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: