# 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<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous | | | |
| Age was collected in relation to the baseline DXA-scans. | | | |
| Units: years<br>arithmetic mean<br>standard deviation | <br>65.4<br>± 8.8 | <br>65.1<br>± 13.2 | <br>68.0<br>± 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<br>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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| vBMD LS | | | |
| Baseline lumbar spine BMD by QCT | | | |
| Units: mg/cm^3<br>arithmetic mean<br>standard deviation | -<br>- | | |
| vBMD distal forearm | | | |
| Bone Mineral Density at the distal forearm by QCT | | | |
| Units: mg/cm^3<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Cortical width . | | | |
| Baseline cortical Width of the distal forearm. | | | |
| Units: mm<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Ionized Calcium | | | |
| Baseline ionized calcium levels. | | | |
| Units: mmol/l<br>arithmetic mean<br>standard deviation | -<br>- | | |
| P-PTH | | | |
| Baseline Parathyroid Hormone level. | | | |
| Units: pmol/l<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Agatston Score | | | |
| Agatston Score Baseline. | | | |
| Units: Score-value<br>median<br>inter-quartile range (Q1-Q3) | -<br>- | | |
| mU-Calcium | | | |
| Baseline urine calcium excretion. | | | |
| Units: mg/d<br>median<br>inter-quartile range (Q1-Q3) | -<br>- | | |
| mU-Phosphorous | | | |
| Baseline daily excretion of phosphorous in urine. | | | |
| Units: mmol/d<br>median<br>inter-quartile range (Q1-Q3) | -<br>- | | |
| P-Phosphorous | | | |
| Baseline p-phosphorous. | | | |
| Units: mmol/l<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Major Depression Inventory score | | | |
| Baseline score | | | |
| Units: MDI-points | | | |

| | | | |
|---|---|---|---|
| median<br>inter-quartile range (Q1-Q3) | -<br> | | |

## 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:<br>Results are given in g/cm^2 | |
| End point type | Primary |
| End point timeframe:<br>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:<br>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:<br>Results are given in g/cm^2 | |
| End point type | Primary |
| End point timeframe:<br>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:<br>Results are given in g/cm^2 | |
| End point type | Primary |
| End point timeframe:<br>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:<br>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:<br>Change in bone turnover marker - level. | |
| End point type | Secondary |
| End point timeframe:<br>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:<br>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:<br>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:<br>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:<br>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