



Clinical trial results:

A Phase 3, Randomized, Double-blind, Parallel-group, Active-controlled Study to Compare the Efficacy, Safety, Pharmacodynamics, Pharmacokinetics and Immunogenicity of Enzene Denosumab (ENZ215) and Prolia® in Postmenopausal Women with Osteoporosis

Summary

EudraCT number	2021-004811-26
Trial protocol	LT DK ES BG PL
Global end of trial date	18 July 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	ALK22/ENZ215-DEN2
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05405725
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alkem Laboratories Ltd.
Sponsor organisation address	ALKEM HOUSE, "Devashish", Adjacent to Matulya centre, Senapati Bapat Marg, Lower Parel, Mumbai, India, 400013
Public contact	Sharma Akhilesh, Alkem Laboratories Ltd, Mumbai, India, +91 22-39829999, Akhilesh.Sharma@alkem.com
Scientific contact	Sharma Akhilesh, Alkem Laboratories Ltd, Mumbai, India, +91 22-39829999, Akhilesh.Sharma@alkem.com
Sponsor organisation name	Enzene Biosciences Ltd.
Sponsor organisation address	Plot No. A-22/A/1/2, MIDC Chakan Industrial Area, Phase II, Vill-Khalumbre, Taluka Khed, Maharashtra, India, 410501
Public contact	Sharma Akhilesh, Alkem Laboratories Ltd., Mumbai, India, +91 20-30674622, Akhilesh.Sharma@alkem.com
Scientific contact	Sharma Akhilesh, Alkem Laboratories Ltd, Mumbai, India, +91 20-30674622, Akhilesh.Sharma@alkem.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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 October 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the efficacy of ENZ215 when compared to Prolia® in patients with postmenopausal osteoporosis, in terms of change in BMD at the lumbar spine from baseline to Month 12
- To compare the AUEC of sCTX levels from baseline to Month 6

Protection of trial subjects:

Safety & Efficacy data reviewed by DMC at predefined timepoints

Background therapy:

Calcium and Vitamin D supplements

Evidence for comparator:

Prolia® (denosumab) to be used as an active comparator; 60 mg/mL solution for injections in PFS for SC administration.

EU marketing authorization holder: Amgen Europe B.V. Minervum 7061, 4817 ZK Breda, The Netherlands

Actual start date of recruitment	21 February 2022
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	Serbia: 39
Country: Number of subjects enrolled	Poland: 230
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Czechia: 134
Country: Number of subjects enrolled	Lithuania: 45
Country: Number of subjects enrolled	Bulgaria: 54
Worldwide total number of subjects	504
EEA total number of subjects	465

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)	204
From 65 to 84 years	300
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 1,061 participants screened for the study, 504 were randomized (253 to ENZ215 and 251 to Prolia®); all these participants were treated. 469 participants overall (93.1%) completed the double-blind treatment period (233 participants [92.1%] in the ENZ215 group and 236 participants [94.0%] in the Prolia group) and 35 participants discontinued.

Pre-assignment

Screening details:

1) Postmenopausal women aged ≥ 55 and ≤ 85 years; 2) Body weight ≥ 50 kg and ≤ 90 kg; 3) Diagnosed with osteoporosis, with absolute BMD consistent with T-scores of ≤ -2.5 and ≥ -4.0 at the lumbar spine (L1-L4 region) as measured by dual-energy X ray absorptiometry (DXA) at screening; 4) At least 5 years of postmenopausal status confirmed by FSH.

Pre-assignment period milestones

Number of subjects started	1061 ^[1]
Intermediate milestone: Number of subjects	Participants who failed screening: 557
Intermediate milestone: Number of subjects	Participants randomized: 504
Number of subjects completed	504

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not meeting criteria: 527
Reason: Number of subjects	other: 30

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Indicated number of patients is a total of patients from screened group, 557 doesn't qualify the Inclusion/exclusion criteria and 504 patients were randomized for participation in the trial.

Period 1

Period 1 title	Double-blind treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

This is a double-blind study (till Month 12) in which patients and Investigators are blinded to study intervention. The IRT has been programmed with blind-breaking instructions. After double-blind part (first 12 months) study analysis were carried out.

Arms

Are arms mutually exclusive?	Yes
Arm title	Biosimilar Denosumab (ENZ215)

Arm description:

Participants received 60 mg ENZ215 on Day 1 and Month 6 as a subcutaneous injection during the double blind treatment period

Arm type	Experimental
Investigational medicinal product name	Biosimilar Denosumab (ENZ215)
Investigational medicinal product code	
Other name	Enzene Denosumab
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg/mL PFS, solution for injections, for SC administration

Arm title	Prolia®
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Arm description:

Participants received 60 mg Prolia® on Day 1 and Month 6 as a subcutaneous injection during the double blind treatment period.

Arm type	Active comparator
Investigational medicinal product name	Prolia®
Investigational medicinal product code	
Other name	Denosumab
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg/mL solution for injection in PFS; for SC administration

Number of subjects in period 1	Biosimilar Denosumab (ENZ215)	Prolia®
Started	253	251
FPFV	253	251
LPLV	239	236
Data Base Lock	253	251
CSR Finalization	253	251
Completed	233	236
Not completed	20	15
Consent withdrawn by subject	14	10
personal reason	2	1
Physician decision	-	1
death	-	1
Adverse event, non-fatal	1	2
Protocol deviation	3	-

Period 2

Period 2 title	Open-label extension period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Biosimilar Denosumab (ENZ215)
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Arm description:

A subset of participants in Prolia® arm who completed the double-blind treatment period, were randomized to receive 60 mg ENZ215 at Month 12 as a subcutaneous injection during the open-label, switch-over period.

Arm type	Experimental
Investigational medicinal product name	Biosimilar Denosumab (ENZ215)
Investigational medicinal product code	
Other name	Enzene Denosumab
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg/mL solutions for injection in PFS; for SC administration

Arm title	Prolia®
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Arm description:

A subset of participants in Prolia® arm who completed the double-blind treatment period, were randomized to receive 60 mg Prolia® at Month 12 as a subcutaneous injection during the open-label, switch-over period.

Arm type	Active comparator
Investigational medicinal product name	Prolia®
Investigational medicinal product code	
Other name	Denosumab
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg/mL solution for injection in PFS; for SC administration

Number of subjects in period 2 ^[2]	Biosimilar Denosumab (ENZ215)	Prolia®
Started	60	60
Completed	60	60

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Open label extension planned for 120 Patients from Prolia group, 60 in ENZ215 arm and 60 in Prolia Arm

Baseline characteristics

Reporting groups

Reporting group title	Biosimilar Denosumab (ENZ215)
Reporting group description: Participants received 60 mg ENZ215 on Day 1 and Month 6 as a subcutaneous injection during the double blind treatment period	
Reporting group title	Prolia®
Reporting group description: Participants received 60 mg Prolia® on Day 1 and Month 6 as a subcutaneous injection during the double blind treatment period.	

Reporting group values	Biosimilar Denosumab (ENZ215)	Prolia®	Total
Number of subjects	253	251	504
Age categorical			
Units: Subjects			
≥55 to < 70 years	171	171	342
≥70 to ≤ 85 years	82	80	162
Age continuous			
Units: years			
median	66.0	66.0	
full range (min-max)	55 to 84	55 to 82	-
Gender categorical			
only female			
Units: Subjects			
Female	253	251	504
Prior use of Bisphosphonate			
Units: Subjects			
yes	44	43	87
no	209	208	417
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	253	250	503
Not stated	0	0	0
Race			
Units: Subjects			
White	253	251	504
Black or African American	0	0	0
Years since menopause			
Units: number			
median	17.0	17.0	
full range (min-max)	5 to 40	5 to 42	-

Subject analysis sets

Subject analysis set title	ITT Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis set consisted of all randomized participants who received at least one dose of study intervention in the double-blind treatment period. In the ITT analysis set, treatment was assigned based on the study intervention to which participants were randomized, regardless of which treatment they actually received.

Reporting group values	ITT Set		
Number of subjects	504		
Age categorical			
Units: Subjects			
≥55 to < 70 years	342		
≥70 to ≤ 85 years	162		
Age continuous			
Units: years			
median	66.0		
full range (min-max)	55 to 84		
Gender categorical			
only female			
Units: Subjects			
Female	504		
Prior use of Bisphosphonate			
Units: Subjects			
yes	87		
no	417		
Ethnicity			
Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	503		
Not stated	0		
Race			
Units: Subjects			
White	504		
Black or African American	0		
Years since menopause			
Units: number			
median	17.0		
full range (min-max)	5 to 42		

End points

End points reporting groups

Reporting group title	Biosimilar Denosumab (ENZ215)
Reporting group description: Participants received 60 mg ENZ215 on Day 1 and Month 6 as a subcutaneous injection during the double blind treatment period	
Reporting group title	Prolia®
Reporting group description: Participants received 60 mg Prolia® on Day 1 and Month 6 as a subcutaneous injection during the double blind treatment period.	
Reporting group title	Biosimilar Denosumab (ENZ215)
Reporting group description: A subset of participants in Prolia® arm who completed the double-blind treatment period, were randomized to receive 60 mg ENZ215 at Month 12 as a subcutaneous injection during the open-label, switch-over period.	
Reporting group title	Prolia®
Reporting group description: A subset of participants in Prolia® arm who completed the double-blind treatment period, were randomized to receive 60 mg Prolia® at Month 12 as a subcutaneous injection during the open-label, switch-over period.	
Subject analysis set title	ITT Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT analysis set consisted of all randomized participants who received at least one dose of study intervention in the double-blind treatment period. In the ITT analysis set, treatment was assigned based on the study intervention to which participants were randomized, regardless of which treatment they actually received.	

Primary: AUEC of sCTX over the initial 6 months (from Day 1 pre-dose to Month 6 pre-dose)

End point title	AUEC of sCTX over the initial 6 months (from Day 1 pre-dose to Month 6 pre-dose)
End point description: AUEC of sCTX over the initial 6 months (from Day 1 pre-dose to Month 6 pre-dose)	
End point type	Primary
End point timeframe: 6 month	

End point values	Biosimilar Denosumab (ENZ215)	Prolia®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	237		
Units: percentage change				
geometric mean (confidence interval 95%)	347382.787 (340087.2488 to 354834.8289)	345858.423 (338640.7259 to 353229.9557)		

Statistical analyses

Statistical analysis title	Double-blind treatment period Analysis Set
Comparison groups	Biosimilar Denosumab (ENZ215) v Prolia®
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≥ 0.05
Method	ANCOVA
Parameter estimate	Ratio of Geometric Means
Point estimate	1.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9748
upper limit	1.0349

Primary: Percentage change in BMD at lumbar spine (L1-L4 region) measured by DXA from baseline to Month 12

End point title	Percentage change in BMD at lumbar spine (L1-L4 region) measured by DXA from baseline to Month 12
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End point description:

The primary endpoint analysis (using a treatment policy estimand in the ITT set) demonstrated equivalence of ENZ215 compared to Prolia® for the percentage change in BMD at lumbar spine (L1-L4 region) measured by DXA from baseline to Month 12: adjusted LS mean (95% CI) of 5.350 (4.7306; 5.9695) in the ENZ215 group and 5.533 (4.9225; 6.1440) in the Prolia group; LS mean difference (95% CI) of -0.183 (-0.9044; 0.5380). Overall, 12 participants (2.4%) experienced ICE1 (defined as "significant BMD assessment delays for > 35 days at Visit 9 [Month 12]"): six participants (2.4%) in each treatment group. Overall, nine participants (1.8%) experienced ICE2 (defined as "participant received other medication alongside the IP, which affected the primary variable [prohibited medications]"): six participants (2.4%) in the ENZ215 group and three participants (1.2%) in the Prolia group.

End point type	Primary
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End point timeframe:

from start of baseline double-blind treatment period (therapy) to Month 12

End point values	Biosimilar Denosumab (ENZ215)	Prolia®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	235		
Units: mean				
least squares mean (confidence interval 95%)	5.530 (4.7306 to 5.9695)	5.533 (4.9225 to 6.1440)		

Statistical analyses

Statistical analysis title	Mixed Model Repeated Measures
Statistical analysis description:	
Analysis was performed with a mixed model repeated measures model with observed %CfB in lumbar spine BMD as the dependent variable model including treatment, age strata, previous treatment with bisphosphonate, visit*treatment interaction and baseline BMD value as covariates.	
Comparison groups	Prolia® v Biosimilar Denosumab (ENZ215)
Number of subjects included in analysis	466
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	LS mean difference
Point estimate	-0.183
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9044
upper limit	0.538

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of informed consent until the end of the study.

Overall, 321 participants (63.7%) experienced 834 TEAEs during the double-blind treatment period.

Overall, 46 participants (38.3%) experienced 66 TEAEs during the open-label extension.

Adverse event reporting additional description:

There was a similar percentage of participants in ENZ215 group and Prolia group who experienced TEAEs, severe TEAEs, study treatment-related TEAEs, TESAEs, treatment-emergent AESIs and TEAEs leading to treatment withdrawal -mild or moderate in severity. There was one SUSAR and one AE/TEAE leading to death, both of which were reported in Prolia.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	ENZ215 Double-blind Treatment Period
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Reporting group description:

Participants received 60 mg ENZ215 on Day 1 and Month 6 as a subcutaneous injection during the double blind treatment period.

Reporting group title	Prolia® Double-Blind Treatment period
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Reporting group description:

Participants received 60 mg Prolia® on Day 1 and Month 6 as a subcutaneous injection during the double blind treatment period.

Reporting group title	ENZ215 Open Label Treatment Period
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Reporting group description:

A subset of participants in Prolia® arm who completed the double-blind treatment period, were randomised to receive 60 mg ENZ215 at Month 12 as a subcutaneous injection during the open-label, switch-over period.

Reporting group title	Prolia® Open Label treatment Period
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Reporting group description:

A subset of participants in Prolia® arm who completed the double-blind treatment period, were randomised to receive 60 mg Prolia® at Month 12 as a subcutaneous injection during the open-label, switch-over period.

Serious adverse events	ENZ215 Double-blind Treatment Period	Prolia® Double-Blind Treatment period	ENZ215 Open Label Treatment Period
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 253 (6.32%)	15 / 251 (5.98%)	0 / 60 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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

Basal cell carcinoma			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Chromophobe renal cell carcinoma			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Meningioma benign			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Investigations			
Red blood cells urine positive			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	3 / 253 (1.19%)	1 / 251 (0.40%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 253 (0.40%)	1 / 251 (0.40%)	0 / 60 (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
Wrist fracture			
subjects affected / exposed	2 / 253 (0.79%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Craniofacial fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Foot fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Forearm fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Fracture displacement			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Humerus fracture			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Lower limb fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Meniscus injury			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Ulna fracture			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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			

Angina pectoris			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Aortic valve stenosis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Myocardial infarction			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Pericarditis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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			
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Myasthenia gravis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Thoracic radiculopathy			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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

Reproductive system and breast disorders			
Genital prolapse			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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			
SAPHO syndrome			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (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
Cystitis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 251 (0.40%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Influenza			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Pneumonia			

subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 251 (0.00%)	0 / 60 (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

Serious adverse events	Prolia® Open Label treatment Period		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chromophobe renal cell carcinoma			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningioma benign			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Investigations			
Red blood cells urine positive			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Craniofacial fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Forearm fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fracture displacement			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Humerus fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meniscus injury			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic valve stenosis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Ischaemic cerebral infarction subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thoracic radiculopathy subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders Gastrooesophageal reflux disease subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders Genital prolapse subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders Bile duct stone subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders SAPHO syndrome subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations COVID-19			

subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	ENZ215 Double-blind Treatment Period	Prolia® Double-Blind Treatment period	ENZ215 Open Label Treatment Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 253 (45.45%)	122 / 251 (48.61%)	23 / 60 (38.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1

Uterine leiomyoma subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	1 / 60 (1.67%) 1
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	9 / 253 (3.56%) 9	12 / 251 (4.78%) 14	0 / 60 (0.00%) 0
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	3 / 253 (1.19%) 3	2 / 251 (0.80%) 2	0 / 60 (0.00%) 0
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	1 / 60 (1.67%) 1
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Upper respiratory tract inflammation subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	1 / 60 (1.67%) 1
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0

Vitamin D decreased subjects affected / exposed occurrences (all)	6 / 253 (2.37%) 6	6 / 251 (2.39%) 6	0 / 60 (0.00%) 0
Injury, poisoning and procedural complications			
Lumbar vertebral fracture subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Meniscus injury subjects affected / exposed occurrences (all)	3 / 253 (1.19%) 3	0 / 251 (0.00%) 0	1 / 60 (1.67%) 1
Thoracic vertebral fracture subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Tooth fracture subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Cardiac disorders			
Atrioventricular block first degree subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	6 / 253 (2.37%) 9	13 / 251 (5.18%) 16	0 / 60 (0.00%) 0
Radiculopathy subjects affected / exposed occurrences (all)	3 / 253 (1.19%) 3	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Blood and lymphatic system disorders			
Leukopenia subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	1 / 60 (1.67%) 1
Neutropenia			

subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0	0 / 251 (0.00%) 0	1 / 60 (1.67%) 1
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	3 / 253 (1.19%) 3	0 / 251 (0.00%) 0	0 / 60 (0.00%) 0
Eye disorders Blepharochalasis subjects affected / exposed occurrences (all) Chalazion subjects affected / exposed occurrences (all) Glaucoma subjects affected / exposed occurrences (all)	0 / 253 (0.00%) 0 0 / 253 (0.00%) 0 0 / 253 (0.00%) 0	0 / 251 (0.00%) 0 0 / 251 (0.00%) 0 0 / 251 (0.00%) 0	1 / 60 (1.67%) 1 1 / 60 (1.67%) 1 1 / 60 (1.67%) 1
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Chronic gastritis subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Gastritis	0 / 253 (0.00%) 0 6 / 253 (2.37%) 6 2 / 253 (0.79%) 2 2 / 253 (0.79%) 2 3 / 253 (1.19%) 3 3 / 253 (1.19%) 3 3 / 253 (1.19%) 3	0 / 251 (0.00%) 0 6 / 251 (2.39%) 6 5 / 251 (1.99%) 6 3 / 251 (1.20%) 3 2 / 251 (0.80%) 3 2 / 251 (0.80%) 2	1 / 60 (1.67%) 1 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0

subjects affected / exposed	5 / 253 (1.98%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences (all)	6	0	0
Nausea			
subjects affected / exposed	0 / 253 (0.00%)	3 / 251 (1.20%)	0 / 60 (0.00%)
occurrences (all)	0	3	0
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Osteoarthritis			
subjects affected / exposed	8 / 253 (3.16%)	4 / 251 (1.59%)	1 / 60 (1.67%)
occurrences (all)	9	4	1
Spinal pain			
subjects affected / exposed	5 / 253 (1.98%)	4 / 251 (1.59%)	2 / 60 (3.33%)
occurrences (all)	7	4	2
Rotator cuff syndrome			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Shoulder girdle pain			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	9 / 253 (3.56%)	9 / 251 (3.59%)	0 / 60 (0.00%)
occurrences (all)	9	13	0

Back pain			
subjects affected / exposed	6 / 253 (2.37%)	6 / 251 (2.39%)	0 / 60 (0.00%)
occurrences (all)	9	6	0
Muscle spasms			
subjects affected / exposed	2 / 253 (0.79%)	3 / 251 (1.20%)	0 / 60 (0.00%)
occurrences (all)	3	3	0
Pain in extremity			
subjects affected / exposed	3 / 253 (1.19%)	2 / 251 (0.80%)	0 / 60 (0.00%)
occurrences (all)	3	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 253 (7.11%)	22 / 251 (8.76%)	5 / 60 (8.33%)
occurrences (all)	21	24	6
Bronchitis			
subjects affected / exposed	11 / 253 (4.35%)	6 / 251 (2.39%)	0 / 60 (0.00%)
occurrences (all)	12	6	0
COVID-19			
subjects affected / exposed	5 / 253 (1.98%)	12 / 251 (4.78%)	1 / 60 (1.67%)
occurrences (all)	5	12	1
Pharyngitis			
subjects affected / exposed	6 / 253 (2.37%)	3 / 251 (1.20%)	2 / 60 (3.33%)
occurrences (all)	7	3	2
Upper respiratory tract infection			
subjects affected / exposed	11 / 253 (4.35%)	16 / 251 (6.37%)	2 / 60 (3.33%)
occurrences (all)	13	19	2
Gastroenteritis			
subjects affected / exposed	5 / 253 (1.98%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences (all)	6	0	0
Herpes zoster			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Lyme disease			

subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	3 / 253 (1.19%)	4 / 251 (1.59%)	0 / 60 (0.00%)
occurrences (all)	3	4	1
Tracheobronchitis			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	8 / 253 (3.16%)	8 / 251 (3.19%)	0 / 60 (0.00%)
occurrences (all)	8	9	0
Cystitis			
subjects affected / exposed	5 / 253 (1.98%)	6 / 251 (2.39%)	0 / 60 (0.00%)
occurrences (all)	5	6	0
Urinary tract infection bacterial			
subjects affected / exposed	3 / 253 (1.19%)	5 / 251 (1.99%)	0 / 60 (0.00%)
occurrences (all)	4	5	0
Respiratory tract infection			
subjects affected / exposed	1 / 253 (0.40%)	5 / 251 (1.99%)	0 / 60 (0.00%)
occurrences (all)	1	6	0
Oral herpes			
subjects affected / exposed	2 / 253 (0.79%)	3 / 251 (1.20%)	0 / 60 (0.00%)
occurrences (all)	2	3	0
Pulpitis dental			
subjects affected / exposed	1 / 253 (0.40%)	3 / 251 (1.20%)	0 / 60 (0.00%)
occurrences (all)	1	3	0
Bronchitis bacterial			

subjects affected / exposed	3 / 253 (1.19%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences (all)	3	0	0
Respiratory tract infection viral			
subjects affected / exposed	3 / 253 (1.19%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences (all)	4	0	0
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Dyslipidaemia			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 253 (0.00%)	0 / 251 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	7 / 253 (2.77%)	6 / 251 (2.39%)	0 / 60 (0.00%)
occurrences (all)	7	6	0
Vitamin D deficiency			
subjects affected / exposed	6 / 253 (2.37%)	4 / 251 (1.59%)	0 / 60 (0.00%)
occurrences (all)	6	4	0
Hypercalcaemia			
subjects affected / exposed	2 / 253 (0.79%)	4 / 251 (1.59%)	0 / 60 (0.00%)
occurrences (all)	2	4	0
Hyperlipidaemia			
subjects affected / exposed	3 / 253 (1.19%)	1 / 251 (0.40%)	0 / 60 (0.00%)
occurrences (all)	3	1	0

Non-serious adverse events	Prolia® Open Label treatment Period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 60 (38.33%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Benign neoplasm subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Uterine leiomyoma subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Upper respiratory tract inflammation subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		

Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Vitamin D decreased subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Injury, poisoning and procedural complications Lumbar vertebral fracture subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Meniscus injury subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Thoracic vertebral fracture subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Tooth fracture subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Headache subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Radiculopathy subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Blood and lymphatic system disorders Leukopenia			

subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0 0 / 60 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Eye disorders Blepharochalasis subjects affected / exposed occurrences (all) Chalazion subjects affected / exposed occurrences (all) Glaucoma subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Chronic gastritis subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Toothache	0 / 60 (0.00%) 0 1 / 60 (1.67%) 1 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0		

subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0		
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Endocrine disorders Autoimmune thyroiditis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Osteoarthritis subjects affected / exposed occurrences (all) Spinal pain subjects affected / exposed occurrences (all) Rotator cuff syndrome subjects affected / exposed occurrences (all) Shoulder girdle pain subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1 1 / 60 (1.67%) 1 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0 1 / 60 (1.67%) 1		

Arthralgia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Bronchitis			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
COVID-19			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Influenza			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Lyme disease			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	0		
Tracheobronchitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Urinary tract infection bacterial			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Pulpitis dental			

subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Bronchitis bacterial			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Respiratory tract infection viral			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Dyslipidaemia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Vitamin D deficiency			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Hyperlipidaemia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2021	Global Protocol Amendment 1 dated 16 December 2021 [Protocol version 1.1] - NS: 1) Change in address of the Co Sponsor; 2) Clarifications in section 5.2 Exclusion Criteria: Exclusion criteria #13 was changed from "Total hip or femoral neck T-score <4.0" to "Total hip or femoral neck T score <-4.0"
08 April 2022	Global Protocol Amendment 2 dated 08 April 2022 [Protocol version 2.0] - NS: This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study. The Global clinical study protocol (CSP) Amendment 2 was prepared in response to queries from the regulatory authority in Czech Republic.
27 July 2022	Country Specific (SPAIN) Protocol Amendment 2.1 dated 27 July 2022 - SM: has been prepared for resubmission after study rejection by Spanish Regulatory Authorities: 1) Section 5.1 Inclusion Criteria: Inclusion criteria #2 for Spain: a) Postmenopausal women aged ≥ 70 years with LS T-score is ≤ -2.5 and ≥ 4.0 or b) Postmenopausal women aged ≥ 55 and < 70 years with either i) LS T-score ≤ -3.0 and ≥ 4.0 or ii) LS T-score is ≤ -2.5 and > 3.0 and they have a prior fragility fracture (except for hip fracture), including non-exclusionary vertebral fractures. 2) Section 8.2.2 Vital Signs: The following text: "Oral temperature, heart rate, respiratory rate, and blood pressure will be assessed" has been updated to "Body temperature, heart rate, respiratory rate, and blood pressure will be assessed." 3)
19 October 2022	Country Specific (SPAIN) Protocol Amendment 2.2 dated 19 October 2022 [Protocol Version 2.2]: SM This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. The clinical study protocol (CSP) Amendment 2.2 was prepared in response to queries from the regulatory authority in Spain. 1) Section 5.1 Inclusion Criteria: Inclusion criteria #2: Postmenopausal women aged ≥ 55 and ≤ 85 years globally, except for Spain. In Spain specifically refer to the below criteria: a. Postmenopausal women aged ≥ 75 and ≤ 85 years with LS T-score ≤ -2.5 or b. Postmenopausal women aged ≥ 65 and < 75 years with LS T-score is ≤ -2.5 and a prior fragility fracture (except for hip fracture), including non-exclusionary vertebral fractures c. In both cases (i.e. criteria a and b), it must also be that these are women who present a contraindication for the use of bisphosphonates or who do not tolerate the oral route.

16 February 2023	Global Protocol Amendment 3 dated 16 February 2023 - NS: This amendment is non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study. The Global clinical study protocol (CSP) Amendment 3.0 was prepared to add clarifications and update typo errors noted in earlier version of the document.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported