events together across the double-blind treatment phase and the follow-up phase there are no significant differences between the two treatment groups.		

subjects affected / exposed	21 / 50 (42.00%)	17 / 47 (36.17%)	
occurrences (all)	46	37	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2012	Amentment 1: Changes/adjustments in protocol and ICF with increase of patients' safety (e.g. expansion blood sampling).
31 August 2012	Amendment 2: minor changes in protocol and ICF, enlargement of time frame for regular study visits +/- 1 week and expansion number of participating trial sites.
05 July 2013	Amendment3: minor changes in protocol and ICF, implementation of an additional investigation (scanning laser Doppler flowmetry) and expansion number of participating trial sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported