# 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 |

**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 |
| Scientific contact | Clinical Trial Information Desk, University Hospital of Wuerzburg, +49 93120143311, hammer_f@klinik.uni-wuerzburg.de |

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 |
| **Arm title** | Spironolactone |

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 |

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 |
|---|---|

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 |

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 |
| 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

| **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) |
|---|---|

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 |
|---|---|

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) |
|---|---|

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 |
|---|---|

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 (± 33.85) | 0.10 (± 27.10) | 3.91 (± 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 (± 6.51) | -0.71 (± 7.32) | 0.44 (± 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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 antihypersensive | 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:

The main safety endpoint was the development of hyperkalemia.
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-$\chi$2-test within a negative binomial model (NB) for count data.
During the double-blind treatment phase mild hyperkalemia (6.0 ≤ 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).
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

| 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 |
|---|---|

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 |
|---|---|

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) |
|---|---|

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 |
|---|---|

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 (± 0.197) | 0.906 (± 0.126) | | |

**Statistical analyses**

| **Statistical analysis title** | Multilevel modelling |
|---|---|
| Statistical analysis description:<br>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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 5.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Spironolactone group |
| Reporting group description: - | |
| Reporting group title | Placebo group |

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:<br>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:<br>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<br>occurrences (all) | 21 / 50 (42.00%)<br>46 | 17 / 47 (36.17%)<br>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