Clinical trial results:
Treatment of Primary Hyperparathyroidism with Denosumab and Cinacalcet

Summary

EudraCT number	2016-001510-20
Trial protocol	DK
Global end of trial date	01 April 2019

Results information

Result version number	v1 (current)
This version publication date	08 April 2020
First version publication date	08 April 2020

Trial information

Trial identification

Sponsor protocol code	180987

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03027557
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aalborg University Hospital
Sponsor organisation address	Moelleparkvej 4, Aalborg, Denmark, 9000
Public contact	Department of Endocrinology, Aalborg University Hospital, p.vestergaard@rn.dk
Scientific contact	Department of Endocrinology, Aalborg University Hospital, p.vestergaard@rn.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	12 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2019
Global end of trial reached?	Yes
Global end of trial date	01 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of Denosumab alone, and in combination with Cinacalcet, as a medical treatment for patients suffering from primary hyperparathyroidism, with mild osteoporosis. Patients included do not meet the criteria for, or have no wish for a surgical procedure.
The main endpoints will be the effect of treatment on BMD and bone structure measured by DXA, VFA and QCT. Calcifications and the effect of treatment here on, in coronary arteries, the pancreas and kidneys will also be evaluated.

Protection of trial subjects:

After completion all participants were referred to continued monitoring and management at the outpatient Clinic of the Department of Endocrinology, Aalborg University Hospital.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2017
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: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	16
From 65 to 84 years	29

85 years and over	1

Subject disposition

Recruitment

Recruitment details:

46 patients were recruited from March 14th 2017 to March 16th 2018. The trial ended with last patient last visit.

Pre-assignment

Screening details:

285 patients were screened for eligibility in relation to a visit in the Outpatient Clinic, the Department of Endocrinology, Aalborg University Hospital. 94 were invited to receive information about the study. 53 participated in a baseline examination and 46 were randomly allocated to the three study arms.

Period 1

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

Blinding implementation details:

All investiagtors, subjects and data-assessors were blinded throughout the study until the end of data-analysis. All handling, distribution, ordering and accounting of medicine was performed by selected unblinded staff under strict division from blinded personelle. Monitors from the GCP-unit were allowed to investigate allocation/randomization and drug-handling. The intervention lasted 52 weeks followed by 2 weeks of followup. Blinding persisted until completion of data-analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Denosumab + Placebo

Arm description:

The participants in this arm were treated with denosumab-injections (60 mg s.c.) at baseline and week 24. They also received placebo for Mimpara (one tablet) daily.

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	2
Other name	Prolia
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg s.c. from a prepacked syringe on the back of the upper arm twice a year.

Investigational medicinal product name	Placebo for Mimpara
Investigational medicinal product code	Placebo 2
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

One coated tablet from an opaque cannister daily throughout the treatment-period.

Arm title	Cinacalcet + Denosumab

Arm description:

The participants received the two active IMPs. Hence, they received Mimpara (cinacalcet, 30 mg, orally) once daily, and Prolia (denosumab, 60 mg, s.c.) at baseline and week 24.

Arm type	Experimental

Investigational medicinal product name	Cinacalcet
Investigational medicinal product code	1
Other name	Mimpara
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Mimpara (one tablet, 30 mg daily) was administered in an opaque cannister (28 pcs each).

Investigational medicinal product name	Denosumab
Investigational medicinal product code	2
Other name	Prolia
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg s.c. from a prepacked syringe on the back of the upper arm twice a year.

Arm title	Placebo

Arm description:

The participants in this arm received placebo for Mimpara (placebo for cinacalcet) daily, and placebo for Prolia (placebo for denosumab) at baseline and week 24.

Arm type	Placebo
Investigational medicinal product name	Placebo for Mimpara
Investigational medicinal product code	Placebo 2
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

One coated tablet from an opaque cannister daily throughout the treatment-period.

Investigational medicinal product name	Placebo for Prolia
Investigational medicinal product code	Placebo 1
Other name	Placebo for denosumab (saline
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The placebo was a saline solution in a prepared syringe. Injections were given at the back of the upper arm at baseline and week 24. Participants were not allowed to see the syringe (which was also the case for the prolia-syringes in the other arms).

Number of subjects in period 1	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo
Started	16	15	15
Completed	16	14	15
Not completed	0	1	0
Adverse event, non-fatal	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Denosumab + Placebo
Reporting group description:	
The participants in this arm were treated with denosumab-injections (60 mg s.c.) at baseline and week 24. They also received placebo for Mimpara (one tablet) daily.	
Reporting group title	Cinacalcet + Denosumab
Reporting group description:	
The participants received the two active IMPs. Hence, they received Mimpara (cinacalcet, 30 mg, orally) once daily, and Prolia (denosumab, 60 mg, s.c.) at baseline and week 24.	
Reporting group title	Placebo
Reporting group description:	
The participants in this arm received placebo for Mimpara (placebo for cinacalcet) daily, and placebo for Prolia (placebo for denosumab) at baseline and week 24.	

Reporting group values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo
Number of subjects	16	15	15
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			
Age was collected in relation to the baseline DXA-scans.			
Units: years arithmetic mean standard deviation	 65.4 ± 8.8	 65.1 ± 13.2	 68.0 ± 7.0
Gender categorical			
Number of subjects			
Units: Subjects			
Female	13	14	12
Male	3	1	3
Nephrolithiasis			
Subjects with nephrolithiasis at baseline.			
Units: Subjects			
Yes	3	0	1
No	13	15	14
Nephrocalcinosis			
Subjects with nephrocalcinosis at baseline.			
Units: Subjects			
Yes	1	2	3

No	15	13	12
Pancreas calcifications			
Subjects with pancreatic calcifications at baseline.			
Units: Subjects			
Yes	1	0	2
No	15	15	13
Fracture by VFA			
Fracture by Vertebral Fracture Assessment at baseline.			
Units: Subjects			
Yes	3	1	2
No	13	14	13
BMI			
Body Mass Index			
Units: kg/m^2			
arithmetic mean	27.4	27.7	28.4
standard deviation	± 4.8	± 3.5	± 3.9
T-score LS			
Baseline T-score of the lumbar spine by DXA.			
Units: T-score			
arithmetic mean	-2.0	-1.9	-1.3
standard deviation	± 0.68	± 0.93	± 0.85
T-score TH			
Baseline T-score Total Hip by DXA.			
Units: T-score			
arithmetic mean	-1.4	-1.4	-1.1
standard deviation	± 0.6	± 0.5	± 0.5
T-score FN			
Baseline T-score femoral neck by DXA.			
Units: T-score			
arithmetic mean	-1.9	-2.0	-1.7
standard deviation	± 0.7	± 0.7	± 0.6
T-score 1/3 FA			
Baseline T-score 1/3 distal forearm by DXA..			
Units: T-score			
arithmetic mean	-2.4	-2.4	-2.8
standard deviation	± 1.2	± 1.2	± 0.9
vBMD LS			
Baseline lumbar spine BMD by QCT			
Units: mg/cm^3			
arithmetic mean	99.7	96.4	94.2
standard deviation	± 24	± 28.1	± 25.4
vBMD distal forearm			
Bone Mineral Density at the distal forearm by QCT			
Units: mg/cm^3			
arithmetic mean	194.9	183.5	181.4
standard deviation	± 37.6	± 32.0	± 35.5
Cortical width .			
Baseline cortical Width of the distal forearm.			
Units: mm			
arithmetic mean	1.19	1.23	1.14
standard deviation	± 0.5	± 0.5	± 0.4

Ionized Calcium			
Baseline ionized calcium levels.			
Units: mmol/l			
arithmetic mean	1.39	1.39	1.39
standard deviation	± 0.078	± 0.08	± 0.08
P-PTH			
Baseline Parathyroid Hormone level.			
Units: pmol/l			
arithmetic mean	13.1	12.1	11.2
standard deviation	± 6.4	± 6.2	± 4.3
Agatston Score			
Agatston Score Baseline.			
Units: Score-value			
median	10.1	4.9	55.7
inter-quartile range (Q1-Q3)	0.3 to 470.3	0.7 to 25.9	6.8 to 144.6
mU-Calcium			
Baseline urine calcium excretion.			
Units: mg/d			
median	276	338	314
inter-quartile range (Q1-Q3)	218 to 555	159 to 419	222 to 373
mU-Phosphorous			
Baseline daily excretion of phosphorous in urine.			
Units: mmol/d			
median	32.2	28.5	35.2
inter-quartile range (Q1-Q3)	26.5 to 37.0	25.7 to 33.6	23.6 to 39.5
P-Phosphorous			
Baseline p-phosphorous.			
Units: mmol/l			
arithmetic mean	0.77	0.77	0.79
standard deviation	± 0.16	± 0.15	± 0.12
Major Depression Inventory score			
Baseline score			
Units: MDI-points			
median	5	5	5
inter-quartile range (Q1-Q3)	1.5 to 8.5	2 to 11	2 to 7

Reporting group values	Total		
Number of subjects	46		
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 was collected in relation to the baseline DXA-scans.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Number of subjects			
Units: Subjects			
Female	39		
Male	7		
Nephrolithiasis			
Subjects with nephrolithiasis at baseline.			
Units: Subjects			
Yes	4		
No	42		
Nephrocalcinosis			
Subjects with nephrocalcinosis at baseline.			
Units: Subjects			
Yes	6		
No	40		
Pancreas calcifications			
Subjects with pancreatic calcifications at baseline.			
Units: Subjects			
Yes	3		
No	43		
Fracture by VFA			
Fracture by Vertebral Fracture Assessment at baseline.			
Units: Subjects			
Yes	6		
No	40		
BMI			
Body Mass Index			
Units: kg/m^2			
arithmetic mean			
standard deviation	-		
T-score LS			
Baseline T-score of the lumbar spine by DXA.			
Units: T-score			
arithmetic mean			
standard deviation	-		
T-score TH			
Baseline T-score Total Hip by DXA.			
Units: T-score			
arithmetic mean			
standard deviation	-		
T-score FN			
Baseline T-score femoral neck by DXA.			
Units: T-score			
arithmetic mean			
standard deviation	-		
T-score 1/3 FA			

Baseline T-score 1/3 distal forearm by DXA..			
Units: T-score arithmetic mean standard deviation	- -		
vBMD LS			
Baseline lumbar spine BMD by QCT			
Units: mg/cm^3 arithmetic mean standard deviation	- -		
vBMD distal forearm			
Bone Mineral Density at the distal forearm by QCT			
Units: mg/cm^3 arithmetic mean standard deviation	- -		
Cortical width .			
Baseline cortical Width of the distal forearm.			
Units: mm arithmetic mean standard deviation	- -		
Ionized Calcium			
Baseline ionized calcium levels.			
Units: mmol/l arithmetic mean standard deviation	- -		
P-PTH			
Baseline Parathyroid Hormone level.			
Units: pmol/l arithmetic mean standard deviation	- -		
Agatston Score			
Agatston Score Baseline.			
Units: Score-value median inter-quartile range (Q1-Q3)	- -		
mU-Calcium			
Baseline urine calcium excretion.			
Units: mg/d median inter-quartile range (Q1-Q3)	- -		
mU-Phosphorous			
Baseline daily excretion of phosphorous in urine.			
Units: mmol/d median inter-quartile range (Q1-Q3)	- -		
P-Phosphorous			
Baseline p-phosphorous.			
Units: mmol/l arithmetic mean standard deviation	- -		
Major Depression Inventory score			
Baseline score			
Units: MDI-points			

median inter-quartile range (Q1-Q3)	- 		

End points

End points reporting groups

Reporting group title	Denosumab + Placebo
Reporting group description:	
The participants in this arm were treated with denosumab-injections (60 mg s.c.) at baseline and week 24. They also received placebo for Mimpara (one tablet) daily.	
Reporting group title	Cinacalcet + Denosumab
Reporting group description:	
The participants received the two active IMPs. Hence, they received Mimpara (cinacalcet, 30 mg, orally) once daily, and Prolia (denosumab, 60 mg, s.c.) at baseline and week 24.	
Reporting group title	Placebo
Reporting group description:	
The participants in this arm received placebo for Mimpara (placebo for cinacalcet) daily, and placebo for Prolia (placebo for denosumab) at baseline and week 24.	

Primary: Change in LS-BMD (DXA)

End point title	Change in LS-BMD (DXA)
End point description:	
End point type	Primary
End point timeframe:	
Baseline - End of Study. (One year of treatment.)	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: g/cm^2				
arithmetic mean (standard error)	0.042 (± 0.009)	0.030 (± 0.009)	-0.016 (± 0.007)	

Statistical analyses

Statistical analysis title	Difference between treatment arms in LS-BMD
Comparison groups	Cinacalcet + Denosumab v Denosumab + Placebo v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	ANOVA
Parameter estimate	Mean difference (net)

Primary: Change in TH-BMD (DXA)	
End point title	Change in TH-BMD (DXA)
End point description: Results are given in g/cm^2	
End point type	Primary
End point timeframe: Baseline - End of Study (One year of treatment.).	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	14	
Units: mg/cm^2				
arithmetic mean (standard error)	0.021 (± 0.003)	0.027 (± 0.006)	-0.013 (± 0.006)	

Statistical analyses

Statistical analysis title	Difference between treatment-arms in TH-BMD
Statistical analysis description: Change in absolute values.	
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	ANOVA
Parameter estimate	Mean difference (net)

Primary: Change in FN-BMD (DXA)	
End point title	Change in FN-BMD (DXA)
End point description: Results are given in g/cm^2	
End point type	Primary
End point timeframe: Baseline - End of Trial (One year of treatment.).	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	14	
Units: mg/cm^2				
arithmetic mean (standard error)	0.020 (± 0.005)	0.023 (± 0.006)	-0.007 (± 0.006)	

Statistical analyses

Statistical analysis title	Absolute change in FN-BMD
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	ANOVA
Parameter estimate	Mean difference (net)

Primary: Change in 1/3 FA-BMD (DXA)

End point title	Change in 1/3 FA-BMD (DXA)
End point description: Results are given in g/cm^2	
End point type	Primary
End point timeframe: Baseline - End of Study (One year of treatment.).	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	14	15	
Units: mg/cm^2				
arithmetic mean (standard error)	0.005 (± 0.003)	0.005 (± 0.003)	-0.005 (± 0.004)	

Statistical analyses

Statistical analysis title	Absolute change in 1/3 FA BMD
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096
Method	ANOVA
Parameter estimate	Mean difference (net)

Primary: Percentage Change in LS-BMD (DXA)

End point title	Percentage Change in LS-BMD (DXA)

End point description:

End point type	Primary

End point timeframe:

Baseline - End of Study (One year of treatment.).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Percentage				
arithmetic mean (standard error)	5.1 (± 1.1)	3.6 (± 1.1)	-1.8 (± 0.8)	

Statistical analyses

Statistical analysis title	Difference in percentage change between groups
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANOVA
Parameter estimate	Mean difference (net)

Primary: Percentage Change in TH-BMD (DXA)

End point title	Percentage Change in TH-BMD (DXA)

End point description:

End point type	Primary

End point timeframe:

Baseline - End of Study (One year of treatment.).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	14	
Units: Percentage				
arithmetic mean (standard error)	2.64 (± 0.41)	3.45 (± 0.72)	-1.50 (± 0.72)	

Statistical analyses

Statistical analysis title	Difference in percentage change in TH-BMD
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	ANOVA
Parameter estimate	Mean difference (net)

Primary: Percentage Change in FN-BMD (DXA)

End point title	Percentage Change in FN-BMD (DXA)

End point description:

End point type	Primary

End point timeframe:

Baseline - End of Study (one year of treatment.).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	14	
Units: Percentage				
arithmetic mean (standard error)	3.03 (± 0.86)	3.70 (± 0.98)	-0.78 (± 0.9)	

Statistical analyses

Statistical analysis title	Difference in FN-BMD in percentage change
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027
Method	ANOVA
Parameter estimate	Mean difference (net)

Primary: Percentage Change in 1/3 FA-BMD (DXA)

End point title	Percentage Change in 1/3 FA-BMD (DXA)

End point description:

End point type	Primary

End point timeframe:

Baseline - End of Study (one year of treatment.).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	14	15	
Units: Percentage				
arithmetic mean (standard error)	0.88 (± 0.5)	0.94 (± 0.7)	-0.91 (± 0.7)	

Statistical analyses

Statistical analysis title	Difference in percentage change of 1/3 FA-BMD
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081
Method	ANOVA
Parameter estimate	Mean difference (net)

Secondary: Change in LS-vBMD (QCT)

End point title	Change in LS-vBMD (QCT)

End point description:

End point type	Secondary

End point timeframe:

Baseline - End of Study (one year of treatment.).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	13	15	
Units: mg/cm^3				
arithmetic mean (standard error)	5.35 (± 1.91)	4.93 (± 2.15)	-2.56 (± 1.6)	

Statistical analyses

Statistical analysis title	Difference in absolute change vBMD-LS
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0071
Method	ANOVA
Parameter estimate	Mean difference (net)

Secondary: Percentage Change in LS-vBMD (QCT)

End point title	Percentage Change in LS-vBMD (QCT)

End point description:

End point type	Secondary

End point timeframe:

Baseline - End of Study (one year of treatment).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	13	15	
Units: Percentage				
arithmetic mean (standard error)	5.66 (± 1.85)	6.18 (± 3.14)	-2.94 (± 1.96)	

Statistical analyses

Statistical analysis title	Difference in percentage change of LS-vBMD
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	ANOVA
Parameter estimate	Mean difference (net)

Secondary: Change in Forearm-BMD (QCT)

End point title	Change in Forearm-BMD (QCT)

End point description:

End point type	Secondary

End point timeframe:

Baseline - End of Study (one year of treatment.).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	12	14	
Units: mg/cm^3				
arithmetic mean (standard error)	9.6 (± 3.7)	1.0 (± 2.1)	-1.1 (± 4.6)	

Statistical analyses

Statistical analysis title	Difference in absolute change in FA-BMD
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0077
Method	ANOVA
Parameter estimate	Mean difference (net)

Secondary: Percentage Change in Forearm-BMD (QCT)

End point title	Percentage Change in Forearm-BMD (QCT)

End point description:

End point type	Secondary

End point timeframe:

Baseline - End of Study (one year of treatment.).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	12	14	
Units: Percentage				
arithmetic mean (standard error)	5.2 (± 1.0)	0.53 (± 1.2)	-0.74 (± 2.6)	

Statistical analyses

Statistical analysis title	Difference in percentage change in FA-BMD
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065
Method	ANOVA
Parameter estimate	Mean difference (net)

Secondary: Change in Cortical Width

End point title	Change in Cortical Width

End point description:

End point type	Secondary

End point timeframe:

Baseline - End of Study (one year of treatment.).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	14	
Units: mm				
arithmetic mean (standard error)	0.02 (± 0.08)	-0.04 (± 0.1)	0.04 (± 0.05)	

Statistical analyses

Statistical analysis title	Difference in change in cortical width
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANOVA
Parameter estimate	Mean difference (net)

Secondary: Mean p-calcium during treatment

End point title	Mean p-calcium during treatment

End point description:

Mean p-ion-calcium thorughout the treatment-period.

End point type	Secondary

End point timeframe:

Baseline - End of Treatment

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[1]	15[2]	15[3]	
Units: mmol/l				
arithmetic mean (standard error)	1.38 (± 0.006)	1.28 (± 0.007)	1.40 (± 0.004)	

Notes:

[1] - 240 measurements

[2] - 210 measurements

[3] - 224 measurements

Statistical analyses

Statistical analysis title	Difference between treatment p-calcium levels
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANOVA
Parameter estimate	Mean difference (net)

Secondary: Mean treatment p-PTH level.

End point title	Mean treatment p-PTH level.

End point description:

End point type	Secondary

End point timeframe:

Baseline - End of Treatment (52 weeks).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[4]	15[5]	15[6]	
Units: pmol/l				
median (confidence interval 95%)	13.4 (12.7 to 14.2)	12.0 (11.1 to 12.9)	9.9 (9.5 to 10.4)	

Notes:

[4] - 240 measurements

[5] - 211 measurements

[6] - 225 measurements

Statistical analyses

Statistical analysis title	Difference in median p-PTH treatment-levels
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Kruskal-wallis
Parameter estimate	Median difference (net)

Secondary: Mean treatment p-phosphate levels

End point title	Mean treatment p-phosphate levels

End point description:

End point type	Secondary

End point timeframe:

Baseline - End of Treatment (52 weeks).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[7]	15[8]	15[9]	
Units: mmol/l				
arithmetic mean (standard error)	0.76 (± 0.012)	0.83 (± 0.013)	0.083 (± 0.011)	

Notes:

[7] - 240 measurements

[8] - 211 measurements

[9] - 225

Statistical analyses

Statistical analysis title	Difference in mean treatment p-phosphate levels
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	ANOVA
Parameter estimate	Mean difference (net)

Secondary: Change in daily u-calcium excretion

End point title	Change in daily u-calcium excretion

End point description:

End point type	Secondary

End point timeframe:

Baseline - End of Treatment (48 weeks).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	14	15	
Units: mg/d				
arithmetic mean (standard error)	4.8 (± 40.0)	-23.1 (± 31.6)	0.2 (± 39.9)	

Statistical analyses

Statistical analysis title	Difference in change in u-calcium excretion
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANOVA
Parameter estimate	Mean difference (net)

Secondary: Change in daily u-phosphate excretion

End point title	Change in daily u-phosphate excretion

End point description:

End point type	Secondary

End point timeframe: Baseline - End of Treatement (48 weeks).

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	14	15	
Units: mmol/d				
arithmetic mean (standard error)	3.21 (± 2.3)	-3.27 (± 3.0)	1.28 (± 1.8)	

Statistical analyses

Statistical analysis title	Difference in change in u-phosphate excretion
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057
Method	ANOVA
Parameter estimate	Mean difference (net)

Secondary: Change in p-CTX	
End point title	Change in p-CTX
End point description: Change in bone turnover marker - level.	
End point type	Secondary
End point timeframe: Baseline vs week 48.	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Percentage				
median (inter-quartile range (Q1-Q3))	-58.2 (-76.7 to -44.3)	-48.7 (-73.2 to -15.8)	11.8 (1.96 to 40.0)	

Statistical analyses

Statistical analysis title	Difference in CTX-development
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Kruskal-wallis
Parameter estimate	Median difference (net)

Secondary: Change in p-P1NP

End point title	Change in p-P1NP

End point description:

End point type	Secondary

End point timeframe:

Baseline vs week 48

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Percentage				
median (inter-quartile range (Q1-Q3))	-66.1 (-75.9 to -55.4)	-63.1 (-66.9 to -57.2)	17.8 (-11.0 to 31.5)	

Statistical analyses

Statistical analysis title	Difference in change in p-P1NP
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Kruskal-wallis
Parameter estimate	Median difference (net)

Secondary: Change in p-Osteocalcin

End point title	Change in p-Osteocalcin

End point description:

End point type	Secondary

End point timeframe: Baseline vs. wk 48

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Percentage				
median (inter-quartile range (Q1-Q3))	-58.9 (-66.9 to -49.0)	-60.0 (-69.8 to -36.9)	7.0 (-0.9 to 36.9)	

Statistical analyses

Statistical analysis title	Difference in change of p-osteocalcin
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANOVA
Parameter estimate	Median difference (net)

Secondary: Change in s- BAP	
End point title	Change in s- BAP
End point description:	
End point type	Secondary
End point timeframe: Baseline vs. week 48	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Percentage				
median (inter-quartile range (Q1-Q3))	-46.3 (-51.5 to -38.4)	-40.0 (-46.3 to -24.1)	9.7 (-7.9 to 32.5)	

Statistical analyses

Statistical analysis title	Difference in change in s-BAP
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Kruskal-wallis
Parameter estimate	Median difference (net)

Secondary: Change in p-Trap5b

End point title	Change in p-Trap5b

End point description:

End point type	Secondary

End point timeframe:

Baseline vs wk 48

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Percentage				
median (inter-quartile range (Q1-Q3))	-36.7 (-51.8 to -16.4)	-27.8 (-34.1 to -2.3)	2.3 (-4.9 to 19.6)	

Statistical analyses

Statistical analysis title	Difference in change in s-Trap5b
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANOVA
Parameter estimate	Median difference (net)

Secondary: Change in p-sclerostin

End point title	Change in p-sclerostin

End point description:

End point type	Secondary

End point timeframe: Baseline vs. wk 48

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Percentage				
median (inter-quartile range (Q1-Q3))	6.5 (0.9 to 15.9)	10.0 (3.1 to 21.1)	4.8 (-2.3 to 13.9)	

Statistical analyses

Statistical analysis title	Difference in change in p-sclerostin
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	Kruskal-wallis
Parameter estimate	Median difference (net)

Secondary: Change in p-FGF23	
End point title	Change in p-FGF23
End point description:	

End point type	Secondary
End point timeframe: Baseline vs wk 48.	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Percentage				
median (inter-quartile range (Q1-Q3))	20.4 (-13.6 to 58.2)	35.8 (0.0 to 52.9)	28.0 (-25.9 to 64.7)	

Statistical analyses

Statistical analysis title	Difference in change in p-FGF23
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	ANOVA
Parameter estimate	Median difference (net)

Secondary: Change in p 25 vit D	
End point title	Change in p 25 vit D
End point description:	
End point type	Secondary
End point timeframe:	
Baseline vs wk 48	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	16.0 (4.1 to 22.0)	22.1 (13.3 to 32.6)	21.2 (8.2 to 30.5)	

Statistical analyses

Statistical analysis title	Difference in change in p-25-vitD
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	ANOVA
Parameter estimate	Median difference (net)

Secondary: Change in s-1,25-vitD	
End point title	Change in s-1,25-vitD
End point description:	
End point type	Secondary

End point timeframe:
Baseline vs wk 48

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: pmol/l				
median (inter-quartile range (Q1-Q3))	4.5 (-15.0 to 25.5)	7.5 (-4.0 to 35.0)	26.0 (14.0 to 36.0)	

Statistical analyses

Statistical analysis title	Difference in change in s-1,25-vitD
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Kruskal-wallis
Parameter estimate	Median difference (net)

Secondary: Median Agatstons Score Final	
End point title	Median Agatstons Score Final
End point description:	
There was no significant difference in agatstons-score development between the arms.	
End point type	Secondary
End point timeframe:	
Baseline vs. End of Study (one year of treatment.).	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	12	13	
Units: Agatston Score				
median (inter-quartile range (Q1-Q3))	24.3 (0.7 to 602.1)	5.0 (0.0 to 78.1)	117.8 (6.8 to 182.6)	

Statistical analyses

Statistical analysis title	Difference in final agaston score
Comparison groups	Denosumab + Placebo v Cinacalcet + Denosumab v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Kruskal-wallis
Parameter estimate	Median difference (net)

Secondary: Patients with nephrolithiasis final scan.

End point title	Patients with nephrolithiasis final scan.

End point description:

No new cases of nephrolithiasis emerged/developed during the study-period. Severity/size similarly remained unchanged.

End point type	Secondary

End point timeframe:

Final scan

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Number of affected patients.	3	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with nephrocalcinosis final scan.

End point title	Patients with nephrocalcinosis final scan.

End point description:

No new cases occured at the final scan. Severity similaly remained unchanged.

End point type	Secondary

End point timeframe:

Final scan

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Number of patients with nephrocalcinosis	1	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with pancreas-calcifications final scan.

End point title	Patients with pancreas-calcifications final scan.
End point description:	
No Development in number or size from baseline.	
End point type	Secondary
End point timeframe:	
Final scan.	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Affected patients	1	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Change MDI-score

End point title	Change MDI-score
End point description:	
Median change in MDI-score	
End point type	Secondary
End point timeframe:	
Baseline vs wk 52	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: MDI-score				
median (inter-quartile range (Q1-Q3))	-0.5 (-4.5 to 1.0)	0.0 (-4.0 to 1.0)	0.0 (-3.0 to 0.0)	

Statistical analyses

Statistical analysis title	Difference in MDI-development.
Comparison groups	Cinacalcet + Denosumab v Placebo v Denosumab + Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	Kruskal-wallis
Parameter estimate	Median difference (net)

Secondary: Vertebral Fracture Assessment - final scan

End point title	Vertebral Fracture Assessment - final scan
End point description:	
No new vertebral fractures emerged during the treatment-period.	
End point type	Secondary
End point timeframe:	
Final scan (week 52).	

End point values	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	14	15	
Units: Number of patients with fractures	3	1	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for each participant from baseline until two weeks after treatment-cessation. Adverse events were thus collected from enrollment of first patient (March 14th 2017) until last patient's last visit (March 28th 2019).

Adverse event reporting additional description:

Patients filled in a questionnaire at every visit (approx. every 4th week). The questionnaire contained prespecified symptoms (nausea and paraesthesia). And spaces for experienced "non-prespecified" symptoms. Patients were also interviewed by a physician at each visit. Reported symptoms (AE and SAE) were collected in an individual AE-report.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Denosumab + Placebo

Reporting group description:

The participants in this arm were treated with denosumab-injections (60 mg s.c.) at baseline and week 24. They also received placebo for Mimpara (one tablet) daily.

Reporting group title	Cinacalcet + Denosumab

Reporting group description:

The participants received the two active IMPs. Hence, they received Mimpara (cinacalcet, 30 mg, orally) once daily, and Prolia (denosumab, 60 mg, s.c.) at baseline and week 24.

Reporting group title	Placebo

Reporting group description:

The participants in this arm received placebo for Mimpara (placebo for cinacalcet) daily, and placebo for Prolia (placebo for denosumab) at baseline and week 24.

Serious adverse events	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	3 / 15 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Angina unstable	Additional description: Treated with PCI.		
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy	Additional description: Investigated (including hospitalization) for atypical focal epilepsy at the department of neurology during her participation. Symptoms were present prior to enrollment in the study, and did not involve seizures or change during participation.		

subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Polycythaemia vera	Additional description: Diagnosed with polycytemia vera during participation. Followed at the department of haematology since.		
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inflammatory bowel disease	Additional description: One patient was diagnosed with Chron's Disease while participating. Symptoms had been present for a long time before enrollment, and continued after discontinuation of the study medicine. Had received treatment >6 months prior to diagnosis.		
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis	Additional description: One participant was hospitalized for observation with suspected gastritis, which was not potentially life threatening or disabling, and the outcome had no sequelae.		
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erysipelas	Additional description: One patient had a traumatic skin-lesion while abroad. Was hospitalized and treated for a potential secondary erysipelas. Despite no fever, and low CRP, she was hospitalized for some days, and treated with antibiotics.		
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Denosumab + Placebo	Cinacalcet + Denosumab	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)	13 / 15 (86.67%)	15 / 15 (100.00%)
Surgical and medical procedures			
Swelling	Additional description: Leg edema		
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	7	1	0

Nervous system disorders			
Paraesthesia hands	Additional description: Paresthesia of the hands.		
subjects affected / exposed	3 / 16 (18.75%)	6 / 15 (40.00%)	4 / 15 (26.67%)
occurrences (all)	15	36	20
Paraesthesia feet	Additional description: Parasthesia of the feet.		
subjects affected / exposed	3 / 16 (18.75%)	4 / 15 (26.67%)	2 / 15 (13.33%)
occurrences (all)	27	17	23
Headache			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	1 / 15 (6.67%)
occurrences (all)	1	4	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	2 / 15 (13.33%)
occurrences (all)	2	2	5
Ear and labyrinth disorders			
Dizziness			
subjects affected / exposed	4 / 16 (25.00%)	1 / 15 (6.67%)	3 / 15 (20.00%)
occurrences (all)	7	3	17
Gastrointestinal disorders			
Nausea	Additional description: Nausea was a prespecified adverse-event as it is a commen side-effect to cinacalcet-treatment.		
subjects affected / exposed	9 / 16 (56.25%)	7 / 15 (46.67%)	4 / 15 (26.67%)
occurrences (all)	21	18	5
Abdominal pain			
subjects affected / exposed	2 / 16 (12.50%)	2 / 15 (13.33%)	1 / 15 (6.67%)
occurrences (all)	6	6	1
Gastroenteritis			
subjects affected / exposed	0 / 16 (0.00%)	3 / 15 (20.00%)	2 / 15 (13.33%)
occurrences (all)	0	5	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 16 (25.00%)	1 / 15 (6.67%)	2 / 15 (13.33%)
occurrences (all)	9	1	2
Dyspnoea			
subjects affected / exposed	2 / 16 (12.50%)	2 / 15 (13.33%)	0 / 15 (0.00%)
occurrences (all)	6	2	0
Renal and urinary disorders			

Cystitis			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	0 / 15 (0.00%)
occurrences (all)	5	2	0
Endocrine disorders			
Hypocalcaemia	Additional description: Hypocalcaemia was an expected effect of the combined treatment.		
subjects affected / exposed	0 / 16 (0.00%)	6 / 15 (40.00%)	0 / 15 (0.00%)
occurrences (all)	0	33	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	Additional description: Muscle and joint pain.		
subjects affected / exposed	6 / 16 (37.50%)	6 / 15 (40.00%)	3 / 15 (20.00%)
occurrences (all)	17	14	20
Back pain	Additional description: These numbers are not included in the musculoskeletal pain reported elsewhere.		
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	1 / 15 (6.67%)
occurrences (all)	1	12	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 16 (37.50%)	5 / 15 (33.33%)	4 / 15 (26.67%)
occurrences (all)	20	12	5

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