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	• New data added to full data set add histomorphology endpoint data

Trial information

Trial identification

Sponsor protocol code	20060289

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

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
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).	

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			
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	-2.81	-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:
• 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 ≥ 3

End point title	Number of Participants with Laboratory Toxicities of Grade ≥

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

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]

End point description:

End point type	Primary

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

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

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

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

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

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

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

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

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

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

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:

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

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

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

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

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

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

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

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:

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

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:

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

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 = 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

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

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

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

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 incudes 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

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

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) Month 84 (n = 0, 19)	1.005 (± 0.242) 99999 (± 99999)	0.904 (± 0.243) 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

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

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 (± 358.238)	1033.416 (± 352.259)		
Month 84 (n = 0, 19)	99999 (± 99999)	708.669 (± 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:

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.

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 (± 51.859)	156.335 (± 48.567)		
Month 84 (n = 0, 19)	99999 (± 99999)	132.965 (± 28.064)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Histomorphometry: Cortical Width

End point title	Bone Histomorphometry: Cortical Width

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

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) Month 84 (n = 0, 21)	622.22 (± 246.7) 99999 (± 99999)	707.69 (± 237.97) 786.19 (± 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

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

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

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

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

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

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

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

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:

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).
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.

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:

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.
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

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: µm				
arithmetic mean (standard deviation)				
Month 24 (n = 13, 25)	43.11 (± 6.08)	49.74 (± 10.51)		
Month 84 (n = 0, 19)	99999 (± 99999)	39.59 (± 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

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

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 (± 0.701)	0.328 (± 0.613)		
Month 84 (n = 0, 19)	99999 (± 99999)	0.511 (± 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

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

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

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) Month 84 (n = 0, 19)	9.6 (± 13.4) 99999 (± 99999)	11 (± 18.5) 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

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

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:

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.
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.

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 avarage 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

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

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: $\mu m^3/\mu m^2$/year				
arithmetic mean (standard deviation)				
Month 24 (n = 5, 10)	0.898 (± 0.706)	2.153 (± 2.468)		
Month 84 (n = 0, 10)	99999 (± 99999)	0.691 (± 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:

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.
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.

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) Month 84 (n = 0, 19)	0.108 (± 0.193) 99999 (± 99999)	0.146 (± 0.382) 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

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)		

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:

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.
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.

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:

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.
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

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Placebo/Denosumab 60 mg Q6M
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
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/Denosumab 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	
Craniocerebral 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 sclerosus			
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	
Spondyloarthropathy			
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/Denosumab 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	460 / 2206 (20.85%)	498 / 2343 (21.25%)	
occurrences (all)	581	606	
Nervous system disorders			
Dizziness			
subjects affected / exposed	173 / 2206 (7.84%)	163 / 2343 (6.96%)	
occurrences (all)	203	193	
Headache			
subjects affected / exposed	121 / 2206 (5.49%)	103 / 2343 (4.40%)	
occurrences (all)	158	120	
Sciatica			
subjects affected / exposed	149 / 2206 (6.75%)	165 / 2343 (7.04%)	
occurrences (all)	175	198	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	141 / 2206 (6.39%)	168 / 2343 (7.17%)	
occurrences (all)	169	194	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	138 / 2206 (6.26%)	140 / 2343 (5.98%)	
occurrences (all)	174	177	
Eye disorders			
Cataract			
subjects affected / exposed	319 / 2206 (14.46%)	317 / 2343 (13.53%)	
occurrences (all)	492	467	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	139 / 2206 (6.30%)	152 / 2343 (6.49%)	
occurrences (all)	169	175	
Constipation			
subjects affected / exposed	141 / 2206 (6.39%)	118 / 2343 (5.04%)	
occurrences (all)	147	134	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	172 / 2206 (7.80%)	168 / 2343 (7.17%)	
occurrences (all)	217	204	
Psychiatric disorders			

Depression			
subjects affected / exposed	135 / 2206 (6.12%)	143 / 2343 (6.10%)	
occurrences (all)	161	161	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	527 / 2206 (23.89%)	541 / 2343 (23.09%)	
occurrences (all)	755	763	
Osteoarthritis			
subjects affected / exposed	332 / 2206 (15.05%)	355 / 2343 (15.15%)	
occurrences (all)	449	484	
Back pain			
subjects affected / exposed	501 / 2206 (22.71%)	493 / 2343 (21.04%)	
occurrences (all)	693	665	
Musculoskeletal pain			
subjects affected / exposed	197 / 2206 (8.93%)	231 / 2343 (9.86%)	
occurrences (all)	243	290	
Pain in extremity			
subjects affected / exposed	264 / 2206 (11.97%)	293 / 2343 (12.51%)	
occurrences (all)	333	387	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	372 / 2206 (16.86%)	385 / 2343 (16.43%)	
occurrences (all)	565	576	
Influenza			
subjects affected / exposed	179 / 2206 (8.11%)	192 / 2343 (8.19%)	
occurrences (all)	225	238	
Cystitis			
subjects affected / exposed	194 / 2206 (8.79%)	212 / 2343 (9.05%)	
occurrences (all)	372	396	
Bronchitis			
subjects affected / exposed	206 / 2206 (9.34%)	226 / 2343 (9.65%)	
occurrences (all)	290	350	
Urinary tract infection			
subjects affected / exposed	242 / 2206 (10.97%)	250 / 2343 (10.67%)	
occurrences (all)	385	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	- Added a PK/PD substudy to provide additional data to characterize the PK and PD profiles at additional time points during the subjecti¦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	- 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	- Added procedures to assess incident vertebral fractures at 2-year intervals starting at year 3.
13 January 2013	- Updated the procedures for reporting adverse events and serious adverse events to IRB/IECs and regulatory authorities.
15 May 2014	- 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