Clinical trial results:
The effect of spironolactone on calcineurin inhibitor induced nephrotoxicity

Summary

EudraCT number	2011-002243-98
Trial protocol	DK
Global end of trial date	08 April 2021

Results information

Result version number	v1 (current)
This version publication date	25 April 2022
First version publication date	25 April 2022

Trial information

Trial identification

Sponsor protocol code	29702

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01602861
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Odense University Hospital
Sponsor organisation address	J.B. Winsløws Vej 4, Odense C, Denmark, 5000
Public contact	Forskerenheden, Department of nephrology, OUH, Odense, DK, +45 30299610, line.mortensen@rsyd.dk
Scientific contact	Forskerenheden, Department of nephrology, OUH, Odense, DK, 30299610 30299610, line.mortensen@rsyd.dk

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	30 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2021
Global end of trial reached?	Yes
Global end of trial date	08 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether renal function in kidney transplant patients can be preserved by the addition of spironolactone to standard treatment

Protection of trial subjects:

Regular scheduled visits
Frequent measurements of plasma potassium after dosage adjustments

Background therapy:

Standard of care
Immunosuppression including a calcineurininhibitor

Evidence for comparator:

Calcineurin inhibitors (CNI) are one of the cornerstones of the immunosuppressive therapy after solid organ transplantation. The introduction of CNI has caused a significant decrease in acute rejections. However, CNI also have severe side effects including renal interstitial fibrosis and tubular atrophy, a term also referred to as CNI nephrotoxicity. In the transplanted kidney this contributes to impaired kidney function and eventually reduced graft survival.
The mineralocorticoid aldosterone may be involved in the development of renal fibrosis. Recent observations suggest that aldosterone plays a central role in the pathogenesis of CNI nephrotoxicity and that the mineralocorticoid-receptor-blocker spironolactone could be a useful agent to prevent it.

Actual start date of recruitment	25 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 180
Worldwide total number of subjects	180
EEA total number of subjects	180

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	148
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Inclusion was performed from February 2013 to April 2021.
Patients were included from outpatient clinics at the four participating sites.

Pre-assignment

Screening details:

Renal transplant patients were identified through the outpatient clinics in the respective sites.
Assessed for eligibility (n=959)
Excluded (n=771), hereof Not meeting inclusion criteria (n= 422), Declined participation (n=270), Eligible, but not approached (n=79)
Included (n=188), hereof Declined after inclusion (n=8)
Randomized (n=180)

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Spironolactone

Arm description:

Spironolactone 25-50 mg OD

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

Dosage and administration details:

25-50 mg once daily

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

1 tablet daily, increased to 2 tablets daily after 3 months if well tolerated

Number of subjects in period 1	Spironolactone	Placebo
Started	90	90
Completed	65	74
Not completed	25	16
Consent withdrawn by subject	2	-
Adverse event, non-fatal	22	16
Death	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Spironolactone
Reporting group description: Spironolactone 25-50 mg OD	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Spironolactone	Placebo	Total
Number of subjects	90	90	180
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	72	76	148
From 65-84 years	18	14	32
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54	53	
standard deviation	± 11	± 12	-
Gender categorical Units: Subjects			
Female	28	35	63
Male	62	55	117
Chrome-EDTA clearance			
Renal function			
Units: mL/min			
arithmetic mean	58	52	
standard deviation	± 23	± 18	-
Systolic blood pressure Units: mmHg			
arithmetic mean	135	133	
standard deviation	± 13	± 12	-
Diastolic blood pressure Units: mmHg			
arithmetic mean	80	79	
standard deviation	± 7	± 7	-
Plasma potassium Units: mmol/L			
arithmetic mean	4.2	4.2	
standard deviation	± 0.4	± 0.5	-

Plasma aldosterone Units: pg/mL			
geometric mean	84.4	78.4	
inter-quartile range (Q1-Q3)	55.9 to 118.8	59.9 to 103.4	-
Age of transplanted kidney Units: Years			
median	4.4	2.0	
inter-quartile range (Q1-Q3)	1.1 to 10.0	0.7 to 6.6	-

End points

End points reporting groups

Reporting group title	Spironolactone
Reporting group description: Spironolactone 25-50 mg OD	
Reporting group title	Placebo
Reporting group description: -	

Primary: Chrome-EDTA clearance

End point title	Chrome-EDTA clearance
End point description: Change from baseline in renal function measured as chrome-EDTA clearance (mL/min) compared to placebo group	
End point type	Primary
End point timeframe: Baseline to 3 years	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	72		
Units: mL/min				
arithmetic mean (confidence interval 95%)	-7.07 (-9.60 to -4.53)	0.12 (-2.27 to 2.52)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Linear mixed effects regressions model using maximum likelihood estimation. The model included fixed effects for time and interaction between the randomization group and time and a random intercept for patient.	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.63
upper limit	-3.75

Secondary: Proteinuria

End point title	Proteinuria

End point description:

Change in 24-hour proteinuria from baseline to 3 years in spironolactone group compared to placebo

End point type	Secondary

End point timeframe:

Baseline to 3 years

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	66		
Units: g/day				
arithmetic mean (confidence interval 95%)	0.07 (-0.87 to 0.22)	0.03 (-0.07 to 0.13)		

Statistical analyses

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Linear mixed effects regressions models using maximum likelihood estimation. The model included fixed effects for time and interaction between the randomization group and time and a random intercept for patient.

Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.22

Secondary: Fibrosis Banff CT score

End point title	Fibrosis Banff CT score
End point description:	
Renal biopsies performed in a subgroup of participants at baseline and after two years (n=48)	
End point type	Secondary
End point timeframe:	
Baseline to two years	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: Number of patients				
CT0	7	8		
CT1	12	12		
CT2	2	4		
CT3	2	1		

Statistical analyses

Statistical analysis title	Statistical analysis 3
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxons matched-pair signed rank test

Secondary: Fibrosis Banff CI score

End point title	Fibrosis Banff CI score
End point description:	
Renal biopsies performed in a subgroup of participants at baseline and after two years (n=48)	
End point type	Secondary
End point timeframe:	
Baseline to two years	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: Number of patients				
CI0	4	3		
CI1	13	14		
CI2	5	7		
CI3	1	1		

Statistical analyses

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Banff scores were tested for changes over two years using Wilcoxons matched-pair signed rank test	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxons matched-pair signed rank test

Secondary: Fibrosis Banff AH score

End point title	Fibrosis Banff AH score
End point description: Renal biopsies at baseline and 2 years in a subgroup (n=48)	
End point type	Secondary
End point timeframe: Baseline to two years	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: Number of patients				
AH0	5	4		
AH1	7	8		
AH2	4	9		
AH3	7	4		

Statistical analyses

Statistical analysis title	Statistical analysis 3
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxons matched-pair signed rank test

Secondary: Fibrosis pointcounting	
End point title	Fibrosis pointcounting
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to two years	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: Percentage fibrosis				
arithmetic mean (confidence interval 95%)	-0.52 (-5.22 to 4.18)	-3.08 (-8.44 to 2.28)		

Statistical analyses

Statistical analysis title	Statistical analysis 4
Comparison groups	Placebo v Spironolactone
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.55
upper limit	4.44
Variability estimate	Standard error of the mean
Dispersion value	3.47

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded during the full 3-year intervention

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	Spironolactone

Reporting group description:

Spironolactone 25-50 mg OD

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Spironolactone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 90 (53.33%)	46 / 90 (51.11%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma in situ cervix uteri			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 90 (2.22%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ishemic ulcer			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected deep vein thrombosis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosed AV-fistula			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurism on brachial artery			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Quinckes edema			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	4 / 90 (4.44%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	4 / 90 (4.44%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Planned operations			
subjects affected / exposed	16 / 90 (17.78%)	19 / 90 (21.11%)	
occurrences causally related to treatment / all	0 / 28	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Electric shock			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 90 (0.00%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knife wound			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bleeding after kidney biopsy			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Digoxin intoxication			

subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azathioprine			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 90 (3.33%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 90 (1.11%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Edema			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	2 / 90 (2.22%)	3 / 90 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 90 (1.11%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired vision			

subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hemolysis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anemia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Intraocular bleeding			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 90 (1.11%)	4 / 90 (4.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bleeding			
subjects affected / exposed	4 / 90 (4.44%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	1 / 90 (1.11%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 90 (3.33%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured spleen			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gall bladder polyp			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystolithiasis			
subjects affected / exposed	1 / 90 (1.11%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rejection in kidney graft			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine increase			

subjects affected / exposed	6 / 90 (6.67%)	9 / 90 (10.00%)	
occurrences causally related to treatment / all	4 / 7	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypocalcemia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone tumor			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	3 / 90 (3.33%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	2 / 90 (2.22%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 90 (7.78%)	7 / 90 (7.78%)	
occurrences causally related to treatment / all	0 / 23	0 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 90 (6.67%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Unknown focus			
subjects affected / exposed	7 / 90 (7.78%)	8 / 90 (8.89%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst infection			
subjects affected / exposed	1 / 90 (1.11%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 90 (3.33%)	4 / 90 (4.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 90 (1.11%)	3 / 90 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegaloviræmia			
subjects affected / exposed	1 / 90 (1.11%)	3 / 90 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 90 (2.22%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection			
subjects affected / exposed	0 / 90 (0.00%)	3 / 90 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	2 / 90 (2.22%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylodiscitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condylomata acuminata			

subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	
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: 0.05 %

Non-serious adverse events	Spironolactone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 90 (94.44%)	88 / 90 (97.78%)	
Injury, poisoning and procedural complications			
Accidents			
subjects affected / exposed	15 / 90 (16.67%)	13 / 90 (14.44%)	
occurrences (all)	19	14	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	6 / 90 (6.67%)	4 / 90 (4.44%)	
occurrences (all)	6	6	
Chest pain			
subjects affected / exposed	1 / 90 (1.11%)	8 / 90 (8.89%)	
occurrences (all)	1	9	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 90 (12.22%)	13 / 90 (14.44%)	
occurrences (all)	14	13	
General disorders and administration site conditions			
Malaise	Additional description: Unspecified malaise		
subjects affected / exposed	34 / 90 (37.78%)	25 / 90 (27.78%)	
occurrences (all)	51	40	
Dizziness			
subjects affected / exposed	23 / 90 (25.56%)	18 / 90 (20.00%)	
occurrences (all)	29	21	

Edema			
subjects affected / exposed	10 / 90 (11.11%)	8 / 90 (8.89%)	
occurrences (all)	11	8	
Hypertension			
subjects affected / exposed	9 / 90 (10.00%)	13 / 90 (14.44%)	
occurrences (all)	10	15	
Hypotension			
subjects affected / exposed	18 / 90 (20.00%)	13 / 90 (14.44%)	
occurrences (all)	25	13	
Acidosis			
subjects affected / exposed	7 / 90 (7.78%)	3 / 90 (3.33%)	
occurrences (all)	7	3	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	17 / 90 (18.89%)	20 / 90 (22.22%)	
occurrences (all)	20	23	
Abdominal pain			
subjects affected / exposed	8 / 90 (8.89%)	8 / 90 (8.89%)	
occurrences (all)	12	8	
Weight increased			
subjects affected / exposed	5 / 90 (5.56%)	7 / 90 (7.78%)	
occurrences (all)	5	10	
Dyspepsia			
subjects affected / exposed	7 / 90 (7.78%)	4 / 90 (4.44%)	
occurrences (all)	8	6	
Nausea			
subjects affected / exposed	4 / 90 (4.44%)	6 / 90 (6.67%)	
occurrences (all)	4	6	
Vomiting			
subjects affected / exposed	6 / 90 (6.67%)	4 / 90 (4.44%)	
occurrences (all)	10	4	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	11 / 90 (12.22%)	12 / 90 (13.33%)	
occurrences (all)	12	14	
Cough			

subjects affected / exposed	4 / 90 (4.44%)	11 / 90 (12.22%)	
occurrences (all)	4	11	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	10 / 90 (11.11%)	6 / 90 (6.67%)	
occurrences (all)	10	8	
Pruritus			
subjects affected / exposed	5 / 90 (5.56%)	6 / 90 (6.67%)	
occurrences (all)	5	6	
Renal and urinary disorders			
Rise in plasma creatinine			
subjects affected / exposed	33 / 90 (36.67%)	21 / 90 (23.33%)	
occurrences (all)	56	27	
Endocrine disorders			
Gynecomasty			
subjects affected / exposed	19 / 90 (21.11%)	12 / 90 (13.33%)	
occurrences (all)	24	16	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	28 / 90 (31.11%)	27 / 90 (30.00%)	
occurrences (all)	38	45	
Gout			
subjects affected / exposed	3 / 90 (3.33%)	8 / 90 (8.89%)	
occurrences (all)	8	9	
Back pain			
subjects affected / exposed	7 / 90 (7.78%)	11 / 90 (12.22%)	
occurrences (all)	7	12	
Infections and infestations			
Infection	Additional description: All bacterial, viral and funghal infections occurring throughout the study		
subjects affected / exposed	64 / 90 (71.11%)	60 / 90 (66.67%)	
occurrences (all)	178	191	
Metabolism and nutrition disorders			
Hyperkalemia			
subjects affected / exposed	16 / 90 (17.78%)	8 / 90 (8.89%)	
occurrences (all)	25	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported