



Clinical trial results:

AspECT - A phase III, randomised study of aspirin and esomeprazole chemoprevention in Barrett's metaplasia & oesophagitis.

Summary

EudraCT number	2004-003836-77
Trial protocol	GB
Global end of trial date	10 August 2017

Results information

Result version number	v1 (current)
This version publication date	26 August 2018
First version publication date	26 August 2018
Summary attachment (see zip file)	AspECT_PrimaryPublication_Lancet_04Aug2018 (AspECT_PrimaryResults_Lancet_PIIS0140673618313886.pdf)

Trial information

Trial identification

Sponsor protocol code	OCTO-003
-----------------------	----------

Additional study identifiers

ISRCTN number	ISRCTN85156844
ClinicalTrials.gov id (NCT number)	NCT00357682
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom, OX4 2PG
Public contact	AspECT Trial Office, Oncology Clinical Trials Unit, University of Oxford, +44 1865 617331, enquiries@oncology.ox.ac.uk
Scientific contact	AspECT Trial Office, Oncology Clinical Trials Unit, University of Oxford, +44 1865 617331, enquiries@oncology.ox.ac.uk

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	31 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2017
Global end of trial reached?	Yes
Global end of trial date	10 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether intervention with aspirin results in a decreased all causes of mortality or conversion rate from Barrett's metaplasia to adenocarcinoma or high grade dysplasia.

To assess whether high dose PPI therapy decreases the all causes of mortality or conversion rate from Barrett's Metaplasia to adenocarcinoma or high grade dysplasia.

Protection of trial subjects:

A data safety monitoring committee was established to review the data at regular intervals and ensure the safety of the trial patients.

Patient information sheets were provided to subjects prior to randomisation. Nurses and consultants also detailed to the patients the option to withdraw from the trial treatment and follow up at any point throughout the trial.

Patients were also provided with contact details of the clinical trial office and were encouraged to reach out if they had any questions at any time.

All adverse events throughout the trial were reported immediately to the trial office and reviewed if deemed serious.

Background therapy:

Proton Pump Inhibitors (PPI) are used in to reduce acid in patients experiencing reflux from the stomach.

Aspirin is a drug mainly used to treat pain, fever, or inflammation.

Evidence for comparator:

It has yet to be determined whether high or low dose PPI is optimal in treating acid reflux and potentially reducing oesophageal cancer.

Long term daily use of aspirin has been seen to reduce the risk of a number of cancers, most notably colon cancer. It is yet unknown for sure if this is the case in oesophageal cancer.

Actual start date of recruitment	04 March 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Ethical reason, Regulatory reason, Scientific research, Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 2491
--------------------------------------	----------------------

Country: Number of subjects enrolled	Canada: 44
Worldwide total number of subjects	2535
EEA total number of subjects	2491

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)	1836
From 65 to 84 years	693
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Eligible participants were recruited from 4th March 2005 to 25th February 2009 in 86 centres in the United Kingdom and 1 centre in Canada. Participants were recruited by gastroenterologists and upper gastrointestinal surgeons at hospitals through clinics and endoscopy lists, including new and existing BE diagnoses.

Pre-assignment

Screening details:

At least 5,726 patients were screened in 87 sites. Of the 5,726 screening records, 2,582 (2083 not meeting exclusion and 499 other reasons) were excluded based on trial exclusion reasons (contraindication to study drug, outside age range etc). Of the 3,100 remaining, 587 declined participation in the trial, leaving 2,557 total patients randomised

Period 1

Period 1 title	Randomisation (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

No blinding was performed

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Low Dose PPI (20mg daily)

Arm type	Active comparator
Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	D9612000000
Other name	Nexium
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20mg/day

Arm title	Arm B
------------------	-------

Arm description:

High Dose PPI (80mg daily)

Arm type	Active comparator
Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	D9612000000
Other name	Nexium
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg/twice daily

Arm title	Arm C
------------------	-------

Arm description:

Low Dose PPI (20mg daily) & Aspirin (300mg daily)

Arm type	Active comparator
----------	-------------------

Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	D9612000000
Other name	Nexium
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20mg/day

Investigational medicinal product name	Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300mg/day

Arm title	Arm D
------------------	-------

Arm description:

High Dose PPI (80mg daily) & Aspirin (300mg daily)

Arm type	Active comparator
Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	D9612000000
Other name	Nexium
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg/twice daily

Investigational medicinal product name	Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300mg/day

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	699	698	566
Completed	699	698	566

Number of subjects in period 1	Arm D
Started	572
Completed	572

Baseline characteristics

Reporting groups

Reporting group title	Arm A
Reporting group description:	
Low Dose PPI (20mg daily)	
Reporting group title	Arm B
Reporting group description:	
High Dose PPI (80mg daily)	
Reporting group title	Arm C
Reporting group description:	
Low Dose PPI (20mg daily) & Aspirin (300mg daily)	
Reporting group title	Arm D
Reporting group description:	
High Dose PPI (80mg daily) & Aspirin (300mg daily)	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	699	698	566
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	495	494	429
From 65-84 years	202	204	134
85 years and over	2	0	3
Age continuous			
Continuous age statistics by treatment arm and primary trial comparisons			
Units: years			
median	59	59	58
inter-quartile range (Q1-Q3)	51 to 65	51 to 66	50 to 64
Gender categorical			
Gender characteristics by treatment arm and primary trial comparisons			
Units: Subjects			
Female	135	136	118
Male	564	562	448

Reporting group values	Arm D	Total	
Number of subjects	572	2535	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	418	1836	
From 65-84 years	153	693	
85 years and over	1	6	
Age continuous			
Continuous age statistics by treatment arm and primary trial comparisons			
Units: years			
median	58		
inter-quartile range (Q1-Q3)	50 to 65	-	
Gender categorical			
Gender characteristics by treatment arm and primary trial comparisons			
Units: Subjects			
Female	124	513	
Male	448	2022	

Subject analysis sets

Subject analysis set title	Aspirin
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients randomised to receive 300mg daily aspirin	
Subject analysis set title	No Aspirin
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomised to receive no aspirin	
Subject analysis set title	Low Dose PPI
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomised to receive 20mg daily PPI	
Subject analysis set title	High Dose PPI
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomised to receive 80mg PPI daily	

Reporting group values	Aspirin	No Aspirin	Low Dose PPI
Number of subjects	1138	1142	1265
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	847	854	924
From 65-84 years	287	287	336
85 years and over	4	1	5

Age continuous			
Continuous age statistics by treatment arm and primary trial comparisons			
Units: years			
median	58	58	59
inter-quartile range (Q1-Q3)	50 to 65	50 to 65	51 to 65
Gender categorical			
Gender characteristics by treatment arm and primary trial comparisons			
Units: Subjects			
Female	242	242	253
Male	896	900	1012

Reporting group values	High Dose PPI		
Number of subjects	1270		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	912		
From 65-84 years	357		
85 years and over	1		
Age continuous			
Continuous age statistics by treatment arm and primary trial comparisons			
Units: years			
median	59		
inter-quartile range (Q1-Q3)	51 to 65		
Gender categorical			
Gender characteristics by treatment arm and primary trial comparisons			
Units: Subjects			
Female	260		
Male	1010		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: Low Dose PPI (20mg daily)	
Reporting group title	Arm B
Reporting group description: High Dose PPI (80mg daily)	
Reporting group title	Arm C
Reporting group description: Low Dose PPI (20mg daily) & Aspirin (300mg daily)	
Reporting group title	Arm D
Reporting group description: High Dose PPI (80mg daily) & Aspirin (300mg daily)	
Subject analysis set title	Aspirin
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients randomised to receive 300mg daily aspirin	
Subject analysis set title	No Aspirin
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects randomised to receive no aspirin	
Subject analysis set title	Low Dose PPI
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects randomised to receive 20mg daily PPI	
Subject analysis set title	High Dose PPI
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects randomised to receive 80mg PPI daily	

Primary: First event of death, oesophageal adenocarcinoma, high grade dysplasia

End point title	First event of death, oesophageal adenocarcinoma, high grade dysplasia
End point description: Death is recorded on a continuous basis through reporting from trial sites. Oesophageal adenocarcinoma is recorded through endoscopies taken every two years or ad-hoc at clinician decision High Grade Dysplasia is recorded through endoscopies taken every two years or ad-hoc at clinician decision	
End point type	Primary
End point timeframe: Events are assessed from the date of randomisation to the end of study which can be patient withdrawal, loss to follow up or study end (8 years or 10 years from randomisation, depending on consent)	

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	699	698	566	572
Units: 20	99	87	75	52

End point values	Aspirin	No Aspirin	Low Dose PPI	High Dose PPI
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1138	1142	1265	1270
Units: 20	127	154	174	139

Statistical analyses

Statistical analysis title	Primary Analysis (PPI)
----------------------------	------------------------

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to primary event in low dose PPI (20mg) patients to high dose PPI (80mg) patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and aspirin randomisation group.

Comparison groups	Low Dose PPI v High Dose PPI
Number of subjects included in analysis	2535
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.068
Method	Accelerated Failure Time
Parameter estimate	Time Ratio
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.57

Notes:

[1] - 5% significance level is considered statistically significant

Statistical analysis title	Primary Analysis (Aspirin)
----------------------------	----------------------------

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to primary event in aspirin patients to non-aspirin patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and PPI randomisation group.

Comparison groups	No Aspirin v Aspirin
Number of subjects included in analysis	2280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	Accelerated Failure Time
Parameter estimate	Time Ratio
Point estimate	1.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.58

Statistical analysis title	Secondary Analysis (PPI All cause mortality)
-----------------------------------	--

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to all cause mortality in low dose PPI (20mg) patients to high dose PPI (80mg) patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and aspirin randomisation group.

Comparison groups	Low Dose PPI v High Dose PPI
Number of subjects included in analysis	2535
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	Accelerated Failure Time
Parameter estimate	Time Ratio
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.82

Statistical analysis title	Secondary Analysis (PPI Oesophageal Adenocarcinoma)
-----------------------------------	---

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to oesophageal adenocarcinoma in low dose PPI (20mg) patients to high dose PPI (80mg) patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and aspirin randomisation group.

Comparison groups	Low Dose PPI v High Dose PPI
Number of subjects included in analysis	2535
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.864
Method	Accelerated Failure Time
Parameter estimate	Time Ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.61

Statistical analysis title	Secondary Analysis (High Grade Dysplasia)
Statistical analysis description:	
Accelerated Failure Time (AFT) analysis comparing time to high grade dysplasia in low dose PPI (20mg) patients to high dose PPI (80mg) patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and aspirin randomisation group.	
Comparison groups	Low Dose PPI v High Dose PPI
Number of subjects included in analysis	2535
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.119
Method	Accelerated Failure Time
Parameter estimate	Time Ratio
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	2.02

Statistical analysis title	Secondary Analysis (Aspirin All Cause Mortality)
Statistical analysis description:	
Accelerated Failure Time (AFT) analysis comparing time to all cause mortality in aspirin patients to non-aspirin patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and PPI randomisation group.	
Comparison groups	Aspirin v No Aspirin
Number of subjects included in analysis	2280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.159
Method	Accelerated Failure Time
Parameter estimate	Time Ratio
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.7

Statistical analysis title	Secondary Analysis (Aspirin and oesophageal adeno)
Statistical analysis description:	
Accelerated Failure Time (AFT) analysis comparing time to oesophageal adenocarcinoma in aspirin patients to non-aspirin patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and PPI randomisation group.	
Comparison groups	Aspirin v No Aspirin

Number of subjects included in analysis	2280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.921
Method	Accelerated Failure Time
Parameter estimate	Time Ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.64

Statistical analysis title	Secondary Analysis (Aspirin High Grade Dysplasia)
-----------------------------------	---

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to high grade dysplasia in aspirin patients to non-aspirin patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and PPI randomisation group.

Comparison groups	Aspirin v No Aspirin
Number of subjects included in analysis	2280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053
Method	Accelerated Failure Time
Parameter estimate	Time Ratio
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.29

Statistical analysis title	Secondary Analysis (PPI Cause Specific Mortality)
-----------------------------------	---

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to cause specific mortality in low dose PPI (20mg) patients to high dose PPI (80mg) patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and aspirin randomisation group.

Cause Specific Mortality: Death due to oesophageal adenocarcinoma

Comparison groups	Low Dose PPI v High Dose PPI
Number of subjects included in analysis	2535
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.336
Method	Accelerated Failure Time
Parameter estimate	Time Ratio
Point estimate	1.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	3.8

Statistical analysis title	Secondary Analysis (Aspirin Cause Specific Death)
-----------------------------------	---

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to cause specific mortality in aspirin patients to non-aspirin patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and PPI randomisation group.

Comparison groups	Aspirin v No Aspirin
Number of subjects included in analysis	2280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.983
Method	Accelerated Failure Time
Parameter estimate	Time Ratio
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	2.69

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse events were reported from the date of randomisation until 30 days after the end of treatment

Adverse event reporting additional description:

Adverse events were reported to the trial team by sites as soon as possible after the events occurred.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20
--------------------	----

Reporting groups

Reporting group title	Arm A
-----------------------	-------

Reporting group description:

Low Dose PPI (20mg daily)

Reporting group title	Arm B
-----------------------	-------

Reporting group description:

High Dose PPI (80mg daily)

Reporting group title	Arm C
-----------------------	-------

Reporting group description:

Low Dose PPI (20mg daily) & Aspirin (300mg daily)

Reporting group title	Arm D
-----------------------	-------

Reporting group description:

High Dose PPI (80mg daily) & Aspirin (300mg daily)

Reporting group title	Aspirin
-----------------------	---------

Reporting group description:

Patients randomised to 300mg daily aspirin treatment

Reporting group title	No Aspirin
-----------------------	------------

Reporting group description:

Patients randomised to received no aspirin treatment

Reporting group title	Low Dose PPI
-----------------------	--------------

Reporting group description:

Patients randomised to 20mg daily PPI treatment

Reporting group title	High Dose PPI
-----------------------	---------------

Reporting group description:

Patients randomised to 80mg daily PPI treatment

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: The reason is that adverse events (non-serious) were only recorded if the event led to the patient withdrawing from study medication. Non serious AE details were not recorded.

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	183 / 699 (26.18%)	195 / 698 (27.94%)	176 / 566 (31.10%)
number of deaths (all causes)	48	42	46
number of deaths resulting from adverse events	39	33	30
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Bile duct cancer			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Cancer			
subjects affected / exposed	1 / 699 (0.14%)	2 / 698 (0.29%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Brain cancer			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Breast cancer			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Colorectal cancer			
subjects affected / exposed	6 / 699 (0.86%)	4 / 698 (0.57%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 7	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 4	0 / 1	0 / 2
Endometrial cancer			
subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder cancer			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric - Adenocarcinoma			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Laryngeal - Squamous cell carcinoma			

subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukemia			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Liposarcoma			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung cancer			
subjects affected / exposed	5 / 699 (0.72%)	7 / 698 (1.00%)	7 / 566 (1.24%)
occurrences causally related to treatment / all	0 / 5	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 4	0 / 5	0 / 7
Lymphoma			
subjects affected / exposed	2 / 699 (0.29%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Mesothelioma			
subjects affected / exposed	1 / 699 (0.14%)	2 / 698 (0.29%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Metastatic cancer unknown origin			
subjects affected / exposed	0 / 699 (0.00%)	2 / 698 (0.29%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Myeloma			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neuroendocrine tumour			

subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal cancer			
subjects affected / exposed	3 / 699 (0.43%)	1 / 698 (0.14%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 2
Oral cancer			
subjects affected / exposed	1 / 699 (0.14%)	2 / 698 (0.29%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic cancer			
subjects affected / exposed	1 / 699 (0.14%)	2 / 698 (0.29%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Prostate cancer			
subjects affected / exposed	4 / 699 (0.57%)	7 / 698 (1.00%)	3 / 566 (0.53%)
occurrences causally related to treatment / all	0 / 4	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	3 / 699 (0.43%)	1 / 698 (0.14%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Skin cancer melanoma			
subjects affected / exposed	0 / 699 (0.00%)	2 / 698 (0.29%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer non-melanoma			

subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Testicular cancer			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hematoma			
subjects affected / exposed	0 / 699 (0.00%)	2 / 698 (0.29%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ruptured aortic arch aneurism			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Thromboembolic event			
subjects affected / exposed	5 / 699 (0.72%)	7 / 698 (1.00%)	6 / 566 (1.06%)
occurrences causally related to treatment / all	0 / 5	0 / 7	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Vasculitis			

subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Fetal death			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flu like symptoms			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localized edema			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	7 / 699 (1.00%)	12 / 698 (1.72%)	7 / 566 (1.24%)
occurrences causally related to treatment / all	0 / 7	0 / 13	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylaxis			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune disorder			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 699 (0.29%)	1 / 698 (0.14%)	3 / 566 (0.53%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			

subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	9 / 566 (1.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	7 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 699 (0.00%)	3 / 698 (0.43%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal stenosis			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			

subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusion			
subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 699 (0.00%)	2 / 698 (0.29%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychosis			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 699 (0.00%)	2 / 698 (0.29%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Investigations			

Blood bilirubin increased			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GGT increased			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental death			
subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Alcohol abuse			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	2 / 699 (0.29%)	2 / 698 (0.29%)	3 / 566 (0.53%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bruising			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cholecystectomy procedural complication			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 699 (0.14%)	3 / 698 (0.43%)	4 / 566 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	2 / 699 (0.29%)	7 / 698 (1.00%)	7 / 566 (1.24%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Head injury			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	6 / 699 (0.86%)	4 / 698 (0.57%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	2 / 6	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraoperative gastrointestinal injury			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative hemorrhage			

subjects affected / exposed	0 / 699 (0.00%)	2 / 698 (0.29%)	3 / 566 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Ruptured spleen			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	2 / 699 (0.29%)	2 / 698 (0.29%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 699 (0.29%)	4 / 698 (0.57%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve disease			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	5 / 699 (0.72%)	5 / 698 (0.72%)	6 / 566 (1.06%)
occurrences causally related to treatment / all	0 / 5	1 / 9	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	2 / 699 (0.29%)	1 / 698 (0.14%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 1
Cardiomyopathy			
subjects affected / exposed	2 / 699 (0.29%)	2 / 698 (0.29%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	6 / 699 (0.86%)	9 / 698 (1.29%)	4 / 566 (0.71%)
occurrences causally related to treatment / all	0 / 6	0 / 12	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart failure			
subjects affected / exposed	4 / 699 (0.57%)	1 / 698 (0.14%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	12 / 699 (1.72%)	12 / 698 (1.72%)	11 / 566 (1.94%)
occurrences causally related to treatment / all	0 / 12	0 / 12	0 / 11
deaths causally related to treatment / all	0 / 4	0 / 3	0 / 3
Pericardial effusion			

subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular dysfunction			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	4 / 566 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disturbance			
subjects affected / exposed	4 / 699 (0.57%)	1 / 698 (0.14%)	4 / 566 (0.71%)
occurrences causally related to treatment / all	1 / 4	1 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 699 (0.14%)	5 / 698 (0.72%)	4 / 566 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hemorrhage			
subjects affected / exposed	3 / 699 (0.43%)	2 / 698 (0.29%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 3	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Ischemia cerebrovascular			
subjects affected / exposed	10 / 699 (1.43%)	7 / 698 (1.00%)	8 / 566 (1.41%)
occurrences causally related to treatment / all	0 / 10	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Motor neurone disease			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple system atrophy			

subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Parkinson's disease			
subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyramidal tract syndrome			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spasticity			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	3 / 699 (0.43%)	1 / 698 (0.14%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischemic attacks			

subjects affected / exposed	3 / 699 (0.43%)	5 / 698 (0.72%)	4 / 566 (0.71%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasovagal reaction			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 699 (0.29%)	4 / 698 (0.57%)	7 / 566 (1.24%)
occurrences causally related to treatment / all	0 / 2	0 / 4	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spleen disorder			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular disorder			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vitreous hemorrhage			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	3 / 699 (0.43%)	3 / 698 (0.43%)	7 / 566 (1.24%)
occurrences causally related to treatment / all	0 / 3	0 / 3	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bloating			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cameron Ulcer			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic hemorrhage			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic obstruction			

subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic perforation			
subjects affected / exposed	1 / 699 (0.14%)	2 / 698 (0.29%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 699 (0.14%)	2 / 698 (0.29%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	3 / 699 (0.43%)	2 / 698 (0.29%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal hemorrhage			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	2 / 699 (0.29%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal haemorrhage			

subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal pain			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 699 (0.00%)	2 / 698 (0.29%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 699 (0.29%)	5 / 698 (0.72%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal pain			

subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhoidal hemorrhage			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhoids			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal obstruction			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Colitis			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss tear			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	5 / 699 (0.72%)	3 / 698 (0.43%)	4 / 566 (0.71%)
occurrences causally related to treatment / all	0 / 10	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Rectal haemorrhage			

subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 699 (0.14%)	2 / 698 (0.29%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Alcoholic Hepatitis			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	6 / 699 (0.86%)	3 / 698 (0.43%)	6 / 566 (1.06%)
occurrences causally related to treatment / all	0 / 6	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder necrosis			

subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gallbladder pain			
subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder perforation			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 699 (0.00%)	3 / 698 (0.43%)	4 / 566 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 4
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 699 (0.14%)	2 / 698 (0.29%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	2 / 699 (0.29%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	3 / 699 (0.43%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal calculi			

subjects affected / exposed	2 / 699 (0.29%)	1 / 698 (0.14%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	3 / 699 (0.43%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	2 / 699 (0.29%)	3 / 698 (0.43%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Avascular necrosis	subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain	subjects affected / exposed	0 / 699 (0.00%)	2 / 698 (0.29%)	1 / 566 (0.18%)
	occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Spondylosis	subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia	subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	2 / 566 (0.35%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint range of motion decreased cervical spine	subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mortons neuroma	subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness lower limb	subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia	subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain				

subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorectal infection			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 699 (0.00%)	2 / 698 (0.29%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			

subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder infection			
subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone infection			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	3 / 699 (0.43%)	6 / 698 (0.86%)	5 / 566 (0.88%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye infection			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inner Ear Infection			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal parasite			

subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint infection			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Kidney infection			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	19 / 699 (2.72%)	12 / 698 (1.72%)	9 / 566 (1.59%)
occurrences causally related to treatment / all	0 / 24	0 / 15	0 / 14
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 1
Pharyngitis			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate infection			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoas abscess			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland infection			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal infection			

subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	7 / 699 (1.00%)	7 / 698 (1.00%)	2 / 566 (0.35%)
occurrences causally related to treatment / all	0 / 7	0 / 10	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory infection			
subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	4 / 699 (0.57%)	0 / 698 (0.00%)	4 / 566 (0.71%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	3 / 699 (0.43%)	3 / 698 (0.43%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acidosis			

subjects affected / exposed	0 / 699 (0.00%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycemia			
subjects affected / exposed	2 / 699 (0.29%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalemia			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricemia			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycemia			
subjects affected / exposed	1 / 699 (0.14%)	0 / 698 (0.00%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalemia			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	1 / 566 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesemia			
subjects affected / exposed	0 / 699 (0.00%)	2 / 698 (0.29%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatremia			
subjects affected / exposed	1 / 699 (0.14%)	1 / 698 (0.14%)	0 / 566 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm D	Aspirin	No Aspirin
Total subjects affected by serious			

adverse events			
subjects affected / exposed	164 / 572 (28.67%)	340 / 1138 (29.88%)	378 / 1142 (33.10%)
number of deaths (all causes)	27	73	90
number of deaths resulting from adverse events	17	47	72
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bile duct cancer			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Bladder Cancer			
subjects affected / exposed	2 / 572 (0.35%)	2 / 1138 (0.18%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Brain cancer			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Breast cancer			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Colorectal cancer			
subjects affected / exposed	4 / 572 (0.70%)	6 / 1138 (0.53%)	10 / 1142 (0.88%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 12
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 5
Endometrial cancer			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder cancer			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Gastric - Adenocarcinoma			

subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Laryngeal - Squamous cell carcinoma			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukemia			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Liposarcoma			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung cancer			
subjects affected / exposed	3 / 572 (0.52%)	10 / 1138 (0.88%)	12 / 1142 (1.05%)
occurrences causally related to treatment / all	0 / 5	0 / 13	0 / 12
deaths causally related to treatment / all	0 / 2	0 / 9	0 / 9
Lymphoma			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 2
Mesothelioma			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Metastatic cancer unknown origin			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Myeloma			

subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Neuroendocrine tumour			
subjects affected / exposed	0 / 572 (0.00%)	2 / 1138 (0.18%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal cancer			
subjects affected / exposed	0 / 572 (0.00%)	2 / 1138 (0.18%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 4
Oral cancer			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic cancer			
subjects affected / exposed	0 / 572 (0.00%)	2 / 1138 (0.18%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 3
Prostate cancer			
subjects affected / exposed	6 / 572 (1.05%)	8 / 1138 (0.70%)	11 / 1142 (0.96%)
occurrences causally related to treatment / all	0 / 6	0 / 9	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal cancer			
subjects affected / exposed	1 / 572 (0.17%)	3 / 1138 (0.26%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Skin cancer melanoma			

subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Skin cancer non-melanoma			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Testicular cancer			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hematoma			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 572 (0.35%)	3 / 1138 (0.26%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ruptured aortic arch aneurism			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Thromboembolic event			

subjects affected / exposed	4 / 572 (0.70%)	10 / 1138 (0.88%)	12 / 1142 (1.05%)
occurrences causally related to treatment / all	0 / 4	0 / 10	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Vasculitis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Fetal death			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flu like symptoms			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localized edema			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	12 / 572 (2.10%)	19 / 1138 (1.67%)	19 / 1142 (1.66%)
occurrences causally related to treatment / all	0 / 14	0 / 21	0 / 20
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pain			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylaxis			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune disorder			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	0 / 572 (0.00%)	3 / 1138 (0.26%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	4 / 572 (0.70%)	13 / 1138 (1.14%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	4 / 4	11 / 13	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal stenosis			

subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusion			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	4 / 572 (0.70%)	4 / 1138 (0.35%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	1 / 4	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychosis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			

subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GGT increased			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental death			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Alcohol abuse			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 572 (0.17%)	4 / 1138 (0.35%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bruising			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy procedural complication			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	3 / 572 (0.52%)	7 / 1138 (0.62%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 4	0 / 8	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Fracture			
subjects affected / exposed	4 / 572 (0.70%)	11 / 1138 (0.97%)	9 / 1142 (0.79%)
occurrences causally related to treatment / all	0 / 4	0 / 12	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Head injury			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 572 (0.17%)	3 / 1138 (0.26%)	10 / 1142 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 3	2 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraoperative gastrointestinal injury			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			

subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative hemorrhage			
subjects affected / exposed	0 / 572 (0.00%)	3 / 1138 (0.26%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Ruptured spleen			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	6 / 572 (1.05%)	7 / 1138 (0.62%)	6 / 1142 (0.53%)
occurrences causally related to treatment / all	0 / 6	0 / 7	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve disease			

subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 572 (0.35%)	8 / 1138 (0.70%)	10 / 1142 (0.88%)
occurrences causally related to treatment / all	0 / 2	0 / 8	1 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 572 (0.00%)	2 / 1138 (0.18%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 572 (0.00%)	2 / 1138 (0.18%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 3
Cardiomyopathy			
subjects affected / exposed	2 / 572 (0.35%)	2 / 1138 (0.18%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	4 / 572 (0.70%)	8 / 1138 (0.70%)	15 / 1142 (1.31%)
occurrences causally related to treatment / all	1 / 4	1 / 8	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart failure			
subjects affected / exposed	3 / 572 (0.52%)	5 / 1138 (0.44%)	5 / 1142 (0.44%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	13 / 572 (2.27%)	24 / 1138 (2.11%)	24 / 1142 (2.10%)
occurrences causally related to treatment / all	0 / 13	0 / 24	0 / 24
deaths causally related to treatment / all	0 / 2	0 / 5	0 / 7
Pericardial effusion			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular dysfunction			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	2 / 572 (0.35%)	6 / 1138 (0.53%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			

subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disturbance			
subjects affected / exposed	2 / 572 (0.35%)	6 / 1138 (0.53%)	5 / 1142 (0.44%)
occurrences causally related to treatment / all	1 / 2	1 / 6	2 / 5
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Dizziness			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 572 (0.00%)	4 / 1138 (0.35%)	6 / 1142 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hemorrhage			
subjects affected / exposed	3 / 572 (0.52%)	5 / 1138 (0.44%)	5 / 1142 (0.44%)
occurrences causally related to treatment / all	3 / 3	4 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Ischemia cerebrovascular			
subjects affected / exposed	10 / 572 (1.75%)	18 / 1138 (1.58%)	17 / 1142 (1.49%)
occurrences causally related to treatment / all	1 / 13	1 / 21	0 / 17
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Memory impairment			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Motor neurone disease			

subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple system atrophy			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Parkinson's disease			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyramidal tract syndrome			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spasticity			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 572 (0.17%)	3 / 1138 (0.26%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischemic attacks			
subjects affected / exposed	6 / 572 (1.05%)	10 / 1138 (0.88%)	8 / 1142 (0.70%)
occurrences causally related to treatment / all	0 / 6	0 / 11	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasovagal reaction			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 572 (0.17%)	8 / 1138 (0.70%)	6 / 1142 (0.53%)
occurrences causally related to treatment / all	0 / 1	7 / 8	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spleen disorder			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 572 (0.35%)	3 / 1138 (0.26%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular disorder			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Retinal detachment			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous hemorrhage			
subjects affected / exposed	2 / 572 (0.35%)	2 / 1138 (0.18%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	3 / 572 (0.52%)	10 / 1138 (0.88%)	6 / 1142 (0.53%)
occurrences causally related to treatment / all	0 / 3	1 / 10	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bloating			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cameron Ulcer			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	3 / 572 (0.52%)	3 / 1138 (0.26%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic hemorrhage			

subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic obstruction			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic perforation			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	2 / 572 (0.35%)	4 / 1138 (0.35%)	5 / 1142 (0.44%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal hemorrhage			
subjects affected / exposed	2 / 572 (0.35%)	2 / 1138 (0.18%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			

subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal haemorrhage			
subjects affected / exposed	1 / 572 (0.17%)	3 / 1138 (0.26%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed	1 / 572 (0.17%)	3 / 1138 (0.26%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal pain			
subjects affected / exposed	0 / 572 (0.00%)	2 / 1138 (0.18%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 572 (0.00%)	2 / 1138 (0.18%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	2 / 572 (0.35%)	4 / 1138 (0.35%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	2 / 2	3 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastritis			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	7 / 1142 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal pain			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhoidal hemorrhage			
subjects affected / exposed	1 / 572 (0.17%)	3 / 1138 (0.26%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhoids			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal obstruction			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Colitis			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss tear			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	5 / 572 (0.87%)	9 / 1138 (0.79%)	8 / 1142 (0.70%)
occurrences causally related to treatment / all	0 / 5	0 / 9	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rectal haemorrhage			
subjects affected / exposed	2 / 572 (0.35%)	2 / 1138 (0.18%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 572 (0.35%)	4 / 1138 (0.35%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	2 / 2	3 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	4 / 572 (0.70%)	6 / 1138 (0.53%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	1 / 4	1 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Alcoholic Hepatitis			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	7 / 572 (1.22%)	13 / 1138 (1.14%)	9 / 1142 (0.79%)
occurrences causally related to treatment / all	0 / 8	0 / 15	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder necrosis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gallbladder pain			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder perforation			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 572 (0.00%)	4 / 1138 (0.35%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 2
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 572 (0.35%)	3 / 1138 (0.26%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			

subjects affected / exposed	2 / 572 (0.35%)	2 / 1138 (0.18%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal calculi			
subjects affected / exposed	0 / 572 (0.00%)	2 / 1138 (0.18%)	3 / 1142 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	2 / 572 (0.35%)	3 / 1138 (0.26%)	5 / 1142 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arthritis			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Avascular necrosis			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Spondylosis			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia			
subjects affected / exposed	2 / 572 (0.35%)	4 / 1138 (0.35%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint range of motion decreased cervical spine			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mortons neuroma			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness lower limb			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			

subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorectal infection			
subjects affected / exposed	2 / 572 (0.35%)	2 / 1138 (0.18%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	3 / 572 (0.52%)	3 / 1138 (0.26%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			

subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder infection			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone infection			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	4 / 572 (0.70%)	9 / 1138 (0.79%)	9 / 1142 (0.79%)
occurrences causally related to treatment / all	3 / 6	3 / 11	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye infection			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inner Ear Infection			

subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal parasite			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint infection			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Kidney infection			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	16 / 572 (2.80%)	25 / 1138 (2.20%)	31 / 1142 (2.71%)
occurrences causally related to treatment / all	0 / 27	0 / 41	0 / 39
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 3
Pharyngitis			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate infection			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoas abscess			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland infection			

subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal infection			
subjects affected / exposed	2 / 572 (0.35%)	2 / 1138 (0.18%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	5 / 572 (0.87%)	7 / 1138 (0.62%)	14 / 1142 (1.23%)
occurrences causally related to treatment / all	0 / 5	0 / 7	0 / 17
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	2 / 572 (0.35%)	2 / 1138 (0.18%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory infection			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	7 / 572 (1.22%)	11 / 1138 (0.97%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 7	0 / 12	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Wound infection			

subjects affected / exposed	0 / 572 (0.00%)	1 / 1138 (0.09%)	6 / 1142 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycemia			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	4 / 1142 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalemia			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricemia			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycemia			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	1 / 1142 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalemia			
subjects affected / exposed	1 / 572 (0.17%)	2 / 1138 (0.18%)	0 / 1142 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesemia			
subjects affected / exposed	1 / 572 (0.17%)	1 / 1138 (0.09%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	1 / 1	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatremia			

subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	2 / 1142 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Low Dose PPI	High Dose PPI	
Total subjects affected by serious adverse events			
subjects affected / exposed	359 / 1265 (28.38%)	359 / 1270 (28.27%)	
number of deaths (all causes)	94	69	
number of deaths resulting from adverse events	69	50	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bile duct cancer			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder Cancer			
subjects affected / exposed	1 / 1265 (0.08%)	4 / 1270 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Brain cancer			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Colorectal cancer			
subjects affected / exposed	8 / 1265 (0.63%)	8 / 1270 (0.63%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 6	0 / 2	
Endometrial cancer			
subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gallbladder cancer			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric - Adenocarcinoma			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Laryngeal - Squamous cell carcinoma			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukemia			
subjects affected / exposed	0 / 1265 (0.00%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Liposarcoma			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung cancer			
subjects affected / exposed	12 / 1265 (0.95%)	10 / 1270 (0.79%)	
occurrences causally related to treatment / all	0 / 13	0 / 12	
deaths causally related to treatment / all	0 / 11	0 / 7	
Lymphoma			
subjects affected / exposed	3 / 1265 (0.24%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
Mesothelioma			
subjects affected / exposed	1 / 1265 (0.08%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Metastatic cancer unknown origin			

subjects affected / exposed	1 / 1265 (0.08%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Myeloma			
subjects affected / exposed	1 / 1265 (0.08%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Neuroendocrine tumour			
subjects affected / exposed	3 / 1265 (0.24%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal cancer			
subjects affected / exposed	5 / 1265 (0.40%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 1	
Oral cancer			
subjects affected / exposed	2 / 1265 (0.16%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cancer			
subjects affected / exposed	3 / 1265 (0.24%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Prostate cancer			
subjects affected / exposed	6 / 1265 (0.47%)	13 / 1270 (1.02%)	
occurrences causally related to treatment / all	0 / 7	0 / 13	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal cancer			

subjects affected / exposed	5 / 1265 (0.40%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Skin cancer melanoma			
subjects affected / exposed	0 / 1265 (0.00%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin cancer non-melanoma			
subjects affected / exposed	3 / 1265 (0.24%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Testicular cancer			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hematoma			
subjects affected / exposed	0 / 1265 (0.00%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 1265 (0.08%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured aortic arch aneurism			

subjects affected / exposed	1 / 1265 (0.08%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Thromboembolic event			
subjects affected / exposed	11 / 1265 (0.87%)	11 / 1270 (0.87%)	
occurrences causally related to treatment / all	0 / 11	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 1	
Vasculitis			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Fetal death			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (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			
Fever			
subjects affected / exposed	0 / 1265 (0.00%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu like symptoms			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site reaction			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localized edema			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	14 / 1265 (1.11%)	24 / 1270 (1.89%)	
occurrences causally related to treatment / all	0 / 14	0 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 1265 (0.00%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylaxis			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune disorder			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 1265 (0.40%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	11 / 1265 (0.87%)	4 / 1270 (0.31%)	
occurrences causally related to treatment / all	7 / 11	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 1265 (0.24%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	2 / 1265 (0.16%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 1265 (0.00%)	4 / 1270 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal stenosis			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion			
subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 1265 (0.00%)	6 / 1270 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychosis			

subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 1265 (0.00%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GGT increased			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental death			
subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Alcohol abuse			
subjects affected / exposed	1 / 1265 (0.08%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Ankle fracture			
subjects affected / exposed	5 / 1265 (0.40%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bruising			
subjects affected / exposed	0 / 1265 (0.00%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy procedural complication			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	5 / 1265 (0.40%)	6 / 1270 (0.47%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fracture			
subjects affected / exposed	9 / 1265 (0.71%)	11 / 1270 (0.87%)	
occurrences causally related to treatment / all	0 / 10	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Head injury			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (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	8 / 1265 (0.63%)	5 / 1270 (0.39%)	
occurrences causally related to treatment / all	2 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraoperative gastrointestinal injury			
subjects affected / exposed	2 / 1265 (0.16%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			

subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative hemorrhage			
subjects affected / exposed	3 / 1265 (0.24%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Ruptured spleen			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (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	3 / 1265 (0.24%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	3 / 1265 (0.24%)	10 / 1270 (0.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			

subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	11 / 1265 (0.87%)	7 / 1270 (0.55%)	
occurrences causally related to treatment / all	0 / 11	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	2 / 1265 (0.16%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	4 / 1265 (0.32%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Cardiomyopathy			
subjects affected / exposed	2 / 1265 (0.16%)	4 / 1270 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	10 / 1265 (0.79%)	13 / 1270 (1.02%)	
occurrences causally related to treatment / all	0 / 10	1 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			

subjects affected / exposed	6 / 1265 (0.47%)	4 / 1270 (0.31%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	23 / 1265 (1.82%)	25 / 1270 (1.97%)	
occurrences causally related to treatment / all	0 / 23	0 / 25	
deaths causally related to treatment / all	0 / 7	0 / 5	
Pericardial effusion			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	4 / 1265 (0.32%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			

subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disturbance			
subjects affected / exposed	8 / 1265 (0.63%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	1 / 8	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dizziness			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	5 / 1265 (0.40%)	5 / 1270 (0.39%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hemorrhage			
subjects affected / exposed	5 / 1265 (0.40%)	5 / 1270 (0.39%)	
occurrences causally related to treatment / all	1 / 5	3 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Ischemia cerebrovascular			
subjects affected / exposed	18 / 1265 (1.42%)	17 / 1270 (1.34%)	
occurrences causally related to treatment / all	0 / 18	1 / 20	
deaths causally related to treatment / all	0 / 1	0 / 0	
Memory impairment			

subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor neurone disease			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple system atrophy			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Parkinson's disease			
subjects affected / exposed	3 / 1265 (0.24%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyramidal tract syndrome			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spasticity			

subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 1265 (0.40%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischemic attacks			
subjects affected / exposed	7 / 1265 (0.55%)	11 / 1270 (0.87%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasovagal reaction			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 1265 (0.71%)	5 / 1270 (0.39%)	
occurrences causally related to treatment / all	7 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spleen disorder			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1265 (0.08%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			

subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 1265 (0.00%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous hemorrhage			
subjects affected / exposed	0 / 1265 (0.00%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	10 / 1265 (0.79%)	6 / 1270 (0.47%)	
occurrences causally related to treatment / all	1 / 10	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bloating			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cameron Ulcer			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 1265 (0.00%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic hemorrhage			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic perforation			
subjects affected / exposed	2 / 1265 (0.16%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 1265 (0.16%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	5 / 1265 (0.40%)	4 / 1270 (0.31%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal hemorrhage			
subjects affected / exposed	0 / 1265 (0.00%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	2 / 1265 (0.16%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	2 / 1265 (0.16%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	3 / 1265 (0.24%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	4 / 1265 (0.32%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal pain			
subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	2 / 1265 (0.16%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	3 / 1265 (0.24%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastritis			

subjects affected / exposed	1 / 1265 (0.08%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 1265 (0.16%)	6 / 1270 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhoidal hemorrhage			
subjects affected / exposed	2 / 1265 (0.16%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhoids			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal obstruction			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Colitis			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss tear			

subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	9 / 1265 (0.71%)	8 / 1270 (0.63%)	
occurrences causally related to treatment / all	0 / 14	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal haemorrhage			
subjects affected / exposed	1 / 1265 (0.08%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 1265 (0.08%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 1265 (0.24%)	4 / 1270 (0.31%)	
occurrences causally related to treatment / all	1 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 1265 (0.16%)	5 / 1270 (0.39%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Alcoholic Hepatitis			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			

subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	12 / 1265 (0.95%)	10 / 1270 (0.79%)	
occurrences causally related to treatment / all	0 / 13	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder necrosis			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gallbladder pain			
subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder perforation			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	4 / 1265 (0.32%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 2	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 1265 (0.16%)	4 / 1270 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			

subjects affected / exposed	2 / 1265 (0.16%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	3 / 1265 (0.24%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal calculi			
subjects affected / exposed	4 / 1265 (0.32%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	4 / 1265 (0.32%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	3 / 1265 (0.24%)	5 / 1270 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	3 / 1265 (0.24%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Avascular necrosis			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 1265 (0.08%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Spondylosis			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	2 / 1265 (0.16%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased cervical spine			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mortons neuroma			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle weakness lower limb			

subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	0 / 1265 (0.00%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	0 / 1265 (0.00%)	5 / 1270 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder infection			
subjects affected / exposed	2 / 1265 (0.16%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone infection			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	8 / 1265 (0.63%)	10 / 1270 (0.79%)	
occurrences causally related to treatment / all	0 / 8	3 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			

subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inner Ear Infection			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal parasite			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint infection			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Kidney infection			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	28 / 1265 (2.21%)	28 / 1270 (2.20%)	
occurrences causally related to treatment / all	0 / 38	0 / 42	
deaths causally related to treatment / all	0 / 4	0 / 2	
Pharyngitis			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate infection			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoas abscess			

subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland infection			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal infection			
subjects affected / exposed	0 / 1265 (0.00%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 1265 (0.16%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	9 / 1265 (0.71%)	12 / 1270 (0.94%)	
occurrences causally related to treatment / all	0 / 9	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 1265 (0.00%)	2 / 1270 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory infection			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	8 / 1265 (0.63%)	7 / 1270 (0.55%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Wound infection			
subjects affected / exposed	4 / 1265 (0.32%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycemia			
subjects affected / exposed	2 / 1265 (0.16%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalemia			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricemia			
subjects affected / exposed	0 / 1265 (0.00%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycemia			
subjects affected / exposed	1 / 1265 (0.08%)	0 / 1270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesemia			

subjects affected / exposed	0 / 1265 (0.00%)	3 / 1270 (0.24%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	1 / 1265 (0.08%)	1 / 1270 (0.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 699 (0.00%)	0 / 698 (0.00%)	0 / 566 (0.00%)

Non-serious adverse events	Arm D	Aspirin	No Aspirin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 572 (0.00%)	0 / 1138 (0.00%)	0 / 1142 (0.00%)

Non-serious adverse events	Low Dose PPI	High Dose PPI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1265 (0.00%)	0 / 1270 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2004	Note that amendments to add sites or change Principal Investigators at active sites have not been listed here.
10 September 2004	Changes to GP letter, PIS and Patient Study Card
01 November 2004	Changes to MREC form, ICF, recruitment flow chart, PIS, GP letter and Patient Study Card
01 February 2005	Changes to ICF, PIS and Patient Study Card
23 March 2005	Drug Distribution
27 July 2005	Protocol_V5 & PIS_V6 Update
17 August 2005	Change of Sponsor from Leicester to Oxford
20 January 2006	Protocol_V6 & Supporting Doc
17 July 2006	Poster
19 January 2007	Drug labelling
05 February 2007	Protocol_V7 & Supporting Docs
09 July 2007	Poster
22 August 2007	Protocol_V8
25 September 2007	Protocol_V9 & Supporting Documents
04 April 2008	Drug labelling
01 September 2008	Appointment of joint CI
10 September 2008	Recruitment extension
23 October 2009	Drug distribution in Northern Ireland
31 March 2010	Letter for patients with overdue endoscopy
30 July 2010	Protocol_V10 & Supporting Documents
02 February 2011	Patient Newsletter

09 May 2014	End of trial PIS and GP letter
20 January 2015	Protocol_V11.0 & Supporting_Documents
26 January 2016	Protocol_V12.0 & Supporting Documents
23 March 2016	Patient Newsletter & PIS V14.0
05 April 2016	Drug labelling
14 June 2017	EndOfTrial_PatientLetter

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30057104>