Clinical trial results:
TECOS: A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control

Summary

EudraCT number	2008-006719-20
Trial protocol	LT NL DE ES HU LV FR CZ GB IE SK BG IT EE FI SE BE
Global end of trial date	30 March 2015

Results information

Result version number	v1
This version publication date	09 April 2016
First version publication date	09 April 2016

Trial information

Trial identification

Sponsor protocol code	MK-0431-082

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00790205
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	30 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2015
Global end of trial reached?	Yes
Global end of trial date	30 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a clinical trial designed to assess the cardiovascular outcome of long-term treatment with sitagliptin used as part of usual care compared to usual care without sitagliptin in participants with Type 2 Diabetes Mellitus having a history of cardiovascular disease and a hemoglobin A1c (HbA1c) of 6.5% to 8.0%.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice (GCP) standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.
The following additional measure defined for this individual study was in place for the protection of trial subjects: in the event that a participant experiences severe hypoglycemia, usual care physicians will be notified and may adjust antihyperglycemic agent (AHA) medications in order to prevent or minimize the occurrence of further hypoglycemia.

Background therapy:

Background therapy included the following: stable doses of either monotherapy or dual combination therapy with metformin, pioglitazone, or a sulfonylurea, or, after a protocol amendment, stable doses of insulin (i.e., ±20% of the scheduled total daily insulin dose) either alone or in combination with metformin, for at least 3 months (i.e., no adjustments to oral antihyperglycemic therapy in the past 3 months).

Evidence for comparator: -

Actual start date of recruitment	10 December 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 542
Country: Number of subjects enrolled	Australia: 427
Country: Number of subjects enrolled	Belgium: 94
Country: Number of subjects enrolled	Brazil: 406
Country: Number of subjects enrolled	Bulgaria: 504
Country: Number of subjects enrolled	Chile: 293
Country: Number of subjects enrolled	China: 31
Country: Number of subjects enrolled	Colombia: 230
Country: Number of subjects enrolled	Canada: 549
Country: Number of subjects enrolled	Czech Republic: 462
Country: Number of subjects enrolled	Estonia: 88
Country: Number of subjects enrolled	Finland: 50

Country: Number of subjects enrolled	France: 86
Country: Number of subjects enrolled	Germany: 503
Country: Number of subjects enrolled	Hong Kong: 360
Country: Number of subjects enrolled	Hungary: 565
Country: Number of subjects enrolled	Israel: 362
Country: Number of subjects enrolled	Italy: 192
Country: Number of subjects enrolled	India: 1817
Country: Number of subjects enrolled	Korea, Republic of: 330
Country: Number of subjects enrolled	Latvia: 401
Country: Number of subjects enrolled	Lithuania: 320
Country: Number of subjects enrolled	Malaysia: 257
Country: Number of subjects enrolled	Netherlands: 309
Country: Number of subjects enrolled	Norway: 43
Country: Number of subjects enrolled	New Zealand: 274
Country: Number of subjects enrolled	Poland: 605
Country: Number of subjects enrolled	Romania: 345
Country: Number of subjects enrolled	Russian Federation: 465
Country: Number of subjects enrolled	Singapore: 91
Country: Number of subjects enrolled	Slovakia: 110
Country: Number of subjects enrolled	South Africa: 406
Country: Number of subjects enrolled	Spain: 202
Country: Number of subjects enrolled	Sweden: 81
Country: Number of subjects enrolled	Taiwan: 210
Country: Number of subjects enrolled	Turkey: 100
Country: Number of subjects enrolled	United Kingdom: 516
Country: Number of subjects enrolled	United States: 2045
Worldwide total number of subjects	14671
EEA total number of subjects	5476

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)	6764
From 65 to 84 years	7804
85 years and over	103

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 14,671 participants were randomized to treatment, provided consent and did not have any GCP deviations.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Sitagliptin

Arm description:

Sitagliptin tablet taken orally once daily in the morning

Arm type	Experimental
Investigational medicinal product name	Sitagliptin phosphate
Investigational medicinal product code	MK-0431
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sitagliptin phosphate, one 50 mg or 100 mg tablet (dose dependant on renal function) orally, once daily

Arm title	Placebo

Arm description:

Matching placebo tablet taken orally once daily in the morning

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet matching the 50 mg or 100 mg sitagliptin phosphate tablet orally, once daily

Number of subjects in period 1	Sitagliptin	Placebo
Started	7332	7339
Treated	7266	7274
Completed	6972	6905
Not completed	360	434

Consent withdrawn by subject	299	363
Lost to follow-up	61	71

Baseline characteristics

Reporting groups	
Reporting group title	Sitagliptin
Reporting group description:	
Sitagliptin tablet taken orally once daily in the morning	
Reporting group title	Placebo
Reporting group description:	
Matching placebo tablet taken orally once daily in the morning	

Reporting group values	Sitagliptin	Placebo	Total
Number of subjects	7332	7339	14671
Age categorical			
Age was unavailable due to regulatory restrictions for 320 participants. The distribution of age in the other study participants was used to impute ages for those 320 participants in the "Age group breakdown for Trial" under the "Population of Trial Subjects" section of the record.			
Units: Subjects			
Adults (18-64 years)	3315	3301	6616
From 65-84 years	3813	3821	7634
85 years and over	46	55	101
Unknown age	158	162	320
Gender, Male/Female Units: Participants			
Female	2134	2163	4297
Male	5198	5176	10374
Estimated glomerular filtration rate (eGFR)			
Sitagliptin, n=7254; Placebo, n=7274			
Units: mL/min/1.73 m^2			
arithmetic mean	74.9	74.9	
standard deviation	± 21.3	± 20.9	-
Hemoglobin A1c (HbA1c)			
Sitagliptin, n=7330; Placebo, n=7336			
Units: Percentage of HbA1c			
arithmetic mean	7.2	7.2	
standard deviation	± 0.5	± 0.5	-
Urine albumin:creatinine ratio			
Sitagliptin, n=2606; Placebo, n=2542			
Units: g/mol Creatinine			
arithmetic mean	8.6	8.4	
standard deviation	± 37.4	± 36	-

End points

End points reporting groups

Reporting group title	Sitagliptin
Reporting group description:	
Sitagliptin tablet taken orally once daily in the morning	
Reporting group title	Placebo
Reporting group description:	
Matching placebo tablet taken orally once daily in the morning	

Primary: Percentage of participants with first confirmed cardiovascular (CV) event of Major Adverse Cardiovascular Event (MACE) plus (Per protocol population)

End point title	Percentage of participants with first confirmed cardiovascular (CV) event of Major Adverse Cardiovascular Event (MACE) plus (Per protocol population)
End point description:	
Primary composite CV endpoint of MACE plus which includes CV-related death, nonfatal myocardial infarction (MI), nonfatal stroke, or unstable angina requiring hospitalization. Per protocol population included all randomized participants who received study medication except those participants who did not contribute at least 1 day of data to the study analysis due to a major protocol violation that excluded all of their data.	
End point type	Primary
End point timeframe:	
Up to 5 years	

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7257	7266		
Units: Percentage of participants				
number (not applicable)	9.6	9.6		

Statistical analyses

Statistical analysis title	Between-treatment difference
Statistical analysis description:	
Hazard Ratio (HR) of Sitagliptin/Placebo: the between-treatment difference in time to the first primary composite CV endpoint was assessed by the HR between the sitagliptin and placebo groups. The confidence interval for the HR was computed and compared to 1.30, the non-inferiority margin.	
Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	14523
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [1]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.09

Notes:

[1] - Model stratified by region with treatment group only as explanatory variable.

Primary: Percentage of participants with first confirmed CV event of MACE plus (Intent to treat population)

End point title	Percentage of participants with first confirmed CV event of MACE plus (Intent to treat population)

End point description:

Primary composite CV endpoint of MACE plus which includes CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization. Intent to treat population included all randomized participants who received study medication, provided consent, and did not have any GCP deviations.

End point type	Primary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7332	7339		
Units: Percentage of participants				
number (not applicable)	11.4	11.6		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

HR of Sitagliptin/Placebo: the between-treatment difference in time to the first primary composite CV endpoint was assessed by the HR between the sitagliptin and placebo groups. The confidence interval for the HR was computed and compared to 1.30, the non-inferiority margin.

Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	14671
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [2]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.08

Notes:

[2] - Model stratified by region with treatment group as the only explanatory variable.

Secondary: Percentage of participants with first confirmed CV event of MACE (Per protocol population)

End point title	Percentage of participants with first confirmed CV event of MACE (Per protocol population)

End point description:

CV composite endpoint of MACE which includes CV-related death, nonfatal MI, or nonfatal stroke. Per protocol population included all randomized participants who received study medication except those participants whodid not contribute at least 1 day of data to the study analysis due to a major protocol violation that excluded all of their data.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7257	7266		
Units: Percentage of participants				
number (not applicable)	8.4	8.3		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

HR of Sitagliptin/Placebo: the between-treatment difference in time to the first primary composite CV endpoint was assessed by the HR between the sitagliptin and placebo groups. The confidence interval for the HR was computed and compared to 1.30, the non-inferiority margin.

Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	14523
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [3]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.11

Notes:

[3] - Model stratified by region with treatment group only as explanatory variable.

Secondary: Percentage of participants with first confirmed CV event of MACE (Intent to treat population)

End point title	Percentage of participants with first confirmed CV event of MACE (Intent to treat population)

End point description:

CV composite endpoint of MACE which includes CV-related death, nonfatal MI, or nonfatal stroke. Intent to treat population included all randomized participants who received study medication, provided consent, and did not have any GCP deviations.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7332	7339		
Units: Percentage of participants				
number (not applicable)	10.2	10.2		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

HR of Sitagliptin/Placebo: the between-treatment difference in time to the first primary composite CV endpoint was assessed by the HR between the sitagliptin and placebo groups. The confidence interval for the HR was computed and compared to 1.30, the non-inferiority margin.

Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	14671
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [4]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.1

Notes:

[4] - Model stratified by region with treatment group only as explanatory variable.

Secondary: Percent incidence of all cause mortality (Per protocol population)

End point title	Percent incidence of all cause mortality (Per protocol population)

End point description:

Percent incidence of all cause mortality is reported as the percentage of participants who died due to any cause. Per protocol population included all randomized participants who received study medication except those participants who did not contribute at least 1 day of data to the study analysis due to a major protocol violation that excluded all of their data.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7257	7266		
Units: Percentage of participants				
number (not applicable)	4.7	4.3		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

HR of Sitagliptin/Placebo: the between-treatment difference in mortality due to all causes was assessed by the HR between the sitagliptin and placebo groups.

Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	14523
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.435
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.24

Secondary: Percent incidence of all cause mortality (Intent to treat population)

End point title	Percent incidence of all cause mortality (Intent to treat population)

End point description:

Percent incidence of all cause mortality is reported as the percentage of participants who died due to any cause. Intent to treat population included all randomized participants who received study medication, provided consent, and did not have any GCP deviations.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7332	7339		
Units: Percentage of participants				
number (not applicable)	7.5	7.3		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

HR of Sitagliptin/Placebo: the between-treatment difference in mortality due to all causes was assessed by the HR between the sitagliptin and placebo groups.

Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	14671
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.875
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.14

Secondary: Percent incidence of congestive heart failure requiring hospitalization (Per protocol population)

End point title	Percent incidence of congestive heart failure requiring hospitalization (Per protocol population)

End point description:

Percent incidence of congestive heart failure requiring hospitalization is reported as the percentage of participants who were admitted to the hospital for congestive heart failure. Per protocol population included all randomized participants who received study medication except those participants who did not contribute at least 1 day of data to the study analysis due to a major protocol violation that excluded all of their data.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7257	7266		
Units: Percentage of participants				
number (not applicable)	2.8	2.8		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Hazard Ratio of Sitagliptin/Placebo: The between-treatment difference in congestive heart failure cases requiring hospitalization was assessed by the hazard ratio between the Sitagliptin and Placebo groups.

Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	14523
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.858 [5]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.19

Notes:

[5] - Model stratified by region with treatment group and history of congestive heart failure at baseline as explanatory variables.

Secondary: Percent incidence of congestive heart failure requiring hospitalization (Intent to treat population)

End point title	Percent incidence of congestive heart failure requiring hospitalization (Intent to treat population)

End point description:

Percent incidence of congestive heart failure requiring hospitalization is reported as the percentage of participants who were admitted to the hospital for congestive heart failure. Intent to treat population included all randomized participants who received study medication, provided consent, and did not have any GCP deviations.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7332	7339		
Units: Percentage of participants				
number (not applicable)	3.1	3.1		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Hazard Ratio of Sitagliptin/Placebo: The between-treatment difference in congestive heart failure cases requiring hospitalization was assessed by the hazard ratio between the Sitagliptin and Placebo groups.

Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	14671
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.983 [6]
Method	Cox poportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.2

Notes:

[6] - Model stratified by region with treatment group and history of congestive heart failure at baseline as explanatory variable.

Secondary: Change from baseline in renal function over time (Per protocol population)

End point title	Change from baseline in renal function over time (Per protocol population)

End point description:

Change in renal function based on estimated glomerular filtration rate [eGFR] using the Modification of Diet in Renal Disease [MDRD] method. Per protocol population included all randomized participants who received study medication except those participants who did not contribute at least 1 day of data to the study analysis due to a major protocol violation that excluded all of their data.

End point type	Secondary

End point timeframe:

Baseline and up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7257	7266		
Units: mL/min/1.73 m^2				
arithmetic mean (standard deviation)				
Month 4; Sitagliptin, n=3859, Placebo, n=3864	-1.9 (± 14.2)	-0.8 (± 14.3)		
Month 8; Sitagliptin, n=3562, Placebo, n=3501	-2.5 (± 14.9)	-0.9 (± 15.1)		
Month 12; Sitagliptin, n=4912, Placebo, n=4778	-1.8 (± 15.8)	-0.5 (± 16.2)		
Month 24; Sitagliptin, n=4782, Placebo, n=4636	-3.1 (± 17.9)	-1.7 (± 17.5)		
Month 36; Sitagliptin, n=2776, Placebo, n=2614	-3.7 (± 18)	-1.6 (± 18.8)		
Month 48; Sitagliptin, n=1096, Placebo, n=1056	-3.7 (± 18.3)	-2.8 (± 18.4)		
Month 60; Sitagliptin, n=79, Placebo, n=88	-3.5 (± 18.2)	-6.4 (± 17.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in renal function over time (Intent to treat population)

End point title	Change from baseline in renal function over time (Intent to treat population)

End point description:

Change in renal function based on estimated glomerular filtration rate [eGFR] using the Modification of Diet in Renal Disease [MDRD] method. Intent to treat population included all randomized participants who received study medication, provided consent, and did not have any GCP deviations.

End point type	Secondary

End point timeframe:

Baseline and up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7332	7339		
Units: mL/min/ 1.73 m^2				
arithmetic mean (standard deviation)				
Month 4; Sitagliptin, n=3949, Placebo, n=3977	-1.8 (± 14.3)	-0.8 (± 14.3)		

Month 8; Sitagliptin, n=3687; Placebo, n=3648	-2.4 (± 14.8)	-0.9 (± 15.2)		
Month 12; Sitagliptin, n=5082, Placebo, n=5015	-1.8 (± 15.8)	-0.5 (± 16.3)		
Month 24; Sitagliptin, n=5157, Placebo, n=5071	-3.2 (± 17.9)	-1.7 (± 17.7)		
Month 36; Sitagliptin, n=3037, Placebo, n=2942	-3.8 (± 18.1)	-1.6 (± 18.7)		
Month 48; Sitagliptin, n=1237, Placebo, n=1210	-4 (± 18.4)	-2.8 (± 18.3)		
Month 60; Sitagliptin, n=93, Placebo, n=106	-4.2 (± 17.4)	-5.7 (± 17.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in HbA1c over time (Per protocol population)

End point title	Change from baseline in HbA1c over time (Per protocol population)

End point description:

HbA1c is a measure of the percentage of glycated hemoglobin in the blood. Estimated mean difference between sitagliptin and placebo controlling for baseline HbA1c and region. Per protocol population included all randomized participants who received study medication except those participants who did not contribute at least 1 day of data to the study analysis due to a major protocol violation that excluded all of their data.

End point type	Secondary

End point timeframe:

Baseline and up to 4 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7257	7266		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)				
Month 4; Sitagliptin, n=6632, Placebo, n=6588	-0.3 (± 0.8)	0.1 (± 0.9)		
Month 8; Sitagliptin, n=6294, Placebo, n=6197	-0.3 (± 0.9)	0.1 (± 1)		
Month 12; Sitagliptin, n=6217, Placebo, n=6092	-0.2 (± 1)	0.1 (± 1)		
Month 24; Sitagliptin, n=5668, Placebo, n=5475	-0.1 (± 1)	0.2 (± 1.1)		
Month 36; Sitagliptin, n=3227, Placebo, n=3083	-0.1 (± 1.1)	0.1 (± 1.1)		
Month 48; Sitagliptin, n=1271, Placebo, n=1224	0 (± 1.1)	0.1 (± 1.2)		
Month 60; Sitagliptin, n=106, Placebo, n=108	-0.1 (± 1)	0 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in HbA1c over time (Intent to treat population)

End point title	Change from baseline in HbA1c over time (Intent to treat population)

End point description:

HbA1c is a measure of the percentage of glycated hemoglobin in the blood. Estimated mean difference between sitagliptin and placebo controlling for baseline HbA1c and region. Intent to treat population included all randomized participants who received study medication, provided consent, and did not have any GCP deviations.

End point type	Secondary

End point timeframe:

Baseline and up to 4 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7332	7339		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)				
Month 4; Sitagliptin, n=6772, Placebo, n=6738	-0.3 (± 0.8)	0.1 (± 0.9)		
Month 8; Sitagliptin, n=6478; Placebo, n=6414	-0.2 (± 0.9)	0.1 (± 1)		
Month 12; Sitagliptin, n=6448; Placebo, n=6384	-0.2 (± 1)	0.1 (± 1)		
Month 24; Sitagliptin, n=6105; Placebo, n=5975	-0.1 (± 1)	0.1 (± 1.1)		
Month 36; Sitagliptin, n=3521; Placebo, n=3439	-0.1 (± 1.1)	0.1 (± 1.1)		
Month 48; Sitagliptin, n=1432; Placebo, n=1383	0 (± 1.1)	0.1 (± 1.2)		
Month 60; Sitagliptin, n=123; Placebo, n=128	0 (± 1)	0 (± 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in urine albumin:creatinine ratio over time (Per protocol population)

End point title	Change from baseline in urine albumin:creatinine ratio over

	time (Per protocol population)

End point description:

Change from baseline reflects the difference between the urine albumin:creatinine ratio reported time point and baseline value. Per protocol population included all randomized participants who received study medication except those participants who did not contribute at least 1 day of data to the study analysis due to a major protocol violation that excluded all of their data.

End point type	Secondary

End point timeframe:

Baseline and up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7257	7266		
Units: g/mol Creatinine				
arithmetic mean (standard deviation)				
Month 4; Sitagliptin, n=664, Placebo, n=688	-2.2 (± 27.7)	-1.4 (± 24.6)		
Month 8; Sitagliptin, n=635, Placebo, n=597	1.7 (± 38.5)	0.2 (± 45.3)		
Month 12; Sitagliptin, n=1126, Placebo, n=1059	0.8 (± 27.7)	1.2 (± 33.1)		
Month 24; Sitagliptin, n=930, Placebo, n=892	0.7 (± 34)	3.2 (± 31.6)		
Month 36; Sitagliptin, n=488, Placebo, n=513	2.5 (± 24)	4 (± 31)		
Month 48; Sitagliptin, n=238, Placebo, n=233	1.3 (± 15.2)	1.5 (± 25.5)		
Month 60; Sitagliptin, n=13, Placebo, n=17	-2.7 (± 10.1)	4.8 (± 15.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in urine albumin:creatinine ratio over time (Intent to treat population)

End point title	Change from baseline in urine albumin:creatinine ratio over time (Intent to treat population)

End point description:

Change from baseline reflects the difference between the urine albumin:creatinine ratio reported time point and baseline value. Intent to treat population included all randomized participants who received study medication, provided consent, and did not have any GCP deviations.

End point type	Secondary

End point timeframe:

Baseline and up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7332	7339		
Units: g/mol Creatinine				
arithmetic mean (standard deviation)				
Month 4; Sitagliptin, n=677, Placebo, n=713	-2.1 (± 27.5)	-1.4 (± 24.1)		
Month 8; Sitagliptin, n=658, Placebo, n=624	2.1 (± 39.4)	0.5 (± 44.5)		
Month 12; Sitagliptin, n=1167, Placebo, n=1115	1.3 (± 30.2)	1.2 (± 32.3)		
Month 24; Sitagliptin, n=1011, Placebo, n=964	0.5 (± 33.1)	3.1 (± 30.7)		
Month 36; Sitagliptin, n=537, Placebo, n=553	2.6 (± 25.8)	3.9 (± 30.3)		
Month 48; Sitagliptin,n=265, Placebo, n=256	1.9 (± 16.3)	1.6 (± 24.5)		
Month 60; Sitagliptin, n=14, Placebo, n=18	-2.5 (± 9.7)	6.4 (± 16.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who initiated chronic insulin therapy (Per protocol population)

End point title	Percentage of participants who initiated chronic insulin therapy (Per protocol population)

End point description:

Chronic insulin therapy is defined as a continuous period of insulin use of more than 3 months. Per protocol population included all randomized participants who received study medication except those participants who did not contribute at least 1 day of data to the study analysis due to a major protocol violation that excluded all of their data.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5554	5601		
Units: Percentage of participants				
number (not applicable)	8.6	11.9		

Statistical analyses

Statistical analysis title	Between-treatment difference
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	11155
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [7]
Method	Cox propotional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.77

Notes:

[7] - Model stratified by region with treatment group only as explanatory variable.

Secondary: Percentage of participants who initiated chronic insulin therapy (Intent to treat population)

End point title	Percentage of participants who initiated chronic insulin therapy (Intent to treat population)

End point description:

Chronic insulin therapy is defined as a continuous period of insulin use of more than 3 months. Intent to treat population included all randomized participants who received study medication, provided consent, and did not have any GCP deviations.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5608	5655		
Units: Percentage of participants				
number (not applicable)	9.7	13.2		

Statistical analyses

Statistical analysis title	Between-treatment difference
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	11263
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [8]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.79

Notes:

[8] - Model stratified by region with treatment group as only explanatory variable.

Secondary: Percentage of participants who initiated a co-interventional agent (Per protocol population)

End point title	Percentage of participants who initiated a co-interventional agent (Per protocol population)

End point description:

In participants not receiving insulin at baseline, addition of first co-interventional agent was the addition of next oral antihyperglycemic agent (AHA) or chronic insulin, where chronic insulin therapy is defined as a continuous period of insulin use of more than 3 months. Per protocol population included all randomized participants whoreceived study medication except those participants who did not contribute at least 1 day of data to the studyanalysis due to a major protocol violation that excluded all of their data.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7257	7266		
Units: Percentage of participants				
number (not applicable)	18.9	24.5		

Statistical analyses

Statistical analysis title	Between-treatment difference
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	14523
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [9]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.75

Notes:

[9] - Model stratified by region with treatment group only as explanatory variable.

Secondary: Percentage of participants who initiated a co-interventional agent (Intent to treat population)

End point title	Percentage of participants who initiated a co-interventional agent (Intent to treat population)

End point description:

In participants not receiving insulin at baseline, addition of first co-interventional agent was the addition of next oral antihyperglycemic agent (AHA) or chronic insulin, where chronic insulin therapy is defined as a continuous period of insulin use of more than 3 months. Intent to treat population included all randomized participants who received study medication, provided consent, and did not have any GCP deviations.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7332	7339		
Units: Percentage of participants				
number (not applicable)	21.7	27.9		

Statistical analyses

Statistical analysis title	Between-treatment difference
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	14671
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [10]
Method	Method Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.77

Notes:

[10] - Model stratified by region with treatment group only as explanatory variable.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Up to 68 months (including up to 28 days after last dose of study drug)

Adverse event reporting additional description:

All participants as treated (APaT) population includes participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Matching placebo tablet taken orally once daily in the morning

Reporting group title	Sitagliptin

Reporting group description:

Sitagliptin tablet taken orally once daily in the morning

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events exceeded the 5% threshold for any treatment group.

Serious adverse events	Placebo	Sitagliptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	909 / 7274 (12.50%)	928 / 7266 (12.77%)	
number of deaths (all causes)	57	54	
number of deaths resulting from adverse events	3	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal neoplasm			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Adenocarcinoma gastric			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma of appendix			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	12 / 7274 (0.16%)	11 / 7266 (0.15%)	
occurrences causally related to treatment / all	1 / 12	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma of salivary gland			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of the cervix			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 2	
Adenoid cystic carcinoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenolymphoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal cancer			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal squamous cell carcinoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaplastic large-cell lymphoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioimmunoblastic T-cell lymphoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	4 / 7274 (0.05%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	55 / 7274 (0.76%)	44 / 7266 (0.61%)	
occurrences causally related to treatment / all	0 / 86	0 / 50	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basosquamous carcinoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign gastric neoplasm			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign salivary gland neoplasm			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct cancer			
subjects affected / exposed	0 / 7274 (0.00%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Bladder cancer			
subjects affected / exposed	10 / 7274 (0.14%)	15 / 7266 (0.21%)	
occurrences causally related to treatment / all	0 / 10	0 / 15	
deaths causally related to treatment / all	0 / 1	0 / 2	
Bladder cancer recurrent			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder papilloma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	6 / 7274 (0.08%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bone cancer			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone sarcoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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	2 / 7274 (0.03%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	5 / 7274 (0.07%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer in situ			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer metastatic			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer recurrent			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	1 / 7274 (0.01%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Carcinoid tumour of the small bowel			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour pulmonary			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lymphoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cervix carcinoma			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	4 / 7274 (0.05%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cholesteatoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	3 / 7274 (0.04%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic lymphocytic leukaemia recurrent			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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	3 / 7274 (0.04%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon adenoma			
subjects affected / exposed	1 / 7274 (0.01%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	14 / 7274 (0.19%)	11 / 7266 (0.15%)	
occurrences causally related to treatment / all	0 / 14	0 / 11	
deaths causally related to treatment / all	0 / 4	0 / 0	
Colon cancer metastatic			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer stage I			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer stage IV			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon neoplasm			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			

subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colorectal cancer			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endometrial adenocarcinoma			
subjects affected / exposed	5 / 7274 (0.07%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder cancer			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric adenoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	2 / 7274 (0.03%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric cancer recurrent			

subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric cancer stage IV			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal cancer metastatic			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma multiforme			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Glioma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hepatic cancer metastatic			

subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic neoplasm			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intraductal papilloma of breast			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular melanoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	4 / 7274 (0.05%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	1 / 4	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Laryngeal cancer			
subjects affected / exposed	4 / 7274 (0.05%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal squamous cell carcinoma			

subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyosarcoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyosarcoma metastatic			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lentigo maligna			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	4 / 7274 (0.05%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Lung adenocarcinoma metastatic			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung adenocarcinoma stage I			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage IV			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung cancer metastatic			
subjects affected / exposed	4 / 7274 (0.05%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Lung carcinoma cell type unspecified stage IV			
subjects affected / exposed	0 / 7274 (0.00%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Lung neoplasm			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	12 / 7274 (0.16%)	12 / 7266 (0.17%)	
occurrences causally related to treatment / all	1 / 12	0 / 12	
deaths causally related to treatment / all	0 / 4	0 / 3	
Lung squamous cell carcinoma stage III			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphocytic leukaemia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant melanoma			
subjects affected / exposed	6 / 7274 (0.08%)	10 / 7266 (0.14%)	
occurrences causally related to treatment / all	0 / 7	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	4 / 7274 (0.05%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of ampulla of Vater			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of renal pelvis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melanocytic naevus			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningeal neoplasm			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma malignant			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastases to liver			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic bronchial carcinoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic malignant melanoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic renal cell carcinoma			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic uterine cancer			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucinous adenocarcinoma of appendix			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 7274 (0.01%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nasal cavity cancer			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngeal cancer			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm recurrence			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma metastatic			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurofibroma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 7274 (0.01%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Non-small cell lung cancer			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer metastatic			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Oesophageal carcinoma			
subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal squamous cell carcinoma			

subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal squamous cell carcinoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian adenoma			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian germ cell teratoma benign			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian granulosa-theca cell tumour			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian neoplasm			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			

subjects affected / exposed	7 / 7274 (0.10%)	8 / 7266 (0.11%)	
occurrences causally related to treatment / all	2 / 7	0 / 8	
deaths causally related to treatment / all	2 / 6	0 / 4	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid tumour benign			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile cancer			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile squamous cell carcinoma			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phaeochromocytoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	6 / 7274 (0.08%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Plasmablastic lymphoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmacytoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleomorphic liposarcoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural mesothelioma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Polycythaemia vera			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	45 / 7274 (0.62%)	36 / 7266 (0.50%)	
occurrences causally related to treatment / all	0 / 45	0 / 36	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer metastatic			

subjects affected / exposed	5 / 7274 (0.07%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 2	
Prostate cancer recurrent			
subjects affected / exposed	2 / 7274 (0.03%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer stage I			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal cancer			
subjects affected / exposed	4 / 7274 (0.05%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer metastatic			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal cancer			

subjects affected / exposed	3 / 7274 (0.04%)	7 / 7266 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer metastatic			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	2 / 7274 (0.03%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma recurrent			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma stage I			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma stage III			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal oncocytoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal cancer			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoma			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Small cell lung cancer			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma			
subjects affected / exposed	38 / 7274 (0.52%)	26 / 7266 (0.36%)	
occurrences causally related to treatment / all	0 / 44	0 / 38	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of head and neck			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	7 / 7274 (0.10%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	20 / 7274 (0.27%)	12 / 7266 (0.17%)	
occurrences causally related to treatment / all	0 / 23	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the oral cavity			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
T-cell lymphoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell prolymphocytic leukaemia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Testis cancer			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thymic cancer metastatic			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue cancer recurrent			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer metastatic			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tracheal cancer			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal neoplasm			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	7 / 7274 (0.10%)	7 / 7266 (0.10%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 1	
Urethral neoplasm			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			

subjects affected / exposed	4 / 7274 (0.05%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Angiodysplasia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bleeding varicose vein			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery aneurysm			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 7274 (0.03%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphorrhoea			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporal arteritis			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 7274 (0.01%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 7274 (0.04%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	8 / 7274 (0.11%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intolerance			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fat necrosis			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
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 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal hyperaemia			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			

subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	26 / 7274 (0.36%)	17 / 7266 (0.23%)	
occurrences causally related to treatment / all	0 / 31	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Puncture site haemorrhage			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Submandibular mass			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Corneal graft rejection			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Atrophic vulvovaginitis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	11 / 7274 (0.15%)	15 / 7266 (0.21%)	
occurrences causally related to treatment / all	0 / 11	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus prostatic			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical polyp			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymal cyst			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital rash			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis noninfective			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic floor muscle weakness			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic obstruction			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatism			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	3 / 7274 (0.04%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterovaginal prolapse			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	5 / 7274 (0.07%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis allergic			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			

subjects affected / exposed	4 / 7274 (0.05%)	8 / 7266 (0.11%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	30 / 7274 (0.41%)	13 / 7266 (0.18%)	
occurrences causally related to treatment / all	0 / 37	0 / 18	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic respiratory disease			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	6 / 7274 (0.08%)	9 / 7266 (0.12%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperventilation			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cyst			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nasal obstruction			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 7274 (0.03%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	4 / 7274 (0.05%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 7274 (0.03%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 7274 (0.00%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus polyp			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal disorder			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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	3 / 7274 (0.04%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	3 / 7274 (0.04%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dissociative disorder			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dependence			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	3 / 7274 (0.04%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nicotine dependence			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoid personality disorder			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Anticoagulation drug level increased			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic specific antigen increased			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	19 / 7274 (0.26%)	17 / 7266 (0.23%)	
occurrences causally related to treatment / all	15 / 19	13 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	3 / 7274 (0.04%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod sting			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Avulsion fracture			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	0 / 7274 (0.00%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns second degree			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns third degree			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical burns of eye			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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	4 / 7274 (0.05%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			

subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	3 / 7274 (0.04%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Delayed recovery from anaesthesia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dislocation of vertebra			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	4 / 7274 (0.05%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	9 / 7274 (0.12%)	9 / 7266 (0.12%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	3 / 7274 (0.04%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femur fracture			
subjects affected / exposed	11 / 7274 (0.15%)	7 / 7266 (0.10%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			

subjects affected / exposed	1 / 7274 (0.01%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 7274 (0.01%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture displacement			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	2 / 7274 (0.03%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat stroke			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	6 / 7274 (0.08%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Humerus fracture			
subjects affected / exposed	9 / 7274 (0.12%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	2 / 7274 (0.03%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	0 / 7274 (0.00%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	2 / 7274 (0.03%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	2 / 7274 (0.03%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth injury			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle injury			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Near drowning			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital haematoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic osteolysis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fistula			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	3 / 7274 (0.04%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prescribed overdose			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary contusion			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haematoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	5 / 7274 (0.07%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 7274 (0.01%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	4 / 7274 (0.05%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 5	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Splinter			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	4 / 7274 (0.05%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haemorrhage			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tendon rupture			
subjects affected / exposed	5 / 7274 (0.07%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular injury			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue injury			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 7274 (0.00%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal injury			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulnar nerve injury			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder rupture			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 7274 (0.00%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hamartoma			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocele			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phimosis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyloric stenosis			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syringomyelia			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitello-intestinal duct remnant			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor pulmonale			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery thrombosis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrhythmia			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Acoustic neuritis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arachnoid cyst			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia haemorrhage			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			

subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical cord compression			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical myelopathy			
subjects affected / exposed	3 / 7274 (0.04%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex partial seizures			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	6 / 7274 (0.08%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cubital tunnel syndrome			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 7274 (0.01%)	7 / 7266 (0.10%)	
occurrences causally related to treatment / all	0 / 1	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness postural			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	3 / 7274 (0.04%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersomnia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 7274 (0.01%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis crisis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve compression			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	3 / 7274 (0.04%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petit mal epilepsy			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Piriformis syndrome			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postictal state			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculitis lumbosacral			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retrograde amnesia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	4 / 7274 (0.05%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory disturbance			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord disorder			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural effusion			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic outlet syndrome			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulnar tunnel syndrome			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS origin			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 7274 (0.32%)	23 / 7266 (0.32%)	
occurrences causally related to treatment / all	0 / 23	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia vitamin B12 deficiency			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	6 / 7274 (0.08%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pernicious anaemia			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoacusis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniere's disease			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden hearing loss			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	2 / 7274 (0.03%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo labyrinthine			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	2 / 7274 (0.03%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angle closure glaucoma			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal degeneration			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryostenosis acquired			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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 / 7274 (0.01%)	0 / 7266 (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 discomfort			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia obstructive			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	0 / 7274 (0.00%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal faeces			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Change of bowel habit			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
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	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic pseudo-obstruction			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 7274 (0.01%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			

subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal polyp			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	3 / 7274 (0.04%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	4 / 7274 (0.05%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 7274 (0.03%)	10 / 7266 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	4 / 7274 (0.05%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			

subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal ulcer			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis haemorrhagic			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	12 / 7274 (0.16%)	11 / 7266 (0.15%)	
occurrences causally related to treatment / all	0 / 14	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7274 (0.00%)	9 / 7266 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	5 / 7274 (0.07%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	11 / 7274 (0.15%)	12 / 7266 (0.17%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia, obstructive			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal perforation			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	2 / 7274 (0.03%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			

subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema mouth			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal achalasia			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal food impaction			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal motility disorder			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer perforation			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontal disease			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngo-oesophageal diverticulum			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			

subjects affected / exposed	3 / 7274 (0.04%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland calculus			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	6 / 7274 (0.08%)	8 / 7266 (0.11%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal ulcer haemorrhage			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue disorder			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			

subjects affected / exposed	2 / 7274 (0.03%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	6 / 7274 (0.08%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Varices oesophageal			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dyskinesia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder polyp			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic congestion			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis contact			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis psoriasiform			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema asteatotic			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkeratosis			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder outlet obstruction			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder stenosis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			

subjects affected / exposed	6 / 7274 (0.08%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	4 / 7274 (0.05%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	6 / 7274 (0.08%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 7274 (0.00%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	9 / 7274 (0.12%)	10 / 7266 (0.14%)	
occurrences causally related to treatment / all	0 / 11	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	4 / 7274 (0.05%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stag horn calculus			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	4 / 7274 (0.05%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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 / 7274 (0.01%)	0 / 7266 (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	6 / 7274 (0.08%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Ankle impingement			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	4 / 7274 (0.05%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			

subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dupuytren's contracture			
subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc displacement			
subjects affected / exposed	2 / 7274 (0.03%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	8 / 7274 (0.11%)	8 / 7266 (0.11%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			

subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	5 / 7274 (0.07%)	13 / 7266 (0.18%)	
occurrences causally related to treatment / all	0 / 5	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	6 / 7274 (0.08%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	3 / 7274 (0.04%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	35 / 7274 (0.48%)	52 / 7266 (0.72%)	
occurrences causally related to treatment / all	0 / 37	0 / 54	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			

subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic arthropathy			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	7 / 7274 (0.10%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	3 / 7274 (0.04%)	4 / 7266 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			

subjects affected / exposed	5 / 7274 (0.07%)	7 / 7266 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis stenosans			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis B			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	2 / 7274 (0.03%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 7274 (0.05%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	4 / 7274 (0.05%)	6 / 7266 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 7274 (0.03%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	0 / 7274 (0.00%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex encephalitis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bites			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	3 / 7274 (0.04%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme disease			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycetoma mycotic			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	0 / 7274 (0.00%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (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	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrub typhus			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			

subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
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	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	8 / 7274 (0.11%)	5 / 7266 (0.07%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	2 / 7274 (0.03%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	5 / 7274 (0.07%)	8 / 7266 (0.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochloraemia			
subjects affected / exposed	1 / 7274 (0.01%)	2 / 7266 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	4 / 7274 (0.05%)	3 / 7266 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	21 / 7274 (0.29%)	8 / 7266 (0.11%)	
occurrences causally related to treatment / all	0 / 21	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 7274 (0.00%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 7274 (0.01%)	0 / 7266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			

subjects affected / exposed	1 / 7274 (0.01%)	1 / 7266 (0.01%)	
occurrences causally related to treatment / all	0 / 1	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	Sitagliptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 7274 (0.00%)	0 / 7266 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2010	Amendment 1: Revised eligibility criteria to include participants on insulin and reduced the minimum number of participants to be recruited on pioglitazone (either as monotherapy or combination therapy) from 2000 to 1000.
05 April 2012	Amendment 2: The non-inferiority margin was revised from 1.20 to 1.30 to provide consistency with current regulatory guidance.
25 September 2013	Amendment 3: The secondary objective related to the analysis of each of the components of the primary composite endpoint was revised to include fatal myocardial infarctions and fatal strokes when analyzing the time to these individual categories of events.
13 March 2014	Amendment 4: The protocol was amended to allow for the collection of new or worsening malignancy and pancreatitis information beyond 28 days after discontinuation of study drug, and indicate that reported events of basal and/or squamous cell carcinoma of the skin will not undergo adjudication by the Clinical Events Classification Committee.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported