



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled, Multi-center Phase 3 Study of Denosumab as Adjuvant Treatment for Women With Early-stage Breast Cancer at High Risk of Recurrence (D-CARE)

Summary

EudraCT number	2009-011299-32
Trial protocol	PT HU GB ES CZ LV FR BE SK NL IE DK SI GR IT BG DE
Global end of trial date	26 March 2018

Results information

Result version number	v1 (current)
This version publication date	10 April 2019
First version publication date	10 April 2019

Trial information

Trial identification

Sponsor protocol code	20060359
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01077154
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	26 March 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the treatment effect of denosumab with that of placebo on prolonging bone metastasis-free survival in subjects with early-stage breast cancer at high risk of disease recurrence.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable federal and local regulations/guidelines.

The protocol, proposed informed consent form (ICF), other written subject information, and any proposed advertising material was submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for written approval before recruitment of subjects in the study and the shipment of investigational product.

The investigator was responsible for obtaining written informed consent after the aims, methods, and potential hazards of the study were adequately explained.

Informed consent was obtained before any protocol-specific screening procedures and before any investigational product was administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 June 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 373
Country: Number of subjects enrolled	Australia: 297
Country: Number of subjects enrolled	United Kingdom: 237
Country: Number of subjects enrolled	Belgium: 228
Country: Number of subjects enrolled	France: 170
Country: Number of subjects enrolled	Greece: 103
Country: Number of subjects enrolled	Ireland: 75
Country: Number of subjects enrolled	Netherlands: 67
Country: Number of subjects enrolled	Denmark: 55
Country: Number of subjects enrolled	Portugal: 51
Country: Number of subjects enrolled	Italy: 46
Country: Number of subjects enrolled	Germany: 41

Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	United States: 715
Country: Number of subjects enrolled	Canada: 287
Country: Number of subjects enrolled	Hungary: 232
Country: Number of subjects enrolled	Czech Republic: 121
Country: Number of subjects enrolled	Russian Federation: 118
Country: Number of subjects enrolled	Poland: 92
Country: Number of subjects enrolled	Latvia: 35
Country: Number of subjects enrolled	Bulgaria: 35
Country: Number of subjects enrolled	Slovakia: 29
Country: Number of subjects enrolled	Romania: 17
Country: Number of subjects enrolled	Slovenia: 9
Country: Number of subjects enrolled	Serbia: 4
Country: Number of subjects enrolled	Japan: 262
Country: Number of subjects enrolled	India: 174
Country: Number of subjects enrolled	Korea, Republic of: 78
Country: Number of subjects enrolled	Taiwan: 43
Country: Number of subjects enrolled	Philippines: 32
Country: Number of subjects enrolled	Hong Kong: 32
Country: Number of subjects enrolled	Malaysia: 15
Country: Number of subjects enrolled	Brazil: 200
Country: Number of subjects enrolled	South Africa: 63
Country: Number of subjects enrolled	Mexico: 53
Country: Number of subjects enrolled	Chile: 34
Country: Number of subjects enrolled	Peru: 28
Country: Number of subjects enrolled	Argentina: 22
Country: Number of subjects enrolled	Turkey: 19
Worldwide total number of subjects	4509
EEA total number of subjects	2016

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)	3919
From 65 to 84 years	588
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 407 centers in Australia, Western Europe, Eastern Europe, Israel, North America, Asia, South America, South Africa, and Turkey from 02 June 2010 to 24 August 2012.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to 1 of 2 groups. Randomization was stratified based on breast cancer therapy/lymph node (LN) status, hormone receptor status, human epidermal growth factor receptor 2 (HER-2) status, age, and geographic region.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants were randomized to receive placebo subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by placebo subcutaneous injections once every 3 months for 4.5 years.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously for up to 5 years.

Arm title	Denosumab
------------------	-----------

Arm description:

Participants were randomized to receive denosumab 120 mg subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by denosumab 120 mg subcutaneous injections once every 3 months for 4.5 years.

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	AMG 162
Other name	XGEVA®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously for up to 5 years.

Number of subjects in period 1	Placebo	Denosumab
Started	2253	2256
Received Study Drug	2229	2230
Completed	27	28
Not completed	2226	2228
Consent withdrawn by subject	369	385
Ineligibility Determined	10	14
Protocol-specified Criteria (Study Ended)	1524	1514
Adverse event, non-fatal	9	9
Protocol Deviation	1	-
Death	215	214
Other	14	11
Administrative Decision	1	6
Lost to follow-up	43	35
Disease Progression	18	20
Noncompliance	22	20

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive placebo subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by placebo subcutaneous injections once every 3 months for 4.5 years.	
Reporting group title	Denosumab
Reporting group description:	
Participants were randomized to receive denosumab 120 mg subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by denosumab 120 mg subcutaneous injections once every 3 months for 4.5 years.	

Reporting group values	Placebo	Denosumab	Total
Number of subjects	2253	2256	4509
Age, Customized			
Units: Subjects			
18 - 64 years	1960	1959	3919
65 - 74 years	259	260	519
75 - 84 years	33	36	69
≥ 85 years	1	1	2
Age Continuous			
Units: years			
arithmetic mean	51.6	51.4	-
standard deviation	± 10.6	± 10.7	-
Sex: Female, Male			
Units: Subjects			
Female	2253	2256	4509
Male	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
White	1692	1676	3368
Asian	222	213	435
Japanese	134	135	269
Hispanic/Latino	112	135	247
Black	70	74	144
Native Hawaiian or Other Pacific Islander	4	3	7
American Indian or Alaska Native	1	0	1
Other	18	20	38
Menopausal Status			
Units: Subjects			
Premenopausal	1165	1195	2360
Postmenopausal	1088	1061	2149
Eastern Cooperative Oncology Group (ECOG) Performance Status			
A scale to assess a patient's disease status. 0 = Fully active, able to carry out all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care, unable to carry out any work activities. Up and about > 50% of waking hours;			

3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours;
4 = Completely disabled, confined to bed or chair;
5 = Dead.

Units: Subjects			
0 (Fully active)	1913	1922	3835
1 (Restricted but ambulatory)	340	329	669
2 (Ambulatory, unable to work)	0	3	3
Missing	0	2	2

Breast Cancer Therapy / Lymph Node Status (Strata per Randomization)			
--	--	--	--

Breast cancer therapy / lymph node (LN) status:
a. neo-adjuvant therapy / any LN status;
b. adjuvant therapy / LN negative (based on axillary LN dissection, or based on sentinel node [SN] status);
c. adjuvant therapy / LN positive

Units: Subjects			
Neo-adjuvant therapy / any lymph node status	550	552	1102
Adjuvant therapy / lymph node negative	68	65	133
Adjuvant therapy / lymph node positive	1635	1639	3274

Hormone Receptor Status (Strata per Randomization)			
--	--	--	--

Hormone receptor (estrogen receptor [ER] / progesterone receptor [PR]) status
a. ER and/or PR positive
b. ER and PR negative

Units: Subjects			
ER and/or PR positive	1740	1747	3487
ER and PR negative	513	509	1022

Human Epidermal Growth Factor Receptor 2 (HER-2) Status (Strata per Randomization)			
--	--	--	--

Units: Subjects			
HER-2 positive	490	492	982
HER-2 negative	1763	1764	3527

Age (Strata per Randomization)			
--------------------------------	--	--	--

Units: Subjects			
< 50 years	1026	1029	2055
≥ 50 years	1227	1227	2454

Geographic Region (Strata per Randomization)			
--	--	--	--

Units: Subjects			
Japan	131	131	262
Other	2122	2125	4247

Molecular Subtypes of Breast Cancer			
-------------------------------------	--	--	--

Hormone receptor (HR; estrogen receptor [ER] / progesterone receptor [PR]); HR positive = ER and/or PR positive; HR negative = ER and PR negative

Units: Subjects			
HR positive and HER-2 positive	288	286	574
HR positive and HER-2 negative	1460	1458	2918
HR negative and HER-2 positive	163	168	331
HR negative and HER-2 negative	341	343	684
Missing	1	1	2

Lymph Node Status			
-------------------	--	--	--

Clinical and pathologic regional lymph node (LN) status (by American Joint Committee on Cancer (AJCC)):

N0 = no LN metastasis or pathologic (p) micrometastases <2.0 mm;
N1 = Ipsilateral level I, II axillary (Ax) LN or p micrometastases >2.0mm or in internal mammary (IM) LN;
N2 = fixed ipsilateral level I, II Ax LNs or clinically detected IM LNs only or pLN metastases in 4-9 Ax LNs;
N3 = ipsilateral level III infraclavicular (IC) LNs or clinically detected IM LNs with other level I/II Ax LNs or supraclavicular (SC) LNs or pLN metastases in ≥10 Ax LNs;
NX = LNs cannot be assessed.

Units: Subjects			
N0	130	131	261
N1	1369	1381	2750
N2	506	505	1011
N3	230	224	454
Nx	18	15	33

Breast Cancer Histopathologic Grade			
-------------------------------------	--	--	--

Tumor grade was determined according to the Nottingham Combined Histological Grading System, based on morphological features (tubule formation, nuclear pleomorphism, and mitotic count), by assigning a value of 1 (favorable) to 3 (unfavorable) for each feature. Scores for the 3 categories were added to give a combined histopathologic grade score:

Grade (G)1 (low grade; favorable) = total score of 3, 4, or 5;

G2 (intermediate) = total score of 6 or 7;

G3 (high; unfavorable) = total score of 8 or 9.

Units: Subjects			
Grade 1 = Low	222	209	431
Grade 2 = Intermediate	1015	1079	2094
Grade 3 = High	938	906	1844
Not Evaluable/Missing	78	62	140

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive placebo subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by placebo subcutaneous injections once every 3 months for 4.5 years.	
Reporting group title	Denosumab
Reporting group description:	
Participants were randomized to receive denosumab 120 mg subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by denosumab 120 mg subcutaneous injections once every 3 months for 4.5 years.	

Primary: Bone Metastasis-free Survival (BMFS)

End point title	Bone Metastasis-free Survival (BMFS)
End point description:	
BMFS time was defined as the time interval from the randomization date to the first occurrence of bone metastasis or death from any cause, whichever came first. Participants last known to be alive with no bone metastasis were censored at their last assessment date, or at the primary analysis data cut-off date, whichever was first. Participants who had first occurrence of bone metastasis before randomization were censored at their randomization date. Bone metastasis must have been confirmed by central imaging analysis or by biopsy. Evidence of disseminated tumor cells in bone marrow was not sufficient for determination of disease recurrence. Development of new primary malignancy in bone was not considered as bone metastasis. Since the median BMFS time could not be estimated due to low number of events, the percentage of participants with an event (i.e., bone metastasis or death) is reported.	
End point type	Primary
End point timeframe:	
From randomization until the primary analysis data cut-off date of 31 August 2017; median (minimum, maximum) time on study was 67.2 (0.0, 85.9) and 67.0 (0.0, 86.6) months in each treatment group respectively.	

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2253	2256		
Units: percentage of participants				
number (confidence interval 95%)	13.5 (12.1 to 15.0)	12.9 (11.6 to 14.3)		

Statistical analyses

Statistical analysis title	Analysis of Bone Metastasis-free Survival
Statistical analysis description:	
The hazard ratio of denosumab compared with placebo and its corresponding 2-sided 95% confidence interval was estimated using a Cox proportional hazards model with treatment groups as the independent variable and stratified by the randomization stratification factors. A hazard ratio < 1 favors denosumab.	
Comparison groups	Placebo v Denosumab

Number of subjects included in analysis	4509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7 ^[1]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.14

Notes:

[1] - Log rank test stratified by breast cancer therapy/LN status, hormone receptor status, HER-2 status, age, and geographic region.

Secondary: Disease-free Survival (DFS)

End point title	Disease-free Survival (DFS)
-----------------	-----------------------------

End point description:

DFS time was defined as the time interval from the randomization date to the date of first observation of disease recurrence or death from any cause, whichever was first. Participants last known to be alive with no disease recurrence were censored at their last assessment date, or at the primary analysis data cut-off date, whichever was first. Participants who had first disease recurrence before randomization were censored at their randomization date. Disease recurrence includes bone metastasis and extraosseous disease (EOD) confirmed by central imaging analysis or by biopsy/cytology. Development of non-breast cancer new primary malignancy was not considered as disease recurrence. Since the median DFS time could not be estimated due to low number of events, the percentage of participants with an event (i.e., disease recurrence or death) is reported.

End point type	Secondary
----------------	-----------

End point timeframe:

From randomization until the primary analysis data cut-off date of 31 August 2017; median (minimum, maximum) time on study was 67.2 (0.0, 85.9) and 67.0 (0.0, 86.6) months in each treatment group respectively.

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2253	2256		
Units: percentage of participants				
number (confidence interval 95%)	19.2 (17.6 to 20.8)	19.6 (18.0 to 21.2)		

Statistical analyses

Statistical analysis title	Analysis of Disease-free Survival
----------------------------	-----------------------------------

Statistical analysis description:

The hazard ratio and its 2-sided 95% CI were estimated using a Cox proportional hazards model with treatment group as the independent variable and stratified by the randomization stratification factors; a hazard ratio < 1 favors denosumab.

Comparison groups	Placebo v Denosumab
-------------------	---------------------

Number of subjects included in analysis	4509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57 ^[2]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.19

Notes:

[2] - Log rank test stratified by breast cancer therapy/LN status, hormone receptor status, HER-2 status, age, and geographic region.

Secondary: Disease-free Survival (DFS) in the Postmenopausal Subset

End point title	Disease-free Survival (DFS) in the Postmenopausal Subset
-----------------	--

End point description:

DFS time was defined as the time interval from the randomization date to the date of first observation of disease recurrence or death from any cause, whichever was first. Participants last known to be alive with no disease recurrence were censored at their last assessment date, or at the primary analysis data cut-off date, whichever was first. Participants who had first disease recurrence before randomization were censored at their randomization date. Disease recurrence includes bone metastasis and extraosseous disease (EOD) confirmed by central imaging analysis or by biopsy/cytology. Development of non-breast cancer new primary malignancy was not considered as disease recurrence. Since the median DFS time in the postmenopausal subset could not be estimated due to low number of events, the percentage of participants with an event (i.e., disease recurrence or death) is reported.

End point type	Secondary
----------------	-----------

End point timeframe:

From randomization until the primary analysis data cut-off date of 31 August 2017; median (minimum, maximum) time on study was 67.2 (0.0, 85.9) and 67.0 (0.0, 86.6) months in each treatment group respectively.

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1088	1061		
Units: percentage of participants				
number (confidence interval 95%)	18.6 (16.3 to 20.9)	20.3 (17.8 to 22.7)		

Statistical analyses

Statistical analysis title	Analysis of DFS in Postmenopausal Subset
----------------------------	--

Statistical analysis description:

The hazard ratio and its 2-sided 95% CI were estimated using a Cox proportional hazards model with treatment group as the independent variable and stratified by the randomization stratification factors; a hazard ratio < 1 favors denosumab.

Comparison groups	Placebo v Denosumab
-------------------	---------------------

Number of subjects included in analysis	2149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26 ^[3]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.36

Notes:

[3] - Log rank test stratified by breast cancer therapy/LN status, hormone receptor status, HER-2 status, age, and geographic region.

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Overall survival (OS) time was defined as the time interval from the randomization date to the date of death from any cause. Participants last known to be alive were censored at their last contact date. Since the median time to overall survival could not be estimated at the time of the final analysis due to low numbers of events, the percentage of participants with an event (i.e., death) is reported.	
End point type	Secondary
End point timeframe:	
From randomization until the end of study; median (minimum, maximum) time on study was 72.7 (0, 92) and 72.3 (0, 92) months in each treatment group respectively.	

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2253	2256		
Units: percentage of participants				
number (confidence interval 95%)	9.5 (8.3 to 10.8)	9.5 (8.3 to 10.7)		

Statistical analyses

Statistical analysis title	Analysis of Overall Survival
Statistical analysis description:	
The hazard ratio and its 2-sided 95% CI were estimated using a Cox proportional hazards model with treatment group as the independent variable and stratified by the randomization stratification factors. A hazard ratio < 1 favors denosumab.	
Comparison groups	Placebo v Denosumab

Number of subjects included in analysis	4509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 ^[4]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.22

Notes:

[4] - Log rank test stratified by breast cancer therapy/LN status, hormone receptor status, HER-2 status, age, and geographic region.

Secondary: Distant Recurrence-free Survival

End point title	Distant Recurrence-free Survival
-----------------	----------------------------------

End point description:

Distant recurrence-free survival (DRFS) was defined as the time interval from the randomization date to the date of first observation of distant disease recurrence or death from any cause, whichever came first. Participants last known to be alive, who had not experienced distant disease recurrence, were censored at their last assessment date, or at the primary analysis data cut-off date, whichever was first. Participants who had first distant recurrence before randomization were censored at their randomization date. Distant disease recurrence includes confirmed bone metastasis and extraosseous disease other than local-regional disease recurrence. Development of non-breast cancer new primary malignancy was not considered as distant disease recurrence. Since the median time to DRFS could not be estimated due to the low number of events, the percentage of participants with an event (i.e., distant recurrence or death) is reported.

End point type	Secondary
----------------	-----------

End point timeframe:

From randomization until the primary analysis data cut-off date of 31 August 2017; median (minimum, maximum) time on study was 67.2 (0.0, 85.9) and 67.0 (0.0, 86.6) months in each treatment group respectively.

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2253	2256		
Units: percentage of participants				
number (confidence interval 95%)	18.0 (16.4 to 19.6)	18.7 (17.1 to 20.3)		

Statistical analyses

Statistical analysis title	Analysis of Distant Recurrence-free Survival
----------------------------	--

Statistical analysis description:

The hazard ratio and its 2-sided 95% CI were estimated using Cox proportional hazards model with treatment group as the independent variable and stratified by the randomization stratification factors. A hazard ratio < 1 favors denosumab.

Comparison groups	Placebo v Denosumab
-------------------	---------------------

Number of subjects included in analysis	4509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41 ^[5]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.21

Notes:

[5] - Log rank test stratified by breast cancer therapy/LN status, hormone receptor status, HER-2 status, age, and geographic region.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 30 days after last dose; median time on treatment was 59 months in each arm. Total deaths includes deaths from first dose of study drug to the end of study date; median time on study was 72.5 months overall.

Adverse event reporting additional description:

Data are reported for all randomized subjects who received ≥ 1 dose of investigational product. Subjects were analyzed according to their actual treatment received; eleven participants randomized to the placebo group received at least 1 dose of denosumab during the study and are counted in the denosumab group for safety analyses.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Participants received placebo subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by placebo subcutaneous injections once every 3 months for 4.5 years.

Reporting group title	Denosumab
-----------------------	-----------

Reporting group description:

Participants received denosumab 120 mg subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by denosumab 120 mg subcutaneous injections once every 3 months for 4.5 years.

Serious adverse events	Placebo	Denosumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	675 / 2218 (30.43%)	702 / 2241 (31.33%)	
number of deaths (all causes)	215	215	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute leukaemia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Adenocarcinoma			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenolipoma			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendix cancer			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell small lymphocytic lymphoma			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	0 / 2218 (0.00%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of thymus			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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 thyroid gland			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma stage III			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone neoplasm			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain cancer metastatic			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	3 / 2218 (0.14%)	8 / 2241 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 3	
Breast cancer metastatic			
subjects affected / exposed	3 / 2218 (0.14%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Breast cancer recurrent			
subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall tumour			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	5 / 2218 (0.23%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenoma			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer stage I			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial stromal sarcoma			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extranodal marginal zone B-cell lymphoma (MALT type)			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fallopian tube cancer			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric neoplasm			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal metastasis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine benign neoplasm			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyoma			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyosarcoma metastatic			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	3 / 2218 (0.14%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lung adenocarcinoma stage IV			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma stage III			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of thorax			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant neoplasm progression			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	3 / 2218 (0.14%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to breast			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	17 / 2218 (0.77%)	15 / 2241 (0.67%)	
occurrences causally related to treatment / all	0 / 20	0 / 17	
deaths causally related to treatment / all	0 / 4	0 / 4	
Metastases to liver			

subjects affected / exposed	4 / 2218 (0.18%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	4 / 2218 (0.18%)	7 / 2241 (0.31%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	3 / 2218 (0.14%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Metastases to ovary			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to skin			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer stage I			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal neoplasm			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian adenoma			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer stage III			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian epithelial cancer			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian neoplasm			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paget's disease of the vulva			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Parathyroid tumour benign			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	1 / 2218 (0.05%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer stage I			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			

subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retro-orbital neoplasm			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine carcinoma			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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 the cervix			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thymoma			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	5 / 2218 (0.23%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Astrocytoma			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloma			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteritis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachiocephalic vein thrombosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	12 / 2218 (0.54%)	9 / 2241 (0.40%)	
occurrences causally related to treatment / all	0 / 12	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	3 / 2218 (0.14%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	6 / 2218 (0.27%)	7 / 2241 (0.31%)	
occurrences causally related to treatment / all	1 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			

subjects affected / exposed	2 / 2218 (0.09%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery thrombosis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 2218 (0.05%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	3 / 2218 (0.14%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Ankle arthroplasty			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast conserving surgery			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast operation			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast reconstruction			
subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer surgery			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter removal			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical polypectomy			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional drainage			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mammoplasty			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oophorectomy bilateral			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophorectomy bilateral			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine dilation and curettage			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastectomy			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Foetal death			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Adverse drug reaction			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Application site pain			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 2218 (0.14%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRCA2 gene mutation			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast complication associated with device			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capsular contracture associated with breast implant			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haematoma			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			

subjects affected / exposed	6 / 2218 (0.27%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	2 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Disease progression			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Drug intolerance			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	4 / 2218 (0.18%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	3 / 2218 (0.14%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granuloma			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiosyncratic drug reaction			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	3 / 2218 (0.14%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (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	1 / 2218 (0.05%)	7 / 2241 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	4 / 2218 (0.18%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	4 / 2218 (0.18%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 4	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudocyst			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	33 / 2218 (1.49%)	37 / 2241 (1.65%)	
occurrences causally related to treatment / all	1 / 40	4 / 42	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	3 / 2218 (0.14%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergy to vaccine			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	2 / 2218 (0.09%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reaction to preservatives			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Bartholin's cyst			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast haematoma			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast inflammation			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Breast mass			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast necrosis			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast pain			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	2 / 2218 (0.09%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystocele			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial disorder			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	4 / 2218 (0.18%)	7 / 2241 (0.31%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital haemorrhage			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital prolapse			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menometrorrhagia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menopausal symptoms			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	7 / 2218 (0.32%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian enlargement			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	2 / 2218 (0.09%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	4 / 2218 (0.18%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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 pulmonary oedema			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			

subjects affected / exposed	3 / 2218 (0.14%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	4 / 2218 (0.18%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 2218 (0.00%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	10 / 2218 (0.45%)	13 / 2241 (0.58%)	
occurrences causally related to treatment / all	0 / 11	1 / 13	
deaths causally related to treatment / all	0 / 1	0 / 3	
Dyspnoea at rest			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperventilation			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngospasm			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	5 / 2218 (0.23%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	0 / 2218 (0.00%)	1 / 2241 (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	2 / 2218 (0.09%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 2218 (0.09%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	20 / 2218 (0.90%)	17 / 2241 (0.76%)	
occurrences causally related to treatment / all	0 / 21	2 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	7 / 2218 (0.32%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	1 / 8	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
Vocal cord polyp			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 2218 (0.00%)	7 / 2241 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			
subjects affected / exposed	3 / 2218 (0.14%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed mood			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	2 / 2218 (0.09%)	8 / 2241 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomania			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persistent depressive disorder			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor retardation			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restlessness			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device expulsion			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Bile duct stone			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	3 / 2218 (0.14%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	4 / 2218 (0.18%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	4 / 2218 (0.18%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gallbladder non-functioning			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatomegaly			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperplastic cholecystopathy			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone scan abnormal			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac murmur			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrin D dimer increased			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			

subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count abnormal			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oestradiol increased			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke volume increased			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cartilage injury			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			

subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposure to radiation			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	3 / 2218 (0.14%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 2218 (0.00%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	6 / 2218 (0.27%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			

subjects affected / exposed	0 / 2218 (0.00%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft complication			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site pain			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 2218 (0.00%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural inflammation			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmastectomy lymphoedema syndrome			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative renal failure			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative thrombosis			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation injury			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation mastitis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	6 / 2218 (0.27%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	6 / 2218 (0.27%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin flap necrosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial rupture			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	2 / 2218 (0.09%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	4 / 2218 (0.18%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrong drug administered			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	3 / 2218 (0.14%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriospasm coronary			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	6 / 2218 (0.27%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac aneurysm			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	4 / 2218 (0.18%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiogenic shock			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic cardiomyopathy			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	4 / 2218 (0.18%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis constrictive			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (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 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	5 / 2218 (0.23%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 2218 (0.05%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar ataxia			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral disorder			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	3 / 2218 (0.14%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fistula			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	6 / 2218 (0.27%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cervical radiculopathy			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma hepatic			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dementia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia with Lewy bodies			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Dizziness			
subjects affected / exposed	4 / 2218 (0.18%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dystonia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epilepsy			

subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial neuralgia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	3 / 2218 (0.14%)	10 / 2241 (0.45%)	
occurrences causally related to treatment / all	1 / 3	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 2218 (0.00%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occipital neuralgia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	4 / 2218 (0.18%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior sagittal sinus thrombosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	9 / 2218 (0.41%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 9	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic stroke			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	4 / 2218 (0.18%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal nerve disorder			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual field defect			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paralysis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	12 / 2218 (0.54%)	17 / 2241 (0.76%)
occurrences causally related to treatment / all	1 / 13	0 / 19
deaths causally related to treatment / all	0 / 0	0 / 1
Anaemia megaloblastic		
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bone marrow failure		
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Febrile neutropenia		
subjects affected / exposed	114 / 2218 (5.14%)	83 / 2241 (3.70%)
occurrences causally related to treatment / all	4 / 128	1 / 98
deaths causally related to treatment / all	0 / 0	0 / 0
Immune thrombocytopenic purpura		
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Leukocytosis		
subjects affected / exposed	3 / 2218 (0.14%)	0 / 2241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Leukopenia		
subjects affected / exposed	5 / 2218 (0.23%)	2 / 2241 (0.09%)
occurrences causally related to treatment / all	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Neutropenia		
subjects affected / exposed	36 / 2218 (1.62%)	35 / 2241 (1.56%)
occurrences causally related to treatment / all	3 / 43	1 / 39
deaths causally related to treatment / all	0 / 0	0 / 0
Pancytopenia		

subjects affected / exposed	4 / 2218 (0.18%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	5 / 2218 (0.23%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 5	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear pain			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
External ear disorder			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 2218 (0.00%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Angle closure glaucoma			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blindness			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	5 / 2218 (0.23%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	3 / 5	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular hole			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy proliferative			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haematoma			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal incarcerated hernia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 2218 (0.09%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	3 / 2218 (0.14%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal prolapse			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	2 / 2218 (0.09%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	24 / 2218 (1.08%)	15 / 2241 (0.67%)	
occurrences causally related to treatment / all	0 / 25	2 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric disorder			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	2 / 2218 (0.09%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival pain			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids thrombosed			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	10 / 2218 (0.45%)	18 / 2241 (0.80%)	
occurrences causally related to treatment / all	0 / 10	2 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising colitis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 2218 (0.05%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	13 / 2218 (0.59%)	24 / 2241 (1.07%)	
occurrences causally related to treatment / all	0 / 14	2 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichen sclerosus			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Onycholysis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain of skin			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash papular			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Segmented hyalinising vasculitis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			

subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 2218 (0.14%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrocalcinosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 2218 (0.14%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis acute			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	1 / 2218 (0.05%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	6 / 2218 (0.27%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	1 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 2218 (0.09%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 4	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw disorder			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint instability			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 2218 (0.05%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	4 / 2218 (0.18%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	4 / 2218 (0.18%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondritis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 2218 (0.00%)	30 / 2241 (1.34%)	
occurrences causally related to treatment / all	0 / 0	29 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 2218 (0.05%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periostitis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	0 / 2218 (0.00%)	1 / 2241 (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 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon disorder			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis stenosans			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	3 / 2218 (0.14%)	7 / 2241 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bartholinitis			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	3 / 2218 (0.14%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	18 / 2218 (0.81%)	20 / 2241 (0.89%)	
occurrences causally related to treatment / all	2 / 20	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 2218 (0.14%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 2218 (0.00%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	30 / 2218 (1.35%)	34 / 2241 (1.52%)	
occurrences causally related to treatment / all	0 / 33	2 / 42	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			

subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis streptococcal			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall abscess			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 2218 (0.09%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	10 / 2218 (0.45%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	1 / 11	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	8 / 2218 (0.36%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	4 / 2218 (0.18%)	14 / 2241 (0.62%)	
occurrences causally related to treatment / all	1 / 5	1 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelothrix infection			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	2 / 2218 (0.09%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal skin infection			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 2218 (0.14%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes simplex			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			

subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 2218 (0.09%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected fistula			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected seroma			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			

subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	5 / 2218 (0.23%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Labyrinthitis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 2218 (0.14%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			

subjects affected / exposed	3 / 2218 (0.14%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	8 / 2218 (0.36%)	12 / 2241 (0.54%)	
occurrences causally related to treatment / all	0 / 9	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis bacterial			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycobacterial infection			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	14 / 2218 (0.63%)	15 / 2241 (0.67%)	
occurrences causally related to treatment / all	0 / 14	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			

subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	2 / 2218 (0.09%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis chronic			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericoronitis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal abscess			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periumbilical abscess			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	30 / 2218 (1.35%)	27 / 2241 (1.20%)	
occurrences causally related to treatment / all	0 / 32	2 / 29	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 2218 (0.00%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	9 / 2218 (0.41%)	7 / 2241 (0.31%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	0 / 2218 (0.00%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 2218 (0.05%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 2218 (0.05%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sebaceous gland infection			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	11 / 2218 (0.50%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 11	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Septic shock			
subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			
subjects affected / exposed	1 / 2218 (0.05%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	2 / 2218 (0.09%)	4 / 2241 (0.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (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	9 / 2218 (0.41%)	7 / 2241 (0.31%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	13 / 2218 (0.59%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 13	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	2 / 2218 (0.09%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	3 / 2218 (0.14%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	3 / 2218 (0.14%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 2218 (0.09%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection bacterial			
subjects affected / exposed	3 / 2218 (0.14%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	3 / 2218 (0.14%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis escherichia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 2218 (0.05%)	3 / 2241 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	8 / 2218 (0.36%)	16 / 2241 (0.71%)	
occurrences causally related to treatment / all	0 / 8	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 2218 (0.05%)	2 / 2241 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	3 / 2218 (0.14%)	5 / 2241 (0.22%)	
occurrences causally related to treatment / all	2 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 2218 (0.05%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 2218 (0.05%)	6 / 2241 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 2218 (0.05%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 2218 (0.09%)	0 / 2241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin D deficiency			
subjects affected / exposed	0 / 2218 (0.00%)	1 / 2241 (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	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2123 / 2218 (95.72%)	2149 / 2241 (95.89%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	645 / 2218 (29.08%)	669 / 2241 (29.85%)	
occurrences (all)	859	929	
Hypertension			
subjects affected / exposed	209 / 2218 (9.42%)	195 / 2241 (8.70%)	
occurrences (all)	275	267	
Lymphoedema			
subjects affected / exposed	350 / 2218 (15.78%)	392 / 2241 (17.49%)	
occurrences (all)	443	498	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	404 / 2218 (18.21%)	407 / 2241 (18.16%)	
occurrences (all)	806	796	
Fatigue			
subjects affected / exposed	893 / 2218 (40.26%)	901 / 2241 (40.21%)	
occurrences (all)	1638	1724	
Influenza like illness			
subjects affected / exposed	145 / 2218 (6.54%)	154 / 2241 (6.87%)	
occurrences (all)	220	284	
Mucosal inflammation			
subjects affected / exposed	278 / 2218 (12.53%)	281 / 2241 (12.54%)	
occurrences (all)	372	373	
Oedema			
subjects affected / exposed	112 / 2218 (5.05%)	106 / 2241 (4.73%)	
occurrences (all)	131	113	
Oedema peripheral			
subjects affected / exposed	397 / 2218 (17.90%)	380 / 2241 (16.96%)	
occurrences (all)	534	498	

Pain			
subjects affected / exposed	178 / 2218 (8.03%)	156 / 2241 (6.96%)	
occurrences (all)	210	190	
Pyrexia			
subjects affected / exposed	342 / 2218 (15.42%)	338 / 2241 (15.08%)	
occurrences (all)	474	458	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	189 / 2218 (8.52%)	178 / 2241 (7.94%)	
occurrences (all)	218	236	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	426 / 2218 (19.21%)	410 / 2241 (18.30%)	
occurrences (all)	549	557	
Dyspnoea			
subjects affected / exposed	268 / 2218 (12.08%)	280 / 2241 (12.49%)	
occurrences (all)	363	369	
Epistaxis			
subjects affected / exposed	151 / 2218 (6.81%)	168 / 2241 (7.50%)	
occurrences (all)	176	192	
Oropharyngeal pain			
subjects affected / exposed	176 / 2218 (7.94%)	157 / 2241 (7.01%)	
occurrences (all)	199	186	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	207 / 2218 (9.33%)	220 / 2241 (9.82%)	
occurrences (all)	248	277	
Depression			
subjects affected / exposed	202 / 2218 (9.11%)	195 / 2241 (8.70%)	
occurrences (all)	245	236	
Insomnia			
subjects affected / exposed	432 / 2218 (19.48%)	429 / 2241 (19.14%)	
occurrences (all)	531	538	
Investigations			

Weight increased subjects affected / exposed occurrences (all)	151 / 2218 (6.81%) 236	167 / 2241 (7.45%) 296	
Injury, poisoning and procedural complications			
Procedural pain subjects affected / exposed occurrences (all)	161 / 2218 (7.26%) 237	170 / 2241 (7.59%) 231	
Radiation skin injury subjects affected / exposed occurrences (all)	351 / 2218 (15.83%) 419	361 / 2241 (16.11%) 432	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	255 / 2218 (11.50%) 336	273 / 2241 (12.18%) 367	
Dysgeusia subjects affected / exposed occurrences (all)	344 / 2218 (15.51%) 460	351 / 2241 (15.66%) 473	
Headache subjects affected / exposed occurrences (all)	567 / 2218 (25.56%) 957	527 / 2241 (23.52%) 844	
Hypoaesthesia subjects affected / exposed occurrences (all)	112 / 2218 (5.05%) 137	112 / 2241 (5.00%) 156	
Neuropathy peripheral subjects affected / exposed occurrences (all)	421 / 2218 (18.98%) 576	417 / 2241 (18.61%) 584	
Paraesthesia subjects affected / exposed occurrences (all)	197 / 2218 (8.88%) 254	216 / 2241 (9.64%) 271	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	177 / 2218 (7.98%) 249	198 / 2241 (8.84%) 289	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	349 / 2218 (15.73%)	354 / 2241 (15.80%)	
occurrences (all)	677	664	
Leukopenia			
subjects affected / exposed	154 / 2218 (6.94%)	145 / 2241 (6.47%)	
occurrences (all)	338	319	
Neutropenia			
subjects affected / exposed	461 / 2218 (20.78%)	441 / 2241 (19.68%)	
occurrences (all)	826	920	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	243 / 2218 (10.96%)	195 / 2241 (8.70%)	
occurrences (all)	276	218	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	242 / 2218 (10.91%)	232 / 2241 (10.35%)	
occurrences (all)	320	296	
Abdominal pain upper			
subjects affected / exposed	199 / 2218 (8.97%)	179 / 2241 (7.99%)	
occurrences (all)	248	218	
Constipation			
subjects affected / exposed	635 / 2218 (28.63%)	626 / 2241 (27.93%)	
occurrences (all)	958	903	
Diarrhoea			
subjects affected / exposed	638 / 2218 (28.76%)	660 / 2241 (29.45%)	
occurrences (all)	1011	1112	
Dyspepsia			
subjects affected / exposed	245 / 2218 (11.05%)	273 / 2241 (12.18%)	
occurrences (all)	317	367	
Nausea			
subjects affected / exposed	1095 / 2218 (49.37%)	1145 / 2241 (51.09%)	
occurrences (all)	2210	2327	
Stomatitis			
subjects affected / exposed	398 / 2218 (17.94%)	399 / 2241 (17.80%)	
occurrences (all)	596	624	

Toothache subjects affected / exposed occurrences (all)	159 / 2218 (7.17%) 184	198 / 2241 (8.84%) 236	
Vomiting subjects affected / exposed occurrences (all)	536 / 2218 (24.17%) 865	536 / 2241 (23.92%) 882	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	923 / 2218 (41.61%) 1129	938 / 2241 (41.86%) 1158	
Dermatitis subjects affected / exposed occurrences (all)	112 / 2218 (5.05%) 132	107 / 2241 (4.77%) 134	
Dry skin subjects affected / exposed occurrences (all)	133 / 2218 (6.00%) 143	125 / 2241 (5.58%) 145	
Erythema subjects affected / exposed occurrences (all)	226 / 2218 (10.19%) 255	260 / 2241 (11.60%) 315	
Nail disorder subjects affected / exposed occurrences (all)	264 / 2218 (11.90%) 303	275 / 2241 (12.27%) 328	
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	114 / 2218 (5.14%) 152	138 / 2241 (6.16%) 201	
Pruritus subjects affected / exposed occurrences (all)	181 / 2218 (8.16%) 223	144 / 2241 (6.43%) 159	
Rash subjects affected / exposed occurrences (all)	372 / 2218 (16.77%) 514	392 / 2241 (17.49%) 540	
Musculoskeletal and connective tissue disorders Arthralgia			

subjects affected / exposed	974 / 2218 (43.91%)	973 / 2241 (43.42%)	
occurrences (all)	1799	1787	
Back pain			
subjects affected / exposed	486 / 2218 (21.91%)	563 / 2241 (25.12%)	
occurrences (all)	657	823	
Bone pain			
subjects affected / exposed	256 / 2218 (11.54%)	288 / 2241 (12.85%)	
occurrences (all)	342	422	
Muscle spasms			
subjects affected / exposed	204 / 2218 (9.20%)	201 / 2241 (8.97%)	
occurrences (all)	247	253	
Musculoskeletal chest pain			
subjects affected / exposed	143 / 2218 (6.45%)	129 / 2241 (5.76%)	
occurrences (all)	179	154	
Musculoskeletal pain			
subjects affected / exposed	308 / 2218 (13.89%)	337 / 2241 (15.04%)	
occurrences (all)	431	444	
Myalgia			
subjects affected / exposed	539 / 2218 (24.30%)	553 / 2241 (24.68%)	
occurrences (all)	838	910	
Neck pain			
subjects affected / exposed	112 / 2218 (5.05%)	106 / 2241 (4.73%)	
occurrences (all)	132	118	
Pain in extremity			
subjects affected / exposed	545 / 2218 (24.57%)	570 / 2241 (25.44%)	
occurrences (all)	815	871	
Pain in jaw			
subjects affected / exposed	124 / 2218 (5.59%)	150 / 2241 (6.69%)	
occurrences (all)	146	182	
Infections and infestations			
Bronchitis			
subjects affected / exposed	112 / 2218 (5.05%)	86 / 2241 (3.84%)	
occurrences (all)	134	112	
Influenza			

subjects affected / exposed	117 / 2218 (5.28%)	117 / 2241 (5.22%)	
occurrences (all)	143	138	
Nasopharyngitis			
subjects affected / exposed	290 / 2218 (13.07%)	292 / 2241 (13.03%)	
occurrences (all)	521	486	
Sinusitis			
subjects affected / exposed	101 / 2218 (4.55%)	113 / 2241 (5.04%)	
occurrences (all)	136	149	
Upper respiratory tract infection			
subjects affected / exposed	195 / 2218 (8.79%)	206 / 2241 (9.19%)	
occurrences (all)	265	283	
Urinary tract infection			
subjects affected / exposed	149 / 2218 (6.72%)	177 / 2241 (7.90%)	
occurrences (all)	211	252	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	289 / 2218 (13.03%)	330 / 2241 (14.73%)	
occurrences (all)	427	486	
Hypocalcaemia			
subjects affected / exposed	73 / 2218 (3.29%)	135 / 2241 (6.02%)	
occurrences (all)	95	181	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2011	- window for screening imaging assessments to document disease extent was increased from 12 to 24 weeks - a second formal interim analysis was added in consideration of the length of time anticipated to reach the primary analysis date - amount of time expected to reach the primary analysis data cutoff date was modified - number of centers was increased from 400 to 500 centers globally - breast density measurements were included as an exploratory outcome (objective and endpoint) for the study
15 August 2012	- collection of skeletal-related event information was extended through the long-term follow-up - objectives and endpoints for skeletal-related events and bone metastasis were modified - fasting requirement from the urine collection for urinary N-telopeptide of type I collagen was removed
18 March 2015	- disease-free survival in the postmenopausal subset as a secondary endpoint was added - hazard ratio of denosumab compared with placebo was added for the postmenopausal subset - pathological variables in tumor tissue from neoadjuvant subjects after surgery was added as an exploratory objective - numbers of subjects with events (any disease recurrence or died, whichever comes last) required for the interim and final analyses was updated - period of time for which subjects must not become pregnant or breastfeed after the end of treatment was updated - duration of the study was changed based on the change in the expected/projected time to primary analysis - atypical femoral fracture was included as an adverse event of interest with adjudication by an independent panel of experts - covariates explored in relation to the primary and secondary efficacy endpoints were updated; primary tumor size and lymph node status were added to the list of covariates - expected event rates at 3 years for bone metastasis-free survival and disease-free survival were updated
17 October 2016	- primary analysis was changed from an event-driven analysis to a landmark (time-based) analysis, triggered when all subjects had the opportunity to complete 5 years treatment with investigational product - second interim analysis from the study was removed - open-label phase from the study was removed - long-term follow-up visit frequency and assessments before and after the primary analysis cutoff date was redefined

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

