



## Clinical trial results:

### The Effect of Spironolactone on Pain in Older People with Osteoarthritis Summary

EudraCT number	2013-002638-19
Trial protocol	GB
Global end of trial date	28 January 2015

#### Results information

Result version number	v1 (current)
This version publication date	23 July 2016
First version publication date	23 July 2016

#### Trial information

##### Trial identification

Sponsor protocol code	2012GR03
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##### Additional study identifiers

ISRCTN number	ISRCTN02046668
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	University of Dundee / NHS Tayside
Sponsor organisation address	TASC, Ninewells Hospital, Dundee, United Kingdom, DD1 9SY
Public contact	Dr Miles Witham, University of Dundee, 44 01382 383086, m.witham@dundee.ac.uk
Scientific contact	Dr Miles Witham, University of Dundee, 44 01382 383086, m.witham@dundee.ac.uk

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	12 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 January 2015
Global end of trial reached?	Yes
Global end of trial date	28 January 2015
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

This pilot study's purpose is to provide preliminary evidence on which to base sample size calculations for a possible future trial which will answer the question: "Is spironolactone more effective than placebo in reducing knee pain in older people with symptomatic osteoarthritis (OA) of the knee, when given in addition to usual analgesia?"

Protection of trial subjects:

Participants were recruited via a range of opt-in strategies to protect confidentiality and prevent unwanted contact. Informed consent was sought after ample time for participants to ask questions prior to engaging in trial procedures.

Participants were enrolled only if they met inclusion and exclusion criteria designed to minimize risk from the IMP - in particular screening checks on renal function, sodium and potassium were conducted, and concomitant use of medications likely to exacerbate side effects of spironolactone (ie ACEi, ARB, NSAID) were exclusion criteria

Frequent checks on blood pressure, renal function and electrolytes were conducted during the trial, and adverse events were sought at each study visit. A DMC was convened to review safety data during the trial.

Background therapy:

Usual analgesic therapy was allowed during the trial as per normal clinical practice. Participants using NSAID medications were excluded from the trial due to the increased risk of interaction with spironolactone.

Evidence for comparator:

Placebo was selected as comparator as the aim of the trial was to test the efficacy of spironolactone as add-on therapy to usual analgesics, rather than as a replacement for usual analgesia.

Aldosterone is known to have pro-inflammatory effects, including stimulation of cytokine production, which might contribute to the low-level chronic inflammation seen in osteoarthritis. Spironolactone, as a blocker of aldosterone, might therefore be able to reverse this process.

Data from a previous trial of spironolactone in older, functionally impaired people suggested an improvement in quality of life and a reduction in pain in the subgroup of participants with osteoarthritis (Am J Med 2013;126:590-7). This previous result provided the evidence that initiated this trial.

Actual start date of recruitment	01 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 86
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Worldwide total number of subjects	86
EEA total number of subjects	86

Notes:

<b>Subjects enrolled per age group</b>	
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)	0
From 65 to 84 years	77
85 years and over	9

## Subject disposition

### Recruitment

Recruitment details:

Recruited from primary care via Scottish Primary care research network; via advertising; via SHARE register

### Pre-assignment

Screening details:

Telephone prescreen, then screening visit to check eligibility criteria. Renal function and potassium checked at screening visit

### Period 1

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

Blinding implementation details:

Matching IMP and placebo (overencapsulated IMP) prepared by an independent provider (Tayside Pharmaceuticals), dispensed in identical bottles with no external indication of allocation group.

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Spironolactone
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Arm description:

Oral spironolactone 25mg once daily

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

Dosage and administration details:

25mg once daily for 12 weeks

<b>Arm title</b>	Placebo
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Arm description:

Matching placebo taken once a day for 12 weeks

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

Dosage and administration details:

Placebo capsule taken orally once per day for 12 weeks

<b>Number of subjects in period 1</b>	Spironolactone	Placebo
Started	43	43
Completed	43	43

## Baseline characteristics

### Reporting groups

Reporting group title	Spironolactone
Reporting group description: Oral spironolactone 25mg once daily	
Reporting group title	Placebo
Reporting group description: Matching placebo taken once a day for 12 weeks	

Reporting group values	Spironolactone	Placebo	Total
Number of subjects	43	43	86
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	77.4	76.1	
standard deviation	± 4.8	± 5.2	-
Gender categorical Units: Subjects			
Female	26	27	53
Male	17	16	33

### Subject analysis sets

Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomised participants (Intention to treat)	

Reporting group values	ITT analysis set		
Number of subjects	86		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	76.7 ± 5		
Gender categorical Units: Subjects			
Female Male	53 33		

## End points

### End points reporting groups

Reporting group title	Spironolactone
Reporting group description: Oral spironolactone 25mg once daily	
Reporting group title	Placebo
Reporting group description: Matching placebo taken once a day for 12 weeks	
Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomised participants (Intention to treat)	

### Primary: WOMAC pain subscale

End point title	WOMAC pain subscale
End point description: Unadjusted	
End point type	Primary
End point timeframe: Change between baseline and 12 weeks	

End point values	Spironolactone	Placebo	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	43	86	
Units: Units				
arithmetic mean (confidence interval 95%)	-1 (-1.6 to -0.4)	-1.7 (-2.3 to -1.2)	-0.01 (-0.9 to 0.88)	

### Statistical analyses

Statistical analysis title	Primary outcome analysis
Statistical analysis description: Between-group mixed-model regression, adjusting for baseline values and for site	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.53



Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	1.33

### Secondary: WOMAC stiffness subscale

End point title	WOMAC stiffness subscale
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to 12 weeks	

End point values	Spironolactone	Placebo	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	43	86	
Units: Units				
arithmetic mean (confidence interval 95%)	-1 (-1.6 to -0.3)	-1.7 (-2.3 to -1.2)	-0.2 (-1.18 to 0.78)	

### Statistical analyses

Statistical analysis title	Secondary outcome
Statistical analysis description:	
Between-group mixed-model regression, adjusting for baseline values and site	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	1.13

### Secondary: WOMAC physical function subscale

End point title	WOMAC physical function subscale
End point description:	
End point type	Secondary
End point timeframe:	
Change between baseline and 12 weeks	

End point values	Spironolactone	Placebo	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	43	86	
Units: Units				
arithmetic mean (confidence interval 95%)	-1 (-1.5 to -0.5)	-1.1 (-1.7 to -0.5)	-0.3 (-1.19 to 0.6)	

### Statistical analyses

Statistical analysis title	Secondary outcome
Statistical analysis description:	
Between-group mixed-model regression, adjusted for baseline values and site	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	0.76

### Secondary: EuroQol EQ5D

End point title	EuroQol EQ5D
End point description:	
End point type	Secondary
End point timeframe:	
Difference between baseline and 12 weeks	

End point values	Spironolactone	Placebo	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	43	86	
Units: Units				
arithmetic mean (confidence interval 95%)	0.02 (-0.05 to 0.09)	0.03 (-0.03 to 0.1)	0.07 (-0.02 to 0.16)	

## Statistical analyses

Statistical analysis title	Secondary outcome
Statistical analysis description:	
Between-group mixed-model regression, adjusted for baseline values, site and use of neuropathic drugs	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.12

## Secondary: EuroQol EQ5D visual analog scale

End point title	EuroQol EQ5D visual analog scale
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to 12 weeks	

End point values	Spironolactone	Placebo	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	43	86	
Units: Units				
arithmetic mean (confidence interval 95%)	0.5 (-4.1 to 5)	0.14 (-5.23 to 5.51)	-2.19 (-9.11 to 4.73)	

## Statistical analyses

<b>Statistical analysis title</b>	Secondary analysis
Statistical analysis description:	
Between-group mixed-model regression, adjusted for baseline values, site and use of neuropathic drugs	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	5.19

## Secondary: Urine CTX II

End point title	Urine CTX II
End point description:	
End point type	Secondary
End point timeframe:	
Change between baseline and 12 weeks	

<b>End point values</b>	Spironolactone	Placebo	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	43	86	
Units: ug/L				
arithmetic mean (confidence interval 95%)	0.1 (-0.8 to 0.9)	-0.03 (-0.81 to 0.75)	0.24 (-0.93 to 1.41)	

## Statistical analyses

<b>Statistical analysis title</b>	Secondary outcome
Statistical analysis description:	
Between-group mixed-model regression, adjusted for baseline values and site	
Comparison groups	Spironolactone v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	1.24

### Secondary: Serum matrix metalloproteinase 3

End point title	Serum matrix metalloproteinase 3
End point description:	
End point type	Secondary
End point timeframe:	
Difference between baseline and 12 weeks	

End point values	Spironolactone	Placebo	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	43	86	
Units: ng/ml				
arithmetic mean (confidence interval 95%)	1 (-2 to 5)	2.86 (-1.34 to 7.07)	-1.44 (-9 to 6.11)	

### Statistical analyses

Statistical analysis title	Secondary outcome
Statistical analysis description:	
Between-group mixed-model regression, adjusted for baseline values and site	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.32
upper limit	3.36

## Secondary: Morning cortisol

End point title	Morning cortisol
End point description:	
End point type	Secondary
End point timeframe:	
Difference between baseline and 12 weeks	

End point values	Spironolactone	Placebo	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	43	86	
Units: ng/ml				
arithmetic mean (confidence interval 95%)	13 (-1 to 27)	8.85 (-2.56 to 20.26)	8.15 (-9.62 to 25.95)	

## Statistical analyses

Statistical analysis title	Secondary outcome
Statistical analysis description:	
Between-group mixed-model regression, adjusted for baseline values and site	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	6.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.66
upper limit	22.73

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

screening visit to 12 week (final) visit

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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### Reporting groups

Reporting group title	Spironolactone
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Reporting group description:

Oral spironolactone 25mg once daily

Reporting group title	Placebo
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Reporting group description:

Matching placebo taken once a day for 12 weeks

Serious adverse events	Spironolactone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 43 (6.98%)	2 / 43 (4.65%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
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 %

<b>Non-serious adverse events</b>	Spironolactone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 43 (58.14%)	24 / 43 (55.81%)	
Investigations			
Blood creatine increased			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	3 / 43 (6.98%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract infection			
subjects affected / exposed	4 / 43 (9.30%)	2 / 43 (4.65%)	
occurrences (all)	5	2	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	3 / 43 (6.98%)	2 / 43 (4.65%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			



Arthralgia			
subjects affected / exposed	4 / 43 (9.30%)	4 / 43 (9.30%)	
occurrences (all)	4	4	
Back pain			
subjects affected / exposed	1 / 43 (2.33%)	2 / 43 (4.65%)	
occurrences (all)	1	2	
Pain in extremity			
subjects affected / exposed	2 / 43 (4.65%)	3 / 43 (6.98%)	
occurrences (all)	2	3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2013	Clarification of Safety assessment procedures.
27 January 2014	Addition of an exclusion criterion.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26413749>