Clinical trial results:
A randomized, double-blind, multicenter integrated phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of GP2411 (proposed biosimilar denosumab) and Prolia® (EU-authorized)

Summary

EudraCT number	2018-003523-11
Trial protocol	CZ ES BG
Global end of trial date	22 April 2022

Results information

Result version number	v1 (current)
This version publication date	23 February 2023
First version publication date	23 February 2023

Trial information

Trial identification

Sponsor protocol code	CGP24112301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03974100
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hexal AG
Sponsor organisation address	Industriestr. 25, Holzkirchen, Germany, 83607
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	22 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the trial were:
• To demonstrate similar efficacy between GP2411 and EU-Prolia, in terms of bone mineral density (BMD)
• To demonstrate similar pharmacodynamics (PD) between GP2411 and EU-Prolia, in terms of the bone resorption marker Carboxy-terminal crosslinked telopeptides of type I collagen (CTX)
• To demonstrate similar pharmacokinetics (PK) between GP2411 and EU-Prolia

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 20
Country: Number of subjects enrolled	Bulgaria: 103
Country: Number of subjects enrolled	Czechia: 160
Country: Number of subjects enrolled	Japan: 46
Country: Number of subjects enrolled	Poland: 170
Country: Number of subjects enrolled	Spain: 28
Worldwide total number of subjects	527
EEA total number of subjects	461

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)	276
From 65 to 84 years	251
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 43 investigative sites in 6 countries.

Pre-assignment

Screening details:

There was a screening period of up to 5 weeks. On Day 1, participants were randomized 1:1 to GP2411 or EU-Prolia for Treatment Period 1 (TP1).
At Week 52, participants in the EU-Prolia group were re-randomized 1:1 to continue with EU-Prolia or switch to GP2411 for Treatment Period 2 (TP2). Participants in GP2411 group continued with GP2411 for TP2

Period 1

Period 1 title	TP1 - Day 1 to Week 52
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	GP2411

Arm description:

Two 60 mg s.c. doses at 26-week intervals of GP2411 (proposed biosimilar denosumab) in TP1

Arm type	Experimental
Investigational medicinal product name	GP2411
Investigational medicinal product code	
Other name	proposed biosimilar denosumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg /mL subcutaneous injection of GP2411 every 6 months (Day 1 and Week 26)

Arm title	EU-Prolia

Arm description:

Two 60 mg s.c. doses at 26-week intervals of EU-Prolia (denosumab) in TP1

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

Dosage and administration details:

60 mg /mL subcutaneous injection of EU-Prolia every 6 months (Day 1 and Week 26)

Number of subjects in period 1	GP2411	EU-Prolia
Started	263	264
Per-Protocol Set (PPS)	233 [1]	230 [2]
TP1 Full Analysis Set (TP1 FAS)	255	257
Pharmacodynamic Analysis Set (PDS)	228 [3]	213 [4]
Pharmacokinetic Analysis Set (PKS)	260	258
TP1 Safety Analysis Set	263	264
Completed	253	249
Not completed	10	15
Physician decision	-	2
Adverse Event	1	3
Subject decision	8	9
Death	1	-
Lost to follow-up	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The intermediate milestones correspond to the Analysis Sets.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The intermediate milestones correspond to the Analysis Sets.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The intermediate milestones correspond to the Analysis Sets.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The intermediate milestones correspond to the Analysis Sets.

Period 2

Period 2 title	TP2- Week 52 to Week 78
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	GP2411/GP2411

Arm description:

Participants treated with GP2411 in TP1 continued with a third dose of GP2411 in TP2

Arm type	Experimental

Investigational medicinal product name	GP2411
Investigational medicinal product code	
Other name	proposed biosimilar denosumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants in GP2411 group in TP1 continued with a third dose of GP2411 in TP2. GP2411 was administered as a 60 mg /mL subcutaneous injection at Week 52.

Arm title	EU-Prolia/EU-Prolia

Arm description:

Participants treated with EU-Prolia in TP1 were re-randomized to continue with a third dose of EU-Prolia in TP2

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

Dosage and administration details:

Participants in EU-Prolia in TP1 were re-randomized to continue with a third dose of EU-Prolia in TP2. EU-Prolia was administered as a 60 mg /mL subcutaneous injection at Week 52.

Arm title	EU-Prolia/GP2411

Arm description:

Participants treated with EU-Prolia in TP1 were re-randomized to switch to GP2411 in TP2

Arm type	Experimental
Investigational medicinal product name	EU-Prolia and GP2411
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants in EU-Prolia in TP1 were re-randomized to switch to GP2411 in TP2. GP2411 was administered as a 60 mg /mL subcutaneous injection at Week 52.

Number of subjects in period 2	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411
Started	253	125	124
TP2 Full Analysis Set (TP2 FAS)	253	124	124
TP2 Safety Analysis Set	253	125	124
Completed	253	123	124
Not completed	0	2	0
Subject decision	-	1	-
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	GP2411
Reporting group description:	
Two 60 mg s.c. doses at 26-week intervals of GP2411 (proposed biosimilar denosumab) in TP1	
Reporting group title	EU-Prolia
Reporting group description:	
Two 60 mg s.c. doses at 26-week intervals of EU-Prolia (denosumab) in TP1	

Reporting group values	GP2411	EU-Prolia	Total
Number of subjects	263	264	527
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
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)	137	139	276
From 65-84 years	126	125	251
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	64.6	64.7	
standard deviation	± 6.08	± 5.78	-
Sex: Female, Male Units: participants			
Female	263	264	527
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Asian	23	24	47
Multiple	1	0	1
White	239	240	479

End points

End points reporting groups

Reporting group title	GP2411
Reporting group description:	
Two 60 mg s.c. doses at 26-week intervals of GP2411 (proposed biosimilar denosumab) in TP1	
Reporting group title	EU-Prolia
Reporting group description:	
Two 60 mg s.c. doses at 26-week intervals of EU-Prolia (denosumab) in TP1	
Reporting group title	GP2411/GP2411
Reporting group description:	
Participants treated with GP2411 in TP1 continued with a third dose of GP2411 in TP2	
Reporting group title	EU-Prolia/EU-Prolia
Reporting group description:	
Participants treated with EU-Prolia in TP1 were re-randomized to continue with a third dose of EU-Prolia in TP2	
Reporting group title	EU-Prolia/GP2411
Reporting group description:	
Participants treated with EU-Prolia in TP1 were re-randomized to switch to GP2411 in TP2	

Primary: Percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 52 – Per-Protocol Set

End point title	Percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 52 – Per-Protocol Set
End point description:	
Bone density measurements were performed by dual energy X-ray absorptiometry (DXA). Lumbar spine scan included L1 through L4 vertebrae. All DXA scans were submitted to a central imaging vendor for analysis. A mixed effect model for repeated measurements (MMRM) was fitted to the changes from baseline in LS-BMD for all post-baseline time points up to Week 52. Values at Week 52 were estimated from the model and are presented in the table.	
End point type	Primary
End point timeframe:	
Baseline (screening), up to Week 52	

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	230		
Units: Percentage change (%)				
least squares mean (standard error)	4.955 (± 0.2634)	5.099 (± 0.2618)		

Statistical analyses

Statistical analysis title	GP2411 vs. EU-Prolia

Statistical analysis description:

MMRM included treatment, prior bisphosphonate use, DXA machine type, visit, visit-treatment interaction, and baseline LS-BMD as a continuous covariate.

Comparison groups	GP2411 v EU-Prolia
Number of subjects included in analysis	463
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Method	Mixed-model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	-0.145
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.798
upper limit	0.509
Variability estimate	Standard error of the mean
Dispersion value	0.3325

Notes:

[1] - Equivalence criteria (analysis set PPS): 95% CI for difference in means contained in [-1.45%, 1.45%]

Primary: Percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 52 – TP1 Full Analysis Set

End point title	Percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 52 – TP1 Full Analysis Set

End point description:

Bone density measurements were performed by DXA. Lumbar spine scan included L1 through L4 vertebrae. All DXA scans were submitted to a central imaging vendor for analysis. A MMRM was fitted to the changes from baseline in LS-BMD for all post-baseline time points up to Week 52. Missing values were assumed to be missing at random (MAR) using the MMRM model. Values at Week 52 were estimated from the model and are presented in the table.

End point type	Primary

End point timeframe:

Baseline (screening), up to Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	257		
Units: Percentage change (%)				
least squares mean (standard error)	4.963 (± 0.2630)	5.140 (± 0.2627)		

Statistical analyses

Statistical analysis title	GP2411 vs. EU-Prolia

Statistical analysis description:

MMRM included treatment, prior bisphosphonate use, DXA machine type, visit, visit-treatment interaction, and baseline LS-BMD as a continuous covariate.

Comparison groups	GP2411 v EU-Prolia

Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Method	Mixed-model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	-0.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	0.475
Variability estimate	Standard error of the mean
Dispersion value	0.3321

Notes:

[2] - Equivalence criteria (analysis set TP1 FAS): 95% CI for difference in means contained in [-1.45%, 1.45%] (criteria 1) or in [-2.00%, 2.00%] (criteria 2)

Primary: Area under the effect-time curve (AUEC) of percentage change from baseline in serum CTX concentrations after first dose – Pharmacodynamic Analysis Set

End point title	Area under the effect-time curve (AUEC) of percentage change from baseline in serum CTX concentrations after first dose – Pharmacodynamic Analysis Set

End point description:

Carboxy-terminal crosslinked telopeptides of type I collagen (CTX) is a bone resorption biomarker. Serum CTX concentration-time data were analyzed by non-compartmental methods. The AUEC of baseline corrected serum CTX concentrations (% change from baseline) was calculated using the linear trapezoidal method. Values below the lower limit of quantification (LLOQ) were imputed with the actual value for the LLOQ.

End point type	Primary

End point timeframe:

Baseline (pre-dose Day 1), up to Week 26

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	213		
Units: percentage change (%)*day				
geometric mean (geometric coefficient of variation)	15700 (± 15.8)	15900 (± 14.0)		

Statistical analyses

Statistical analysis title	GP2411 vs. EU-Prolia - 90% CI

Statistical analysis description:

ANCOVA was performed on log-transformed AUEC including treatment and log baseline CTX value as a continuous covariate.

Comparison groups	GP2411 v EU-Prolia

Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.98
upper limit	1.01

Notes:

[3] - Equivalence criteria (analysis set PDS): 90% CI for ratio of geometric means contained in [0.80, 1.25%]

Statistical analysis title	GP2411 vs. EU-Prolia - 95%CI

Statistical analysis description:

ANCOVA was performed on log-transformed AUEC including treatment and log baseline CTX value as a continuous covariate.

Comparison groups	GP2411 v EU-Prolia
Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	equivalence[4]
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.01

Notes:

[4] - Equivalence criteria (analysis set PDS): 95% CI for ratio of geometric means contained in [0.80, 1.25%]

Primary: Maximum observed serum concentration (Cmax) of denosumab after first dose

End point title	Maximum observed serum concentration (Cmax) of denosumab after first dose

End point description:

Serum denosumab concentration-time data were analyzed by non-compartmental methods. Missing denosumab serum concentrations or concentrations below the LLOQ were not imputed and handled as missing values, except for the pre-dose sample which were treated as zero.

End point type	Primary

End point timeframe:

Baseline (pre-dose Day 1), up to Week 26

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260	258		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	6970 (± 45.8)	7050 (± 44.2)		

Statistical analyses

Statistical analysis title	GP2411 vs. EU-Prolia

Statistical analysis description:

ANCOVA was performed on log-transformed Cmax including treatment and weight as a continuous covariate.

Comparison groups	GP2411 v EU-Prolia
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	equivalence[5]
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	0.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1.03

Notes:

[5] - Equivalence criteria (analysis set PKS): 90% CI for ratio of geometric means contained in [0.80, 1.25%]

Primary: Area under the serum concentration-time curve from time zero to infinity (AUCinf) of denosumab after first dose

End point title	Area under the serum concentration-time curve from time zero to infinity (AUCinf) of denosumab after first dose

End point description:

Serum denosumab concentration-time data were analyzed by non-compartmental methods. Missing denosumab serum concentrations or concentrations below the LLOQ were not imputed and handled as missing values, except for the pre-dose sample which were treated as zero. The linear-up log-down trapezoidal method was used for the AUCinf calculation.

End point type	Primary

End point timeframe:

Baseline (pre-dose Day 1), up to Week 26

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	246		
Units: day*ng/mL				
geometric mean (geometric coefficient of variation)	370000 (± 47.8)	365000 (± 43.3)		

Statistical analyses

Statistical analysis title	GP2411 vs. EU-Prolia

Statistical analysis description:

ANCOVA was performed on log-transformed AUCinf including treatment and weight as a continuous covariate.

Comparison groups	GP2411 v EU-Prolia
Number of subjects included in analysis	493
Analysis specification	Pre-specified
Analysis type	equivalence[6]
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	0.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.93
upper limit	1.05

Notes:

[6] - Equivalence criteria (analysis set PKS): 90% CI for ratio of geometric means contained in [0.80, 1.25%]

Secondary: Percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 26 – Treatment Period 1 (Per-Protocol Set)

End point title	Percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 26 – Treatment Period 1 (Per-Protocol Set)

End point description:

Bone density measurements were performed by DXA. Lumbar spine scan included L1 through L4 vertebrae. All DXA scans were submitted to a central imaging vendor for analysis.

End point type	Secondary

End point timeframe:

Baseline (screening), Week 26

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	229		
Units: percentage change (%)				
arithmetic mean (standard deviation)	3.6501 (± 3.76952)	3.6700 (± 3.68816)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 26 – Treatment Period 1 (TP1 Full Analysis Set)

End point title	Percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 26 – Treatment Period 1 (TP1 Full Analysis Set)

End point description:

Bone density measurements were performed by DXA. Lumbar spine scan included L1 through L4 vertebrae. All DXA scans were submitted to a central imaging vendor for analysis.

End point type	Secondary

End point timeframe:

Baseline (screening), Week 26

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	256		
Units: percentage change (%)				
arithmetic mean (standard deviation)	3.5877 (± 3.73579)	3.7144 (± 3.89730)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 78 – Treatment Period 2 (TP2 Full Analysis Set)

End point title	Percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 78 – Treatment Period 2 (TP2 Full Analysis Set)

End point description:

Bone density measurement were performed by DXA. Lumbar spine scan included L1 through L4 vertebrae. All DXA scans were submitted to a central imaging vendor for analysis.

End point type	Secondary

End point timeframe:

Baseline (screening), Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249	123	122	
Units: Percentage change (%)				
arithmetic mean (standard deviation)	6.8222 (± 3.95225)	7.0694 (± 4.72955)	6.4212 (± 4.47102)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in femoral neck bone mineral density (FN-BMD) at Week 26 and Week 52 – Treatment Period 1 (Per-Protocol Set)

End point title	Percent change from baseline in femoral neck bone mineral density (FN-BMD) at Week 26 and Week 52 – Treatment Period 1 (Per-Protocol Set)

End point description:

Bone density measurements were performed by DXA. For proximal femur, the left side was to be used for all DXA scans at all study visits. If the right side had to be used (e.g., due to implants) or was inadvertently used at baseline, then it was to be used consistently throughout the study. All DXA scans were submitted to a central imaging vendor for analysis.

End point type	Secondary

End point timeframe:

Baseline (screening), Week 26 and Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	230		
Units: percentage change (%)				
arithmetic mean (standard deviation)				
Week 26 (n=232,229)	2.0818 (± 3.38039)	1.8087 (± 3.18505)		
Week 52 (n=233,229)	2.4200 (± 3.70552)	2.6157 (± 3.26119)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in femoral neck bone mineral density (FN-BMD) at Week 26 and Week 52 – Treatment Period 1 (TP1 Full Analysis Set)

End point title	Percent change from baseline in femoral neck bone mineral density (FN-BMD) at Week 26 and Week 52 – Treatment Period 1 (TP1 Full Analysis Set)

End point description:

Bone density measurements were performed by DXA. For proximal femur, the left side was to be used for all DXA scans at all study visits. If the right side had to be used (e.g., due to implants) or was inadvertently used at baseline, then it was to be used consistently throughout the study. All DXA scans were submitted to a central imaging vendor for analysis.

End point type	Secondary

End point timeframe:

Baseline (screening), Week 26 and Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	257		
Units: percentage change (%)				
arithmetic mean (standard deviation)				
Week 26 (n=254,256)	2.0343 (± 3.43682)	1.8210 (± 3.11073)		
Week 52 (n=253,248)	2.3686 (± 3.69145)	2.5717 (± 3.29726)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in femoral neck bone mineral density (FN-BMD) at Week 78 – Treatment Period 2 (TP2 Full Analysis Set)

End point title	Percent change from baseline in femoral neck bone mineral density (FN-BMD) at Week 78 – Treatment Period 2 (TP2 Full Analysis Set)

End point description:

Bone density measurements were performed by DXA. For proximal femur, the left side was to be used for all DXA scans at all study visits. If the right side had to be used (e.g., due to implants) or was inadvertently used at baseline, then it was to be used consistently throughout the study. All DXA scans were submitted to a central imaging vendor for analysis.

End point type	Secondary

End point timeframe:

Baseline (screening), Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	122	122	
Units: Percentage change (%)				
arithmetic mean (standard deviation)	3.2220 (± 4.03733)	2.9406 (± 3.92115)	2.6857 (± 3.64193)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in total hip bone mineral density (TH-

BMD) at Week 26 and Week 52 – Treatment Period 1 (Per-Protocol Set)

End point title	Percent change from baseline in total hip bone mineral density (TH-BMD) at Week 26 and Week 52 – Treatment Period 1 (Per-Protocol Set)

End point description:

Bone density measurements were performed by DXA. For total hip, the left side was to be used for all DXA scans at all study visits. If the right side had to be used (e.g., due to implants) or was inadvertently used at baseline, then it was to be used consistently throughout the study. All DXA scans were submitted to a central imaging vendor for analysis.

End point type	Secondary

End point timeframe:

Baseline (screening), Week 26 and Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	230		
Units: percentage change (%)				
arithmetic mean (standard deviation)				
Week 26 (n=232,229)	2.6475 (± 2.43928)	2.1178 (± 2.44627)		
Week 52 (n=233,229)	3.4289 (± 2.71152)	3.3211 (± 2.59266)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in total hip bone mineral density (TH-BMD) at Week 26 and Week 52 – Treatment Period 1 (TP1 Full Analysis Set)

End point title	Percent change from baseline in total hip bone mineral density (TH-BMD) at Week 26 and Week 52 – Treatment Period 1 (TP1 Full Analysis Set)

End point description:

Bone density measurements were performed by DXA. For total hip, the left side was to be used for all DXA scans at all study visits. If the right side had to be used (e.g., due to implants) or was inadvertently used at baseline, then it was to be used consistently throughout the study. All DXA scans were submitted to a central imaging vendor for analysis.

End point type	Secondary

End point timeframe:

Baseline (screening), Week 26 and Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	257		
Units: percentage change (%)				
arithmetic mean (standard deviation)				
Week 26 (n=254,256)	2.5280 (± 2.46669)	2.0595 (± 2.51811)		
Week 52 (n=253,248)	3.2882 (± 2.70260)	3.2234 (± 2.64633)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in total hip bone mineral density (TH-BMD) at Week 78 – Treatment Period 2 (TP2 Full Analysis Set)

End point title	Percent change from baseline in total hip bone mineral density (TH-BMD) at Week 78 – Treatment Period 2 (TP2 Full Analysis Set)

End point description:

Bone density measurements were performed by DXA. For total hip, the left side was to be used for all DXA scans at all study visits. If the right side had to be used (e.g., due to implants) or was inadvertently used at baseline, then it was to be used consistently throughout the study.

End point type	Secondary

End point timeframe:

Baseline (screening), Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	122	122	
Units: Percentage change (%)				
arithmetic mean (standard deviation)	3.8270 (± 3.28071)	4.0898 (± 2.96530)	3.9987 (± 3.33311)	

Statistical analyses

No statistical analyses for this end point

Secondary: CTX serum concentrations as per visit schedule up to Week 52 - Treatment Period 1

End point title	CTX serum concentrations as per visit schedule up to Week 52 - Treatment Period 1

End point description:

CTX is a bone resorption biomarker. Serum samples were analyzed for CTX concentrations. CTX serum concentrations were determined by a validated ligand-binding immunoassay. Values below the LLOQ were imputed with the actual value for the LLOQ.

End point type	Secondary

End point timeframe:

Baseline (pre-dose Day 1), Day 2, Day 4, Week 8, Week 18, Week 22, Week 26, Week 39 and Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	213		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=228,213)	0.437 (± 0.249)	0.450 (± 0.264)		
Day 2 (n=226,212)	0.0904 (± 0.110)	0.0859 (± 0.0923)		
Day 4 (n=226,211)	0.0383 (± 0.0272)	0.0407 (± 0.0537)		
Week 8 (n=222,206)	0.0339 (± 0.0134)	0.0332 (± 0.00334)		
Week 18 (n=219,200)	0.0355 (± 0.0205)	0.0362 (± 0.0225)		
Week 22 (n=226,211)	0.0428 (± 0.0546)	0.0422 (± 0.0406)		
Week 26 (n=228,213)	0.0661 (± 0.0954)	0.0651 (± 0.0708)		
Week 39 (n=227,206)	0.0342 (± 0.0116)	0.0345 (± 0.0110)		
Week 52 (n=224,207)	0.0845 (± 0.116)	0.0807 (± 0.0883)		

Statistical analyses

No statistical analyses for this end point

Secondary: CTX serum concentrations as per visit schedule from Week 52 up to Week 78 - Treatment Period 2

End point title	CTX serum concentrations as per visit schedule from Week 52 up to Week 78 - Treatment Period 2

End point description:

CTX is a bone resorption biomarker. Serum samples were analyzed for CTX concentrations. CTX serum concentrations were determined by a validated ligand-binding immunoassay. Values below the LLOQ were imputed with the actual value for the LLOQ.

End point type	Secondary

End point timeframe:

Week 56, Week 65 and Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	124	124	
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 56 (n=247,116,117)	0.0335 (± 0.00685)	0.0358 (± 0.0259)	0.0330 (± 0.00)	
Week 65 (n=246,117,118)	0.0335 (± 0.00714)	0.0352 (± 0.0159)	0.0359 (± 0.0281)	
Week 78 (n=248,117,117)	0.125 (± 0.190)	0.144 (± 0.155)	0.101 (± 0.149)	

Statistical analyses

No statistical analyses for this end point

Secondary: PINP serum concentrations as per visit schedule up to Week 52 - Treatment Period 1

End point title	PINP serum concentrations as per visit schedule up to Week 52 - Treatment Period 1

End point description:

Procollagen I N-terminal propeptide (PINP) is a bone formation biomarker. Serum samples were analyzed for PINP concentrations. PINP serum concentrations were determined by a validated ligand-binding immunoassay. Values below the LLOQ were imputed with the actual value for the LLOQ.

End point type	Secondary

End point timeframe:

Baseline (pre-dose Day 1), Day 2, Day 4, Week 8, Week 18, Week 22, Week 26, Week 39 and Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	213		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=228,213)	60.3 (± 27.1)	62.2 (± 30.0)		
Day 2 (n=228,213)	58.5 (± 25.9)	60.2 (± 29.3)		
Day 4 (n=227,213)	56.8 (± 23.2)	58.8 (± 26.8)		
Week 8 (n=223,207)	21.2 (± 9.53)	21.0 (± 7.58)		
Week 18 (n=221,200)	12.1 (± 4.52)	12.6 (± 5.10)		
Week 22 (n=227,212)	13.5 (± 5.92)	13.3 (± 4.59)		
Week 26 (n=228,213)	15.4 (± 7.44)	15.9 (± 6.71)		
Week 39 (n=227,208)	10.5 (± 3.14)	10.7 (± 3.43)		
Week 52 (n=225,207)	15.0 (± 5.95)	15.7 (± 7.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: PINP serum concentrations as per visit schedule from Week 52 up to Week 78 - Treatment Period 2

End point title	PINP serum concentrations as per visit schedule from Week 52 up to Week 78 - Treatment Period 2

End point description:

PINP is a bone formation biomarker. Serum samples were analyzed for PINP concentrations. PINP serum concentrations were determined by a validated ligand-binding immunoassay. Values below the LLOQ were imputed with the actual value for the LLOQ.

End point type	Secondary

End point timeframe:

Week 56, Week 65 and Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	124	124	
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 56 (n=252,122,124)	13.7 (± 8.06)	13.9 (± 5.39)	14.4 (± 11.0)	
Week 65 (n=250,123,123)	10.5 (± 3.40)	10.9 (± 3.43)	11.1 (± 3.85)	
Week 78 (n=252,123,124)	17.5 (± 14.1)	20.3 (± 20.4)	17.1 (± 8.37)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs up to Week 52 - Treatment Period 1

End point title	Number of participants with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs up to Week 52 - Treatment Period 1

End point description:

Number of participants with TEAEs and serious TEAEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs during Treatment Period 1. The number of participants in each category is reported in the table.

End point type	Secondary

End point timeframe:

From first dose of study treatment on Day 1 up to pre-dose at Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	264		
Units: participants				
TEAE	157	181		
Treatment-related TEAE	36	49		
Serious TEAE	12	8		
Treatment-related serious TEAE	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs from Week 52 up to Week 78 - Treatment Period 2

End point title	Number of participants with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs from Week 52 up to Week 78 - Treatment Period 2

End point description:

Number of participants with TEAEs and serious TEAEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs during Treatment Period 2. The number of participants in each category is reported in the table.

End point type	Secondary

End point timeframe:

From dosing of study treatment at Week 52 up to Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	125	124	
Units: participants				
TEAE	68	47	48	
Treatment-related TEAE	7	7	5	
Serious TEAE	4	2	0	
Treatment-related serious TEAE	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with vertebral fractures up to Week 52 - Treatment Period 1

End point title	Number of participants with vertebral fractures up to Week 52 - Treatment Period 1

End point description:

Vertebral fractures were assessed by independent radiologists at the central imaging vendor. The

radiologists assessed lateral thoracic (vertebrae T4 to T12) and lumbar (vertebrae L1 to L4) spine radiographs for vertebral fractures. New and worsening vertebral fractures are defined as occurrence of new fracture (i.e. change in Genant score from 0 at baseline to 1 or higher at a later time point) or worsening fracture (i.e. increase in Genant score from baseline at a later time point) in any assessed vertebra. The Genant classification of vertebral fractures is based on the vertebral shape, with respect to vertebral height loss involving the anterior, posterior, and/or middle vertebral body and ranges between 0 (normal) and 3 (severe fracture, >40% loss of height).
The number of participants in each category is reported in the table.

End point type	Secondary

End point timeframe:

Baseline (screening) and Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	264		
Units: participants				
At least one vertebral fracture at baseline	123	116		
New vertebral fractures at Week 52	15	24		
Worsening vertebral fractures at Week 52	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with vertebral fractures from Week 52 up to Week 78 - Treatment Period 2

End point title	Number of participants with vertebral fractures from Week 52 up to Week 78 - Treatment Period 2

End point description:

Vertebral fractures were assessed by independent radiologists at the central imaging vendor. The radiologists assessed lateral thoracic (vertebrae T4 to T12) and lumbar (vertebrae L1 to L4) spine radiographs for vertebral fractures. New and worsening vertebral fractures are defined as occurrence of new fracture (i.e. change in Genant score from 0 at Week 52 to 1 or higher at a later time point) or worsening fracture (i.e. increase in Genant score from Week 52 at a later time point) in any assessed vertebra. The Genant classification of vertebral fractures is based on the vertebral shape, with respect to vertebral height loss involving the anterior, posterior, and/or middle vertebral body and ranges between 0 (normal) and 3 (severe fracture, >40% loss of height).
The number of participants in each category is reported in the table.

End point type	Secondary

End point timeframe:

Week 52 and Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	125	124	
Units: participants				
At least one vertebral fracture at Week 52	126	57	65	
New vertebral fractures at Week 78	12	3	8	
Worsening vertebral fractures at Week 78	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with nonvertebral fractures up to Week 52 - Treatment Period 1

End point title	Number of participants with nonvertebral fractures up to Week 52 - Treatment Period 1

End point description:

Information about any nonvertebral fractures while on study were recorded as adverse events. The diagnosis of nonvertebral fractures did not require central X-ray reading and was based on local radiology reports.
The number of participants in each category is reported in the table.

End point type	Secondary

End point timeframe:

From first dose of study treatment on Day 1 up to pre-dose at Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	264		
Units: participants				
Hip fracture	2	0		
Femoral neck fracture	1	0		
Femur fracture	0	1		
Ankle fracture	1	1		
Wrist fracture	1	0		
Radius fracture	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with nonvertebral fractures from Week 52 up to Week 78 - Treatment Period 2

End point title	Number of participants with nonvertebral fractures from Week

	52 up to Week 78 - Treatment Period 2

End point description:

Information about any nonvertebral fractures while on study were recorded as adverse events. The diagnosis of nonvertebral fractures did not require central X-ray reading and was based on local radiology reports.
The number of participants in each category is reported in the table.

End point type	Secondary

End point timeframe:

From dosing of study treatment at Week 52 up to Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	125	124	
Units: participants				
Hip fracture	1	0	0	
Fibula fracture	1	0	0	
Hand fracture	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Injection Site Reactions (ISRs) up to Week 52 - Treatment Period 1

End point title	Number of participants with Injection Site Reactions (ISRs) up to Week 52 - Treatment Period 1

End point description:

The injection site reaction (ISR) assessment was done by the investigator/designee. It consisted of grading the severity of each injection reaction based on criteria the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The ISR grading was defined as follows:
• Grade 1: Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)
• Grade 2: Pain; lipodystrophy; edema; phlebitis
• Grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated
• Grade 4: Life-threatening consequences; urgent intervention indicated
The number of participants in each category is reported in the table.

End point type	Secondary

End point timeframe:

From first dose of study treatment on Day 1 up to pre-dose at Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	264		
Units: participants				
ISR Grade 1	6	9		
ISR Grade 2	1	1		
ISR Grade 3	0	0		

ISR Grade 4	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Injection Site Reactions (ISRs) from Week 52 up to Week 78 - Treatment Period 2

End point title	Number of participants with Injection Site Reactions (ISRs) from Week 52 up to Week 78 - Treatment Period 2

End point description:

The injection site reaction (ISR) assessment was done by the investigator/designee. It consisted of grading the severity of each injection reaction based on criteria the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The ISR grading was defined as follows:
• Grade 1: Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)
• Grade 2: Pain; lipodystrophy; edema; phlebitis
• Grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated
• Grade 4: Life-threatening consequences; urgent intervention indicated
The number of participants in each category is reported in the table.

End point type	Secondary

End point timeframe:

From dosing of study treatment at Week 52 up to Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	125	124	
Units: participants				
ISR Grade 1	1	0	0	
ISR Grade 2	0	0	0	
ISR Grade 3	0	0	0	
ISR Grade 4	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with anti-drug antibodies (ADA) up to Week 52 - Treatment Period 1

End point title	Number of participants with anti-drug antibodies (ADA) up to Week 52 - Treatment Period 1

End point description:

Immunogenicity was evaluated in serum. Samples were screened for potential anti-drug antibodies (ADA) and positive screen results were confirmed using a confirmatory assay. For confirmed ADA positive samples, titers were determined. Confirmed ADAs were also analyzed for their neutralization potential. Patient ADA status was defined as follows:

• ADA Positive: ADA-positive sample at any time point during TP1
• ADA Positive, Persistent: 'Persistent' indicates a subject experiencing a positive ADA result at the final visit and with at least 2 consecutive positive ADA results
• ADA Positive, Transient: 'Transient' indicates a subject experiencing positive ADA result but not qualifying as 'Persistent'
• ADA titer positive: ADA-positive sample with a titer result ≥ 20 ng/mL
• NAb Positive: ADA-positive sample with presence of neutralizing antibodies (NAb)
The number of participants in each category is reported in the table.

End point type	Secondary

End point timeframe:

From Week 2 up to Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	264		
Units: participants				
ADA Positive	93	108		
ADA Positive, Persistent	7	4		
ADA Positive, Transient	86	104		
ADA titer positive	2	2		
NAb positive	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with anti-drug antibodies (ADA) from Week 52 up to Week 78 - Treatment Period 2

End point title	Number of participants with anti-drug antibodies (ADA) from Week 52 up to Week 78 - Treatment Period 2

End point description:

Immunogenicity was evaluated in serum. Samples were screened for potential anti-drug antibodies (ADA) and positive screen results were confirmed using a confirmatory assay. For confirmed ADA positive samples, titers were determined. Confirmed ADAs were also analyzed for their neutralization potential. Patient ADA status was defined as follows:
• ADA Positive: ADA-positive sample at any time point during TP1
• ADA Positive, Persistent: 'Persistent' indicates a subject experiencing a positive ADA result at the final visit and with at least 2 consecutive positive ADA results
• ADA Positive, Transient: 'Transient' indicates a subject experiencing positive ADA result but not qualifying as 'Persistent'
• ADA titer positive: ADA-positive sample with a titer result ≥ 20 ng/mL
• NAb Positive: ADA-positive sample with presence of neutralizing antibodies (NAb)
The number of participants in each category is reported in the table.

End point type	Secondary

End point timeframe:

From Week 56 up to Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	125	124	
Units: participants				
ADA Positive	42	26	26	
ADA Positive, Persistent	3	3	0	
ADA Positive, Transient	39	23	26	
ADA titer positive	0	1	0	
NAb positive	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Denosumab serum concentrations as per visit schedule up to Week 52 - Treatment Period 1

End point title	Denosumab serum concentrations as per visit schedule up to Week 52 - Treatment Period 1

End point description:

Serum samples were analyzed for concentrations of free denosumab by using a validated ligand binding assay. Briefly, the concentration of free denosumab was determined by binding to coated ligand molecules.
Denosumab concentrations below the LLOQ were set to zero in order to calculate arithmetic means.

End point type	Secondary

End point timeframe:

Baseline (pre-dose Day 1), Day 4, Week 1, Week 2, Week 8, Week 14, Week 18, Week 22, Week 26, Week 39 and Week 52

End point values	GP2411	EU-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260	258		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=256,257)	0.00 (± 0.00)	0.928 (± 14.9)		
Day 4 (n=258,258)	4930 (± 2530)	5250 (± 2660)		
Week 1 (n=259,254)	6820 (± 3220)	6890 (± 3320)		
Week 2 (n=259,256)	6940 (± 3040)	6760 (± 2890)		
Week 8 (n=253,251)	3160 (± 1500)	3070 (± 1510)		
Week 14 (n=250,249)	1130 (± 740)	1090 (± 797)		
Week 18 (n=248,241)	536 (± 516)	495 (± 487)		
Week 22 (n=256,254)	208 (± 277)	198 (± 392)		
Week 26 (n=252,253)	95.9 (± 415)	47.9 (± 114)		
Week 39 (n=250,245)	1490 (± 902)	1390 (± 787)		
Week 52 (n=250,244)	91.9 (± 186)	58.3 (± 126)		

Statistical analyses

No statistical analyses for this end point

Secondary: Denosumab serum concentrations as per visit schedule from Week 52 up to Week 78 - Treatment Period 2

End point title	Denosumab serum concentrations as per visit schedule from Week 52 up to Week 78 - Treatment Period 2

End point description:

Serum samples were analyzed for concentrations of free denosumab by using a validated ligand binding assay. Briefly, the concentration of free denosumab was determined by binding to coated ligand molecules.
Denosumab concentrations below the LLOQ were set to zero in order to calculate arithmetic means.

End point type	Secondary

End point timeframe:

Week 56, Week 65 and Week 78

End point values	GP2411/GP2411	EU-Prolia/EU-Prolia	EU-Prolia/GP2411	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	124	124	
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 56 (n=252,122,124)	6010 (± 2200)	5550 (± 1900)	6220 (± 2130)	
Week 65 (n=250,123,122)	1540 (± 880)	1330 (± 753)	1640 (± 962)	
Week 78 (n=251,123,124)	122 (± 406)	53.2 (± 133)	147 (± 652)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study treatment on Day 1 up to Week 78.	
Adverse event reporting additional description:	
Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	EU-Prolia
Reporting group description:	
Two 60 mg s.c. doses at 26-week intervals of EU-Prolia (denosumab) in TP1	
Reporting group title	GP2411
Reporting group description:	
Two 60 mg s.c. doses at 26-week intervals of GP2411 (proposed biosimilar denosumab) in TP1	
Reporting group title	EU-Prolia/EU-Prolia
Reporting group description:	
Participants treated with EU-Prolia in TP1 were re-randomized to continue with a third dose of EU-Prolia in TP2	
Reporting group title	EU-Prolia/GP2411
Reporting group description:	
Participants treated with EU-Prolia in TP1 were re-randomized to switch to GP2411 in TP2	
Reporting group title	GP2411/GP2411
Reporting group description:	
Participants treated with GP2411 in TP1 continued with a third dose of GP2411 in TP2	

Serious adverse events	EU-Prolia	GP2411	EU-Prolia/EU-Prolia
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 264 (3.03%)	12 / 263 (4.56%)	2 / 125 (1.60%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			

subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 125 (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
Malignant neoplasm of ampulla of Vater			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 125 (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
Metastatic neoplasm			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 125 (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
Ovarian cancer			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 125 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 125 (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
Femoral neck fracture			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 125 (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
Hip fracture			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 125 (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

Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 125 (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
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Eye disorders			
Epiretinal membrane			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 125 (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
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 125 (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 erosive			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 125 (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 inflammation			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 125 (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
Pancreatic fistula			

subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 125 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 125 (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			
Pneumothorax spontaneous			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 125 (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
Pulmonary embolism			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 125 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 125 (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
Gastrointestinal candidiasis			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	EU-Prolia/GP2411	GP2411/GP2411	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 124 (0.00%)	4 / 253 (1.58%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 124 (0.00%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of ampulla of Vater			
subjects affected / exposed	0 / 124 (0.00%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (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			
Ankle fracture			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 124 (0.00%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (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			
Syncope			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Epiretinal membrane			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Chronic gastritis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 124 (0.00%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic fistula			
subjects affected / exposed	0 / 124 (0.00%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (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			
Pneumothorax spontaneous			
subjects affected / exposed	0 / 124 (0.00%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (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 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal candidiasis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 253 (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: 3 %

Non-serious adverse events	EU-Prolia	GP2411	EU-Prolia/EU-Prolia
Total subjects affected by non-serious adverse events			
subjects affected / exposed	119 / 264 (45.08%)	89 / 263 (33.84%)	29 / 125 (23.20%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 264 (2.27%)	3 / 263 (1.14%)	1 / 125 (0.80%)
occurrences (all)	6	3	1
Spinal compression fracture			

subjects affected / exposed	5 / 264 (1.89%)	1 / 263 (0.38%)	2 / 125 (1.60%)
occurrences (all)	6	1	3
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 264 (4.92%)	6 / 263 (2.28%)	2 / 125 (1.60%)
occurrences (all)	16	6	2
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	10 / 264 (3.79%)	7 / 263 (2.66%)	0 / 125 (0.00%)
occurrences (all)	10	7	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 264 (2.65%)	3 / 263 (1.14%)	4 / 125 (3.20%)
occurrences (all)	11	3	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 264 (3.03%)	12 / 263 (4.56%)	5 / 125 (4.00%)
occurrences (all)	9	15	5
Spinal osteoarthritis			
subjects affected / exposed	9 / 264 (3.41%)	4 / 263 (1.52%)	2 / 125 (1.60%)
occurrences (all)	10	4	2
Back pain			
subjects affected / exposed	9 / 264 (3.41%)	10 / 263 (3.80%)	2 / 125 (1.60%)
occurrences (all)	10	14	2
Infections and infestations			
COVID-19			
subjects affected / exposed	13 / 264 (4.92%)	9 / 263 (3.42%)	7 / 125 (5.60%)
occurrences (all)	13	9	7
Cystitis			
subjects affected / exposed	9 / 264 (3.41%)	1 / 263 (0.38%)	0 / 125 (0.00%)
occurrences (all)	10	2	0
Nasopharyngitis			
subjects affected / exposed	16 / 264 (6.06%)	23 / 263 (8.75%)	4 / 125 (3.20%)
occurrences (all)	17	26	4
Upper respiratory tract infection			

subjects affected / exposed	8 / 264 (3.03%)	4 / 263 (1.52%)	2 / 125 (1.60%)
occurrences (all)	8	4	3
Urinary tract infection			
subjects affected / exposed	10 / 264 (3.79%)	5 / 263 (1.90%)	2 / 125 (1.60%)
occurrences (all)	12	7	2
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	26 / 264 (9.85%)	28 / 263 (10.65%)	0 / 125 (0.00%)
occurrences (all)	26	29	0
Vitamin D deficiency			
subjects affected / exposed	12 / 264 (4.55%)	7 / 263 (2.66%)	3 / 125 (2.40%)
occurrences (all)	12	7	3

Non-serious adverse events	EU-Prolia/GP2411	GP2411/GP2411	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 124 (19.35%)	33 / 253 (13.04%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 124 (3.23%)	1 / 253 (0.40%)	
occurrences (all)	4	1	
Spinal compression fracture			
subjects affected / exposed	4 / 124 (3.23%)	2 / 253 (0.79%)	
occurrences (all)	4	2	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 124 (2.42%)	1 / 253 (0.40%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	0 / 124 (0.00%)	1 / 253 (0.40%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 124 (0.00%)	1 / 253 (0.40%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 124 (1.61%)	7 / 253 (2.77%)	
occurrences (all)	3	11	
Spinal osteoarthritis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 253 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 124 (0.81%)	2 / 253 (0.79%)	
occurrences (all)	1	2	
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 124 (1.61%)	6 / 253 (2.37%)	
occurrences (all)	2	6	
Cystitis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 253 (0.40%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	6 / 124 (4.84%)	5 / 253 (1.98%)	
occurrences (all)	6	5	
Upper respiratory tract infection			
subjects affected / exposed	2 / 124 (1.61%)	1 / 253 (0.40%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	0 / 124 (0.00%)	2 / 253 (0.79%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	0 / 124 (0.00%)	1 / 253 (0.40%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	3 / 124 (2.42%)	2 / 253 (0.79%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2018	The main purpose of this amendment was to use appropriate terminology, e.g. when referring to US-licensed Prolia and EU-authorized Prolia.
15 March 2019	The following main changes were implemented: • The sample size calculations were updated to change the CI for the LS-BMD for the FDA requirements to use a 95% CI in the similarity assessment of the primary endpoint. • The inclusion and exclusion criteria were updated, additional PK, PD and ADA sampling time points were added, the definition of the analysis sets was updated, handling of missing ecacy values was clarified, and a sensitivity analysis was planned. In addition, severity grading of ISRs and other AEs was updated. • Severity grading of ISRs was updated to align with the CTCAE classification.
21 February 2020	The following changes were made: • SD estimate of %CfB in LS-BMD at Week 52 was updated and analysis set for the primary analysis of %CfB in LS-BMD for FDA was updated from PPS to TP1 FAS, which resulted in a reduction of the sample size. • This amendment also changed the calcium assessment by shifting from the parameter "albumin adjusted serum calcium" to the parameter "total serum calcium". • Screening period was prolonged from 28 to 35 days.
30 October 2020	Following changes were made: • The statistical testing strategy was updated from one overall study testing strategy to three separate testing strategies which address dierent health authority requirements •Details were added on the MMRM model, and the handling and statistical analysis of missing data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported