



Clinical trial results:

Multicenter, Randomized, Double-blind, Placebo-controlled Study to Compare the Efficacy and Safety of Romosozumab With Placebo in Men With Osteoporosis

Summary

EudraCT number	2013-005551-32
Trial protocol	CZ BE DK PL
Global end of trial date	20 April 2016

Results information

Result version number	v1 (current)
This version publication date	13 April 2017
First version publication date	13 April 2017

Trial information

Trial identification

Sponsor protocol code	20110174
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02186171
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, 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	20 April 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of treatment with romosozumab for 12 months compared with placebo on percent changes from baseline in bone mineral density (BMD) at the lumbar spine as assessed by dual-energy x-ray absorptiometry (DXA) in men with osteoporosis.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

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	16 June 2014
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: 47
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	Denmark: 35
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Switzerland: 15
Country: Number of subjects enrolled	Colombia: 35
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	245
EEA total number of subjects	127

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)	42
From 65 to 84 years	197
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 31 centers in Europe, North America, Latin America, and Japan. Participants were enrolled from 16 June 2014 to 27 January 2015.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to receive 210 mg romosozumab or matched placebo in a blinded fashion for the duration of the 12-month treatment period. Randomization was stratified by geographic region (Europe, North America, Latin America, and Japan).

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo subcutaneous injections once a month (QM) for 12 months.

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

Dosage and administration details:

Administered by subcutaneous injection once a month

Arm title	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:

Administered by subcutaneous injection once a month

Number of subjects in period 1	Placebo	Romosozumab
Started	82	163
Received Treatment	81	163
Completed	78	148
Not completed	4	15
Consent withdrawn by subject	1	9
Death	1	2
Lost to follow-up	2	2
Protocol-specified criteria	-	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneous injections once a month (QM) 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.	

Reporting group values	Placebo	Romosozumab	Total
Number of subjects	82	163	245
Age Categorical			
Units: Subjects			
Adults (18-64 years)	11	31	42
From 65-74 years	42	62	104
75 years and over	29	70	99
Age Continuous			
Units: years			
arithmetic mean	71.5	72.4	-
standard deviation	± 6.9	± 7.4	-
Gender Categorical			
Units: Subjects			
Female	0	0	0
Male	82	163	245
Race			
Units: Subjects			
White	60	120	180
Asian	9	18	27
Black or African American	0	1	1
Other	13	23	36
Multiple	0	1	1
Geographic Region			
Units: Subjects			
Europe	54	108	162
Japan	9	18	27
Latin America	12	23	35
North America	7	14	21
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	-2.33	-2.22	-
standard deviation	± 1.41	± 1.19	-
Total Hip BMD T-score			
Units: T-score			
arithmetic mean	-1.92	-1.92	-

standard deviation	± 0.65	± 0.59	-
Femoral Neck BMD T-score			
Units: T-score			
arithmetic mean	-2.3	-2.34	
standard deviation	± 0.52	± 0.52	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneous injections once a month (QM) 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 in Lumbar Spine Bone Mineral Density (BMD) at Month 12

End point title	Percent Change From Baseline in Lumbar Spine Bone Mineral Density (BMD) at Month 12
End point description:	
Lumbar spine bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center. This endpoint was analyzed using the primary efficacy analysis subset which includes all randomized participants who had a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement at the lumbar spine; last observation carried forward (LOCF) imputation was used.	
End point type	Primary
End point timeframe:	
Baseline and month 12	

End point values	Placebo	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	157		
Units: percent change				
least squares mean (standard error)	1.2 (\pm 0.5)	12.1 (\pm 0.5)		

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Romosozumab
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[1]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	10.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	9.6
upper limit	12.2
Variability estimate	Standard error of the mean
Dispersion value	0.6

Notes:

[1] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

Secondary: Percent Change from Baseline in BMD at the Total Hip at Month 12

End point title	Percent Change from Baseline in BMD at the Total Hip at Month 12
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End point description:

Total hip bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

This endpoint was analyzed using the primary efficacy analysis subset which includes all randomized participants who had a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement at the total hip; LOCF imputation was used.

End point type	Secondary
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End point timeframe:

Baseline and month 12

End point values	Placebo	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	158		
Units: percent change				
least squares mean (standard error)	-0.5 (± 0.3)	2.5 (± 0.2)		

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Romosozumab
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.0001 ^[3]
Method	ANCOVA
Parameter estimate	LS Mean Treatment Difference
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	3.7

Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

[2] - The Hochberg procedure was employed to control the overall type 1 error for the percent change from baseline at 12 months in total hip and femoral neck to maintain the overall significance level at 0.05.

[3] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

Secondary: Percent Change from Baseline in BMD at the Femoral Neck at Month 12

End point title	Percent Change from Baseline in BMD at the Femoral Neck at Month 12
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End point description:

Femoral neck bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

This endpoint was analyzed using the primary efficacy analysis subset which includes all randomized participants who had a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement at the femoral neck; LOCF imputation was used.

End point type	Secondary
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End point timeframe:

Baseline and month 12

End point values	Placebo	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	158		
Units: percent change				
least squares mean (standard error)	-0.2 (± 0.4)	2.2 (± 0.4)		

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Romosozumab
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.0001 ^[5]
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	0.5

Notes:

[4] - The Hochberg procedure was employed to control the overall type 1 error for the percent change from baseline at 12 months in total hip and femoral neck to maintain the overall significance level at 0.05.

[5] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

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
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End point description:

Lumbar spine bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center. This endpoint was analyzed using the primary efficacy analysis subset with available data at baseline and month 6.

End point type	Secondary
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End point timeframe:

Baseline and month 6

End point values	Placebo	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	156		
Units: percent change				
least squares mean (standard error)	0.3 (± 0.4)	9 (± 0.4)		

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Romosozumab
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	< 0.0001 ^[7]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.6
upper limit	9.7
Variability estimate	Standard error of the mean
Dispersion value	0.5

Notes:

[6] - The Hochberg procedure was employed to control the overall type 1 error for the percent change from baseline at 6 months at the lumbar spine, total hip and femoral neck BMD in order to maintain the overall significance level at 0.05.

[7] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-

baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

Secondary: Percent Change from Baseline in BMD at the Total Hip at Month 6

End point title	Percent Change from Baseline in BMD at the Total Hip at Month 6
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End point description:

Bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

This endpoint was analyzed using the primary efficacy analysis subset with available data at baseline and month 6.

End point type	Secondary
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End point timeframe:

Baseline and month 6

End point values	Placebo	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	157		
Units: percent change				
least squares mean (standard error)	0.2 (\pm 0.2)	1.6 (\pm 0.2)		

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Romosozumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	< 0.0001 ^[9]
Method	ANCOVA
Parameter estimate	LS Mean Treatment Difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	0.3

Notes:

[8] - The Hochberg procedure was employed to control the overall type 1 error for the percent change from baseline at 6 months at the lumbar spine, total hip and femoral neck BMD in order to maintain the overall significance level at 0.05.

[9] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

Secondary: Percent Change from Baseline in BMD at the Femoral Neck at Month 6

End point title	Percent Change from Baseline in BMD at the Femoral Neck at Month 6
End point description:	Bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center. This endpoint was analyzed using the primary efficacy analysis subset with available data at baseline and month 6.
End point type	Secondary
End point timeframe:	Baseline and month 6

End point values	Placebo	Romosozumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	157		
Units: percent change				
least squares mean (standard error)	0 (\pm 0.4)	1.2 (\pm 0.3)		

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Romosozumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.0033 ^[11]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	2.1
Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

[10] - The Hochberg procedure was employed to control the overall type 1 error for the percent change from baseline at 6 months at the lumbar spine, total hip and femoral neck BMD in order to maintain the overall significance level at 0.05.

[11] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

15 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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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	Placebo
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Reporting group description:

Participants received placebo subcutaneous injections once a month (QM) for 12 months.

Serious adverse events	Romosozumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 163 (14.11%)	10 / 81 (12.35%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal cancer			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve disease			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wolff-Parkinson-White syndrome			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid arteriosclerosis			

subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Implant site haematoma			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intra-abdominal haemorrhage subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depressed mood subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Osteoarthritis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (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 %

Non-serious adverse events	Romosozumab	Placebo
Total subjects affected by non-serious adverse events		
subjects affected / exposed	122 / 163 (74.85%)	65 / 81 (80.25%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal cell carcinoma		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Benign lung neoplasm		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Benign neoplasm of adrenal gland		
subjects affected / exposed	0 / 163 (0.00%)	2 / 81 (2.47%)
occurrences (all)	0	2
Benign renal neoplasm		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Lipoma		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Paranasal sinus benign neoplasm		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Prostatic adenoma		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Seborrhoeic keratosis		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Skin papilloma		

subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	3	0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 163 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Aortic dilatation			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	2	
Arteriosclerosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Essential hypertension			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	3 / 163 (1.84%)	0 / 81 (0.00%)	
occurrences (all)	3	0	
Hypertension			
subjects affected / exposed	14 / 163 (8.59%)	5 / 81 (6.17%)	
occurrences (all)	17	5	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Peripheral venous disease			
subjects affected / exposed	4 / 163 (2.45%)	0 / 81 (0.00%)	
occurrences (all)	4	0	
Subclavian artery stenosis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Varicose vein			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences (all)	1	1	

Surgical and medical procedures			
Osteosynthesis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Application site dermatitis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	0 / 163 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Chills			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Discomfort			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Drug withdrawal syndrome			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	3 / 163 (1.84%)	4 / 81 (4.94%)	
occurrences (all)	3	4	
Influenza like illness			
subjects affected / exposed	6 / 163 (3.68%)	0 / 81 (0.00%)	
occurrences (all)	6	0	
Injection site bruising			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Injection site erythema			
subjects affected / exposed	3 / 163 (1.84%)	1 / 81 (1.23%)	
occurrences (all)	5	1	
Injection site haematoma			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Injection site hypersensitivity			

subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Injection site induration subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Injection site pain subjects affected / exposed occurrences (all)	4 / 163 (2.45%) 9	0 / 81 (0.00%) 0	
Injection site pruritus subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 3	2 / 81 (2.47%) 2	
Injection site swelling subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Local swelling subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Malaise subjects affected / exposed occurrences (all)	2 / 163 (1.23%) 2	0 / 81 (0.00%) 0	
Non-cardiac chest pain subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 2	1 / 81 (1.23%) 1	
Immune system disorders			
Allergy to arthropod bite subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
House dust allergy subjects affected / exposed occurrences (all)	2 / 163 (1.23%) 2	0 / 81 (0.00%) 0	
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	2 / 81 (2.47%) 2	

Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Benign prostatic hyperplasia			
subjects affected / exposed	5 / 163 (3.07%)	0 / 81 (0.00%)	
occurrences (all)	5	0	
Breast pain			
subjects affected / exposed	0 / 163 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Breast swelling			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Nipple disorder			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Prostatitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Allergic pharyngitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Asthma			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Bronchiectasis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Cough			
subjects affected / exposed	5 / 163 (3.07%)	1 / 81 (1.23%)	
occurrences (all)	5	1	

Dyspnoea			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Dyspnoea exertional			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Emphysema			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 163 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Productive cough			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Pulmonary embolism			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	2	
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Affective disorder			

subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Confusional state			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Insomnia			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Personality change due to a general medical condition			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Blood uric acid increased			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Cardiac murmur			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Heart rate irregular			

subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Vitamin D decreased subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Vitamin D increased subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Injury, poisoning and procedural complications			
Arthropod bite subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Arthropod sting subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Chest injury subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Contusion subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	3 / 81 (3.70%) 3	
Face injury subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Fall subjects affected / exposed occurrences (all)	6 / 163 (3.68%) 7	2 / 81 (2.47%) 4	
Head injury subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Joint injury subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Laceration			

subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Meniscus injury			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Post procedural haematoma			
subjects affected / exposed	2 / 163 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Post procedural haemorrhage			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Procedural pain			
subjects affected / exposed	8 / 163 (4.91%)	6 / 81 (7.41%)	
occurrences (all)	9	7	
Skin abrasion			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Tendon rupture			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	3	
Congenital, familial and genetic disorders			
Hydrocele			

subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Cardiac disorders			
Angina pectoris subjects affected / exposed occurrences (all)	2 / 163 (1.23%) 2	0 / 81 (0.00%) 0	
Aortic valve incompetence subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Arteriosclerosis coronary artery subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	1 / 81 (1.23%) 1	
Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	1 / 81 (1.23%) 1	
Atrial flutter subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Atrioventricular block first degree subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Cardiac failure chronic subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	1 / 81 (1.23%) 1	
Extrasystoles subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Left atrial dilatation subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Mitral valve incompetence subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Myocardial ischaemia subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	

Palpitations			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Cerebral arteriosclerosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Cognitive disorder			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Disturbance in attention			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	5 / 163 (3.07%)	1 / 81 (1.23%)	
occurrences (all)	5	1	
Dysaesthesia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	10 / 163 (6.13%)	6 / 81 (7.41%)	
occurrences (all)	12	7	
Hypoaesthesia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
IIIrd nerve paralysis			

subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
IVth nerve paralysis		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Loss of consciousness		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Migraine		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Paraesthesia		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Polyneuropathy		
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)
occurrences (all)	1	1
Radicular syndrome		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Radiculopathy		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Sciatica		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Seizure		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Somnolence		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Syncope		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Transient ischaemic attack		

subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Vlth nerve paralysis subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	2 / 81 (2.47%) 2	
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Vertigo subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Vertigo positional subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Eye disorders			
Arteriosclerotic retinopathy subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Blepharitis subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Cataract subjects affected / exposed occurrences (all)	4 / 163 (2.45%) 4	1 / 81 (1.23%) 1	
Conjunctivitis allergic subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Ectropion			

subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Eye allergy			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Glaucoma			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Macular degeneration			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Abdominal hernia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	3 / 163 (1.84%)	0 / 81 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	3 / 163 (1.84%)	0 / 81 (0.00%)	
occurrences (all)	5	0	
Ascites			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Cheilitis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	

Cheilosis		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Coeliac artery stenosis		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Constipation		
subjects affected / exposed	9 / 163 (5.52%)	1 / 81 (1.23%)
occurrences (all)	10	1
Dental caries		
subjects affected / exposed	3 / 163 (1.84%)	0 / 81 (0.00%)
occurrences (all)	3	0
Diarrhoea		
subjects affected / exposed	6 / 163 (3.68%)	4 / 81 (4.94%)
occurrences (all)	6	4
Diverticulum		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Diverticulum intestinal		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Dyspepsia		
subjects affected / exposed	3 / 163 (1.84%)	3 / 81 (3.70%)
occurrences (all)	4	4
Eructation		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Functional gastrointestinal disorder		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Gastric ulcer		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Haemorrhagic erosive gastritis		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0

Haemorrhoids		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Hiatus hernia		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Inguinal hernia		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Intestinal dilatation		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Irritable bowel syndrome		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Large intestine polyp		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Loose tooth		
subjects affected / exposed	0 / 163 (0.00%)	2 / 81 (2.47%)
occurrences (all)	0	2
Mesenteric artery stenosis		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Nausea		
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)
occurrences (all)	1	1
Odynophagia		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Oesophagitis		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Pancreatic cyst		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1

Periodontal disease subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Stomatitis subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Teeth brittle subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Toothache subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Truncus coeliacus thrombosis subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Vomiting subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	2 / 81 (2.47%) 2	
Gallbladder polyp subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Hepatic cyst subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Hepatomegaly subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Skin and subcutaneous tissue disorders Actinic keratosis subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Blister			

subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Dermatitis allergic		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Dermatitis contact		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Dry skin		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Ecchymosis		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Eczema		
subjects affected / exposed	0 / 163 (0.00%)	2 / 81 (2.47%)
occurrences (all)	0	2
Erythema		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Hyperhidrosis		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Miliaria		
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)
occurrences (all)	1	1
Papule		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Pruritus		
subjects affected / exposed	2 / 163 (1.23%)	1 / 81 (1.23%)
occurrences (all)	2	1
Pruritus generalised		
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)
occurrences (all)	1	1
Psoriasis		

subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Rash			
subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	1 / 81 (1.23%) 1	
Rosacea			
subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Seborrhoeic dermatitis			
subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Skin mass			
subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Urticaria			
subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Vitiligo			
subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Haematuria			
subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Nephrolithiasis			
subjects affected / exposed occurrences (all)	1 / 163 (0.61%) 1	0 / 81 (0.00%) 0	
Nephropathy			
subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 1	
Renal artery stenosis			
subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0	1 / 81 (1.23%) 2	

Renal cyst			
subjects affected / exposed	3 / 163 (1.84%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Renal injury			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Urinary bladder polyp			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 163 (6.13%)	8 / 81 (9.88%)	
occurrences (all)	13	9	
Arthritis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	15 / 163 (9.20%)	4 / 81 (4.94%)	
occurrences (all)	15	4	
Bone pain			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Bursa disorder			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Intervertebral disc degeneration			

subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Intervertebral disc disorder		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Limb discomfort		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Muscle spasms		
subjects affected / exposed	3 / 163 (1.84%)	5 / 81 (6.17%)
occurrences (all)	3	7
Muscular weakness		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Musculoskeletal chest pain		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Musculoskeletal pain		
subjects affected / exposed	5 / 163 (3.07%)	0 / 81 (0.00%)
occurrences (all)	7	0
Myalgia		
subjects affected / exposed	4 / 163 (2.45%)	5 / 81 (6.17%)
occurrences (all)	6	5
Osteitis deformans		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Osteoarthritis		
subjects affected / exposed	8 / 163 (4.91%)	2 / 81 (2.47%)
occurrences (all)	8	2
Pain in extremity		
subjects affected / exposed	6 / 163 (3.68%)	2 / 81 (2.47%)
occurrences (all)	7	2
Periarthritis		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	3	0
Rheumatoid arthritis		

subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Rib deformity			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 163 (0.61%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Spinal pain			
subjects affected / exposed	2 / 163 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Trigger finger			
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	3 / 163 (1.84%)	3 / 81 (3.70%)	
occurrences (all)	3	3	
Bronchitis viral			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Fungal infection			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Furuncle			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	

Gastroenteritis		
subjects affected / exposed	3 / 163 (1.84%)	2 / 81 (2.47%)
occurrences (all)	4	4
Gastroenteritis viral		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Herpes zoster		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Influenza		
subjects affected / exposed	4 / 163 (2.45%)	0 / 81 (0.00%)
occurrences (all)	4	0
Laryngitis		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Localised infection		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Lower respiratory tract infection		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Nasopharyngitis		
subjects affected / exposed	35 / 163 (21.47%)	22 / 81 (27.16%)
occurrences (all)	45	23
Onychomycosis		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Oral fungal infection		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Otitis externa		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Otitis externa bacterial		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1

Otitis media		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Paronychia		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Periodontitis		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	4 / 163 (2.45%)	1 / 81 (1.23%)
occurrences (all)	4	1
Pharyngitis streptococcal		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Pulpitis dental		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Pneumonia		
subjects affected / exposed	4 / 163 (2.45%)	0 / 81 (0.00%)
occurrences (all)	4	0
Respiratory tract infection viral		
subjects affected / exposed	0 / 163 (0.00%)	2 / 81 (2.47%)
occurrences (all)	0	2
Respiratory tract infection		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Rhinitis		
subjects affected / exposed	1 / 163 (0.61%)	2 / 81 (2.47%)
occurrences (all)	1	2
Sinusitis		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	3	0
Tonsillitis		
subjects affected / exposed	0 / 163 (0.00%)	2 / 81 (2.47%)
occurrences (all)	0	2

Tooth abscess			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 163 (3.07%)	4 / 81 (4.94%)	
occurrences (all)	5	4	
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 163 (0.61%)	3 / 81 (3.70%)	
occurrences (all)	2	4	
Urinary tract infection			
subjects affected / exposed	1 / 163 (0.61%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Viral infection			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Viral rhinitis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Wound infection			
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Wound infection staphylococcal			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Diabetes mellitus inadequate control			

subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Dyslipidaemia		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Glucose tolerance impaired		
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)
occurrences (all)	1	1
Gout		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	2
Hypercholesterolaemia		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Hyperglycaemia		
subjects affected / exposed	2 / 163 (1.23%)	0 / 81 (0.00%)
occurrences (all)	2	0
Hypermagnesaemia		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0
Hypomagnesaemia		
subjects affected / exposed	0 / 163 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	1
Type 2 diabetes mellitus		
subjects affected / exposed	1 / 163 (0.61%)	1 / 81 (1.23%)
occurrences (all)	1	1
Vitamin B12 deficiency		
subjects affected / exposed	1 / 163 (0.61%)	0 / 81 (0.00%)
occurrences (all)	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2014	- Inclusion criteria: Number 103: added assessment by the central imaging vendor at screening for BMD T-scores - Exclusion criteria and Excluded treatments: deleted tibolone. - Study procedures: Clarified intervals for DXA scans taken for the screening period; defined day 1 and subsequent visit dates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported