Clinical trial results:
BONATHIAD - Bone Association with Thiazide Diuretics.

Summary

EudraCT number	2015-001059-63
Trial protocol	DK
Global end of trial date	05 March 2019

Results information

Result version number	v1 (current)
This version publication date	07 October 2020
First version publication date	07 October 2020

Trial information

Trial identification

Sponsor protocol code	2015.009

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aalborg University Hospital
Sponsor organisation address	Mølleparkvej 4, Aalborg, Denmark,
Public contact	Peter Vestergaard, Aalborg University, 45 99403791, pev@dcm.aau.dk
Scientific contact	Peter Vestergaard, Aalborg University, 45 99403791, pev@dcm.aau.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	03 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 March 2019
Global end of trial reached?	Yes
Global end of trial date	05 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To examine if bendroflumethiazide with potassium supplements augment the effect of oral bisphosphonates on preventing progression of osteoporosis.

Protection of trial subjects:

No painful procedures were performed. The trial was overseen by licensed doctors, any discrepancies from normal results in CT or DXA scans or biochemical abnormalities led to appropriate supplementary diagnostics and treatment and the participants were referred to specialist or GP for follow-up. Results of DXA scans were communicated to the patients GPs at study end.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2015
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	Denmark: 139
Worldwide total number of subjects	139
EEA total number of subjects	139

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)	71
From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from the osteoporosis clinic at Aalborg University Hospital in Denmark from July 2016 to March 2018.

Pre-assignment

Screening details:

The study population included postmenopausal women over the age of 50 years with osteoporosis diagnosed using traditional dual energy x-ray absorptiometry (DXA) scans. All participants were treated with oral bisphosphonates prior to inclusion and throughout the study.

Period 1

Period 1 title	overall trial (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:

Active and placebo tablet made to look exactly similar

Arms

Are arms mutually exclusive?	Yes
Arm title	24 wks placebo

Arm description:

24 weeks placebo, 24 weeks washout

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:

Placebo

Arm title	24 wks active

Arm description:

24 weeks bendroflumethiazide followed by 24 weeks of washout

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

Dosage and administration details:

2.5 mg bendroflumethiazide and 573 mg potassium chloride p.o. once daily

Arm title	48 wks active

Arm description:

48 weeks bendroflumethiazide

Arm type	Active comparator

Investigational medicinal product name	Bendroflumethiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg bendroflumethiazide and 573 mg potassium chloride p.o. once daily

Arm title	48 wks placebo

Arm description:

Placebo for 48 weeks

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:

Placebo

Number of subjects in period 1	24 wks placebo	24 wks active	48 wks active
Started	27	25	44
Completed	17	23	35
Not completed	10	2	9
Lost to follow-up	10	2	9

Number of subjects in period 1	48 wks placebo
Started	43
Completed	34
Not completed	9
Lost to follow-up	9

Baseline characteristics

Reporting groups	
Reporting group title	24 wks placebo
Reporting group description:	
24 weeks placebo, 24 weeks washout	
Reporting group title	24 wks active
Reporting group description:	
24 weeks bendroflumethiazide followed by 24 weeks of washout	
Reporting group title	48 wks active
Reporting group description:	
48 weeks bendroflumethiazide	
Reporting group title	48 wks placebo
Reporting group description:	
Placebo for 48 weeks	

Reporting group values	24 wks placebo	24 wks active	48 wks active
Number of subjects	27	25	44
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	65.0	63.7	65.0
standard deviation	± 1.3	± 1.5	± 1.0
Gender categorical Units: Subjects			
Female	27	25	44
Male	0	0	0

Reporting group values	48 wks placebo	Total	
Number of subjects	43	139	
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	64.9		
standard deviation	± 1.1	-	
Gender categorical			
Units: Subjects			
Female	43	139	
Male	0	0	

End points

End points reporting groups	
Reporting group title	24 wks placebo
Reporting group description: 24 weeks placebo, 24 weeks washout	
Reporting group title	24 wks active
Reporting group description: 24 weeks bendroflumethiazide followed by 24 weeks of washout	
Reporting group title	48 wks active
Reporting group description: 48 weeks bendroflumethiazide	
Reporting group title	48 wks placebo
Reporting group description: Placebo for 48 weeks	

Primary: Change in femoral neck BMD after 48 weeks	
End point title	Change in femoral neck BMD after 48 weeks
End point description: Change in femoral neck BMD from baseline to 48 weeks	
End point type	Primary
End point timeframe: 48 weeks	

End point values	24 wks placebo	24 wks active	48 wks active	48 wks placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	23	35	34
Units: Femoral neck BMD				
arithmetic mean (standard error)	0.016 (± 0.0034)	0.0086 (± 0.0043)	-0.00035 (± 0.0046)	0.012 (± 0.004)

Statistical analyses

Statistical analysis title	t test
Comparison groups	24 wks placebo v 24 wks active v 48 wks active v 48 wks placebo
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 5
Method	ANOVA
Parameter estimate	Mean difference (final values)

Primary: Change in total hip BMD after 48 weeks	
End point title	Change in total hip BMD after 48 weeks
End point description: Change in total hip BMD after 48 weeks	
End point type	Primary
End point timeframe: 48 weeks	

End point values	24 wks placebo	24 wks active	48 wks active	48 wks placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	23	35	34
Units: Total hip BMd (g/cm2)				
arithmetic mean (standard error)	0.012 (± 0.0039)	0.0081 (± 0.0035)	0.0066 (± 0.0096)	0.011 (± 0.0028)

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	24 wks placebo v 24 wks active v 48 wks active v 48 wks placebo
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 5
Method	ANOVA

Primary: Change in lumber spine BMD (g/cm2) 48 weeks	
End point title	Change in lumber spine BMD (g/cm2) 48 weeks
End point description: Change in lumbar spine BMD from baseline to 48 weeks	
End point type	Primary
End point timeframe: 48 weeks	

End point values	24 wks placebo	24 wks active	48 wks active	48 wks placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	23	35	34
Units: Change in lumbar spine BMD				
arithmetic mean (standard error)	0.015 (± 0.0087)	0.015 (± 0.0075)	0.020 (± 0.006)	0.016 (± 0.0055)

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	24 wks placebo v 24 wks active v 48 wks active v 48 wks placebo
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 5
Method	ANOVA
Parameter estimate	Mean difference (final values)

Primary: Change in lumbar spine QCT 48 weeks

End point title	Change in lumbar spine QCT 48 weeks
End point description:	
Change from baseline to 48 weeks in lumbar spine QCT (mg/cm3)	
End point type	Primary
End point timeframe:	
48 weeks	

End point values	24 wks placebo	24 wks active	48 wks active	48 wks placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	23	35	34
Units: Change in spine QCT (mg/cm3) at 48 weeks				
arithmetic mean (standard error)	0.07 (± 0.2)	-0.1 (± 0.1)	3.26 (± 1.63)	-3.55 (± 2.01)

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	24 wks placebo v 24 wks active v 48 wks active v 48 wks placebo

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 5
Method	ANOVA

Primary: Change in femoral neck QCT (mg/cm3)at 48 weeks

End point title	Change in femoral neck QCT (mg/cm3)at 48 weeks
End point description:	
Change in femoral neck QCT from baseline to 48 weeks in femoral neck QCT (mg/cm3)	
End point type	Primary
End point timeframe:	
48 weeks	

End point values	24 wks placebo	24 wks active	48 wks active	48 wks placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	23	35	34
Units: Change in femoral neck QCT (mg/cm3)				
arithmetic mean (standard error)	0.0093 (± 0.0096)	0.011 (± 0.019)	0.0059 (± 0.010)	0.0022 (± 0.0018)

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	24 wks placebo v 24 wks active v 48 wks active v 48 wks placebo
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 5
Method	ANOVA
Parameter estimate	Mean difference (final values)

Secondary: Change in serum sodium 48 weeks

End point title	Change in serum sodium 48 weeks
End point description:	
Change in serum sodium from baseline to 48 weeks (mmol/l)	
End point type	Secondary
End point timeframe:	
48 weeks	

End point values	24 wks placebo	24 wks active	48 wks active	48 wks placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	23	35	34
Units: Change in serum sodium 48 weeks				
arithmetic mean (standard error)	0.2 (± 0.4)	0.4 (± 0.6)	-0.08 (± 0.6)	-0.1 (± 0.4)

Statistical analyses

No statistical analyses for this end point

Secondary: change in serum calcium 48 weeks

End point title	change in serum calcium 48 weeks

End point description:

End point type	Secondary

End point timeframe:

Change in serum albumin adjusted calcium from baseline to 48 weeks (mmol/l)

End point values	24 wks placebo	24 wks active	48 wks active	48 wks placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	23	35	34
Units: change in serum calcium 48 weeks				
arithmetic mean (standard error)	-0.02 (± 0.02)	0.0007 (± 0.03)	0.02 (± 0.02)	-0.003 (± 0.02)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
48 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	1

Reporting groups	
Reporting group title	48 weeks active
Reporting group description: -	
Reporting group title	48 weeks placebo
Reporting group description: -	
Reporting group title	24 weeks placebo, 24 weeks washout
Reporting group description: -	
Reporting group title	24 weeks active, 24 weeks washout
Reporting group description: -	

Serious adverse events	48 weeks active	48 weeks placebo	24 weeks placebo, 24 weeks washout
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 27 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	24 weeks active, 24 weeks washout		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	48 weeks active	48 weeks placebo	24 weeks placebo, 24 weeks washout
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	1 / 27 (3.70%)
Infections and infestations			

Influenza subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1	1 / 43 (2.33%) 1	1 / 27 (3.70%) 1

Non-serious adverse events	24 weeks active, 24 weeks washout		
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 25 (4.00%)		
Infections and infestations Influenza subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 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