Clinical trial results:
Oral potassium supplementation in healthy men - interactions with the renin-angiotensin-aldosterone system and the sympathetic nervous system

Summary

EudraCT number	2013-004460-66
Trial protocol	DK
Global end of trial date	21 December 2016

Results information

Result version number	v1 (current)
This version publication date	15 February 2020
First version publication date	15 February 2020

Trial information

Trial identification

Sponsor protocol code	KARAASS-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02380157
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Jørgen Jeppesen
Sponsor organisation address	Valdemar Hansens Vej 1-23, Glostup, Denmark, 2600
Public contact	Rasmus Dreier, Rasmus Dreier, rasmus.dreier.01@regionh.dk
Scientific contact	Rasmus Dreier, Rasmus Dreier, rasmus.dreier.01@regionh.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	24 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2016
Global end of trial reached?	Yes
Global end of trial date	21 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to test whether oral potassium supplementation, administered as Kaleorid, interacts with the renin-angiotensin-aldosterone system and the sympathetic nervous system.

Protection of trial subjects:

Participants were treated with an oral potassium supplement (90 mmol potassium per day). To secure that hyperkalemia was not developed plasma potassium was systematically measured.

Background therapy:

No background therapy. All participants were healthy men not taking any medication.

Evidence for comparator:

We tested a potassium supplement (90 mmol per day) against placebo as the comparator, primarily to minimize bias.

Actual start date of recruitment	24 March 2015
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: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	32
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited through announcement on the Danish website: www.forsoegsperson.dk, a website where researchers can announce their project for potential trial participants. Following recruitment a screening visit was arranged.

Pre-assignment

Screening details:

The screening consisted of a medical interview and baseline testing including physical examination, office blood pressure measurement, electrocardiogram and blood sampling.
Only healthy normotensive men were included.

Period 1

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

Blinding implementation details:

Treatment was blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Potassium then Placebo

Arm description:

Cross-over study.
This arm received 4 weeks potassium supplement in period 1 followed by 4 weeks placebo in period 2. The two periods was separated by 2 weeks washout.

Arm type	Cross-over study
Investigational medicinal product name	Kaleorid, 750mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

3 tablets 3 times daily equivalent to 90 mmol potassium per day

Arm title	Placebo then Potassium

Arm description:

Cross-over study.
This arm received Placebo for 4 weeks in Period 1 followed by Potassium for 4 weeks in Period 2. The two periods was separated by 2 weeks washout.

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

Dosage and administration details:

3 tablets 3 times daily

Number of subjects in period 1	Potassium then Placebo	Placebo then Potassium
Started	16	16
Completed	13	12
Not completed	3	4
Adverse event, non-fatal	1	1
Protocol deviation	2	3

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Treatment was blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Potassium then Placebo

Arm description:

Cross-over study.
This arm received 4 weeks potassium supplement in period 1 followed by 4 weeks placebo in period 2. The two periods was separated by 2 weeks washout.

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

Dosage and administration details:

3 tablets 3 times daily

Arm title	Placebo then Potassium

Arm description:

Cross-over study.
This arm received Placebo for 4 weeks in Period 1 followed by Potassium for 4 weeks in Period 2. The two periods was separated by 2 weeks washout.

Arm type	Cross-over study
Investigational medicinal product name	Kaleorid, 750mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

3 tablets 3 times daily equivalent to 90 mmol potassium per day

Number of subjects in period 2	Potassium then Placebo	Placebo then Potassium
Started	13	12
Completed	13	12

Baseline characteristics

Reporting groups	
Reporting group title	Period 1
Reporting group description:	
Baseline characteristics are only for the 25 subjects who completed the study.	

Reporting group values	Period 1	Total	
Number of subjects	32	32	
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			
Age for the 25 men who completed the study			
Units: years			
median	25.7		
inter-quartile range (Q1-Q3)	23.1 to 34.4	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	32	32	
Body Mass Index (BMI)			
BMI of the 25 men who completed the study			
Units: kilogram(s)/square meter			
arithmetic mean	24.8		
standard deviation	± 2.3	-	
Office Systolic Blood Pressure			
Office Systolic Blood Pressure of the 25 men who completed the study.			
Units: mm Hg			
arithmetic mean	119.7		
standard deviation	± 6.9	-	
Office Diastolic Blood Pressure			
Office Diastolic Blood Pressure of the 25 men who completed the study.			
Units: mm Hg			
arithmetic mean	72.6		
standard deviation	± 7.1	-	
Plasma Creatinine			
Plasma Creatinine of the 25 men who completed the study.			
Units: micromole(s)/litre			

arithmetic mean	84.7		
standard deviation	± 12.3	-	
Plasma Sodium			
Plasma Sodium of the 25 men who completed the study.			
Units: millimole(s)/litre			
arithmetic mean	142.1		
standard deviation	± 1.1	-	
Plasma Potassium			
Plasma Potassium of the 25 men who completed the study.			
Units: millimole(s)/litre			
arithmetic mean	4.2		
standard deviation	± 0.2	-	

End points

End points reporting groups

Reporting group title	Potassium then Placebo
Reporting group description:	
Cross-over study. This arm received 4 weeks potassium supplement in period 1 followed by 4 weeks placebo in period 2. The two periods was separated by 2 weeks washout.	
Reporting group title	Placebo then Potassium
Reporting group description:	
Cross-over study. This arm received Placebo for 4 weeks in Period 1 followed by Potassium for 4 weeks in Period 2. The two periods was separated by 2 weeks washout.	
Reporting group title	Potassium then Placebo
Reporting group description:	
Cross-over study. This arm received 4 weeks potassium supplement in period 1 followed by 4 weeks placebo in period 2. The two periods was separated by 2 weeks washout.	
Reporting group title	Placebo then Potassium
Reporting group description:	
Cross-over study. This arm received Placebo for 4 weeks in Period 1 followed by Potassium for 4 weeks in Period 2. The two periods was separated by 2 weeks washout.	
Subject analysis set title	Crossover: Potassium
Subject analysis set type	Per protocol
Subject analysis set description:	
Crossover study, We here report the results after 4 weeks on potassium.	
Subject analysis set title	Crossover: Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
Crossover study. We here report the results after 4 weeks on placebo.	

Primary: Angiotensin II stimulated P-aldosterone

End point title	Angiotensin II stimulated P-aldosterone
End point description:	
Angiotensin II (Ang II) was infused in each subject and P-aldosterone was measured before, during and after the infusion. The aim was to test if the aldosterone respons to Ang II was different after 4 weeks on potassium compared with after 4 weeks on placebo. The result is presented as a graph.	
End point type	Primary
End point timeframe:	
This was measured at the end of each treatment period, after 4 weeks on potassium and after 4 weeks on placebo.	

End point values	Crossover: Potassium	Crossover: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: pmol/L				
arithmetic mean (standard error)	0 (± 0)	0 (± 0)		

Attachments (see zip file)	Angiotensin II stimulated P-Aldosterone/A_Aldosterone.tif

Statistical analyses

Statistical analysis title	Linear mixed model for repeated measurements

Statistical analysis description:

In this analysis the effect of time was equal to the effect of the Ang II infusion, and if there was a significant interaction between time and treatment, then the response to Ang II was different between the two treatments (Potassium and Placebo).

Comparison groups	Crossover: Potassium v Crossover: Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	Mixed models analysis

Secondary: Angiotensin II stimulated blood pressure (Systolic BP)

End point title	Angiotensin II stimulated blood pressure (Systolic BP)

End point description:

Angiotensin II (Ang II) was infused in each subject and systolic BP (blood pressure) was measured before, during and after the infusion. The aim was to test if the systolic BP response to Ang II was different after 4 weeks on potassium compared with after 4 weeks on placebo. The result is presented as a graph.

End point type	Secondary

End point timeframe:

This was measured at the end of each treatment period, after 4 weeks on potassium and after 4 weeks on placebo.

End point values	Crossover: Potassium	Crossover: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: mm Hg				
arithmetic mean (standard error)	0 (± 0)	0 (± 0)		

Attachments (see zip file)	Angiotensin II stimulated systolic BP/B_TFM_systolicBP.tif

Statistical analyses

Statistical analysis title	Linear mixed model for repeated measurements

Statistical analysis description:

In this analysis the effect of time was equal to the effect of the Ang II infusion, and if there was a significant interaction between time and treatment, then the response to Ang II was different between the two treatments (Potassium and Placebo).

Comparison groups	Crossover: Potassium v Crossover: Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.885
Method	Mixed models analysis

Other pre-specified: 24-hour SBP (systolic blood pressure)

End point title	24-hour SBP (systolic blood pressure)

End point description:

This endpoint is one of the 24-hour ambulatory blood pressure variables.

End point type	Other pre-specified

End point timeframe:

This was measured at the end of each treatment period, after 4 weeks on potassium and after 4 weeks on placebo.

End point values	Crossover: Potassium	Crossover: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: mm Hg				
arithmetic mean (standard deviation)	117.6 (± 5.8)	118.2 (± 5.2)		

Statistical analyses

Statistical analysis title	Linear mixed model for repeated measurements
Comparison groups	Crossover: Potassium v Crossover: Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.48
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	1.1

Other pre-specified: 24-hour DBP (diastolic blood pressure)	
End point title	24-hour DBP (diastolic blood pressure)
End point description: This end point is one of the 24-hour ambulatory blood pressure variables.	
End point type	Other pre-specified
End point timeframe: This was measured at the end of each treatment period, after 4 weeks on potassium and after 4 weeks on placebo.	

End point values	Crossover: Potassium	Crossover: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: mm Hg				
arithmetic mean (standard deviation)	70.8 (± 6.2)	70.8 (± 6.3)		

Statistical analyses

Statistical analysis title	Linear mixed model for repeated measurements
Comparison groups	Crossover: Potassium v Crossover: Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.97
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	1.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were registered for each individual from the first day of experimental treatment until their last visit.

Assessment type	Systematic

Dictionary used

Dictionary name	None used
Dictionary version	1

Reporting groups

Reporting group title	Crossover: Potassium

Reporting group description:

We here report adverse events during potassium treatment.

Reporting group title	Crossover: Placebo

Reporting group description:

We here report adverse events during placebo treatment.

Serious adverse events	Crossover: Potassium	Crossover: Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Crossover: Potassium	Crossover: Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 25 (76.00%)	17 / 25 (68.00%)	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 25 (4.00%)	4 / 25 (16.00%)	
occurrences (all)	1	4	
Abdominal pain			
subjects affected / exposed	5 / 25 (20.00%)	3 / 25 (12.00%)	
occurrences (all)	5	3	
Flatulence	Additional description: Flatus		

subjects affected / exposed	9 / 25 (36.00%)	5 / 25 (20.00%)	
occurrences (all)	9	5	
Diarrhoea	Additional description: Diarrhea		
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Reflux gastritis	Additional description: Acid reflux		
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Itching			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Rash			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	

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