# Clinical trial results:
# A Double-blind, Randomized, Active-controlled, Phase 3 Study to Compare Efficacy, Pharmacokinetics, Pharmacodynamics, and Safety of CT-P41 and US-licensed Prolia in Postmenopausal Women with Osteoporosis.

## Summary

| | |
|---|---|
| EudraCT number | 2020-005974-91 |
| Trial protocol | LV EE |
| Global end of trial date | 16 November 2023 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 31 July 2024 |
| First version publication date | 31 July 2024 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CT-P41_3.1 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | CELLTRION, Inc. |
| Sponsor organisation address | 23, Academy-ro, Yeonsu-gu, Incheon, Korea, Republic of, 22014 |
| Public contact | Head Clinical Planning Department, Celltrion, Inc, +82 328504167, JeeHye.Suh@celltrion.com |
| Scientific contact | Head Clinical Planning Department, Celltrion, Inc, +82 328504167, JeeHye.Suh@celltrion.com |

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 | 16 November 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 May 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 November 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

- To demonstrate the equivalence of CT-P41 to US licensed Prolia in terms of efficacy in postmenopausal women with osteoporosis as determined by percent change from baseline in BMD for lumbar spine (L1 to L4) at Week 52
- To demonstrate the PD similarity in terms of area under the effect curve (AUEC) of serum carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) over the initial 6 months (from Day 1 predose to Week 26 predose) between CT-P41 and US-licensed Prolia

Protection of trial subjects:

The study was performed following the ethical principles that have their origin in the Declaration of Helsinki (WMA 2013), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) harmonised tripartite guideline E6 (R2): Good Clinical Practice (GCP), and all applicable regulations. All investigators agreed to conduct all aspects of this study by national, state, local laws and regulations.
Hypersensitivity/allergic reactions monitoring was assessed before the start of the study drug administration (within 15 minutes) and at 1 hour (± 10 minutes) after the end of the study drug administration by additional vital sign measurements including blood pressure, heart and respiratory rates, and body temperature.
If patients had signs and symptoms of hypersensitivity/allergic reactions at home (hives, difficulty breathing, or swelling of face, eyes, lips, or mouth or any symptoms of cardiac origin), patients or caregivers were to be advised to call the study center or get immediate help.
In addition, hypersensitivity could be monitored by routine continuous clinical monitoring including patient-reported signs and symptoms. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation was available and any types of ECG could be performed.
For patients who experience or develop life-threatening treatment-related hypersensitivity/allergic reactions, the study drug was to be stopped immediately and the patient was to be withdrawn from the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 18 May 2021 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 339 |
| Country: Number of subjects enrolled | Estonia: 53 |
| Country: Number of subjects enrolled | Latvia: 9 |
| Country: Number of subjects enrolled | Ukraine: 78 |

| | |
|---|---|
| Worldwide total number of subjects | 479 |
| EEA total number of subjects | 401 |

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) | 202 |
| From 65 to 84 years | 277 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The recruitment was conducted in 20 study centers in 4 countries.

### Pre-assignment

Screening details:

The screening period was up to 28 days. On Day 1, participants were randomized in a 1:1 ratio to receive CT-P41 or US-denosumab during Treatment Period (TP) I. At Week 52, participants in the US-denosumab group were re-randomized 1:1 to continue US-denosumab or transition to CT-P41. The participants in CT-P41 group continued with CT-P41 for TP II.

### Period 1

| | |
|---|---|
| Period 1 title | TP I - Week 0 Day 1 to Week 52 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | CT-P41 |

Arm description:

A total of 2 subcutaneous administration of 60 mg CT-P41 (proposed denosumab biosimilar) at Week 0 and Week 26 (26-week intervals) in TP I.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CT-P41 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

A total of 2 subcutaneous administration of 60 mg CT-P41 (proposed denosumab biosimilar) at Week 0 and Week 26 (26-week intervals) in TP I. CT-P41 was administered as 60 mg/mL single dose, solution for injection in a pre-filled syringe (PFS).

| | |
|---|---|
| **Arm title** | US-licensed Prolia |

Arm description:

A total of 2 subcutaneous administrations of 60 mg US-licensed Prolia (denosumab) at Week 0 and Week 26 (26-week intervals) in TP I.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | US-licensed Prolia |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

A total of 2 subcutaneous administrations of 60 mg US-licensed Prolia (denosumab) at Week 0 and Week 26 (26-week intervals) in TP I. US-licensed Prolia was administered as 60 mg/mL single dose, solution for injection in PFS.

| Number of subjects in period 1 | CT-P41 | US-licensed Prolia |
|---|---|---|
| Started | 240 | 239 |
| Completed | 221 | 201 |
| Not completed | 19 | 38 |
| Consent withdrawn by subject | 8 | 24 |
| Physician decision | 1 | - |
| Disease progression | - | 1 |
| Terminated the study before treamtent initiation | 1 | 1 |
| Adverse event, non-fatal | 4 | 5 |
| Lost to follow-up | - | 3 |
| Protocol deviation | 5 | 4 |

| Period 2 | |
|---|---|
| Period 2 title | TP II - Week 52 to Week 78 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

**Arms**

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | CT-P41 maintenance |

Arm description:

Participants treated with CT-P41 in TP I continued the treatment with CT-P41 as a third dose at Week 52 in TP II.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CT-P41 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants treated with CT-P41 in TP I continued the treatment with CT-P41 as a third dose at Week 52 in TP II

| | |
|---|---|
| **Arm title** | US-licensed Prolia maintenance |

Arm description:

Participants treated with US-licensed Prolia in TP I were re-randomized to continue the treatment with US-licensed Prolia as a third dose at Week 52 in TP II

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | US-licensed Prolia |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants treated with US-licensed Prolia in TP I were re-randomized to continue the treatment with US-licensed Prolia as a third dose at Week 52 in TP II

| **Arm title** | Switched to CT-P41 |
|---|---|

Arm description:

Participants treated with US-licensed Prolia in TP I were re-randomized to switch to CT-P41 as a third dose at Week 52 in TP II

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CT-P41 and US-licensed Prolia |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants treated with US-licensed Prolia in TP I were re-randomized to switch to CT-P41 as a third dose at Week 52 in TP II

| **Number of subjects in period 2** | CT-P41 maintenance | US-licensed Prolia maintenance | Switched to CT-P41 |
|---|---|---|---|
| Started | 221 | 100 | 101 |
| Completed | 220 | 100 | 101 |
| Not completed | 1 | 0 | 0 |
| non-fatal AE, not treated but completed the study | 1 | - | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | CT-P41 |
| Reporting group description: | |
| A total of 2 subcutaneous administration of 60 mg CT-P41 (proposed denosumab biosimilar) at Week 0 and Week 26 (26-week intervals) in TP I. | |
| Reporting group title | US-licensed Prolia |
| Reporting group description: | |
| A total of 2 subcutaneous administrations of 60 mg US-licensed Prolia (denosumab) at Week 0 and Week 26 (26-week intervals) in TP I. | |

| Reporting group values | CT-P41 | US-licensed Prolia | Total |
|---|---|---|---|
| Number of subjects | 240 | 239 | 479 |
| Age categorical | | | |
| Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 101 | 101 | 202 |
| From 65-84 years | 139 | 138 | 277 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 66.0 | 66.0 | |
| full range (min-max) | 50 to 79 | 51 to 79 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 240 | 239 | 479 |
| Male | 0 | 0 | 0 |
| Race | | | |
| Units: Subjects | | | |
| White | 240 | 239 | 479 |
| Ethinicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 3 | 3 |
| Non-Hispanic or NonLatino | 240 | 236 | 476 |
| Body mass index | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 24.92 | 25.23 | |
| standard deviation | ± 4.230 | ± 4.328 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | CT-P41 |
| Reporting group description: | |
| A total of 2 subcutaneous administration of 60 mg CT-P41 (proposed denosumab biosimilar) at Week 0 and Week 26 (26-week intervals) in TP I. | |
| Reporting group title | US-licensed Prolia |
| Reporting group description: | |
| A total of 2 subcutaneous administrations of 60 mg US-licensed Prolia (denosumab) at Week 0 and Week 26 (26-week intervals) in TP I. | |
| Reporting group title | CT-P41 maintenance |
| Reporting group description: | |
| Participants treated with CT-P41 in TP I continued the treatment with CT-P41 as a third dose at Week 52 in TP II. | |
| Reporting group title | US-licensed Prolia maintenance |
| Reporting group description: | |
| Participants treated with US-licensed Prolia in TP I were re-randomized to continue the treatment with US-licensed Prolia as a third dose at Week 52 in TP II | |
| Reporting group title | Switched to CT-P41 |
| Reporting group description: | |
| Participants treated with US-licensed Prolia in TP I were re-randomized to switch to CT-P41 as a third dose at Week 52 in TP II | |

### Primary: Percent Change From Baseline in Lumbar Spine Bone Mineral Density (BMD) at Week 52 - Full Analysis Set

| | |
|---|---|
| End point title | Percent Change From Baseline in Lumbar Spine Bone Mineral Density (BMD) at Week 52 - Full Analysis Set |
| End point description: | |
| Bone mineral density was assessed by dual-energy X-ray absorptiometry (DXA) and assessments of the lumbar spine (L1 to L4) were performed at a central imaging vendor. To evaluate the difference between 2 groups in the primary efficacy endpoint, the percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 was analyzed using an analysis of covariance (ANCOVA) model coupled with multiple imputation assuming the data to be missing at random (MAR). The total number of participants in full analysis set (FAS) was 239 and 238 in the CT-P41 and US-licensed Prolia groups, respectively. | |
| End point type | Primary |
| End point timeframe: | |
| baseline (screening), Week 52 predose | |

| End point values | CT-P41 | US-licensed Prolia | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222[1] | 212[2] | | |
| Units: percentage change (%) | | | | |
| least squares mean (standard error) | 4.9317 (± 0.31508) | 5.0706 (± 0.32714) | | |

Notes:

[1] - The number of participants in FAS who had a BMD result for the lumbar spine by DXA at Week 52.

[2] - The number of participants in FAS who had a BMD result for the lumbar spine by DXA at Week 52.

### Statistical analyses

| Statistical analysis title | CT-P41 vs. US-licensed Prolia - 95% CI |
|---|---|

Statistical analysis description:

An ANCOVA was performed with the treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine, and prior bisphosphonates therapy (yes versus no) as covariates.

| | |
|---|---|
| Comparison groups | CT-P41 v US-licensed Prolia |
| Number of subjects included in analysis | 434 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence[3] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.139 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.826 |
| upper limit | 0.548 |

Notes:

[3] - Equivalence criteria (analysis set FAS): 95% CI for the treatment difference in means contained in [-1.503%, 1.503%]

## Primary: Area under the effect curve of s-CTX (AUEC of s-CTX) over the initial 6 months - Full Analysis Set

| End point title | Area under the effect curve of s-CTX (AUEC of s-CTX) over the initial 6 months - Full Analysis Set |
|---|---|

End point description:

The AUEC of serum Concentration of serum carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) was calculated by non-compartmental analysis method from the concentration-time data. The effect used in the AUEC was based on the percent change from baseline (or also defined as % inhibition). Serum concentration below the LLoQ was set to the LLoQ in the PD parameter estimation.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Week 0 Day 1), up to Week 26

| End point values | CT-P41 | US-licensed Prolia | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 227[4] | 221[5] | | |
| Units: day*% | | | | |
| arithmetic mean (standard deviation) | 14603.5726 (± 2869.78700) | 14871.2730 (± 2158.17748) | | |

Notes:

[4] - The number of participants who had the result of AUEC of s-CTX in FAS

[5] - The number of participants who had the result of AUEC of s-CTX in FAS

### Statistical analyses

| Statistical analysis title | CT-P41 vs. US-licensed Prolia - 95% CI |
|---|---|

Statistical analysis description:

An ANCOVA was performed with the natural log-transformed AUEC of s-CTX as the dependent variable, treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine, prior bisphosphonates therapy (Yes versus No), and baseline s-CTX level as covariates.

| | |
|---|---|
| Comparison groups | CT-P41 v US-licensed Prolia |

| | |
|---|---|
| Number of subjects included in analysis | 448 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence[6] |
| Parameter estimate | Geometric Least Square Mean Ratio |
| Point estimate | 94.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 90.75 |
| upper limit | 99.32 |

Notes:

[6] - Equivalence criteria (analysis set: FAS): 95% CI for ratio of geometric least square means contained in [80, 125%]

## Primary: Percent Change From Baseline in Lumbar Spine BMD at Week 52 - Per-protocol Set

| | |
|---|---|
| End point title | Percent Change From Baseline in Lumbar Spine BMD at Week 52 - Per-protocol Set |

End point description:

Bone mineral density was assessed by DXA and assessments of the lumbar spine (L1 to L4) were performed at a central imaging vendor. To evaluate the difference between 2 groups in the primary efficacy endpoint, the percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 was analyzed using an ANCOVA model coupled with multiple imputation assuming the data to be MAR.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

baseline (screening), Week 52 predose

| **End point values** | CT-P41 | US-licensed Prolia | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 215[7] | 202[8] | | |
| Units: percentage change (%) | | | | |
| least squares mean (standard error) | 5.0330 (± 0.31640) | 5.3125 (± 0.33505) | | |

Notes:

[7] - The number of participants in per-protocol set (PPS)

[8] - The number of participants in PPS

### Statistical analyses

| **Statistical analysis title** | CT-P41 vs. US-licensed Prolia - 95% CI |
|---|---|

Statistical analysis description:

An ANCOVA was performed with the treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine, and prior bisphosphonates therapy (yes versus no) as covariates.

| | |
|---|---|
| Comparison groups | CT-P41 v US-licensed Prolia |

| | |
|---|---|
| Number of subjects included in analysis | 417 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence[9] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.973 |
| upper limit | 0.414 |

Notes:

[9] - Equivalence criteria (analysis set PPS): 95% CI for the treatment difference in means contained in [-1.503%, 1.503%]

## Secondary: Percent Change From Baseline in Lumbar Spine, Total Hip, and Femoral Neck BMD at Week 52 - Full Analysis Set

| | |
|---|---|
| End point title | Percent Change From Baseline in Lumbar Spine, Total Hip, and Femoral Neck BMD at Week 52 - Full Analysis Set |

End point description:

Bone mineral density was assessed by DXA and assessments of the lumbar spine (L1 to L4), total hip, and femoral neck were performed at a central imaging vendor.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

baseline (screening), Week 52 predose

| End point values | CT-P41 | US-licensed Prolia | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 239[10] | 238[11] | | |
| Units: percentage change (%) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Lumbar spine | 5.4913 (± 3.79907) | 5.6621 (± 3.75768) | | |
| Total hip | 2.7914 (± 2.87044) | 2.4253 (± 2.84061) | | |
| Femoral neck | 2.2295 (± 4.02031) | 1.9476 (± 3.86739) | | |

Notes:

[10] - The total number of participants in the FAS

[11] - The total number of participants in the FAS

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Lumbar Spine, Total Hip, and Femoral Neck BMD at Week 78 - Full Analysis Set-TP II Subset

| | |
|---|---|
| End point title | Percent Change From Baseline in Lumbar Spine, Total Hip, and Femoral Neck BMD at Week 78 - Full Analysis Set-TP II Subset |

End point description:

Bone mineral density was assessed by DXA and assessments of the lumbar spine (L1 to L4), total hip, and femoral neck BMD were performed at a central imaging vendor.

| End point type | Secondary |
|---|---|
| End point timeframe: baseline (screening), Week 78 | |

| End point values | CT-P41 maintenance | US-licensed Prolia maintenance | Switched to CT-P41 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 220[12] | 100[13] | 101[14] | |
| Units: percentage change (%) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Lumbar spine | 6.8588 (± 4.12795) | 6.5745 (± 3.40437) | 7.0532 (± 3.55985) | |
| Total hip | 3.4706 (± 2.81017) | 2.7947 (± 2.79862) | 3.3837 (± 2.92786) | |
| Femoral neck | 2.9995 (± 3.73072) | 2.4429 (± 3.61786) | 2.8226 (± 4.02021) | |

Notes:

[12] - The total number of participants in the FAS-TP II subset

[13] - The total number of participants in the FAS-TP II subset

[14] - The total number of participants in the FAS-TP II subset

### Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of New Vertebral, Nonvertebral, and Hip Fractures During TP I - Full Analysis Set

| End point title | Incidence of New Vertebral, Nonvertebral, and Hip Fractures During TP I - Full Analysis Set |
|---|---|

End point description:

Efficacy analysis of new vertebral fractures included only vertebral fractures occurring from T4 to L4 and confirmed by the central imaging vendor. A new vertebral fracture was defined as an increase of ≥1 grade in any vertebra from T4 to L4 that was normal at screening.
The nonvertebral fractures endpoint included fractures other than those of the vertebrae, excluding the skull, facial bones, mandible, metacarpals, and phalanges (fingers or toes) since they are not associated with decreased BMD, and excluded pathologic fractures and those associated with severe trauma acquired from a fall (from a height higher than a stool, chair, or first rung of a ladder) or otherwise. Only nonvertebral fractures confirmed by the central imaging vendor were included in the efficacy analysis. The fractures occurring at the site of femur neck, femur intertrochanter, or femur subtrochanter were considered as a hip fracture.

| End point type | Secondary |
|---|---|
| End point timeframe: up to Week 52 predose | |

| End point values | CT-P41 | US-licensed Prolia | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 239[15] | 238[16] | | |
| Units: participants | | | | |
| New vertebral fracture | 1 | 1 | | |
| Nonvertebral fracture | 2 | 4 | | |
| Hip fracture | 0 | 0 | | |

Notes:

[15] - The total number of participants in FAS

[16] - The total number of participants in FAS

### Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of New Vertebral, Nonvertebral, and Hip Fractures During TP II - Full Analysis Set-TP II Subset

| End point title | Incidence of New Vertebral, Nonvertebral, and Hip Fractures During TP II - Full Analysis Set-TP II Subset |
|---|---|

End point description:

Efficacy analysis of new vertebral fractures included only vertebral fractures occurring from T4 to L4 and confirmed by the central imaging vendor. A new vertebral fracture was defined as an increase of ≥1 grade in any vertebra from T4 to L4 that was normal at screening.
The nonvertebral fractures endpoint included fractures other than those of the vertebrae, excluding the skull, facial bones, mandible, metacarpals, and phalanges (fingers or toes) since they are not associated with decreased BMD, and excluded pathologic fractures and those associated with severe trauma acquired from a fall (from a height higher than a stool, chair, or first rung of a ladder) or otherwise. Only nonvertebral fractures confirmed by the central imaging vendor were included in the efficacy analysis. The fractures occurring at the site of femur neck, femur intertrochanter, or femur subtrochanter were considered as a hip fracture.

| End point type | Secondary |
|---|---|

End point timeframe:

from Week 52 to Week 78

| End point values | CT-P41 maintenance | US-licensed Prolia maintenance | Switched to CT-P41 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 220[17] | 100[18] | 101[19] | |
| Units: participants | | | | |
| New vertebral fracture | 1 | 0 | 0 | |
| Nonvertebral fracture | 2 | 0 | 1 | |
| Hip fracture | 0 | 0 | 0 | |

Notes:

[17] - The total number of participants in FAS-TP II subset

[18] - The total number of participants in FAS-TP II subset

[19] - The total number of participants in FAS-TP II subset

### Statistical analyses

No statistical analyses for this end point

## Secondary: Trough Serum Concentration (Ctrough) of Denosumab at Weeks 0 and 26 - Pharmacokinetic Set

| End point title | Trough Serum Concentration (Ctrough) of Denosumab at Weeks 0 and 26 - Pharmacokinetic Set |
|---|---|

End point description:

The Ctrough, a concentration before the next study drug administration, was calculated by non-compartmental analysis method from the concentration-time data. All serum concentrations below the lower limit of quantification (LLoQ) was set to 0 in the descriptive summaries of pharmacokinetics (PK) parameter estimation. In TP I, the Ctrough of denosumab at Weeks 0 and 26 was assessed as the serum concentration at Weeks 26 and 52 before the study drug administration, respectively.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 0 Day 1 predose, Week 26 predose

| **End point values** | CT-P41 | US-licensed Prolia | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 237[20] | 236[21] | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 0 Day 1 | 46.79 (± 105.102) | 31.69 (± 73.253) | | |
| Week 26 | 75.64 (± 154.630) | 63.99 (± 140.912) | | |

Notes:

[20] - The total number of participants in PK Set

[21] - The total number of participants in PK Set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Ctrough of Denosumab at Week 52 - Pharmacokinetics -TP II Subset

| End point title | Ctrough of Denosumab at Week 52 - Pharmacokinetics -TP II Subset |
|---|---|

End point description:

The Ctrough, a concentration before the next study drug administration, was calculated by non-compartmental analysis method from the concentration-time data. All serum concentrations below the LLoQ was set to 0 in the descriptive summaries of PK parameter estimation. In TP II, the Ctrough of denosumab at Week 52 was assessed as the serum concentration at Week 78.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 52

| End point values | CT-P41 maintenance | US-licensed Prolia maintenance | Switched to CT-P41 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 214[22] | 96[23] | 98[24] | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 52 | 70.24 (± 126.852) | 66.60 (± 129.573) | 126.15 (± 508.689) | |

Notes:

[22] - The number of participants in the PK-TP II subset who had the Ctrough data at Week 52.

[23] - The number of participants in the PK-TP II subset who had the Ctrough data at Week 52.

[24] - The number of participants in the PK-TP II subset who had the Ctrough data at Week 52.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With at Least 1 Anti-drug Antibodies (ADA)/Neutralizing Antibodies (NAb) Result After the First Study Drug Administration of TP I - Safety Set

| End point title | Number of Participants With at Least 1 Anti-drug Antibodies (ADA)/Neutralizing Antibodies (NAb) Result After the First Study Drug Administration of TP I - Safety Set |
|---|---|

End point description:

Samples that were positive in the ADA confirmatory assay were analyzed further to conduct a NAb assessment. The test outcomes for the screening assay were 'Positive' or 'Negative'. The number of patients with at least one ADA/NAb positive result after the first study drug administration of each treatment period including scheduled and unscheduled visits (Treatment Period I: Week 0 / Treatment Period II: Week 52) regardless of their ADA status at baseline were presented.

| End point type | Secondary |
|---|---|

End point timeframe:

up to Week 52 predose

| End point values | CT-P41 | US-licensed Prolia | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 239[25] | 238[26] | | |
| Units: participants | | | | |
| ADA positive | 233 | 234 | | |
| NAb positive | 0 | 0 | | |

Notes:

[25] - The number of participants in the Safety Set.

[26] - The number of participants in the Safety Set.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With at Least 1 ADA/NAb Result After the First Study Drug Administration of TP II - Safety-TP II Subset

| End point title | Number of Participants With at Least 1 ADA/NAb Result After the First Study Drug Administration of TP II - Safety-TP II |
|---|---|

| | |
|---|---|
| | Subset |

End point description:

Samples that were positive in the ADA confirmatory assay were analyzed further to conduct a NAb assessment. The test outcomes for the screening assay were 'Positive' or 'Negative'. The number of patients with at least one ADA/NAb positive result after the first study drug administration of each treatment period including scheduled and unscheduled visits (Treatment Period I: Week 0 / Treatment Period II: Week 52) regardless of their ADA status at baseline were presented.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

from Week 52 to Week 78

| **End point values** | CT-P41 maintenance | US-licensed Prolia maintenance | Switched to CT-P41 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 220[27] | 100[28] | 101[29] | |
| Units: participants | | | | |
| ADA positive | 208 | 92 | 93 | |
| NAb positive | 0 | 0 | 0 | |

Notes:

[27] - the number of participants in the Safety-TP II subset

[28] - the number of participants in the Safety-TP II subset

[29] - the number of participants in the Safety-TP II subset

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Through Week 78
- TP I: Adverse event (AE) start date before the study drug administration in TP II
- TP II: AE start date on or after the date of study drug administration in TP II.

Adverse event reporting additional description:

Among the 240 and 239 in the CT-P41 and US-licensed Prolia groups who initiated TP I, 1 subject each terminated the study participation before the treatment initiation. Since the AE results in TP I were summarized in the safety set who received at least 1 dose of the study drug during TP I, the total number of subjects exposed was 239 and 238.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | CT-P41 |

Reporting group description:

A total of 2 subcutaneous administration of 60 mg CT-P41 (proposed denosumab biosimilar) at Week 0 and Week 26 (26-week intervals) in TP I
CT-P41: 60 mg/mL single dose, Solution for injection in PFS

| | |
|---|---|
| Reporting group title | US-licensed Prolia |

Reporting group description:

A total of 2 subcutaneous administration of 60 mg US-licensed Prolia (denosumab) at Week 0 and Week 26 (26-week intervals) in TP I
US-licensed Prolia: 60 mg/mL single dose, Solution for injection in PFS

| | |
|---|---|
| Reporting group title | CT-P41 Maintenance |

Reporting group description:

Participants treated with CT-P41 in TP I continued the treatment with CT-P41 as a third dose at Week 52 in TP II

| | |
|---|---|
| Reporting group title | US-licensed Prolia Maintenance |

Reporting group description:

Participants treated with US-licensed Prolia in TP I were re-randomized to continue the treatment with US-licensed Prolia as a third dose at Week 52 in TP II

| | |
|---|---|
| Reporting group title | Switched to CT-P41 |

Reporting group description:

Participants treated with US-licensed Prolia in TP I were re-randomized to switch to CT-P41 as a third dose at Week 52 in TP II

| **Serious adverse events** | CT-P41 | US-licensed Prolia | CT-P41 Maintenance |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 239 (2.93%) | 10 / 238 (4.20%) | 8 / 220 (3.64%) |
| number of deaths (all causes) | 1 | 0 | 1 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Hormone level abnormal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 0 / 220 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 |
| Benign neoplasm of adrenal gland | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 0 / 220 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Borderline ovarian tumour | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 1 / 220 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Genital neoplasm malignant female | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 1 / 220 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Invasive breast carcinoma | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 238 (0.00%) | 0 / 220 (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 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 238 (0.00%) | 0 / 220 (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 |
| Squamous cell carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 1 / 220 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 |
| Vascular disorders | | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 238 (0.00%) | 0 / 220 (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 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 1 / 220 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 2 / 220 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 1 / 220 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 238 (0.00%) | 0 / 220 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Nervous system disorders | | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 0 / 220 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Crohn’s disease | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 238 (0.00%) | 0 / 220 (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 |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 |
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 perforation | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 1 / 220 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 |
| Reproductive system and breast disorders | | | |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 238 (0.00%) | 0 / 220 (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 |
| Vulval leukoplakia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 238 (0.00%) | 0 / 220 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 0 / 220 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 0 / 238 (0.00%) | 1 / 220 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 238 (0.00%) | 0 / 220 (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 |
| Pain in extremity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 238 (0.42%) | 0 / 220 (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 |

| **Serious adverse events** | US-licensed Prolia Maintenance | Switched to CT-P41 | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 100 (3.00%) | 0 / 101 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Hormone level abnormal | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign neoplasm of adrenal gland | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Borderline ovarian tumour | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Genital neoplasm malignant female | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive breast carcinoma | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Crohn’s disease | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum intestinal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal stenosis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Reproductive system and breast disorders** | | | |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulval leukoplakia | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Epistaxis | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 101 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | CT-P41 | US-licensed Prolia | CT-P41 Maintenance |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 98 / 239 (41.00%) | 86 / 238 (36.13%) | 44 / 220 (20.00%) |
| Immune system disorders | | | |
| COVID-19 | | | |
| subjects affected / exposed | 28 / 239 (11.72%) | 26 / 238 (10.92%) | 8 / 220 (3.64%) |
| occurrences (all) | 28 | 26 | 8 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| Arthralgia | | | |
| subjects affected / exposed | 24 / 239 (10.04%) | 21 / 238 (8.82%) | 7 / 220 (3.18%) |
| occurrences (all) | 29 | 24 | 7 |
| Osteoarthritis | | | |
| subjects affected / exposed | 9 / 239 (3.77%) | 13 / 238 (5.46%) | 2 / 220 (0.91%) |
| occurrences (all) | 10 | 14 | 2 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 10 / 239 (4.18%) | 12 / 238 (5.04%) | 4 / 220 (1.82%) |
| occurrences (all) | 10 | 13 | 4 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 25 / 239 (10.46%) | 20 / 238 (8.40%) | 13 / 220 (5.91%) |
| occurrences (all) | 28 | 27 | 16 |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | 4 / 238 (1.68%) | 6 / 220 (2.73%) |
| occurrences (all) | 13 | 5 | 6 |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 15 / 239 (6.28%) | 5 / 238 (2.10%) | 6 / 220 (2.73%) |
| occurrences (all) | 15 | 5 | 7 |

| **Non-serious adverse events** | US-licensed Prolia Maintenance | Switched to CT-P41 | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 100 (14.00%) | 29 / 101 (28.71%) | |
| Immune system disorders | | | |
| COVID-19 | | | |
| subjects affected / exposed | 3 / 100 (3.00%) | 6 / 101 (5.94%) | |
| occurrences (all) | 3 | 6 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) | |
| occurrences (all) | 0 | 1 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 2 / 101 (1.98%) | |
| occurrences (all) | 1 | 2 | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 100 (3.00%) | 4 / 101 (3.96%) | |
| occurrences (all) | 3 | 4 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 100 (4.00%) | 11 / 101 (10.89%) | |
| occurrences (all) | 4 | 11 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 3 / 101 (2.97%) | |
| occurrences (all) | 0 | 3 | |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 3 / 100 (3.00%) | 4 / 101 (3.96%) | |
| occurrences (all) | 3 | 6 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 08 April 2021 | Inclusion and exclusion criteria were updated; secondary efficacy and safety endpoints and assessments were updated; the statistical assumption was updated to change the CI from 90% to 95% for the EMA requirement and the sample size was revised to 440 from 416; analysis set for primary and secondary efficacy endpoints and primary PD endpoints were updated for the EMA requirement; FAS-Treatment Period II subset was added; rationale for historical data selection was added for the EMA requirement; transition to another anti-resorptive therapy for the patients who discontinued the treatment or terminated the study participation for the FDA requirement. |
| 30 July 2021 | the number of study centers and countries was updated; exclusion criteria were updated; prohibited therapy was updated; analysis of the listing of patients whose trial participation was impacted by COVID-19 was updated to reflect the FDA guidance. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Notes: