



**Clinical trial results:**

**An Open-label, Randomized, Teriparatide-controlled Study to Evaluate the Effect of Treatment With Romosozumab in Postmenopausal Women With Osteoporosis Previously Treated With Bisphosphonate Therapy**

**Summary**

EudraCT number	2012-002948-24
Trial protocol	BE DK ES GB CZ HU
Global end of trial date	23 April 2015

**Results information**

Result version number	v1 (current)
This version publication date	13 August 2016
First version publication date	13 August 2016

**Trial information**

**Trial identification**

Sponsor protocol code	20080289
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01796301
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ-Medical Info - Clinical Trials, Amgen (Europe) GmbH, MedinfoInternational@amgen.com
Scientific contact	IHQ-Medical Info - Clinical Trials, Amgen (Europe) GmbH, MedinfoInternational@amgen.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	23 April 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 April 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Evaluate the effect of treatment with romosozumab for 12 months, compared with teriparatide (TPTD), on total hip bone mineral density (BMD), as assessed by dual energy X-ray absorptiometry (DXA), in postmenopausal women with osteoporosis, previously treated with bisphosphonate therapy.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2013
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	Poland: 11
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	United Kingdom: 80
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Czech Republic: 91
Country: Number of subjects enrolled	Denmark: 69
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Colombia: 47
Country: Number of subjects enrolled	Argentina: 32
Country: Number of subjects enrolled	United States: 20
Country: Number of subjects enrolled	Canada: 12
Worldwide total number of subjects	436
EEA total number of subjects	325

Notes:

<b>Subjects enrolled per age group</b>	
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)	98
From 65 to 84 years	320
85 years and over	18

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 46 sites in North America, Latin America, and Europe. Participants were enrolled from 31 January 2013 to 29 April 2014.

### Pre-assignment

Screening details:

A total of 777 subjects were screened for participation; 341 (43.9%) were excluded prior to randomization, primarily due to not meeting inclusion/exclusion criteria (306 [39.4%] subjects). A total of 436 subjects were randomized into the study.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Teriparatide

Arm description:

Participants received teriparatide 20 µg/day administered by subcutaneous injection for 12 months.

Arm type	Active comparator
Investigational medicinal product name	Teriparatide
Investigational medicinal product code	
Other name	Forteo
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

20 µg administered by subcutaneous injection once a day.

<b>Arm title</b>	Romosozumab
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Arm description:

Participants received 210 mg romosozumab administered by subcutaneous injection once a month for 12 months.

Arm type	Experimental
Investigational medicinal product name	Romosozumab
Investigational medicinal product code	AMG 785
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

210 mg administered subcutaneously once a month.

<b>Number of subjects in period 1</b>	Teriparatide	Romosozumab
Started	218	218
Received Treatment	214	218
Completed	200	198
Not completed	18	20
Consent withdrawn by subject	15	15
Death	-	1
Lost to follow-up	3	3
Sponsor decision	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Teriparatide
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Reporting group description:

Participants received teriparatide 20 µg/day administered by subcutaneous injection for 12 months.

Reporting group title	Romosozumab
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Reporting group description:

Participants received 210 mg romosozumab administered by subcutaneous injection once a month for 12 months.

Reporting group values	Teriparatide	Romosozumab	Total
Number of subjects	218	218	436
Age categorical			
Units: Subjects			
< 65 years	48	50	98
≥ 65 to < 75 years	96	83	179
≥ 75 years	74	85	159
Age continuous			
Units: years			
arithmetic mean	71.2	71.8	-
standard deviation	± 7.7	± 7.4	-
Gender categorical			
Units: Subjects			
Female	218	218	436
Male	0	0	0
Race			
Units: Subjects			
White	196	191	387
Other	18	23	41
American Indian or Alaska Native	1	4	5
Asian	2	0	2
Multiple	1	0	1
Prior Fracture			
Units: Subjects			
Yes	217	218	435
No	1	0	1
Lumbar Spine BMD T-score			
The T-score is the bone mineral density (BMD) at the site when compared to that of a healthy thirty-year-old. Normal is a T-score of -1.0 or higher; Osteopenia is defined as between -1.0 and -2.5; Osteoporosis is defined as -2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.			
Units: T-score			
arithmetic mean	-2.87	-2.83	-
standard deviation	± 1.04	± 1.1	-
Total Hip BMD T-score			
Units: T-score			
arithmetic mean	-2.21	-2.27	-
standard deviation	± 0.72	± 0.75	-
Femoral Neck BMD T-score			

Units: T-score			
arithmetic mean	-2.43	-2.49	
standard deviation	± 0.66	± 0.67	-
Serum Type 1 Collagen C-telopeptide (sCTX)			
Units: ng/L			
arithmetic mean	260.1	252.3	
standard deviation	± 124.9	± 136.4	-

## End points

### End points reporting groups

Reporting group title	Teriparatide
Reporting group description: Participants received teriparatide 20 µg/day administered by subcutaneous injection for 12 months.	
Reporting group title	Romosozumab
Reporting group description: Participants received 210 mg romosozumab administered by subcutaneous injection once a month for 12 months.	

### Primary: Percent Change From Baseline Through Month 12 in Total Hip Bone Mineral Density (BMD)

End point title	Percent Change From Baseline Through Month 12 in Total Hip Bone Mineral Density (BMD)
End point description: Bone mineral density was measured by dual-energy X-ray absorptiometry (DXA). Percent change from baseline through month 12 is the average of the treatment effect at months 6 and 12. The primary efficacy analysis set includes randomized subjects with a non-missing baseline and at least one post-baseline measurement.	
End point type	Primary
End point timeframe: Baseline, month 6 and month 12	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	206		
Units: percent change				
least squares mean (standard error)	-0.6 (± 0.2)	2.6 (± 0.2)		

### Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description: The primary analysis to assess the treatment difference (Romosozumab – Teriparatide) employed a linear mixed effects model for repeated measures. The model included main effects for treatment group, visit (categorical), baseline sCTX, baseline hip DXA BMD value, machine type (categorical), and machine type-by-baseline value interaction (to adjust for the effect of machine type on baseline DXA BMD value) as fixed main effects using an unstructured within-subject variance-covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	< 0.0001
Method	Linear mixed effects model for repeated
Parameter estimate	Treatment difference
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.7
upper limit	3.8
Variability estimate	Standard error of the mean
Dispersion value	0.3

Notes:

[1] - A two-step, step-down, fixed-sequential testing procedure was used to test the primary and key secondary efficacy endpoints for the comparison of romosozumab to teriparatide groups in the order presented for multiplicity adjustment to maintain the overall significance level at 0.05

### Secondary: Percent Change From Baseline in Total Hip BMD at Month 6

End point title	Percent Change From Baseline in Total Hip BMD at Month 6
End point description:	
Bone mineral density was measured by dual-energy X-ray absorptiometry (DXA). The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe:	
Baseline and month 6	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203 <sup>[2]</sup>	203 <sup>[3]</sup>		
Units: percent change				
least squares mean (standard error)	-0.8 (± 0.2)	2.3 (± 0.2)		

Notes:

[2] - Participants with values at baseline and month 6

[3] - Participants with values at baseline and month 6

### Statistical analyses

Statistical analysis title	Difference from Teriparatide
Statistical analysis description:	
Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, baseline BMD value, machine type, baseline BMD value-by machine type interaction, treatment-by-visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	0.3

### Secondary: Percent Change From Baseline in Total Hip BMD at Month 12

End point title	Percent Change From Baseline in Total Hip BMD at Month 12
End point description: Bone mineral density was measured by dual-energy X-ray absorptiometry (DXA). The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 12	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202 <sup>[4]</sup>	197 <sup>[5]</sup>		
Units: percent				
least squares mean (standard error)	-0.5 (± 0.2)	2.9 (± 0.2)		

Notes:

[4] - Participants with values at baseline and month 12

[5] - Participants with values at baseline and month 12

### Statistical analyses

Statistical analysis title	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, baseline BMD value, machine type, baseline BMD value-by machine type interaction, treatment-by-visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	4
Variability estimate	Standard error of the mean
Dispersion value	0.3

### Secondary: Percent Change From Baseline in Cortical BMD by Quantitative Computed Tomography (QCT) at the Total Hip at Month 6

End point title	Percent Change From Baseline in Cortical BMD by Quantitative Computed Tomography (QCT) at the Total Hip at Month 6
End point description: Cortical BMD was measured by quantitative computed tomography (QCT) at the total hip. The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 6	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156 <sup>[6]</sup>	163 <sup>[7]</sup>		
Units: percent change				
least squares mean (standard error)	-2.7 (± 0.2)	0.7 (± 0.2)		

Notes:

[6] - Participants with values at baseline and month 6

[7] - Participants with values at baseline and month 6

### Statistical analyses

<b>Statistical analysis title</b>	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	4
Variability estimate	Standard error of the mean
Dispersion value	0.3

### Secondary: Percent Change From Baseline in Cortical BMD by QCT at the Total Hip at Month 12

End point title	Percent Change From Baseline in Cortical BMD by QCT at the Total Hip at Month 12
End point description: Cortical BMD was measured by quantitative computed tomography (QCT) at the total hip. The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 12	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159 <sup>[8]</sup>	163 <sup>[9]</sup>		
Units: percent change				
least squares mean (standard error)	-3.6 (± 0.3)	1.1 (± 0.3)		

Notes:

[8] - Participants with values at baseline and month 12

[9] - Participants with values at baseline and month 12

### Statistical analyses

Statistical analysis title	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	5.3
Variability estimate	Standard error of the mean
Dispersion value	0.4

### Secondary: Percent Change From Baseline in Integral BMD by QCT at the Total Hip at Month 6

End point title	Percent Change From Baseline in Integral BMD by QCT at the Total Hip at Month 6
End point description: Integral BMD was measured by quantitative computed tomography (QCT) at the total hip. The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 6	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156 <sup>[10]</sup>	163 <sup>[11]</sup>		
Units: percent change				
least squares mean (standard error)	-0.8 (± 0.2)	2.3 (± 0.2)		

Notes:

[10] - Participants with values at baseline and month 6

[11] - Participants with values at baseline and month 6

### Statistical analyses

<b>Statistical analysis title</b>	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	3.6
Variability estimate	Standard error of the mean
Dispersion value	0.3

### Secondary: Percent Change From Baseline in Integral BMD by QCT at the Total Hip at Month 12

End point title	Percent Change From Baseline in Integral BMD by QCT at the Total Hip at Month 12
End point description: Integral BMD was measured by quantitative computed tomography (QCT) at the total hip. The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 12	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159 <sup>[12]</sup>	163 <sup>[13]</sup>		
Units: percent change				
least squares mean (standard error)	-0.2 (± 0.2)	3.4 (± 0.2)		

Notes:

[12] - Participants with values at baseline and month 12

[13] - Participants with values at baseline and month 12

### Statistical analyses

<b>Statistical analysis title</b>	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.9
upper limit	4.2
Variability estimate	Standard error of the mean
Dispersion value	0.3

### Secondary: Percent Change From Baseline in Estimated Strength by FEA at the Total Hip at Month 6

End point title	Percent Change From Baseline in Estimated Strength by FEA at the Total Hip at Month 6
End point description: Total hip estimated strength was assessed by finite element analysis (FEA) of QCT scans. The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 6	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163 <sup>[14]</sup>	164 <sup>[15]</sup>		
Units: percent change				
least squares mean (standard error)	-1 (± 0.2)	2.1 (± 0.2)		

Notes:

[14] - Participants with values at baseline and month 6

[15] - Participants with values at baseline and month 6

### Statistical analyses

<b>Statistical analysis title</b>	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.4
upper limit	3.8
Variability estimate	Standard error of the mean
Dispersion value	0.3

### Secondary: Percent Change From Baseline in Estimated Strength by FEA at the Total Hip at Month 12

End point title	Percent Change From Baseline in Estimated Strength by FEA at the Total Hip at Month 12
End point description:	
End point type	Secondary
End point timeframe: Baseline and month 12	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 <sup>[16]</sup>	159 <sup>[17]</sup>		
Units: percent change				
least squares mean (standard error)	-0.7 (± 0.4)	2.5 (± 0.4)		

Notes:

[16] - Participants with values at baseline and month 12

[17] - Participants with values at baseline and month 12

### Statistical analyses

Statistical analysis title	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	4.3
Variability estimate	Standard error of the mean
Dispersion value	0.6

### Secondary: Percent Change From Baseline in Total Hip Integral Bone Mineral Content (BMC) by QCT at Month 6

End point title	Percent Change From Baseline in Total Hip Integral Bone Mineral Content (BMC) by QCT at Month 6
End point description: Total hip integral BMC was measured using quantitative computed tomography (QCT). The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 6	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156 <sup>[18]</sup>	163 <sup>[19]</sup>		
Units: percent change				
least squares mean (standard error)	-0.7 (± 0.2)	2.4 (± 0.2)		

Notes:

[18] - Participants with values at baseline and month 6

[19] - Participants with values at baseline and month 6

### Statistical analyses

Statistical analysis title	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	3.6
Variability estimate	Standard error of the mean
Dispersion value	0.3

### Secondary: Percent Change From Baseline in Total Hip Integral Bone Mineral Content (BMC) by QCT at Month 12

End point title	Percent Change From Baseline in Total Hip Integral Bone Mineral Content (BMC) by QCT at Month 12
End point description: Total hip integral BMC was measured using quantitative computed tomography (QCT). The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 12	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159 <sup>[20]</sup>	163 <sup>[21]</sup>		
Units: percent change				
least squares mean (standard error)	0 (± 0.2)	3.6 (± 0.2)		

Notes:

[20] - Participants with values at baseline and month 12

[21] - Participants with values at baseline and month 12

### Statistical analyses

<b>Statistical analysis title</b>	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.9
upper limit	4.2
Variability estimate	Standard error of the mean
Dispersion value	0.3

### Secondary: Percent Change From Baseline in Femoral Neck BMD at Month 6

End point title	Percent Change From Baseline in Femoral Neck BMD at Month 6
End point description: Femoral neck BMD was measured by DXA. The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 6	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203 <sup>[22]</sup>	203 <sup>[23]</sup>		
Units: percent change				
least squares mean (standard error)	-1.1 (± 0.3)	2.1 (± 0.3)		

Notes:

[22] - Participants with values at baseline and month 6

[23] - Participants with values at baseline and month 6

### Statistical analyses

<b>Statistical analysis title</b>	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	3.9
Variability estimate	Standard error of the mean
Dispersion value	0.4

### Secondary: Percent Change From Baseline in Femoral Neck BMD at Month 12

End point title	Percent Change From Baseline in Femoral Neck BMD at Month 12
End point description: Femoral neck BMD was measured by DXA. The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 12	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202 <sup>[24]</sup>	197 <sup>[25]</sup>		
Units: percent change				
least squares mean (standard error)	-0.2 (± 0.3)	3.2 (± 0.3)		

Notes:

[24] - Participants with values at baseline and month 12

[25] - Participants with values at baseline and month 12

### Statistical analyses

<b>Statistical analysis title</b>	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	4.2
Variability estimate	Standard error of the mean
Dispersion value	0.4

### Secondary: Percent Change From Baseline in Lumbar Spine BMD at Month 6

End point title	Percent Change From Baseline in Lumbar Spine BMD at Month 6
End point description: Lumbar spine BMD was measured by DXA. The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 6	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204 <sup>[26]</sup>	203 <sup>[27]</sup>		
Units: percent change				
least squares mean (standard error)	3.5 (± 0.3)	7.2 (± 0.3)		

Notes:

[26] - Participants with values at baseline and month 6

[27] - Participants with values at baseline and month 6

### Statistical analyses

Statistical analysis title	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.9
upper limit	4.6
Variability estimate	Standard error of the mean
Dispersion value	0.4

### Secondary: Percent Change From Baseline in Lumbar Spine BMD at Month 12

End point title	Percent Change From Baseline in Lumbar Spine BMD at Month 12
End point description: Lumbar spine BMD was measured by DXA. The primary efficacy analysis set was used for this analysis.	
End point type	Secondary
End point timeframe: Baseline and month 12	

End point values	Teriparatide	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201 <sup>[28]</sup>	197 <sup>[29]</sup>		
Units: percent change				
least squares mean (standard error)	5.4 (± 0.4)	9.8 (± 0.4)		

Notes:

[28] - Participants with values at baseline and month 12

[29] - Participants with values at baseline and month 12

### Statistical analyses

<b>Statistical analysis title</b>	Difference from Teriparatide
Statistical analysis description: Treatment difference (Romosozumab – Teriparatide) was analyzed using a linear mixed effects model for repeated measures adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, parameter baseline value, treatment-by visit interaction, and using an unstructured variance covariance structure.	
Comparison groups	Romosozumab v Teriparatide

Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effects repeated measures
Parameter estimate	Treatment difference
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	5.4
Variability estimate	Standard error of the mean
Dispersion value	0.5

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

12 months

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	Romosozumab
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Reporting group description:

Participants received 210 mg romosozumab administered by subcutaneous injection once a month for 12 months.

Reporting group title	Teriparatide
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Reporting group description:

Participants received teriparatide 20 µg/day administered by subcutaneous injection for 12 months.

<b>Serious adverse events</b>	Romosozumab	Teriparatide	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 218 (7.80%)	23 / 214 (10.75%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign soft tissue neoplasm			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			

subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Myeloid leukaemia</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ovarian cancer stage III</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vascular disorders</b>			
<b>Haemorrhage</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
<b>Hypertension</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Surgical and medical procedures</b>			
<b>Medical device removal</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>General disorders and administration site conditions</b>			
<b>Non-cardiac chest pain</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pyrexia</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural nausea			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Tibia fracture</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ulna fracture</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cardiac disorders</b>			
<b>Angina pectoris</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Arrhythmia supraventricular</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Atrial fibrillation</b>			
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bifascicular block</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bradycardia</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cardiac arrest</b>			

subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radicular pain			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radicular syndrome			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Syncope</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Transient ischaemic attack</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>VIIth nerve paralysis</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Blood and lymphatic system disorders</b>			
<b>Bone marrow failure</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ear and labyrinth disorders</b>			
<b>Vertigo</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
<b>Abdominal pain</b>			
subjects affected / exposed	0 / 218 (0.00%)	2 / 214 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Abdominal pain lower</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestinal ulcer			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Diverticulitis</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Influenza</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pneumonia</b>			
subjects affected / exposed	1 / 218 (0.46%)	2 / 214 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pneumonia bacterial</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Urinary tract infection fungal</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
<b>Hyperglycaemia</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hypernatraemia</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Romosozumab	Teriparatide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	160 / 218 (73.39%)	146 / 214 (68.22%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Benign neoplasm of thyroid gland			
subjects affected / exposed	3 / 218 (1.38%)	0 / 214 (0.00%)	
occurrences (all)	3	0	
Benign renal neoplasm			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Colon adenoma			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Haemangioma of bone			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Keratoacanthoma			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Lipoma			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Melanocytic naevus			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Uterine leiomyoma			

subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
<b>Vascular disorders</b>			
Circulatory collapse subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Haematoma subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	0 / 214 (0.00%) 0	
Hot flush subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	0 / 214 (0.00%) 0	
Hypertension subjects affected / exposed occurrences (all)	7 / 218 (3.21%) 7	5 / 214 (2.34%) 5	
Hypertensive crisis subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 2	0 / 214 (0.00%) 0	
Hypotension subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Phlebitis subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Thrombophlebitis superficial subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Varicose vein subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
<b>Surgical and medical procedures</b>			
Breast prosthesis implantation subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Cataract operation			

subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Dermabrasion subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Large intestinal polypectomy subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Medical device removal subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Toe amputation subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Tooth extraction subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	2 / 214 (0.93%) 2	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	4 / 218 (1.83%) 4	1 / 214 (0.47%) 1	
Chest pain subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Drug intolerance subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 2	
Fatigue subjects affected / exposed occurrences (all)	5 / 218 (2.29%) 5	9 / 214 (4.21%) 9	
Feeling cold subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	0 / 214 (0.00%) 0	
Gait disturbance			

subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	2	0
Implant site reaction		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Influenza like illness		
subjects affected / exposed	2 / 218 (0.92%)	2 / 214 (0.93%)
occurrences (all)	2	2
Injection site bruising		
subjects affected / exposed	2 / 218 (0.92%)	1 / 214 (0.47%)
occurrences (all)	2	1
Injection site erythema		
subjects affected / exposed	3 / 218 (1.38%)	2 / 214 (0.93%)
occurrences (all)	11	3
Injection site haemorrhage		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Injection site inflammation		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Injection site pain		
subjects affected / exposed	8 / 218 (3.67%)	2 / 214 (0.93%)
occurrences (all)	10	2
Injection site pruritus		
subjects affected / exposed	3 / 218 (1.38%)	0 / 214 (0.00%)
occurrences (all)	6	0
Injection site rash		
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)
occurrences (all)	2	0
Injection site reaction		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Injection site swelling		
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)
occurrences (all)	2	0
Injection site warmth		

subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Medical device complication subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Oedema subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	2 / 214 (0.93%) 2	
Pain subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Vaccination site bruising subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	2 / 214 (0.93%) 2	

Reproductive system and breast disorders			
Urogenital prolapse			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Uterine prolapse			
subjects affected / exposed	0 / 218 (0.00%)	2 / 214 (0.93%)	
occurrences (all)	0	2	
Vaginal discharge			
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)	
occurrences (all)	2	0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 218 (0.00%)	2 / 214 (0.93%)	
occurrences (all)	0	2	
Vulva cyst			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal pruritus			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)	
occurrences (all)	2	0	
Bronchial hyperreactivity			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Catarrh			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)	
occurrences (all)	1	3	
Cough			
subjects affected / exposed	7 / 218 (3.21%)	9 / 214 (4.21%)	
occurrences (all)	7	9	

Dysphonia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Dyspnoea		
subjects affected / exposed	1 / 218 (0.46%)	2 / 214 (0.93%)
occurrences (all)	1	2
Dyspnoea exertional		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Epistaxis		
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)
occurrences (all)	1	1
Nasal congestion		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Nasal obstruction		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Oropharyngeal pain		
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)
occurrences (all)	1	1
Pleural effusion		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Productive cough		
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)
occurrences (all)	1	1
Pulmonary hypertension		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Rhinitis allergic		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Rhinorrhoea		
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)
occurrences (all)	1	1

Wheezing subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	2 / 214 (0.93%) 2	
Depressed mood subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Depression subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	5 / 214 (2.34%) 5	
Insomnia subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	3 / 214 (1.40%) 3	
Investigations			
Arthroscopy subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Blood calcium decreased subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	0 / 214 (0.00%) 0	
Blood cholesterol increased subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Blood potassium increased subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Cardiac murmur subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Liver function test abnormal subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Weight decreased			

subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Weight increased subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	2 / 214 (0.93%) 2	
White blood cells urine positive subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Injury, poisoning and procedural complications			
Arthropod bite subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	2 / 214 (0.93%) 2	
Chest injury subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Concussion subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	0 / 214 (0.00%) 0	
Contusion subjects affected / exposed occurrences (all)	10 / 218 (4.59%) 14	8 / 214 (3.74%) 11	
Epicondylitis subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Excoriation subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Face injury subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Fall subjects affected / exposed occurrences (all)	12 / 218 (5.50%) 15	5 / 214 (2.34%) 5	
Foot fracture			

subjects affected / exposed	2 / 218 (0.92%)	1 / 214 (0.47%)
occurrences (all)	2	1
Forearm fracture		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Head injury		
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)
occurrences (all)	3	0
Humerus fracture		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Incisional hernia		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Joint dislocation		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Joint injury		
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)
occurrences (all)	2	0
Laceration		
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)
occurrences (all)	1	1
Ligament sprain		
subjects affected / exposed	5 / 218 (2.29%)	4 / 214 (1.87%)
occurrences (all)	5	5
Limb injury		
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)
occurrences (all)	1	1
Lip injury		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Muscle injury		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Overdose		

subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Post-traumatic neck syndrome		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Postoperative hernia		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Procedural pain		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Pubis fracture		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	2
Radius fracture		
subjects affected / exposed	0 / 218 (0.00%)	2 / 214 (0.93%)
occurrences (all)	0	2
Rib fracture		
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)
occurrences (all)	2	0
Scratch		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Skin abrasion		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Sternal fracture		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Subcutaneous haematoma		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	2
Tendon rupture		
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)
occurrences (all)	1	1
Tooth fracture		

subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	3 / 218 (1.38%)	0 / 214 (0.00%)	
occurrences (all)	3	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)	
occurrences (all)	2	0	
Aortic valve calcification			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Aortic valve incompetence			
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)	
occurrences (all)	1	1	
Bundle branch block left			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Bundle branch block right			
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)	
occurrences (all)	2	0	
Cardiac failure			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Cardiac failure congestive			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Cardiac hypertrophy			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Diastolic dysfunction			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Heart valve calcification			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	

Left atrial dilatation subjects affected / exposed occurrences (all)	3 / 218 (1.38%) 3	0 / 214 (0.00%) 0	
Left ventricular dysfunction subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Left ventricular hypertrophy subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Mitral valve calcification subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Mitral valve incompetence subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	1 / 214 (0.47%) 1	
Palpitations subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	2 / 214 (0.93%) 2	
Supraventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Tachycardia subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Tricuspid valve incompetence subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Nervous system disorders			
Akathisia subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Amnesia subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Aphonia			

subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Balance disorder		
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)
occurrences (all)	3	0
Burning sensation		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Carpal tunnel syndrome		
subjects affected / exposed	2 / 218 (0.92%)	1 / 214 (0.47%)
occurrences (all)	2	1
Cerebral ischaemia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	2	0
Dizziness		
subjects affected / exposed	9 / 218 (4.13%)	5 / 214 (2.34%)
occurrences (all)	12	6
Dysaesthesia		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Facial neuralgia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Headache		
subjects affected / exposed	14 / 218 (6.42%)	9 / 214 (4.21%)
occurrences (all)	15	10
Hypoaesthesia		
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)
occurrences (all)	2	0
Lethargy		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Migraine		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Neuralgia		

subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	4 / 218 (1.83%)	3 / 214 (1.40%)	
occurrences (all)	4	3	
Parkinson's disease			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)	
occurrences (all)	1	1	
Restless legs syndrome			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	2 / 218 (0.92%)	2 / 214 (0.93%)	
occurrences (all)	3	3	
Seizure			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	2 / 218 (0.92%)	2 / 214 (0.93%)	
occurrences (all)	2	2	
Transient ischaemic attack			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
White matter lesion			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 218 (1.83%)	3 / 214 (1.40%)	
occurrences (all)	4	3	
Bone marrow oedema syndrome			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	

Eosinophilia subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Ear and labyrinth disorders			
Ear congestion subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Ear disorder subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Ear pain subjects affected / exposed occurrences (all)	3 / 218 (1.38%) 3	0 / 214 (0.00%) 0	
Hypoacusis subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Meniere's disease subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Mixed deafness subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Tinnitus subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Vertigo subjects affected / exposed occurrences (all)	4 / 218 (1.83%) 5	4 / 214 (1.87%) 4	
Vertigo positional subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Eye disorders			
Blepharospasm subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Cataract			

subjects affected / exposed	1 / 218 (0.46%)	2 / 214 (0.93%)
occurrences (all)	1	2
Conjunctival haemorrhage		
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)
occurrences (all)	2	0
Dry eye		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Eye disorder		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Eye haemorrhage		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Eye irritation		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Eyelid oedema		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Glaucoma		
subjects affected / exposed	1 / 218 (0.46%)	2 / 214 (0.93%)
occurrences (all)	1	2
Macular fibrosis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Photopsia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Retinal fibrosis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Visual acuity reduced		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Gastrointestinal disorders		

Abdominal discomfort		
subjects affected / exposed	4 / 218 (1.83%)	0 / 214 (0.00%)
occurrences (all)	4	0
Abdominal distension		
subjects affected / exposed	3 / 218 (1.38%)	2 / 214 (0.93%)
occurrences (all)	3	2
Abdominal pain		
subjects affected / exposed	4 / 218 (1.83%)	5 / 214 (2.34%)
occurrences (all)	5	5
Abdominal pain lower		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Abdominal pain upper		
subjects affected / exposed	1 / 218 (0.46%)	3 / 214 (1.40%)
occurrences (all)	1	3
Cheilitis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Constipation		
subjects affected / exposed	4 / 218 (1.83%)	4 / 214 (1.87%)
occurrences (all)	5	4
Dental caries		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Diarrhoea		
subjects affected / exposed	4 / 218 (1.83%)	9 / 214 (4.21%)
occurrences (all)	4	9
Diverticulum		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Diverticulum intestinal		
subjects affected / exposed	2 / 218 (0.92%)	1 / 214 (0.47%)
occurrences (all)	2	1
Dyspepsia		
subjects affected / exposed	2 / 218 (0.92%)	2 / 214 (0.93%)
occurrences (all)	2	2

Enterocolitis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Flatulence		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Food poisoning		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Frequent bowel movements		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Gastric disorder		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Gastric polyps		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Gastritis		
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)
occurrences (all)	2	0
Gastrointestinal disorder		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	2
Gastrointestinal ulcer		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Gingival pain		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Glossodynia		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Haemorrhoids		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0

Hiatus hernia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Inguinal hernia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Loose tooth			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	8 / 218 (3.67%)	10 / 214 (4.67%)	
occurrences (all)	8	11	
Noninfective gingivitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Periodontal disease			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Tooth loss			
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)	
occurrences (all)	1	3	
Vomiting			
subjects affected / exposed	1 / 218 (0.46%)	2 / 214 (0.93%)	
occurrences (all)	1	3	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Cholelithiasis			
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)	
occurrences (all)	1	1	
Hepatic steatosis			

subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Hepatitis toxic subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
<b>Skin and subcutaneous tissue disorders</b>			
Acne subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Actinic keratosis subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Alopecia subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	4 / 214 (1.87%) 4	
Dermatitis subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Dermatitis contact subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Drug eruption subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 2	
Dry skin subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Eczema subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	3 / 214 (1.40%) 3	
Erythema subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	

Hair growth abnormal		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Hyperkeratosis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Night sweats		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Photosensitivity reaction		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Pruritus		
subjects affected / exposed	3 / 218 (1.38%)	1 / 214 (0.47%)
occurrences (all)	3	1
Pruritus generalised		
subjects affected / exposed	0 / 218 (0.00%)	2 / 214 (0.93%)
occurrences (all)	0	2
Rash		
subjects affected / exposed	3 / 218 (1.38%)	2 / 214 (0.93%)
occurrences (all)	3	2
Rash macular		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Skin discolouration		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Skin exfoliation		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Skin fibrosis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Skin lesion		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0

Stasis dermatitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)	
occurrences (all)	2	0	
Bladder irritation			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Bladder wall calcification			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Chronic kidney disease			
subjects affected / exposed	2 / 218 (0.92%)	1 / 214 (0.47%)	
occurrences (all)	2	1	
Dysuria			
subjects affected / exposed	0 / 218 (0.00%)	2 / 214 (0.93%)	
occurrences (all)	0	2	
Haematuria			
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)	
occurrences (all)	1	1	
Nephrolithiasis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)	
occurrences (all)	0	1	
Renal cyst			
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)	
occurrences (all)	1	1	
Renal failure			

subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	2 / 214 (0.93%) 2	
Endocrine disorders			
Hyperthyroidism subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Hypothyroidism subjects affected / exposed occurrences (all)	3 / 218 (1.38%) 3	0 / 214 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	22 / 218 (10.09%) 28	13 / 214 (6.07%) 14	
Arthritis subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	2 / 214 (0.93%) 2	
Back pain subjects affected / exposed occurrences (all)	19 / 218 (8.72%) 21	12 / 214 (5.61%) 13	
Bone pain subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	1 / 214 (0.47%) 1	
Bursitis subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	2 / 214 (0.93%) 3	
Fibromyalgia subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Foot deformity subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Gouty arthritis			

subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Groin pain		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Intervertebral disc degeneration		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Intervertebral disc protrusion		
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)
occurrences (all)	1	1
Joint crepitation		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Joint swelling		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Lumbar spinal stenosis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Muscle contracture		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Muscle spasms		
subjects affected / exposed	3 / 218 (1.38%)	6 / 214 (2.80%)
occurrences (all)	3	7
Muscle tightness		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Muscular weakness		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Musculoskeletal chest pain		
subjects affected / exposed	3 / 218 (1.38%)	1 / 214 (0.47%)
occurrences (all)	4	1
Musculoskeletal pain		

subjects affected / exposed	11 / 218 (5.05%)	5 / 214 (2.34%)
occurrences (all)	12	6
Musculoskeletal stiffness		
subjects affected / exposed	2 / 218 (0.92%)	1 / 214 (0.47%)
occurrences (all)	2	1
Myalgia		
subjects affected / exposed	9 / 218 (4.13%)	4 / 214 (1.87%)
occurrences (all)	9	4
Osteitis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Osteoarthritis		
subjects affected / exposed	5 / 218 (2.29%)	6 / 214 (2.80%)
occurrences (all)	7	6
Osteonecrosis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Pain in extremity		
subjects affected / exposed	11 / 218 (5.05%)	4 / 214 (1.87%)
occurrences (all)	14	4
Pain in jaw		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Periarthritis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Spinal osteoarthritis		
subjects affected / exposed	3 / 218 (1.38%)	1 / 214 (0.47%)
occurrences (all)	3	1
Spinal pain		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Synovitis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Tendonitis		

subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Trigger finger subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
<b>Infections and infestations</b>			
Borrelia infection subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	3 / 218 (1.38%) 3	1 / 214 (0.47%) 1	
Cellulitis subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	1 / 214 (0.47%) 1	
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	4 / 214 (1.87%) 4	
Cystitis subjects affected / exposed occurrences (all)	3 / 218 (1.38%) 4	2 / 214 (0.93%) 3	
Diverticulitis subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Ear infection subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	2 / 214 (0.93%) 2	
Eczema infected subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 214 (0.00%) 0	
Erysipelas subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 1	
Eye infection subjects affected / exposed occurrences (all)	0 / 218 (0.00%) 0	1 / 214 (0.47%) 2	

Eye infection bacterial		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	2
Folliculitis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Gastric infection		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Gastroenteritis		
subjects affected / exposed	5 / 218 (2.29%)	1 / 214 (0.47%)
occurrences (all)	5	1
Gastroenteritis viral		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Genital infection fungal		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Genital infection viral		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Gingivitis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Helicobacter gastritis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Herpes virus infection		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Herpes zoster		
subjects affected / exposed	2 / 218 (0.92%)	3 / 214 (1.40%)
occurrences (all)	2	3
Hordeolum		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0

Influenza		
subjects affected / exposed	8 / 218 (3.67%)	8 / 214 (3.74%)
occurrences (all)	10	8
Labyrinthitis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Laryngitis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Localised infection		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Lower respiratory tract infection		
subjects affected / exposed	2 / 218 (0.92%)	3 / 214 (1.40%)
occurrences (all)	2	3
Nasopharyngitis		
subjects affected / exposed	28 / 218 (12.84%)	22 / 214 (10.28%)
occurrences (all)	30	25
Omphalitis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Oral bacterial infection		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Oral herpes		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Oral infection		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Otitis media		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Paronychia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0

Parotitis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)
occurrences (all)	1	1
Pneumonia		
subjects affected / exposed	4 / 218 (1.83%)	3 / 214 (1.40%)
occurrences (all)	4	3
Respiratory tract infection		
subjects affected / exposed	1 / 218 (0.46%)	2 / 214 (0.93%)
occurrences (all)	2	2
Rhinitis		
subjects affected / exposed	3 / 218 (1.38%)	0 / 214 (0.00%)
occurrences (all)	3	0
Sinusitis		
subjects affected / exposed	5 / 218 (2.29%)	1 / 214 (0.47%)
occurrences (all)	6	1
Tonsillitis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	2
Tooth abscess		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Tooth infection		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Upper respiratory tract infection		
subjects affected / exposed	11 / 218 (5.05%)	9 / 214 (4.21%)
occurrences (all)	11	10
Upper respiratory tract infection bacterial		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Urethritis		

subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Urinary tract infection		
subjects affected / exposed	9 / 218 (4.13%)	10 / 214 (4.67%)
occurrences (all)	9	19
Varicella		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Viral infection		
subjects affected / exposed	4 / 218 (1.83%)	6 / 214 (2.80%)
occurrences (all)	4	6
Wound infection		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Metabolism and nutrition disorders		
Decreased appetite		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Dehydration		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	2	0
Diabetes mellitus		
subjects affected / exposed	1 / 218 (0.46%)	1 / 214 (0.47%)
occurrences (all)	1	1
Dyslipidaemia		
subjects affected / exposed	2 / 218 (0.92%)	0 / 214 (0.00%)
occurrences (all)	2	0
Gout		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Hyper HDL cholesterolaemia		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1
Hypercalcaemia		
subjects affected / exposed	2 / 218 (0.92%)	22 / 214 (10.28%)
occurrences (all)	2	29

Hypercholesterolaemia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Hyperlipidaemia		
subjects affected / exposed	3 / 218 (1.38%)	0 / 214 (0.00%)
occurrences (all)	3	0
Hypoalbuminaemia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Hypocalcaemia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Hypokalaemia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Hypophosphataemia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Iron deficiency		
subjects affected / exposed	1 / 218 (0.46%)	0 / 214 (0.00%)
occurrences (all)	1	0
Vitamin B12 deficiency		
subjects affected / exposed	0 / 218 (0.00%)	1 / 214 (0.47%)
occurrences (all)	0	1

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2013	<ul style="list-style-type: none"><li>- Added assessments for formation of anti-romosozumab antibodies at the month 1 and month 3 visits to allow a more comprehensive characterization of the anti-romosozumab antibody response.</li><li>- Eligibility criteria were modified to allow participation of a wider range of patients; the minimum age was lowered from 60 to 55 years and the protocol-mandated off-treatment times for exclusionary medications were revised.</li><li>- Retesting of serum calcium would be permitted within the screening window if the initial test indicated an elevated level of serum calcium within 1.1 times the upper limit of normal set by the central laboratory to account for the imprecision of serum calcium laboratory measurements.</li><li>- Added a subset of up to 20 subjects to be recruited to undergo a transiliac bone biopsy at the month 12 visit to assess the effect of romosozumab treatment on parameters of bone histology and histomorphometry.</li><li>- Added detail to the justification for romosozumab treatment duration and dosing regimen.</li><li>- Expectations for serious adverse event reporting were redefined.</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported