



Clinical trial results:

An Open Label, Single Arm, Extension Study to Evaluate the Long Term Safety and Sustained Efficacy of Denosumab (AMG162) in the Treatment of Postmenopausal Osteoporosis

Summary

EudraCT number	2007-001041-17
Trial protocol	DK SE EE DE LV GB LT HU AT FI BE MT CZ FR ES GR IT BG SK
Global end of trial date	29 July 2015

Results information

Result version number	v2 (current)
This version publication date	01 April 2017
First version publication date	04 August 2016
Version creation reason	<ul style="list-style-type: none">• New data added to full data setadd histomorphology endpoint data

Trial information

Trial identification

Sponsor protocol code	20060289
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00523341
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	29 July 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to describe the safety and tolerability of up to 10 years or 7 years denosumab administration as measured by adverse event monitoring, immunogenicity and safety laboratory parameters in participants who previously received denosumab or placebo, respectively.

Protection of trial subjects:

This study was conducted in accordance with the principles of the Food and Drug Administration (FDA) and 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	07 August 2007
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: 496
Country: Number of subjects enrolled	Denmark: 898
Country: Number of subjects enrolled	Czech Republic: 381
Country: Number of subjects enrolled	United Kingdom: 327
Country: Number of subjects enrolled	Estonia: 296
Country: Number of subjects enrolled	Brazil: 287
Country: Number of subjects enrolled	Argentina: 211
Country: Number of subjects enrolled	United States: 178
Country: Number of subjects enrolled	Spain: 165
Country: Number of subjects enrolled	Hungary: 132
Country: Number of subjects enrolled	Italy: 132
Country: Number of subjects enrolled	Germany: 116
Country: Number of subjects enrolled	Norway: 98
Country: Number of subjects enrolled	Austria: 86
Country: Number of subjects enrolled	Belgium: 84

Country: Number of subjects enrolled	France: 83
Country: Number of subjects enrolled	Sweden: 78
Country: Number of subjects enrolled	Latvia: 75
Country: Number of subjects enrolled	Mexico: 72
Country: Number of subjects enrolled	Canada: 66
Country: Number of subjects enrolled	Slovakia: 52
Country: Number of subjects enrolled	Lithuania: 45
Country: Number of subjects enrolled	Switzerland: 40
Country: Number of subjects enrolled	New Zealand: 33
Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	Bulgaria: 25
Country: Number of subjects enrolled	Finland: 19
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Malta: 15
Country: Number of subjects enrolled	Serbia: 15
Country: Number of subjects enrolled	Romania: 5
Worldwide total number of subjects	4550
EEA total number of subjects	3623

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)	107
From 65 to 84 years	4304
85 years and over	139

Subject disposition

Recruitment

Recruitment details:

This was an extension study open to participants who had completed core study 20030216 (NCT00089791). The study was conducted at 178 centers in North America, South America, Europe, Australia, and New Zealand. Participants were enrolled from 7 August 2007 to 20 June 2008.

Pre-assignment

Screening details:

All participants received open-label denosumab during this study. Results are reported by the Study 20030216 randomized treatment groups (placebo versus denosumab).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo / Denosumab

Arm description:

Participants who were randomized to placebo in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study.

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	AMG 162
Other name	Prolia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once every 6 months.

Arm title	Denosumab / Denosumab
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Arm description:

Participants who were randomized to denosumab in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study (total of 10 years treatment).

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	AMG 162
Other name	Prolia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once every 6 months.

Number of subjects in period 1	Placebo / Denosumab	Denosumab / Denosumab
Started	2207	2343
Received Treatment	2206	2343
Completed	1283	1343
Not completed	924	1000
Consent withdrawn by subject	399	427
Physician decision	14	13
Ineligibility Determined	3	4
Adverse event, non-fatal	122	155
Protocol Deviation	6	5
Other	181	198
Death	101	110
Non-compliance	20	13
Lost to follow-up	73	61
Requirement for Alternative Therapy	4	14
Disease Progression	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo / Denosumab
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Reporting group description:

Participants who were randomized to placebo in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study.

Reporting group title	Denosumab / Denosumab
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Reporting group description:

Participants who were randomized to denosumab in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study (total of 10 years treatment).

Reporting group values	Placebo / Denosumab	Denosumab / Denosumab	Total
Number of subjects	2207	2343	4550
Age, Customized Units: participants			
60 - 64 years	58	49	107
65 - 69 years	326	320	646
70 - 74 years	672	716	1388
≥ 75 years	1151	1258	2409
Age Continuous Units: years			
arithmetic mean	74.8	74.9	-
standard deviation	± 5.1	± 5	-
Gender, Male/Female Units: participants			
Female	2207	2343	4550
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	2063	2169	4232
Black	16	19	35
Hispanic or Latino	121	145	266
Asian	2	3	5
Japanese	3	5	8
Native Hawaiian or Other Pacific Islander	1	0	1
Other	1	2	3
Bone Mineral Density T-score Lumbar spine			
<p>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.</p>			
Units: T-score			
arithmetic mean	-2.81	-2.14	-
standard deviation	± 0.75	± 0.8	-
Bone Mineral Density T-score Total hip			

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	-1.93	-1.5	-
standard deviation	± 0.8	± 0.79	-
Bone Mineral Density T-score Femoral neck			

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	-2.17	-1.83	-
standard deviation	± 0.72	± 0.75	-
Bone Mineral Density T-score at Study 20030216 Baseline Lumbar spine			
Units: T-score			
arithmetic mean	-2.84	-2.83	-
standard deviation	± 0.68	± 0.67	-
Bone Mineral Density T-score at Study 20030216 Baseline Total hip			
Units: T-score			
arithmetic mean	-1.85	-1.85	-
standard deviation	± 0.79	± 0.79	-
Bone Mineral Density T-score at Study 20030216 Baseline Femoral neck			
Units: T-score			
arithmetic mean	-2.11	-2.11	-
standard deviation	± 0.71	± 0.71	-

End points

End points reporting groups

Reporting group title	Placebo / Denosumab
Reporting group description:	
Participants who were randomized to placebo in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study.	
Reporting group title	Denosumab / Denosumab
Reporting group description:	
Participants who were randomized to denosumab in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study (total of 10 years treatment).	

Primary: Number of participants with Adverse Events (AEs)

End point title	Number of participants with Adverse Events (AEs) ^[1]
End point description:	
A serious adverse event (SAE) is defined as an AE that:	
<ul style="list-style-type: none"> • is fatal • is life threatening • requires in-patient hospitalization or prolongation of existing hospitalization • results in persistent or significant disability/incapacity • is a congenital anomaly/birth defect • is other significant medical hazard. 	
Treatment-related adverse events includes only events for which the investigator indicated there was a reasonable possibility they may have been caused by study drug. The following were classified as adverse events of interest (events that are considered to be identified or potential risks of denosumab treatment): positively adjudicated osteonecrosis of the jaw, positively adjudicated atypical femoral fracture, hypocalcemia, adverse events potentially related to hypersensitivity, serious infection (including bacterial cellulitis), malignancy, cardiac disorders, vascular disorders, fracture healing complications, eczema, acute pancreatitis, and musculoskeletal pain.	
End point type	Primary
End point timeframe:	
84 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical testing was performed.

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2206	2343		
Units: participants				
number (not applicable)				
Any adverse event (AE)	2070	2173		
Serious adverse event	945	1014		
Fatal adverse event	101	108		
AE leading to study discontinuation	145	173		
AE leading to discontinuation of denosumab	184	216		
Treatment-related adverse events (TRAE)	185	188		
Serious treatment-related adverse events	26	28		

Fatal treatment-related adverse events	1	0		
TRAE leading to study discontinuation	16	9		
TRAE leading to discontinuation of denosumab	30	25		
Positively adjudicated osteonecrosis of the jaw	6	7		
Positively adjudicated atypical femoral fracture	1	1		
Hypocalcaemia	10	6		
AEs potentially related to hypersensitivity	260	280		
Serious infections	161	185		
Serious bacterial cellulitis	7	12		
Malignancy	227	237		
Cardiac disorders	449	492		
Vascular disorders	693	732		
Fracture healing complications	0	1		
Eczema	99	115		
Acute pancreatitis	4	8		
Musculoskeletal pain	1125	1206		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Laboratory Toxicities of Grade \geq 3

End point title	Number of Participants with Laboratory Toxicities of Grade \geq
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End point description:

Laboratory toxicity grading was based on Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Grade 3 indicates severe toxicity and Grade 4 indicates life-threatening toxicity.

End point type	Primary
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End point timeframe:

84 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical testing was performed.

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2206	2343		
Units: participants				
number (not applicable)				
Low sodium - Grade 3	28	25		
Low sodium - Grade 4	1	0		
High potassium - Grade 3	9	11		
High potassium - Grade 4	0	3		
Low potassium - Grade 3	7	7		
Low magnesium - Grade 3	1	1		
Low magnesium - Grade 4	0	1		

High calcium - Grade 3	2	3		
High calcium - Grade 4	0	2		
High corrected calcium - Grade 3	2	3		
High corrected calcium - Grade 4	0	2		
Low phosphorus - Grade 3	3	1		
High Creatinine - Grade 3	0	1		
High aspartate amino transferase (AST) - Grade 3	5	11		
High aspartate amino transferase (AST) - Grade 4	1	0		
High alanine amino transferase (ALT) - Grade 3	8	10		
High alanine amino transferase (ALT) - Grade 4	1	0		
High total bilirubin - Grade 3	2	3		
Low albumin - Grade 3	0	1		
High glucose - Grade 3	35	37		
High glucose - Grade 4	0	1		
Low glucose - Grade 3	4	1		
Low glucose - Grade 4	1	1		
Low hemoglobin - Grade 3	6	4		
Low platelets - Grade 3	3	7		
Low platelets - Grade 4	2	4		
Low white blood cells - Grade 3	5	7		
Low white blood cells - Grade 4	0	1		
Low lymphocytes - Grade 3	17	16		
Low lymphocytes - Grade 4	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Antibodies to Denosumab

End point title	Number of Participants with Antibodies to Denosumab ^[3]
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End point description:

End point type	Primary
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End point timeframe:

Every 12 months through Month 84

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical testing was performed.

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2206	2343		
Units: participants				
number (not applicable)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Lumbar Spine Bone Mineral Density by Visit

End point title	Percent Change From Baseline in Lumbar Spine Bone Mineral Density by Visit
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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. Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline (of extension study) and months 12, 24, 36, 60 and 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2210		
Units: percent change				
least squares mean (confidence interval 95%)				
Month 12 (n = 2040, 2168)	5.2 (5 to 5.3)	2 (1.8 to 2.2)		
Month 24 (n = 1935, 2061)	7.7 (7.5 to 7.9)	3.5 (3.4 to 3.7)		
Month 36 (n = 1497, 1607)	9.4 (9.1 to 9.6)	4.9 (4.7 to 5.1)		
Month 60 (n = 1472, 1567)	13 (12.7 to 13.3)	7.9 (7.6 to 8.2)		
Month 84 (n = 1223, 1264)	16.5 (16.1 to 16.9)	10.8 (10.4 to 11.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Total Hip Bone Mineral Density by Visit

End point title	Percent Change From Baseline in Total Hip Bone Mineral Density by Visit
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End point description:

Total hip bone mineral density was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center. Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

End point type	Secondary
End point timeframe:	
Baseline (of extension study) and months 12, 24, 36, 60 and 84	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2210		
Units: percent change				
least squares mean (confidence interval 95%)				
Month 12 (n = 2029, 2160)	3 (2.8 to 3.1)	0.8 (0.7 to 0.9)		
Month 24 (n = 1918, 2045)	4.1 (4 to 4.2)	1.4 (1.3 to 1.5)		
Month 36 (n = 1475, 1591)	4.9 (4.7 to 5)	1.8 (1.7 to 2)		
Month 60 (n = 1439, 1538)	6.2 (6 to 6.4)	2.6 (2.4 to 2.8)		
Month 84 (n = 1200, 1232)	7.4 (7.1 to 7.6)	3.4 (3.2 to 3.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Femoral Neck Bone Mineral Density by Visit

End point title	Percent Change From Baseline in Femoral Neck Bone Mineral Density by Visit
End point description:	
Femoral neck bone mineral density was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.	
Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.	
End point type	Secondary
End point timeframe:	
Baseline (of extension study) and months 12, 24, 36, 60 and 84	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2210		
Units: percent change				
least squares mean (confidence interval 95%)				
Month 12 (n = 2029, 2160)	2.1 (1.9 to 2.3)	0.8 (0.7 to 1)		
Month 24 (n = 1918, 2045)	3.2 (3.1 to 3.4)	1.2 (1 to 1.4)		
Month 36 (n = 1475, 1591)	4 (3.8 to 4.3)	1.7 (1.5 to 1.9)		
Month 60 (n = 1439, 1538)	5.7 (5.4 to 5.9)	2.8 (2.6 to 3.1)		
Month 84 (n = 1200, 1232)	7.1 (6.8 to 7.4)	3.8 (3.5 to 4.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in 1/3 Radius Bone Mineral Density by Visit

End point title	Percent Change From Baseline in 1/3 Radius Bone Mineral Density by Visit
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End point description:

1/3 radius bone mineral density was measured in a subset of participants by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

Analysis includes participants in the DXA substudy with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline (of extension study) and months 12, 24, 36, 60 and 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	467		
Units: percent change				
least squares mean (confidence interval 95%)				
Month 12 (n = 114, 134)	0.3 (-0.2 to 0.9)	0.6 (0.1 to 1.2)		
Month 24 (n = 108, 127)	0.2 (-0.4 to 0.9)	0.2 (-0.4 to 0.8)		
Month 36 (n = 73, 93)	1.3 (0.5 to 2)	0.6 (-0.1 to 1.3)		
Month 60 (n = 59, 84)	1.8 (0.9 to 2.7)	1.4 (0.6 to 2.2)		
Month 84 (n = 39, 56)	2.2 (0.9 to 3.6)	1 (-0.1 to 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Study 20030216 Baseline in Lumbar Spine Bone Mineral Density by Visit

End point title	Percent Change From Study 20030216 Baseline in Lumbar Spine Bone Mineral Density by Visit
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End point description:

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

Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Study 20030216 baseline and extension study months 12, 24, 36, 60 and 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2210		
Units: percent change				
least squares mean (confidence interval 95%)				
Month 12 (n = 2030, 2148)	5.9 (5.6 to 6.1)	11.9 (11.7 to 12.2)		
Month 24 (n = 1924, 2041)	8.4 (8.1 to 8.7)	13.7 (13.4 to 13.9)		
Month 36 (n = 1487, 1589)	10.1 (9.8 to 10.4)	15.2 (14.9 to 15.5)		
Month 60 (n = 1464, 1551)	13.8 (13.4 to 14.1)	18.4 (18.1 to 18.8)		
Month 84 (n = 1216, 1251)	17.3 (16.8 to 17.8)	21.7 (21.2 to 22.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Study 20030216 Baseline in Total Hip BMD by Visit

End point title	Percent Change From Study 20030216 Baseline in Total Hip BMD by Visit
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End point description:

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

Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Study 20030216 baseline and extension study months 12, 24, 36, 60 and 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2210		
Units: percent change				
least squares mean (confidence interval 95%)				
Month 12 (n = 2006, 2132)	1.7 (1.6 to 1.9)	6.4 (6.3 to 6.6)		
Month 24 (n = 1895, 2017)	2.9 (2.7 to 3)	7.1 (6.9 to 7.2)		
Month 36 (n = 1457, 1567)	3.6 (3.4 to 3.8)	7.5 (7.3 to 7.7)		
Month 60 (n = 1424, 1518)	4.9 (4.7 to 5.2)	8.4 (8.1 to 8.6)		
Month 84 (n = 1189, 1215)	6.1 (5.8 to 6.4)	9.2 (8.9 to 9.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Study 20030216 Baseline in Femoral Neck BMD by Visit

End point title	Percent Change From Study 20030216 Baseline in Femoral Neck BMD by Visit
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End point description:

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

Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Study 20030216 baseline and extension study months 12, 24, 36, 60 and 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2210		
Units: percent change				
least squares mean (confidence interval 95%)				
Month 12 (n = 2006, 2132)	1.4 (1.2 to 1.7)	5.8 (5.6 to 6)		
Month 24 (n = 1895, 2017)	2.6 (2.3 to 2.8)	6.2 (6 to 6.5)		
Month 36 (n = 1457, 1567)	3.4 (3.1 to 3.6)	6.7 (6.5 to 7)		
Month 60 (n = 1424, 1518)	5 (4.7 to 5.3)	7.9 (7.6 to 8.2)		
Month 84 (n = 1189, 1215)	6.4 (6 to 6.8)	9 (8.6 to 9.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Study 20030216 Baseline in 1/3 Radius BMD by Visit

End point title	Percent Change From Study 20030216 Baseline in 1/3 Radius BMD by Visit
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End point description:

1/3 radius BMD was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

Analysis includes participants in the DXA substudy with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Study 20030216 baseline and extension study months 12, 24, 36, 60, and 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	467		
Units: percent change				
least squares mean (confidence interval 95%)				
Month 12 (n = 113, 133)	-1 (-1.7 to -0.3)	2.6 (1.9 to 3.2)		
Month 24 (n = 107, 127)	-1.2 (-1.9 to -0.4)	2.1 (1.4 to 2.8)		
Month 36 (n = 73, 92)	-0.2 (-1.1 to 0.7)	2.4 (1.6 to 3.2)		
Month 60 (n = 59, 83)	0.3 (-0.7 to 1.3)	3.3 (2.4 to 4.2)		
Month 84 (n = 39, 56)	0.6 (-0.8 to 2.1)	2.8 (1.6 to 4.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With New Vertebral Fractures

End point title	Number of Participants With New Vertebral Fractures
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End point description:

A new vertebral fracture, assessed by lateral spine X-ray using Genant semiquantitative scoring method, was identified as an ≥ 1 grade increase from the previous grade of 0 in any vertebra from T4 to L4, excluding any fracture associated with high trauma severity or a pathologic fracture.

Analysis includes all participants enrolled in the extension study who have vertebral X-ray assessment at the extension baseline and at least 1 post-extension baseline visit.

End point type	Secondary
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End point timeframe:

84 months

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1991	2116		
Units: participants				
number (not applicable)	145	149		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Non-Vertebral Fractures

End point title	Number of Participants With Non-Vertebral Fractures
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End point description:

Non-vertebral fractures (osteoporotic) were defined as a fracture present on a copy of radiographs or other diagnostic images such as computerized tomography (CT) or magnetic resonance imaging (MRI) confirming the fracture, and/or documented in a copy of the radiology report, surgical report, or discharge summary, excluding skull, facial, mandible, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, metacarpus, finger phalanges, and toe phalanges. In addition, fractures associated with high trauma severity or pathologic fractures were excluded.

Analysis includes all enrolled participants.

End point type	Secondary
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End point timeframe:

84 months

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2207	2343		
Units: participants				
number (not applicable)	219	172		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in C-Telopeptide 1 (CTX-1) by Visit

End point title	Percent Change From Baseline in C-Telopeptide 1 (CTX-1) by Visit
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End point description:

Bone turnover markers were collected in a subset of participants who participated in the 20030216 Bone Marker sub-study and in new participants continuing beyond month 24 who were not previously in the Bone Turnover Markers sub-study.

End point type	Secondary
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End point timeframe:

Baseline (of extension study), day 10, and months 6, 12, 24, 36, 48, 60, 72, and 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	342		
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Day 10 (n = 26, 47)	-90 (-93 to -85)	-72 (-86 to -47)		
Month 6 (n = 30, 56)	-85 (-91 to -73)	-26 (-63 to 1)		
Month 12 (n = 27, 56)	-75 (-90 to -54)	-13 (-37 to 24)		
Month 24 (n = 27, 47)	-67 (-84 to -29)	10 (-27 to 55)		
Month 36 (n = 68, 81)	-59 (-84 to -28)	2 (-32 to 68)		
Month 48 (n = 62, 75)	-58 (-84 to -12)	0 (-46 to 56)		
Month 60 (n = 59, 70)	-65 (-90 to -19)	0 (-47 to 83)		
Month 72 (n = 56, 62)	-60 (-85 to -16)	-1 (-47 to 76)		
Month 84 (n = 41, 41)	-64 (-86 to -28)	-6 (-26 to 68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Procollagen Type 1 N-telopeptide (P1NP) by Visit

End point title	Percent Change From Baseline in Procollagen Type 1 N-telopeptide (P1NP) by Visit
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End point description:

Bone turnover markers were collected in a subset of participants who participated in the 20030216 Bone Marker sub-study and in new participants continuing beyond month 24 who were not previously in the Bone Turnover Markers sub-study.

End point type	Secondary
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End point timeframe:

Baseline (of extension study), day 10, and months 6, 12, 24, 36, 48, 60, 72, and 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	342		
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Day 10 (n = 30, 51)	6 (-5 to 30)	14 (-1 to 25)		
Month 6 (n = 30, 53)	-71 (-78 to -62)	-23 (-50 to -2)		
Month 12 (n = 26, 56)	-67 (-76 to -57)	7 (-15 to 30)		
Month 24 (n = 27, 47)	-63 (-77 to -41)	11 (-17 to 42)		
Month 36 (n = 69, 83)	-57 (-67 to -29)	29 (-6 to 91)		
Month 48 (n = 61, 73)	-60 (-70 to -41)	8 (-21 to 49)		
Month 60 (n = 61, 71)	-54 (-72 to -35)	30 (-6 to 67)		
Month 72 (n = 55, 64)	-50 (-60 to -36)	44 (3 to 103)		
Month 84 (n = 48, 50)	-59 (-73 to -40)	32 (-4 to 75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Study 20030216 Baseline in CTX-1 by Visit

End point title	Percent Change From Study 20030216 Baseline in CTX-1 by Visit
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End point description:

Bone turnover markers were collected in a subset of participants who participated in the 20030216 Bone Marker sub-study and in new participants continuing beyond month 24 who were not previously in the Bone Turnover Markers sub-study.

End point type	Secondary
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End point timeframe:

Study 20030216 Baseline and extension study day 10, and months 6, 12, 24, 36, 48, 60, 72, and 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	342		
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Day 10 (n = 26, 56)	-90 (-91 to -78)	-91 (-93 to -86)		
Month 6 (n = 32, 72)	-83 (-90 to -72)	-77 (-87 to -49)		
Month 12 (n = 27, 65)	-77 (-91 to -45)	-63 (-87 to -11)		

Month 24 (n = 28, 60)	-65 (-80 to -24)	-53 (-82 to 0)		
Month 36 (n = 289, 313)	-71 (-88 to -40)	-52 (-86 to -4)		
Month 48 (n = 274, 290)	-70 (-88 to -36)	-61 (-85 to -24)		
Month 60 (n = 268, 276)	-67 (-88 to -25)	-53 (-86 to -18)		
Month 72 (n = 243, 248)	-69 (-88 to -32)	-59 (-86 to -21)		
Month 84 (n = 217, 216)	-63 (-88 to -19)	-53 (-84 to -12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Study 20030216 Baseline in P1NP by Visit

End point title	Percent Change From Study 20030216 Baseline in P1NP by Visit
End point description:	Bone turnover markers were collected in a subset of participants who participated in the 20030216 Bone Marker sub-study and in new participants continuing beyond month 24 who were not previously in the Bone Turnover Markers sub-study.
End point type	Secondary
End point timeframe:	Study 20030216 Baseline and extension study day 10, and months 6, 12, 24, 36, 48, 60, 72, and 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	342		
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Day 10 (n = 30, 51)	9 (-14 to 34)	-59 (-74 to -22)		
Month 6 (n = 32, 57)	-74 (-80 to -67)	-75 (-80 to -55)		
Month 12 (n = 26, 56)	-74 (-79 to -51)	-63 (-76 to -36)		
Month 24 (n = 28, 51)	-67 (-75 to -51)	-56 (-72 to -30)		
Month 36 (n = 70, 83)	-59 (-75 to -37)	-60 (-71 to -40)		
Month 48 (n = 61, 73)	-67 (-75 to -46)	-63 (-77 to -42)		
Month 60 (n = 61, 71)	-62 (-75 to -42)	-55 (-74 to -30)		
Month 72 (n = 56, 67)	-62 (-71 to -35)	-55 (-70 to -27)		
Month 84 (n = 49, 53)	-68 (-78 to -56)	-57 (-74 to -38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Albumin-adjusted Serum Calcium at Day 10

End point title	Percent Change From Baseline in Albumin-adjusted Serum Calcium at Day 10
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End point description:

Analysis includes participants who had a calcium corrected by albumin measurement within the Day 10 visit window up to May 31, 2008.

End point type	Secondary
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End point timeframe:

Baseline (of extension study) and day 10

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2027	2154		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-3.1 (-6.1 to 0)	-2 (-5.1 to 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Denosumab Concentration

End point title	Serum Denosumab Concentration
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End point description:

Serum concentrations of denosumab were measured by a validated conventional sandwich enzyme-linked immunosorbent assay (ELISA). The lower limit of quantification (LLOQ) was 0.8 ng/mL. Values of 0 in the table below indicate data below the lower limit of quantification.

Analysis includes participants who participated in the Study 20030216 PK substudy, for whom dosing information was not missing and for whom sampling was within 14 days of specified sampling times.

End point type	Secondary
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End point timeframe:

Baseline (pre-dose in extension study), day 10, and Months 3, 4 and 6 (pre-dose)

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	113		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n = 97, 113)	0 (± 0)	113 (± 107)		
Day 10 (n = 92, 106)	5890 (± 2010)	6010 (± 2530)		
Month 3 (n = 81, 92)	1000 (± 560)	1190 (± 690)		
Month 4 (n = 87, 104)	429 (± 378)	554 (± 480)		
Month 6 (n = 87, 103)	20.8 (± 61.7)	66 (± 147.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Cancellous Bone Volume

End point title	Bone Histomorphometry: Cancellous Bone Volume
End point description:	Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Cancellous (trabecular) bone volume is the percent of the total marrow cavity that is occupied by cancellous bone (both mineralized and non-mineralized) measured by quantitative histomorphometry. The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available cancellous bone volume data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.
End point type	Secondary
End point timeframe:	Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: percentage of total bone tissue volume				
arithmetic mean (standard deviation)				
Month 24 (n=13, 25)	15.253 (± 6.065)	14.64 (± 6.979)		
Month 84 (n=0, 19)	99999 (± 99999)	16.358 (± 4.438)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Trabecular Number

End point title	Bone Histomorphometry: Trabecular Number
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Trabecular number is the number of trabeculae present per lineal mm and is calculated as trabecular bone volume/trabecular thickness. Trabecular number is a measure of trabecular connectivity and decreases with bone loss.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available trabecular number data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: 1/mm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	1.005 (± 0.242)	0.904 (± 0.243)		
Month 84 (n = 0, 19)	99999 (± 99999)	1.235 (± 0.254)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Trabecular Separation

End point title	Bone Histomorphometry: Trabecular Separation
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Trabecular separation is the mean distance between trabeculae (measured by integrated computer graphics). Trabecular separation increases with trabecular bone loss.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available trabecular separation data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: μm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	919.693 (\pm 358.238)	1033.416 (\pm 352.259)		
Month 84 (n = 0, 19)	99999 (\pm 99999)	708.669 (\pm 171.782)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Trabecular Thickness

End point title	Bone Histomorphometry: Trabecular Thickness
End point description:	
<p>Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Mean trabecular thickness is a measure of trabecular structure and is calculated as the reciprocal of total bone (trabecular) surfaces. Trabecular thickness is reduced by aging and osteoporosis. The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available trabecular thickness data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.</p>	
End point type	Secondary
End point timeframe:	
Month 24 and month 84	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: μm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	153.878 (\pm 51.859)	156.335 (\pm 48.567)		
Month 84 (n = 0, 19)	99999 (\pm 99999)	132.965 (\pm 28.064)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Cortical Width

End point title	Bone Histomorphometry: Cortical Width
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Cortical width is the average width of both inner and outer cortices. Analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available cortical width data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	45		
Units: μm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 28)	622.22 (\pm 246.7)	707.69 (\pm 237.97)		
Month 84 (n = 0, 21)	99999 (\pm 99999)	786.19 (\pm 279.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Cancellous Bone Volume by TRAP Histomorphometry

End point title	Bone Histomorphometry: Cancellous Bone Volume by TRAP Histomorphometry
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Cancellous (trabecular) bone volume is the percent of the total marrow cavity that is occupied by cancellous bone (both mineralized and non-mineralized) measured by tartrate-resistant acid phosphatase (TRAP) staining histomorphometry.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available cancellous bone volume data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: percentage of total bone tissue volume				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	16.678 (± 7.27)	15.606 (± 6.986)		
Month 84 (n = 0, 19)	99999 (± 99999)	17.631 (± 4.387)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Surface Density

End point title	Bone Histomorphometry: Surface Density
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Surface density is calculated by total bone (trabecular) surfaces / total tissue volume.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available surface density data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: mm ² /mm ³				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	2.009 (± 0.486)	1.807 (± 0.486)		
Month 84 (n = 0, 19)	99999 (± 99999)	2.472 (± 0.506)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Osteoblast - Osteoid Interface

End point title	Bone Histomorphometry: Osteoblast - Osteoid Interface
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoblast - osteoid interface is calculated as osteoblast surface / osteoid surface * 100. Analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoblast - osteoid interface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: percentage of osteoid surface				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	22.124 (± 34.879)	17.813 (± 28.381)		
Month 84 (n = 0, 19)	99999 (± 99999)	5.951 (± 15.223)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Osteoid Surface

End point title	Bone Histomorphometry: Osteoid Surface
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoid surface is the percent of bone surface covered in osteoid. The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoid surface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: percentage of total bone surface				
arithmetic mean (standard deviation)				

Month 24 (n = 13, 25)	0.915 (± 1.382)	0.982 (± 2.489)		
Month 84 (n = 0, 19)	99999 (± 99999)	0.421 (± 1.068)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Osteoid Thickness

End point title	Bone Histomorphometry: Osteoid Thickness
End point description:	
<p>Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoid thickness (width) is the mean thickness of osteoid seams on cancellous surfaces. Osteoid thickness is normally <12.5 µm. Increased osteoid thickness suggests abnormal mineralization (osteomalacia).</p> <p>The analysis included participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoid thickness data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.</p>	
End point type	Secondary
End point timeframe:	
Month 24 and month 84	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: µm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	5.139 (± 3.261)	4.548 (± 4.973)		
Month 84 (n = 0, 19)	99999 (± 99999)	4.108 (± 3.476)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Wall Thickness

End point title	Bone Histomorphometry: Wall Thickness
End point description:	
<p>Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Wall thickness is the average thickness of trabecular bone structural units (BSU) and is used to assess the overall balance between resorption and formation.</p> <p>The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available wall thickness data. Biopsies were only</p>	

collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: μm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	43.11 (\pm 6.08)	49.74 (\pm 10.51)		
Month 84 (n = 0, 19)	99999 (\pm 99999)	39.59 (\pm 7.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Eroded Surface/Bone Surface

End point title	Bone Histomorphometry: Eroded Surface/Bone Surface
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Eroded surface/bone surface is the percentage of bone surface occupied by eroded (resorption) cavities (Howships lacunae), with or without osteoclasts.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available eroded surface/bone surface data.

Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: percentage of bone surface				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	0.414 (\pm 0.701)	0.328 (\pm 0.613)		
Month 84 (n = 0, 19)	99999 (\pm 99999)	0.511 (\pm 0.579)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Osteoclast Number - Length Based

End point title | Bone Histomorphometry: Osteoclast Number - Length Based

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoclast number was measured by quantitative histomorphometry and is expressed per mm of bone. The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoclast number data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type | Secondary

End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: 1/mm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	0.086 (± 0.119)	0.107 (± 0.198)		
Month 84 (n = 0, 19)	99999 (± 99999)	0.074 (± 0.101)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Osteoclast Number - Surface Based

End point title | Bone Histomorphometry: Osteoclast Number - Surface Based

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoclast number was measured by quantitative histomorphometry and is expressed per 100 mm of bone surface.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoclast number data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
End point timeframe:	
Month 24 and month 84	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: 1/100 mm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	8.6 (± 11.9)	10.7 (± 19.8)		
Month 84 (n = 0, 19)	99999 (± 99999)	7.4 (± 10.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Osteoclast Number by TRAP - Length Based

End point title	Bone Histomorphometry: Osteoclast Number by TRAP - Length Based
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoclast number was measured using TRAP staining and is expressed per mm of bone.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoclast number data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
End point timeframe:	
Month 24 and month 84	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: 1/mm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	0.096 (± 0.134)	0.11 (± 0.185)		
Month 84 (n = 0, 19)	99999 (± 99999)	0.077 (± 0.107)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Osteoclast Number by TRAP - Surface Based

End point title	Bone Histomorphometry: Osteoclast Number by TRAP - Surface Based
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoclast number was measured using TRAP staining and is expressed per 100 mm of bone surface. The analysis included participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoclast number data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: 1/100 mm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	9.6 (± 13.4)	11 (± 18.5)		
Month 84 (n = 0, 19)	99999 (± 99999)	7.7 (± 10.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Single-label Surface

End point title	Bone Histomorphometry: Single-label Surface
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. A single label is deposited if formation either started or ended during the interval between the uses of the two courses of tetracycline administration. Single-label surface is expressed as a percentage of total bone surface.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available single-label surface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: percentage of bone surface				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 10)	0.304 (± 0.302)	0.643 (± 0.661)		
Month 84 (n = 0, 10)	99999 (± 99999)	0.611 (± 0.726)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Double-label Surface

End point title	Bone Histomorphometry: Double-label Surface
End point description:	<p>Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. The presence of double labels indicates that normal bone mineralization was actively occurring over the entire labeling interval. Double-label surface is expressed as a percentage of total bone surface.</p> <p>The analysis includes Participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available double-label surface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.</p>
End point type	Secondary
End point timeframe:	Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: percentage of bone surface				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 10)	0.258 (± 0.207)	0.356 (± 0.295)		
Month 84 (n = 0, 10)	99999 (± 99999)	0.106 (± 0.237)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Mineralizing Surface

End point title | Bone Histomorphometry: Mineralizing Surface

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. Total mineralizing surfaces (MS) include all double and half of single-labeled surfaces. MS is expressed as a percentage of total bone surface.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available mineralizing surface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type | Secondary

End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: percentage of bone surface				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 10)	0.406 (± 0.323)	0.681 (± 0.453)		
Month 84 (n = 0, 10)	99999 (± 99999)	0.412 (± 0.458)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Mineral Apposition Rate

End point title | Bone Histomorphometry: Mineral Apposition Rate

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. The mineral apposition rate (MAR) is the average rate at which new bone mineral is being added on any actively forming surface. MAR is calculated as the average distance between visible labels, divided by the labeling interval.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available mineral apposition rate data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type | Secondary

End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: µm/day				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 10)	0.616 (± 0.219)	0.722 (± 0.573)		
Month 84 (n = 0, 10)	99999 (± 99999)	0.394 (± 0.233)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Adjusted Apposition Rate

End point title	Bone Histomorphometry: Adjusted Apposition Rate
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. MAR is the average rate at which new bone mineral is being added on any actively forming surface. Adjusted MAR is calculated as: (average distance between visible labels / labeling interval) * (total mineralizing surface/total bone surface).

Analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or 84 and with available adjusted apposition rate data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
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End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	19		
Units: µm/day				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 9)	0.394 (± 0.471)	0.517 (± 0.537)		
Month 84 (n = 0, 10)	99999 (± 99999)	0.818 (± 1.207)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Bone Formation Rate - Surface Based

End point title | Bone Histomorphometry: Bone Formation Rate - Surface Based

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. Bone formation rate - surface based is the calculated rate at which cancellous bone surface is being replaced annually, derived from the Mineral Appositional Rate * 365 * (relative mineralizing surface / total bone surface).

The analysis included participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available bone formation rate data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type | Secondary

End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: $\mu\text{m}^3/\mu\text{m}^2/\text{year}$				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 10)	0.898 (\pm 0.706)	2.153 (\pm 2.468)		
Month 84 (n = 0, 10)	99999 (\pm 99999)	0.691 (\pm 0.868)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Bone Formation Rate - Volume Based

End point title | Bone Histomorphometry: Bone Formation Rate - Volume Based

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. Bone formation rate - volume based is the calculated rate at which cancellous bone volume is being replaced annually, derived from the Mineral Appositional Rate * 365 * (relative mineralizing surface / total bone volume).

The analyses includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available bone formation rate data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type | Secondary

End point timeframe:
Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: percent of bone volume per year				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 10)	1.454 (± 1.265)	3.162 (± 3.773)		
Month 84 (n = 0, 10)	99999 (± 99999)	1.071 (± 1.308)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Activation Frequency

End point title	Bone Histomorphometry: Activation Frequency
End point description:	
<p>Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. The average time that it takes for a new remodeling cycle to begin on any point on a cancellous surface is called the activation frequency. Activation frequency is calculated as the bone formation rate / wall width.</p> <p>The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available activation frequency data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.</p>	
End point type	Secondary
End point timeframe:	
Month 24 and month 84	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: /year				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 10)	0.022 (± 0.019)	0.045 (± 0.049)		
Month 84 (n = 0, 10)	99999 (± 99999)	0.014 (± 0.024)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Formation Period

End point title | Bone Histomorphometry: Formation Period

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. Formation period (FP) is the mean time required to rebuild a new bone structural unit or osteon from the cement line back to the bone surface at a single location, and is given by wall width / adjusted apposition rate.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available formation period data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type | Secondary

End point timeframe:

Month 24 and month 84

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: days				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 10)	593.5 (± 996.8)	287.3 (± 391.5)		
Month 84 (n = 0, 10)	99999 (± 99999)	229.7 (± 512)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Osteoid Volume

End point title | Bone Histomorphometry: Osteoid Volume

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoid volume is the percentage of a given volume of bone tissue that consists of unmineralized bone (osteoid).

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of

denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoid volume data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
End point timeframe:	
Month 24 and month 84	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: percentage of total bone tissue				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	0.108 (± 0.193)	0.146 (± 0.382)		
Month 84 (n = 0, 19)	99999 (± 99999)	0.048 (± 0.133)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Mineralization Lag Time

End point title	Bone Histomorphometry: Mineralization Lag Time
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End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. Mineralization lag time is the average time interval between osteoid formation and its subsequent mineralization and is calculated by dividing the osteoid width by the apposition rate. The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available mineralization lag time data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

End point type	Secondary
End point timeframe:	
Month 24 and month 84	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: days				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 10)	84.9 (± 136.8)	54.3 (± 76.1)		

Month 84 (n = 0, 10)	99999 (± 99999)	52.3 (± 114.5)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histology at Month 24

End point title	Bone Histology at Month 24
End point description:	
<p>Bone biopsy samples were prepared according to standard procedures for bone histology to determine if there were any histological abnormalities in the bone. Results are reported for the number of biopsies with normal bone micro-architecture: normal lamellar bone, normal mineralization, and osteoid, and biopsies with abnormal bone histology: osteomalacia, marrow fibrosis, or woven bone.</p> <p>Analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, and had at least 1 evaluable bone biopsy at extension month 24.</p>	
End point type	Secondary
End point timeframe:	
Month 24	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	28		
Units: biopsies				
Normal lamellar bone	13	28		
Normal mineralization	13	28		
Osteoid	13	23		
Osteomalacia	0	0		
Marrow fibrosis	0	0		
Woven bone	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histology at Month 84

End point title	Bone Histology at Month 84
End point description:	
<p>Bone biopsy samples were prepared according to standard procedures for bone histology to determine if there were any histological abnormalities in the bone. Results are reported for the number of biopsies with normal bone micro-architecture: normal lamellar bone, normal mineralization, and osteoid, and biopsies with abnormal bone histology: osteomalacia, marrow fibrosis, or woven bone.</p> <p>Analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, and had at least 1 evaluable bone biopsy at extension month</p>	

84.

End point type	Secondary
End point timeframe:	
Month 84	

End point values	Placebo / Denosumab	Denosumab / Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[4]	22		
Units: biopsies				
Normal lamellar bone		22		
Normal mineralization		22		
Osteoid		18		
Osteomalacia		0		
Marrow fibrosis		0		
Woven bone		0		

Notes:

[4] - No participants had biopsies collected at month 84

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

84 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	Placebo/Denosumab 60 mg Q6M
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Reporting group description:

Participants who were randomized to placebo in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study.

Reporting group title	Denosumab/Denosumab 60 mg Q6M
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Reporting group description:

Participants who were randomized to denosumab in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study (total of 10 years treatment).

Serious adverse events	Placebo/Denosumab 60 mg Q6M	Denosumab/Denosu mab 60 mg Q6M	
Total subjects affected by serious adverse events			
subjects affected / exposed	945 / 2206 (42.84%)	1014 / 2343 (43.28%)	
number of deaths (all causes)	101	108	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	4 / 2206 (0.18%)	5 / 2343 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Adenoma benign		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Adrenal adenoma		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Adenosquamous cell lung cancer		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Adrenal neoplasm		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Anal cancer		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
B-cell lymphoma		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Benign breast neoplasm		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Basal cell carcinoma		

subjects affected / exposed	16 / 2206 (0.73%)	14 / 2343 (0.60%)
occurrences causally related to treatment / all	0 / 17	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0
Benign hepatic neoplasm		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Benign lung neoplasm		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Benign gastrointestinal neoplasm		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Benign neoplasm of bladder		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Benign neoplasm		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Benign neoplasm of thyroid gland		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Benign pancreatic neoplasm		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Benign neoplasm of skin		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Benign salivary gland neoplasm		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Benign vulval neoplasm		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bladder cancer		
subjects affected / exposed	2 / 2206 (0.09%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Brain cancer metastatic		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Brain neoplasm malignant		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Breast cancer metastatic		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Breast cancer		
subjects affected / exposed	21 / 2206 (0.95%)	24 / 2343 (1.02%)
occurrences causally related to treatment / all	0 / 21	1 / 26
deaths causally related to treatment / all	0 / 0	0 / 1
Bronchial carcinoma		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Breast neoplasm		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Breast cancer recurrent		
subjects affected / exposed	3 / 2206 (0.14%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Carcinoma in situ of skin		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cervix carcinoma		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Central nervous system lymphoma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cholangiocarcinoma		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cholesteatoma		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic lymphocytic leukaemia		

subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Colon adenoma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colon cancer		
subjects affected / exposed	7 / 2206 (0.32%)	12 / 2343 (0.51%)
occurrences causally related to treatment / all	0 / 7	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 3
Colon cancer metastatic		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1
Colon neoplasm		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Colorectal cancer		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dermatofibrosarcoma protuberans		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Colorectal adenocarcinoma		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diffuse large B-cell lymphoma		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diffuse large B-cell lymphoma stage IV		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Endometrial adenocarcinoma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Follicular thyroid cancer		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Endometrial cancer		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal stromal tumour		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric cancer		
subjects affected / exposed	1 / 2206 (0.05%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1
Gallbladder cancer		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal tract adenoma		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gingival cancer		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hairy cell leukaemia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatic cancer		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1
Hepatic neoplasm		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intraductal proliferative breast lesion		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatocellular carcinoma		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Invasive ductal breast carcinoma		
subjects affected / exposed	10 / 2206 (0.45%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	1 / 11	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Invasive papillary breast carcinoma		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Invasive breast carcinoma		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Leiomyosarcoma		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Laryngeal papilloma		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Leukaemia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Lip neoplasm malignant stage unspecified		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lentigo maligna		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lipoma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
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	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung cancer metastatic		
subjects affected / exposed	4 / 2206 (0.18%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 2
Lung carcinoma cell type unspecified recurrent		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung neoplasm		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lymphocytic leukaemia		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Lung neoplasm malignant		
subjects affected / exposed	11 / 2206 (0.50%)	13 / 2343 (0.55%)
occurrences causally related to treatment / all	0 / 11	0 / 13
deaths causally related to treatment / all	0 / 3	0 / 2
Lung squamous cell carcinoma stage 0		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Malignant melanoma		
subjects affected / exposed	3 / 2206 (0.14%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Lymphoma		

subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of spinal cord			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant peritoneal neoplasm			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mantle cell lymphoma			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant urinary tract neoplasm			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesothelioma			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Metastases to liver		
subjects affected / exposed	3 / 2206 (0.14%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1
Metastases to lung		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Metastases to peritoneum		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Metastases to lymph nodes		
subjects affected / exposed	2 / 2206 (0.09%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Metastatic carcinoma of the bladder		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Metastatic gastric cancer		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastasis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastatic neoplasm		

subjects affected / exposed	3 / 2206 (0.14%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Metastatic renal cell carcinoma		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastatic squamous cell carcinoma		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Monoclonal gammopathy		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Muscle neoplasm		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Myeloproliferative disorder		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Neoplasm malignant		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0
Neoplasm progression		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Neuroendocrine carcinoma		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Neuroma		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Nodular fasciitis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Non-Hodgkin's lymphoma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Non-small cell lung cancer		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Non-Hodgkin's lymphoma stage IV		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal adenocarcinoma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal squamous cell carcinoma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oral neoplasm		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal carcinoma		
subjects affected / exposed	0 / 2206 (0.00%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Ovarian adenoma		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Ovarian cancer		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0
Ovarian cancer metastatic		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ovarian cancer stage III		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ovarian fibroma		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ovarian epithelial cancer		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic carcinoma		

subjects affected / exposed	6 / 2206 (0.27%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 6	1 / 5
deaths causally related to treatment / all	0 / 2	0 / 2
Pancreatic neoplasm		
subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1
Pelvic neoplasm		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Parathyroid tumour benign		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Papillary thyroid cancer		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Plasma cell myeloma		
subjects affected / exposed	3 / 2206 (0.14%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0
Phyllodes tumour		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Plasmacytoma		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Polycythaemia vera		

subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal adenocarcinoma		
subjects affected / exposed	5 / 2206 (0.23%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal adenoma		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal cancer		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Renal cancer		
subjects affected / exposed	2 / 2206 (0.09%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0
Rectosigmoid cancer		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal neoplasm		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Renal cell carcinoma		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Skin cancer		

subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Squamous cell carcinoma		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Squamous cell carcinoma of lung		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Squamous cell carcinoma of skin		
subjects affected / exposed	3 / 2206 (0.14%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Squamous cell carcinoma of the oral cavity		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Thyroid adenoma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Transitional cell carcinoma		
subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Thyroid cancer		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	6 / 2206 (0.27%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cancer			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	1 / 2206 (0.05%)	5 / 2343 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Aortic dissection			
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arterial disorder			

subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Aortic stenosis		
subjects affected / exposed	5 / 2206 (0.23%)	8 / 2343 (0.34%)
occurrences causally related to treatment / all	0 / 5	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Arterial haemorrhage		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Arterial occlusive disease		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriosclerosis		
subjects affected / exposed	5 / 2206 (0.23%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1
Circulatory collapse		
subjects affected / exposed	3 / 2206 (0.14%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Deep vein thrombosis		
subjects affected / exposed	8 / 2206 (0.36%)	8 / 2343 (0.34%)
occurrences causally related to treatment / all	0 / 10	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Embolism venous		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Essential hypertension		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Femoral artery occlusion		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Femoral artery aneurysm		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhage		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haematoma		
subjects affected / exposed	2 / 2206 (0.09%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertension		
subjects affected / exposed	18 / 2206 (0.82%)	21 / 2343 (0.90%)
occurrences causally related to treatment / all	0 / 23	0 / 23
deaths causally related to treatment / all	0 / 0	0 / 0
Hypotension		
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive crisis		
subjects affected / exposed	7 / 2206 (0.32%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 12	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hypovolaemic shock		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Intermittent claudication		
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemia		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Orthostatic hypotension		
subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral arterial occlusive disease		
subjects affected / exposed	4 / 2206 (0.18%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral artery stenosis		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral embolism		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral vascular disorder		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral venous disease		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebolith			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery occlusion			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporal arteritis			
subjects affected / exposed	2 / 2206 (0.09%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	4 / 2206 (0.18%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	5 / 2206 (0.23%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis necrotising			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arthrodesis			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anticoagulant therapy			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign tumour excision			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker replacement			

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Chemotherapy		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hip arthroplasty		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hospitalisation		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hysterectomy		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Joint arthroplasty		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Knee arthroplasty		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal decompression		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rehabilitation therapy		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral operation			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth extraction			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 2206 (0.14%)	4 / 2343 (0.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	9 / 2206 (0.41%)	8 / 2343 (0.34%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	16 / 2206 (0.73%)	13 / 2343 (0.55%)	
occurrences causally related to treatment / all	0 / 16	0 / 13	
deaths causally related to treatment / all	0 / 16	0 / 13	
Device dislocation			
subjects affected / exposed	3 / 2206 (0.14%)	5 / 2343 (0.21%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic fatigue syndrome			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Device failure		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Device malfunction		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Foreign body reaction		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fatigue		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Face oedema		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
General physical health deterioration		
subjects affected / exposed	4 / 2206 (0.18%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1
Gait disturbance		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Inflammation		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Incarcerated hernia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hernia		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Malaise		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemic ulcer		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Medical device complication		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Multi-organ failure		
subjects affected / exposed	2 / 2206 (0.09%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 3
Nodule		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Non-cardiac chest pain		

subjects affected / exposed	7 / 2206 (0.32%)	5 / 2343 (0.21%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 2206 (0.18%)	5 / 2343 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyp			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	4 / 2206 (0.18%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
Sudden cardiac death			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ulcer haemorrhage			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune disorder			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Physical assault			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Activities of daily living impaired			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	11 / 2206 (0.50%)	5 / 2343 (0.21%)	
occurrences causally related to treatment / all	0 / 12	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Breast mass			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colpocele			
subjects affected / exposed	2 / 2206 (0.09%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial atrophy			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial metaplasia			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrocystic breast disease			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital prolapse			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mammary duct ectasia			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ovarian cyst		
subjects affected / exposed	4 / 2206 (0.18%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Rectocele		
subjects affected / exposed	4 / 2206 (0.18%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Uterine cyst		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Uterine polyp		
subjects affected / exposed	4 / 2206 (0.18%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Uterine haemorrhage		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Uterine prolapse		
subjects affected / exposed	9 / 2206 (0.41%)	9 / 2343 (0.38%)
occurrences causally related to treatment / all	0 / 9	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0
Vaginal cyst		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Vaginal prolapse		

subjects affected / exposed	5 / 2206 (0.23%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval leukoplakia			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	4 / 2206 (0.18%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchial hyperreactivity			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	4 / 2206 (0.18%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			

subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchitis chronic		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchiectasis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Dysphonia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchomalacia		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic obstructive pulmonary disease		
subjects affected / exposed	14 / 2206 (0.63%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 20	0 / 8
deaths causally related to treatment / all	0 / 1	0 / 0
Dyspnoea		
subjects affected / exposed	6 / 2206 (0.27%)	7 / 2343 (0.30%)
occurrences causally related to treatment / all	0 / 6	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 1
Dyspnoea exertional		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Epistaxis		

subjects affected / exposed	2 / 2206 (0.09%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Haemoptysis		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Emphysema		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hydrothorax		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Interstitial lung disease		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lung infiltration		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung disorder		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Laryngeal cyst		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nasal ulcer		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mediastinal cyst		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Painful respiration		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (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 / 2206 (0.05%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Pleurisy		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonitis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia aspiration		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary congestion		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary embolism		

subjects affected / exposed	19 / 2206 (0.86%)	13 / 2343 (0.55%)
occurrences causally related to treatment / all	0 / 19	1 / 16
deaths causally related to treatment / all	0 / 4	0 / 1
Pneumothorax		
subjects affected / exposed	2 / 2206 (0.09%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary mass		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary oedema		
subjects affected / exposed	6 / 2206 (0.27%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 3	0 / 1
Pulmonary fibrosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory arrest		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory failure		
subjects affected / exposed	3 / 2206 (0.14%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0
Tonsillar cyst		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tracheomalacia		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Emotional distress			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	6 / 2206 (0.27%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	11 / 2206 (0.50%)	9 / 2343 (0.38%)	
occurrences causally related to treatment / all	0 / 12	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			

subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia, paranoid type			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 2206 (0.00%)	4 / 2343 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			

subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Biliary colic		
subjects affected / exposed	2 / 2206 (0.09%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1
Cholangitis		
subjects affected / exposed	4 / 2206 (0.18%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Biliary cirrhosis primary		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cholelithiasis		
subjects affected / exposed	22 / 2206 (1.00%)	30 / 2343 (1.28%)
occurrences causally related to treatment / all	0 / 25	0 / 31
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis acute		
subjects affected / exposed	4 / 2206 (0.18%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis		
subjects affected / exposed	6 / 2206 (0.27%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Gallbladder oedema		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gallbladder necrosis		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder polyp			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Jaundice cholestatic			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Antinuclear antibody positive		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Carcinoembryonic antigen increased		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Blood pressure orthostatic		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Occult blood positive		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatic enzyme increased		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Investigation		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Troponin increased		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Protein total decreased		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	3 / 2206 (0.14%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fissure			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbon monoxide poisoning			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cartilage injury			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cervical vertebral fracture		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cataract traumatic		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Concussion		
subjects affected / exposed	7 / 2206 (0.32%)	8 / 2343 (0.34%)
occurrences causally related to treatment / all	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Contusion		
subjects affected / exposed	4 / 2206 (0.18%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dislocation of vertebra		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cranio-cerebral injury		
subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1
Coronary artery restenosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Facial bones fracture		

subjects affected / exposed	0 / 2206 (0.00%)	9 / 2343 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0
Eye penetration		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Femoral neck fracture		
subjects affected / exposed	16 / 2206 (0.73%)	15 / 2343 (0.64%)
occurrences causally related to treatment / all	1 / 16	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 0
Fall		
subjects affected / exposed	13 / 2206 (0.59%)	16 / 2343 (0.68%)
occurrences causally related to treatment / all	0 / 13	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 0
Fibula fracture		
subjects affected / exposed	14 / 2206 (0.63%)	11 / 2343 (0.47%)
occurrences causally related to treatment / all	0 / 14	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0
Foot fracture		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Femur fracture		
subjects affected / exposed	16 / 2206 (0.73%)	12 / 2343 (0.51%)
occurrences causally related to treatment / all	0 / 16	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0
Fractured sacrum		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal stoma complication		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Graft complication		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hand fracture		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Head injury		
subjects affected / exposed	4 / 2206 (0.18%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Humerus fracture		
subjects affected / exposed	13 / 2206 (0.59%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 13	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Hip fracture		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Injury corneal		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Incisional hernia		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ilium fracture		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Joint dislocation		
subjects affected / exposed	7 / 2206 (0.32%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Joint injury		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ligament rupture		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ligament injury		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Laceration		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Limb crushing injury		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ligament sprain		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Meniscus injury		

subjects affected / exposed	5 / 2206 (0.23%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbar vertebral fracture		
subjects affected / exposed	4 / 2206 (0.18%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Muscle rupture		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Overdose		
subjects affected / exposed	3 / 2206 (0.14%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Multiple injuries		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Patella fracture		
subjects affected / exposed	5 / 2206 (0.23%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Perineal injury		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumothorax traumatic		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural complication		

subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural haematoma		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural haemorrhage		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative hernia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative ileus		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Procedural hypotension		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Procedural pain		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pubis fracture		
subjects affected / exposed	3 / 2206 (0.14%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	1 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Radiation mucositis		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rib fracture		
subjects affected / exposed	7 / 2206 (0.32%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 7	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Road traffic accident		
subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2
Radius fracture		
subjects affected / exposed	25 / 2206 (1.13%)	22 / 2343 (0.94%)
occurrences causally related to treatment / all	0 / 26	0 / 22
deaths causally related to treatment / all	0 / 0	0 / 0
Scar		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Shunt malfunction		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Skull fracture		
subjects affected / exposed	5 / 2206 (0.23%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Skeletal injury		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Skin abrasion		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Soft tissue injury		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Subdural haematoma		
subjects affected / exposed	8 / 2206 (0.36%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 8	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Subdural haemorrhage		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tendon rupture		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Thermal burn		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Thoracic vertebral fracture		
subjects affected / exposed	1 / 2206 (0.05%)	9 / 2343 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0
Tibia fracture		
subjects affected / exposed	17 / 2206 (0.77%)	12 / 2343 (0.51%)
occurrences causally related to treatment / all	0 / 17	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0
Transplant dysfunction		

subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	4 / 2206 (0.18%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ulna fracture			
subjects affected / exposed	9 / 2206 (0.41%)	9 / 2343 (0.38%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulnar nerve injury			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital ureteric anomaly			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer gene carrier			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal dystrophy			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular dystrophy			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	8 / 2206 (0.36%)	18 / 2343 (0.77%)	
occurrences causally related to treatment / all	0 / 8	0 / 19	
deaths causally related to treatment / all	0 / 2	0 / 4	
Acute coronary syndrome			
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	7 / 2206 (0.32%)	12 / 2343 (0.51%)	
occurrences causally related to treatment / all	0 / 7	1 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	17 / 2206 (0.77%)	19 / 2343 (0.81%)	
occurrences causally related to treatment / all	0 / 17	0 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adams-Stokes syndrome			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Aortic valve incompetence		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Aortic valve disease		
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Aortic valve stenosis		
subjects affected / exposed	4 / 2206 (0.18%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Arrhythmia supraventricular		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Arrhythmia		
subjects affected / exposed	3 / 2206 (0.14%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriosclerosis coronary artery		
subjects affected / exposed	3 / 2206 (0.14%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial fibrillation		
subjects affected / exposed	50 / 2206 (2.27%)	40 / 2343 (1.71%)
occurrences causally related to treatment / all	4 / 69	0 / 47
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block		

subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial flutter		
subjects affected / exposed	0 / 2206 (0.00%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block second degree		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Bradycardia		
subjects affected / exposed	5 / 2206 (0.23%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0
Atrioventricular block complete		
subjects affected / exposed	5 / 2206 (0.23%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac arrest		
subjects affected / exposed	4 / 2206 (0.18%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 2
Bundle branch block left		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure		
subjects affected / exposed	15 / 2206 (0.68%)	21 / 2343 (0.90%)
occurrences causally related to treatment / all	0 / 17	0 / 24
deaths causally related to treatment / all	0 / 3	0 / 5
Cardiac failure acute		

subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1
Cardiac disorder		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure chronic		
subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1
Cardiac failure congestive		
subjects affected / exposed	10 / 2206 (0.45%)	9 / 2343 (0.38%)
occurrences causally related to treatment / all	0 / 11	0 / 9
deaths causally related to treatment / all	0 / 3	0 / 1
Cardiac fibrillation		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (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 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac valve sclerosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiogenic shock		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2
Cardio-respiratory arrest		

subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2
Cardiomyopathy		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiopulmonary failure		
subjects affected / exposed	4 / 2206 (0.18%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 1
Chronic right ventricular failure		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiovascular insufficiency		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery occlusion		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery disease		
subjects affected / exposed	9 / 2206 (0.41%)	17 / 2343 (0.73%)
occurrences causally related to treatment / all	0 / 9	0 / 19
deaths causally related to treatment / all	0 / 0	0 / 1
Coronary artery insufficiency		
subjects affected / exposed	3 / 2206 (0.14%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Extrasystoles		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery stenosis		
subjects affected / exposed	1 / 2206 (0.05%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive heart disease		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Heart valve calcification		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Heart valve incompetence		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Left atrial dilatation		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemic cardiomyopathy		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Left ventricular failure		
subjects affected / exposed	2 / 2206 (0.09%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1
Mitral valve disease		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mitral valve disease mixed		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mitral valve incompetence		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Myocardial infarction		
subjects affected / exposed	21 / 2206 (0.95%)	24 / 2343 (1.02%)
occurrences causally related to treatment / all	0 / 26	1 / 27
deaths causally related to treatment / all	0 / 3	0 / 2
Myocardial ischaemia		
subjects affected / exposed	4 / 2206 (0.18%)	13 / 2343 (0.55%)
occurrences causally related to treatment / all	0 / 4	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 1
Pericardial effusion		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Palpitations		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pericardial haemorrhage		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pericarditis		

subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Right ventricular failure		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Sinus arrest		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Sinoatrial block		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Sinus node dysfunction		
subjects affected / exposed	6 / 2206 (0.27%)	10 / 2343 (0.43%)
occurrences causally related to treatment / all	0 / 6	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0
Supraventricular extrasystoles		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sinus bradycardia		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Supraventricular tachycardia		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Supraventricular tachyarrhythmia		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tachycardia		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tachyarrhythmia		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tachycardia induced cardiomyopathy		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tricuspid valve disease		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ventricular arrhythmia		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ventricular extrasystoles		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ventricular fibrillation		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ventricular tachycardia		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Acoustic neuritis			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Akinesia			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	3 / 2206 (0.14%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (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 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Carotid artery thrombosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Carpal tunnel syndrome		
subjects affected / exposed	1 / 2206 (0.05%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Cauda equina syndrome		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebellar haemorrhage		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebellar infarction		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral artery embolism		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral arteriosclerosis		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral atrophy		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral haemorrhage		
subjects affected / exposed	5 / 2206 (0.23%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 2
Cerebral infarction		
subjects affected / exposed	5 / 2206 (0.23%)	17 / 2343 (0.73%)
occurrences causally related to treatment / all	0 / 5	1 / 17
deaths causally related to treatment / all	0 / 0	0 / 1
Cerebral thrombosis		
subjects affected / exposed	8 / 2206 (0.36%)	8 / 2343 (0.34%)
occurrences causally related to treatment / all	0 / 9	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral ischaemia		
subjects affected / exposed	6 / 2206 (0.27%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 8	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral microangiopathy		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (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	22 / 2206 (1.00%)	29 / 2343 (1.24%)
occurrences causally related to treatment / all	0 / 23	0 / 30
deaths causally related to treatment / all	0 / 6	0 / 3
Cerebrovascular disorder		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebrovascular insufficiency		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cervicogenic headache		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cognitive disorder		
subjects affected / exposed	3 / 2206 (0.14%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Coma		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cubital tunnel syndrome		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Dementia		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic hyperosmolar coma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dementia Alzheimer's type		
subjects affected / exposed	2 / 2206 (0.09%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1
Dysaesthesia		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic neuropathy		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dizziness		
subjects affected / exposed	5 / 2206 (0.23%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Embolic stroke		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Encephalopathy		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Extrapyramidal disorder		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Epilepsy		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhage intracranial		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2
Facial paresis		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hemiparesis		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhagic stroke		
subjects affected / exposed	3 / 2206 (0.14%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 1
Headache		
subjects affected / exposed	4 / 2206 (0.18%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoaesthesia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypotonia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive encephalopathy		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoxic-ischaemic encephalopathy		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intercostal neuralgia		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intracranial aneurysm		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemic cerebral infarction		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Loss of consciousness		
subjects affected / exposed	2 / 2206 (0.09%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemic stroke		
subjects affected / exposed	11 / 2206 (0.50%)	9 / 2343 (0.38%)
occurrences causally related to treatment / all	0 / 13	0 / 10
deaths causally related to treatment / all	0 / 1	0 / 1
Lacunar infarction		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbar radiculopathy		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Mental impairment		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Motor neurone disease		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Motor dysfunction		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mononeuropathy multiplex		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Myasthenia gravis		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nervous system disorder		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Optic neuritis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Paraesthesia		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Parkinson's disease		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Parkinsonism		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Partial seizures		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pseudoradicular syndrome		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Polyneuropathy		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Presyncope		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Radicular syndrome		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Radiculitis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pyramidal tract syndrome		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Radiculopathy		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sciatica		
subjects affected / exposed	6 / 2206 (0.27%)	12 / 2343 (0.51%)
occurrences causally related to treatment / all	0 / 6	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0
Seizure		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Senile dementia		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal cord compression		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Subarachnoid haemorrhage		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Sensory disturbance		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tarsal tunnel syndrome		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Syncope		

subjects affected / exposed	18 / 2206 (0.82%)	20 / 2343 (0.85%)
occurrences causally related to treatment / all	0 / 18	0 / 21
deaths causally related to treatment / all	0 / 0	0 / 0
Thrombotic cerebral infarction		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Transient global amnesia		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Trigeminal neuralgia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
VIIth nerve paralysis		
subjects affected / exposed	3 / 2206 (0.14%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Transient ischaemic attack		
subjects affected / exposed	21 / 2206 (0.95%)	19 / 2343 (0.81%)
occurrences causally related to treatment / all	0 / 24	0 / 21
deaths causally related to treatment / all	0 / 0	0 / 0
Vascular dementia		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vascular headache		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Vertebrobasilar insufficiency		

subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 2206 (0.50%)	11 / 2343 (0.47%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic disorder			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow oedema			
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	3 / 2206 (0.14%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			

subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenomegaly			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytosis			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 2206 (0.14%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniere's disease			

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoacusis			
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	14 / 2206 (0.63%)	8 / 2343 (0.34%)	
occurrences causally related to treatment / all	0 / 18	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otosclerosis			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blepharochalasis			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blindness unilateral			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cataract		
subjects affected / exposed	17 / 2206 (0.77%)	15 / 2343 (0.64%)
occurrences causally related to treatment / all	0 / 26	0 / 19
deaths causally related to treatment / all	0 / 0	0 / 0
Cataract diabetic		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Detachment of macular retinal pigment epithelium		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diplopia		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Eye haemorrhage		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ectropion		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Glaucoma		
subjects affected / exposed	3 / 2206 (0.14%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Keratopathy		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Iridocyclitis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Macular fibrosis		
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Retinal detachment		
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Maculopathy		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Open angle glaucoma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Retinal tear		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Retinal haemorrhage		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Retinal vascular thrombosis		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	4 / 2206 (0.18%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia obstructive			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal pain		
subjects affected / exposed	10 / 2206 (0.45%)	8 / 2343 (0.34%)
occurrences causally related to treatment / all	0 / 10	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal rigidity		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Acquired oesophageal web		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Anal haemorrhage		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Anal prolapse		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Anal sphincter atony		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Colitis		
subjects affected / exposed	3 / 2206 (0.14%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic gastritis		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Coeliac disease		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colitis microscopic		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Colitis ischaemic		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Colitis ulcerative		
subjects affected / exposed	3 / 2206 (0.14%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Constipation		
subjects affected / exposed	8 / 2206 (0.36%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 8	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Crohn's disease		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diaphragmatic hernia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (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	9 / 2206 (0.41%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 10	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulum intestinal		
subjects affected / exposed	1 / 2206 (0.05%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulum		
subjects affected / exposed	3 / 2206 (0.14%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticular perforation		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenal stenosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulum oesophageal		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenal ulcer haemorrhage		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenal ulcer		
subjects affected / exposed	5 / 2206 (0.23%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Dyspepsia		

subjects affected / exposed	3 / 2206 (0.14%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenal ulcer perforation		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenitis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Enteritis		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dysphagia		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Faecal incontinence		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Epigastric discomfort		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Enterocolitis haemorrhagic		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Femoral hernia		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Faeces discoloured		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric ulcer		
subjects affected / exposed	6 / 2206 (0.27%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis		
subjects affected / exposed	4 / 2206 (0.18%)	9 / 2343 (0.38%)
occurrences causally related to treatment / all	0 / 4	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric ulcer haemorrhage		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroduodenal ulcer		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis erosive		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal haemorrhage		
subjects affected / exposed	6 / 2206 (0.27%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal motility disorder		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal inflammation		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal mucosal disorder		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal obstruction		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal stenosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrooesophageal reflux disease		
subjects affected / exposed	3 / 2206 (0.14%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Haematemesis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haematochezia		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhoids		

subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hiatus hernia		
subjects affected / exposed	2 / 2206 (0.09%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Ileus		
subjects affected / exposed	7 / 2206 (0.32%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 11	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hernial eventration		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Inguinal hernia		
subjects affected / exposed	14 / 2206 (0.63%)	7 / 2343 (0.30%)
occurrences causally related to treatment / all	0 / 14	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal angina		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal fistula		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal haemorrhage		
subjects affected / exposed	4 / 2206 (0.18%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal ischaemia		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Intestinal obstruction		
subjects affected / exposed	5 / 2206 (0.23%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	1 / 5	0 / 1
deaths causally related to treatment / all	1 / 2	0 / 0
Intestinal perforation		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal strangulation		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Irritable bowel syndrome		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Large intestinal haemorrhage		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Large intestine polyp		
subjects affected / exposed	4 / 2206 (0.18%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Large intestinal stenosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Malabsorption		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lower gastrointestinal haemorrhage		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mesenteric artery embolism		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Mechanical ileus		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Melaena		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal polyp		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophagitis		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nausea		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic cyst		

subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic necrosis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis		
subjects affected / exposed	0 / 2206 (0.00%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1
Pancreatitis acute		
subjects affected / exposed	1 / 2206 (0.05%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis chronic		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peptic ulcer		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis necrotising		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peritoneal perforation		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pharyngo-oesophageal diverticulum		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Periodontal disease		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal haemorrhage		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal polyp		
subjects affected / exposed	2 / 2206 (0.09%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Small intestinal obstruction		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Retroperitoneal haematoma		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal prolapse		
subjects affected / exposed	1 / 2206 (0.05%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Subileus		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Stomatitis		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toothache			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue oedema			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus of small bowel			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 2206 (0.18%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Decubitus ulcer		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Dermatitis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic foot		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dermatitis allergic		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Drug eruption		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lichenoid keratosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lichen sclerosis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pemphigoid		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pruritic			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	3 / 2206 (0.14%)	5 / 2343 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder disorder			
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder irritation			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			

subjects affected / exposed	1 / 2206 (0.05%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Bladder prolapse		
subjects affected / exposed	0 / 2206 (0.00%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Calculus bladder		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Calculus ureteric		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Calculus urethral		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic kidney disease		
subjects affected / exposed	3 / 2206 (0.14%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Diabetic nephropathy		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cystitis interstitial		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hydronephrosis		

subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Incontinence		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haematuria		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Mixed incontinence		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Nephrolithiasis		
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Renal failure		
subjects affected / exposed	3 / 2206 (0.14%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 2
Nephropathy		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal colic		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Stress urinary incontinence		

subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tubulointerstitial nephritis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ureteric stenosis		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urethral disorder		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Urethral stenosis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary bladder polyp		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Urge incontinence		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary incontinence		
subjects affected / exposed	4 / 2206 (0.18%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract obstruction		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			
subjects affected / exposed	6 / 2206 (0.27%)	5 / 2343 (0.21%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basedow's disease			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic nodular goitre			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (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			
Arthralgia			
subjects affected / exposed	10 / 2206 (0.45%)	15 / 2343 (0.64%)	
occurrences causally related to treatment / all	1 / 10	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acquired claw toe			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	6 / 2206 (0.27%)	4 / 2343 (0.17%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	16 / 2206 (0.73%)	10 / 2343 (0.43%)	
occurrences causally related to treatment / all	0 / 17	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone loss			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone disorder			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Chondrocalcinosis		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bursitis		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Compartment syndrome		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dupuytren's contracture		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Chondropathy		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fistula		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fibromyalgia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Fracture pain		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemarthrosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Foot deformity		
subjects affected / exposed	4 / 2206 (0.18%)	7 / 2343 (0.30%)
occurrences causally related to treatment / all	0 / 7	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral disc disorder		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral disc degeneration		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral disc protrusion		
subjects affected / exposed	12 / 2206 (0.54%)	7 / 2343 (0.30%)
occurrences causally related to treatment / all	0 / 15	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0
Joint effusion		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Joint swelling		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbar spinal stenosis		

subjects affected / exposed	4 / 2206 (0.18%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	1 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Kyphosis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Mobility decreased		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Monarthritis		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Morphoea		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Muscle disorder		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Muscular weakness		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal chest pain		
subjects affected / exposed	1 / 2206 (0.05%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal pain		

subjects affected / exposed	4 / 2206 (0.18%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	1 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Myopathy		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nodal osteoarthritis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Neck pain		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Osteoarthropathy		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Osteochondrosis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Osteoarthritis		
subjects affected / exposed	79 / 2206 (3.58%)	99 / 2343 (4.23%)
occurrences causally related to treatment / all	1 / 87	0 / 118
deaths causally related to treatment / all	0 / 0	0 / 0
Osteonecrosis of jaw		
subjects affected / exposed	3 / 2206 (0.14%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	3 / 3	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Osteonecrosis		

subjects affected / exposed	5 / 2206 (0.23%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pain in extremity		
subjects affected / exposed	5 / 2206 (0.23%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Osteoporosis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pain in jaw		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Periarthritis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Plica syndrome		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Polymyalgia rheumatica		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pseudarthrosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rhabdomyolysis		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rotator cuff syndrome		
subjects affected / exposed	4 / 2206 (0.18%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Rheumatoid arthritis		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Sacroiliitis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Seronegative arthritis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Sjogren's syndrome		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal column stenosis		
subjects affected / exposed	14 / 2206 (0.63%)	22 / 2343 (0.94%)
occurrences causally related to treatment / all	0 / 15	1 / 27
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal osteoarthritis		
subjects affected / exposed	4 / 2206 (0.18%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 4	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal pain		

subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondyloarthritis			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial disorder			
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal sepsis			

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Abdominal abscess		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Abscess		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Abscess limb		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Appendiceal abscess		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Abscess neck		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Appendicitis		
subjects affected / exposed	4 / 2206 (0.18%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Appendicitis perforated		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Arthritis bacterial		

subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Atypical pneumonia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Arthritis infective		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bacteraemia		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bacterial infection		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bacterial pyelonephritis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchopneumonia		
subjects affected / exposed	6 / 2206 (0.27%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 1
Bronchitis		
subjects affected / exposed	8 / 2206 (0.36%)	7 / 2343 (0.30%)
occurrences causally related to treatment / all	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchitis fungal		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cellulitis		
subjects affected / exposed	3 / 2206 (0.14%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis infective		
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Clostridium difficile infection		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic tonsillitis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic sinusitis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dengue fever		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cystitis		
subjects affected / exposed	6 / 2206 (0.27%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 7	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Device related infection		

subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ear infection		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulitis		
subjects affected / exposed	11 / 2206 (0.50%)	10 / 2343 (0.43%)
occurrences causally related to treatment / all	0 / 15	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0
Endocarditis		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Enterocolitis bacterial		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Erysipelas		
subjects affected / exposed	4 / 2206 (0.18%)	9 / 2343 (0.38%)
occurrences causally related to treatment / all	0 / 6	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis		
subjects affected / exposed	9 / 2206 (0.41%)	9 / 2343 (0.38%)
occurrences causally related to treatment / all	0 / 9	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0
Gangrene		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis viral		

subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal infection		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Helicobacter gastritis		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haemophilus infection		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
H1N1 influenza		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis C		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatic cyst infection		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Herpes zoster		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Infected skin ulcer		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Infection		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Influenza		
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Klebsiella infection		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Klebsiella bacteraemia		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Liver abscess		
subjects affected / exposed	0 / 2206 (0.00%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Listeriosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Laryngitis		

subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Localised infection		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lobar pneumonia		
subjects affected / exposed	2 / 2206 (0.09%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0
Lower respiratory tract infection		
subjects affected / exposed	2 / 2206 (0.09%)	6 / 2343 (0.26%)
occurrences causally related to treatment / all	0 / 2	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 1
Lymph node tuberculosis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung infection		
subjects affected / exposed	3 / 2206 (0.14%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Meningitis viral		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Meningitis aseptic		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mycobacterium avium complex infection		

subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Neutropenic sepsis		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Necrotising fasciitis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Onychomycosis		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis		
subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	2 / 3	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Otitis media		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Parotitis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peritonitis		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Pneumonia		

subjects affected / exposed	44 / 2206 (1.99%)	48 / 2343 (2.05%)
occurrences causally related to treatment / all	0 / 52	0 / 59
deaths causally related to treatment / all	0 / 5	0 / 2
Pneumonia bacterial		
subjects affected / exposed	3 / 2206 (0.14%)	4 / 2343 (0.17%)
occurrences causally related to treatment / all	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia influenzal		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia pneumococcal		
subjects affected / exposed	3 / 2206 (0.14%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia haemophilus		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia pseudomonal		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia staphylococcal		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia streptococcal		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural infection		

subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative wound infection		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pseudomembranous colitis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary tuberculosis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis		
subjects affected / exposed	5 / 2206 (0.23%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis acute		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Salmonellosis		
subjects affected / exposed	1 / 2206 (0.05%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis chronic		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory tract infection		

subjects affected / exposed	2 / 2206 (0.09%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Salpingo-oophoritis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Salpingitis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Septic shock		
subjects affected / exposed	5 / 2206 (0.23%)	5 / 2343 (0.21%)
occurrences causally related to treatment / all	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 3	0 / 3
Sepsis		
subjects affected / exposed	6 / 2206 (0.27%)	15 / 2343 (0.64%)
occurrences causally related to treatment / all	0 / 7	0 / 16
deaths causally related to treatment / all	0 / 2	0 / 2
Skin infection		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sinusitis		
subjects affected / exposed	3 / 2206 (0.14%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Small intestine gangrene		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Soft tissue infection		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Staphylococcal bacteraemia		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Staphylococcal sepsis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Stenotrophomonas infection		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tick-borne viral encephalitis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Subcutaneous abscess		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Subdural empyema		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tonsillitis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tooth infection		

subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tuberculosis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tracheobronchitis		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tracheitis		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Upper respiratory tract infection		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Tuberculosis of peripheral lymph nodes		
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
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	13 / 2206 (0.59%)	11 / 2343 (0.47%)
occurrences causally related to treatment / all	0 / 15	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0
Urosepsis		
subjects affected / exposed	6 / 2206 (0.27%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Vaginal infection		

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	3 / 2206 (0.14%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	6 / 2206 (0.27%)	7 / 2343 (0.30%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetes mellitus			
subjects affected / exposed	2 / 2206 (0.09%)	3 / 2343 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypercalcaemia		
subjects affected / exposed	1 / 2206 (0.05%)	3 / 2343 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Electrolyte imbalance		
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperglycaemia		
subjects affected / exposed	1 / 2206 (0.05%)	1 / 2343 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypercholesterolaemia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypocalcaemia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoglycaemia		
subjects affected / exposed	0 / 2206 (0.00%)	2 / 2343 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperkalaemia		
subjects affected / exposed	1 / 2206 (0.05%)	0 / 2343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hyponatraemia		

subjects affected / exposed	4 / 2206 (0.18%)	2 / 2343 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	2 / 2206 (0.09%)	0 / 2343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 2206 (0.09%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 2206 (0.00%)	1 / 2343 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo/Denosumab 60 mg Q6M	Denosumab/Denosu mab 60 mg Q6M	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1809 / 2206 (82.00%)	1920 / 2343 (81.95%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	240 / 2206 (10.88%)	268 / 2343 (11.44%)	
occurrences (all)	338	373	
Contusion			
subjects affected / exposed	181 / 2206 (8.20%)	176 / 2343 (7.51%)	
occurrences (all)	251	245	
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	460 / 2206 (20.85%) 581	498 / 2343 (21.25%) 606	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Sciatica subjects affected / exposed occurrences (all)	173 / 2206 (7.84%) 203 121 / 2206 (5.49%) 158 149 / 2206 (6.75%) 175	163 / 2343 (6.96%) 193 103 / 2343 (4.40%) 120 165 / 2343 (7.04%) 198	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	141 / 2206 (6.39%) 169	168 / 2343 (7.17%) 194	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	138 / 2206 (6.26%) 174	140 / 2343 (5.98%) 177	
Eye disorders Cataract subjects affected / exposed occurrences (all)	319 / 2206 (14.46%) 492	317 / 2343 (13.53%) 467	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	139 / 2206 (6.30%) 169 141 / 2206 (6.39%) 147	152 / 2343 (6.49%) 175 118 / 2343 (5.04%) 134	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	172 / 2206 (7.80%) 217	168 / 2343 (7.17%) 204	
Psychiatric disorders			

Depression subjects affected / exposed occurrences (all)	135 / 2206 (6.12%) 161	143 / 2343 (6.10%) 161	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	527 / 2206 (23.89%) 755	541 / 2343 (23.09%) 763	
Osteoarthritis subjects affected / exposed occurrences (all)	332 / 2206 (15.05%) 449	355 / 2343 (15.15%) 484	
Back pain subjects affected / exposed occurrences (all)	501 / 2206 (22.71%) 693	493 / 2343 (21.04%) 665	
Musculoskeletal pain subjects affected / exposed occurrences (all)	197 / 2206 (8.93%) 243	231 / 2343 (9.86%) 290	
Pain in extremity subjects affected / exposed occurrences (all)	264 / 2206 (11.97%) 333	293 / 2343 (12.51%) 387	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	372 / 2206 (16.86%) 565	385 / 2343 (16.43%) 576	
Influenza subjects affected / exposed occurrences (all)	179 / 2206 (8.11%) 225	192 / 2343 (8.19%) 238	
Cystitis subjects affected / exposed occurrences (all)	194 / 2206 (8.79%) 372	212 / 2343 (9.05%) 396	
Bronchitis subjects affected / exposed occurrences (all)	206 / 2206 (9.34%) 290	226 / 2343 (9.65%) 350	
Urinary tract infection subjects affected / exposed occurrences (all)	242 / 2206 (10.97%) 385	250 / 2343 (10.67%) 389	

Pneumonia			
subjects affected / exposed	137 / 2206 (6.21%)	167 / 2343 (7.13%)	
occurrences (all)	217	246	
Upper respiratory tract infection			
subjects affected / exposed	139 / 2206 (6.30%)	128 / 2343 (5.46%)	
occurrences (all)	169	159	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	215 / 2206 (9.75%)	200 / 2343 (8.54%)	
occurrences (all)	223	207	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2007	<ul style="list-style-type: none">- Added a PK/PD substudy to provide additional data to characterize the PK and PD profiles at additional time points during the subject's dosing interval.- Incorporated investigational product from a new manufacturing facility (BIP) to be administered by prefilled syringe.- Added an assessment of antidenosumab antibodies at extension month 6 in subjects who received investigational product from BIP to evaluate the immunogenicity for BIP drug substance in prefilled syringes.
09 March 2009	<ul style="list-style-type: none">- Extended the study beyond extension month 24 for 5 additional years to allow reporting of descriptive analyses of safety and assessments of the cumulative effect of denosumab on BMD, BTMs, and vertebral and nonvertebral fractures following up to ten years of therapy.
01 September 2010	<ul style="list-style-type: none">- Added procedures to assess incident vertebral fractures at 2-year intervals starting at year 3.
13 January 2013	<ul style="list-style-type: none">- Updated the procedures for reporting adverse events and serious adverse events to IRB/IECs and regulatory authorities.
15 May 2014	<ul style="list-style-type: none">- Added quantitative computer tomography assessments for a subset of approximately 30 subjects who had participated in a similar substudy in Study 20030216.- Added blood sample collection to analyze bone turnover markers CTX-1 and P1NP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported