Clinical trial results:
A Double-Blind, Placebo Controlled, Multicenter Study to Assess the Effect of Evolocumab on Cognitive Function in Patients with Clinically Evident Cardiovascular Disease and Receiving Statin Background Lipid Lowering Therapy: A Study for Subjects Enrolled in the FOURIER (Study 20110118) Trial

Summary

EudraCT number	2014-001976-75
Trial protocol	SE GR IT FI EE SK LV DE LT CZ PT BE HU DK ES NL
Global end of trial date	11 November 2016

Results information

Result version number	v2 (current)
This version publication date	19 January 2018
First version publication date	26 November 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	20130385

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02207634
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate change over time in executive function, as assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM) strategy index of executive function, in subjects receiving statin therapy in combination with evolocumab, compared with subjects receiving statin therapy in combination with placebo.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP. The study and all amendments were reviewed by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) at each center.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

Background therapy:

Participants were required to be on a stable, high- to moderate-intensity statin background therapy consisting of an effective statin dose, ie, at least atorvastatin 20 mg daily or equivalent, and where locally approved, highly effective statin therapy (defined as at least atorvastatin 40 mg daily or equivalent) was recommended.

Evidence for comparator: -

Actual start date of recruitment	10 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 28
Country: Number of subjects enrolled	Japan: 39
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	New Zealand: 16
Country: Number of subjects enrolled	South Africa: 51
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czech Republic: 161
Country: Number of subjects enrolled	Denmark: 44
Country: Number of subjects enrolled	Estonia: 35
Country: Number of subjects enrolled	Finland: 54
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Germany: 75
Country: Number of subjects enrolled	Greece: 5

Country: Number of subjects enrolled	Hungary: 93
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Latvia: 33
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Netherlands: 23
Country: Number of subjects enrolled	Norway: 16
Country: Number of subjects enrolled	Poland: 254
Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Russian Federation: 209
Country: Number of subjects enrolled	Slovakia: 80
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Turkey: 31
Country: Number of subjects enrolled	United Kingdom: 118
Country: Number of subjects enrolled	Canada: 63
Country: Number of subjects enrolled	United States: 416
Worldwide total number of subjects	1974
EEA total number of subjects	1119

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)	1088
From 65 to 84 years	883
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants enrolled in Study 20110118 (FOURIER; NCT01764633) at select sites in select countries (based on study start-up timelines) were invited to participate in this cognitive function study. Participants were enrolled at 340 centers in 29 countries in Europe, North America, and Asia Pacific from September 2014 to July 2015.

Pre-assignment

Screening details:

There was no separate randomization in this study; each participant received their assigned treatment per Protocol 20110118. Data were analyzed according to Study 20110118 randomized treatment arm.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo subcutaneous injections either once every 2 weeks (Q2W) or once a month (QM) according to their own preference. Participants continued with their background statin therapy during the course of the study.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously using a spring-based prefilled 1.0 mL autoinjector/pen.

Arm title	Evolocumab

Arm description:

Participants received evolocumab 140 mg Q2W or 420 mg QM subcutaneous injections according to their own preference. Participants continued with their background statin therapy during the course of the study.

Arm type	Experimental
Investigational medicinal product name	Evolocumab
Investigational medicinal product code	AMG 145
Other name	Repatha
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously using a spring-based prefilled 1.0 mL autoinjector/pen.

Number of subjects in period 1	Placebo	Evolocumab
Started	990	984
Received Treatment	990	983
Completed	968	953
Not completed	22	31
Consent withdrawn by subject	21	31
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneous injections either once every 2 weeks (Q2W) or once a month (QM) according to their own preference. Participants continued with their background statin therapy during the course of the study.	
Reporting group title	Evolocumab
Reporting group description:	
Participants received evolocumab 140 mg Q2W or 420 mg QM subcutaneous injections according to their own preference. Participants continued with their background statin therapy during the course of the study.	

Reporting group values	Placebo	Evolocumab	Total
Number of subjects	990	984	1974
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	62.7	62.9	
standard deviation	± 8.7	± 8.7	-
Gender Categorical Units: Subjects			
Female	274	269	543
Male	716	715	1431
Race Units: Subjects			
American Indian or Alaska Native	2	1	3
Asian	28	31	59
Black or African American	32	28	60
Native Hawaiian or Other Pacific Islander	0	3	3
White	910	908	1818
Multiple	1	1	2
Other	17	12	29
Ethnicity Units: Subjects			
Hispanic/Latino	14	9	23
Not Hispanic/Latino	976	975	1951
Spatial Working Memory (SWM) Strategy Index of Executive Function Raw Score			
CANTAB is a series of computerized tests to assess cognitive function. The SWM test assesses the cognitive domain of executive function (high-level thinking and decision making). Patients search for colored tokens hidden inside boxes on the screen. Tokens were never hidden inside the same box twice, so patients must not return to a box where a token was already found. The SWM strategy index of executive function represents the number of times a patient began a search with a different box. A high score represents an inefficient use of strategy and planning. The raw score ranges from 4 to 28.			
Units: units on a scale			
arithmetic mean	17.8	17.8	

standard deviation	± 3.4	± 3.5	-
Spatial Working Memory (SWM) Strategy Index of Executive Function Z Score			
The CANTAB SWM test assesses the cognitive domain of executive function (high-level thinking and decision making). Patients search for colored tokens hidden inside boxes on the screen. Tokens were never hidden inside the same box twice, so patients must not return to a box where a token was already found. The SWM strategy index of executive function represents the number of times a patient began a search with a different box. The Z score represents the standardized measure of how far an individual deviates from the study cohort average at baseline. A higher Z score reflects better performance.			
Units: Z score			
arithmetic mean	-0.0106	0.0166	
standard deviation	± 0.9910	± 1.0066	-
Spatial Working Memory Between Errors Raw Score			
The CANTAB Spatial Working Memory (SWM) between-errors score test assesses the cognitive domain of working memory (holding material in mind while that material is being actively processed). Patients search for colored tokens hidden inside boxes on the screen. Tokens were never hidden inside the same box twice, so patients must not return to a box where a token was already found. The SWM between-errors score is the number of times that a patient revisited a box in which a token had previously been found. A lower score indicates better performance. The raw score ranges from 0 to 279.			
Units: units on a scale			
arithmetic mean	21.0	20.9	
standard deviation	± 10.6	± 10.2	-
Paired Associates Learning (PAL) Total Errors Adjusted Raw Score			
The CANTAB PAL test assesses memory function (storing/retrieving information by associating an event with a time and place). Boxes on the screen open in turn to reveal a number of patterns. After all the boxes were opened, each pattern was shown in a randomized order and the patient asked to touch the box where they think the pattern was hidden. The PAL total errors adjusted score is the number of errors made plus an adjustment for the estimated number of errors the patient would have made on any stages not reached. A lower score indicates better performance. The raw score ranges from 0 to 70.			
Units: units on a scale			
arithmetic mean	25.2	26.5	
standard deviation	± 18.4	± 19.3	-
Spatial Working Memory Between Errors Z Score			
The CANTAB Spatial Working Memory (SWM) between-errors score test assesses the cognitive domain of working memory (holding material in mind while that material is being actively processed). Patients search for colored tokens hidden inside boxes on the screen. Tokens were never hidden inside the same box twice, so patients must not return to a box where a token was already found. The SWM between-errors score is the number of times a patient revisited a box in which a token had already been found. A higher Z score reflects better performance.			
Units: Z score			
arithmetic mean	-0.0130	0.0024	
standard deviation	± 1.0075	± 0.9675	-
Paired Associates Learning Total Errors Adjusted Z Score			
The CANTAB PAL test assesses memory function (storing/retrieving information by associating an event with a time and place). Boxes on the screen open in turn to reveal a number of patterns. After all the boxes have been opened, each pattern was shown in a randomized order and the patient asked to touch the box where they think each pattern was hidden. The PAL total errors adjusted is the number of errors committed plus an adjustment for the estimated number of errors the patient would have made on any stages not reached. Higher Z scores indicate better performance.			
Units: Z score			
arithmetic mean	0.0442	-0.0272	
standard deviation	± 0.9834	± 1.0294	-
Reaction Time Median 5-Choice Reaction Time Raw Score			
The CANTAB Reaction Time (RTI) test assessed psychomotor speed (detecting and responding to a stimulus). Participants held down a button until a spot appeared in 1 of 5 circles on the screen. As soon			

as possible after the spot flashed up, the patient lifted their finger from the button and touched the circle in which the spot appeared. The RTI median 5-choice reaction time was the median duration between the onset of the stimulus and the release of the button. A lower score indicates better performance. The raw score ranges from 100 to 5100 msec.			
Units: msec			
arithmetic mean	355.10	356.74	
standard deviation	± 77.60	± 65.01	-
Reaction Time Median 5-Choice Reaction Time Z Score			
The CANTAB Reaction Time (RTI) test assessed psychomotor speed (detecting and responding to a stimulus). Participants held down a button until a spot appeared in 1 of 5 circles on the screen. As soon as possible after the spot flashed up, the patient moved their finger from the button to the circle in which the spot appeared. The RTI median 5-choice reaction time is the median duration between the onset of the stimulus and the release of the button. A higher Z score reflects better performance.			
Units: Z score			
arithmetic mean	-0.0271	-0.0500	
standard deviation	± 1.0829	± 0.9072	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo subcutaneous injections either once every 2 weeks (Q2W) or once a month (QM) according to their own preference. Participants continued with their background statin therapy during the course of the study.

Reporting group title	Evolocumab

Reporting group description:

Participants received evolocumab 140 mg Q2W or 420 mg QM subcutaneous injections according to their own preference. Participants continued with their background statin therapy during the course of the study.

Primary: Mean Change from Baseline in Spatial Working Memory Strategy Index of Executive Function (6-8 boxes) Z Score

End point title	Mean Change from Baseline in Spatial Working Memory Strategy Index of Executive Function (6-8 boxes) Z Score

End point description:

Assessments were performed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), a language-independent battery of computerized tests that is used to assess cognitive function.
The Spatial Working Memory (SWM) test assesses the cognitive domain of executive function (high-level thinking and decision making). Patients search for colored tokens hidden inside boxes on the screen by touching them. The critical instruction is that once a token has been found inside a box, there will never be a token hidden inside that box again, so patients must not return to a box where a token has been found.
The SWM strategy index of executive function represented the number of times a subject began a search with a different box. The Z score represents the standardized measure of how far an individual subject deviates from the study cohort average at baseline. A higher Z score reflects better performance. The mean change from baseline averaged across all the visits is reported.

End point type	Primary

End point timeframe:

Assessments were conducted at Baseline and at weeks 24, 48, 96, 144 and end of study visit (median time on study was 19.4 months).

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	616[1]	586[2]		
Units: Z score				
least squares mean (confidence interval 95%)	0.1206 (0.0535 to 0.1877)	0.1134 (0.0449 to 0.1820)		

Notes:

[1] - Cognitive function assessments after an on-study stroke event were excluded from the analysis.

[2] - Cognitive function assessments after an on-study stroke event were excluded from the analysis.

Statistical analyses

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

A repeated measures mixed-effect linear model was used to estimate treatment difference (placebo - evolocumab) in change from baseline and associated 95% confidence intervals (CI). The model included stratification factors for Study 20110118 (final screening low-density lipoprotein cholesterol [LDL-C] and geographical region), age, education level, baseline SWM strategy index Z score, treatment group, visit, and treatment by visit interaction.

Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	1202
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Treatment Difference
Point estimate	0.0072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0664
upper limit	0.0808
Variability estimate	Standard error of the mean
Dispersion value	0.0375

Notes:

[3] - The non-inferiority margin was 0.19, calculated as 20% of the observed common standard deviation, which was estimated from observations in the placebo group by a repeated measured mixed-effect linear model with visit as a covariate. If the upper bound of the 95% CI for the difference between the placebo and evolocumab group in mean change from baseline for Z score averaged across the visits was less than the non-inferiority margin non-inferiority criteria were met.

Secondary: Mean Change from Baseline in Spatial Working Memory (SWM) Between-errors Z Score

End point title	Mean Change from Baseline in Spatial Working Memory (SWM) Between-errors Z Score

End point description:

Assessments were performed with the CANTAB, a language-independent battery of computerized tests that is used to assess cognitive function. The Spatial Working Memory (SWM) between-errors test assesses the cognitive domain of working memory (holding material in mind while that material is being actively processed). Patients search for colored tokens hidden inside boxes on the screen by touching them. The critical instruction is that once a token has been found inside a box, there will never be a token hidden inside that box again, so patients must not return to a box where a token has been found. The SWM between-errors score is the number of times that a patient revisited a box in which a token had previously been found. The Z score represents the standardized measure of how far an individual participant deviates from the study cohort average at baseline. A higher Z score reflects better performance. The mean change from baseline averaged across all the visits is reported.

End point type	Secondary

End point timeframe:

Assessments were conducted at Baseline and at weeks 24, 48, 96, 144 and end of study visit (median time on study was 19.4 months).

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	616[4]	586[5]		
Units: Z score				
least squares mean (confidence interval 95%)	0.1024 (0.0373 to 0.1675)	0.0691 (0.0026 to 0.1355)		

Notes:

[4] - Cognitive function assessments after an on-study stroke event were excluded from the analysis.

[5] - Cognitive function assessments after an on-study stroke event were excluded from the analysis.

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

A repeated measures mixed-effect linear model was used to estimate treatment difference (placebo - evolocumab) in change from baseline and associated 95% confidence intervals (CI). The model included stratification factors for Study 20110118 (final screening LDL-C and geographical region), age, education level, baseline SWM between-errors Z score, treatment group, visit, and treatment by visit interaction.

Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	1202
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment Difference
Point estimate	0.0333
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0378
upper limit	0.1045
Variability estimate	Standard error of the mean
Dispersion value	0.0363

Secondary: Mean Change from Baseline in Paired Associated Learning (PAL) Total Errors Adjusted Z Score

End point title	Mean Change from Baseline in Paired Associated Learning (PAL) Total Errors Adjusted Z Score

End point description:

The CANTAB PAL test assesses visuospatial episodic memory (storing/retrieving information by associating an event with a time and place). Boxes on the screen opened up one at a time to reveal a number of patterns. Participants were asked to remember the location of each pattern. After all the boxes had been opened, each pattern was then shown in the center of the screen in a randomized order, and the patient should touch the box where they think each pattern was hidden. The PAL total errors adjusted comprised the number of errors committed by a patient plus an adjustment for the estimated number of errors the patient would have made on any stages that were not reached.
Z score represents the standardized measure of how far an individual patient deviates from the study cohort average at baseline. A higher Z score indicated better performance. The mean change from baseline averaged across all the visits is reported.

End point type	Secondary

End point timeframe:

Assessments were conducted at Baseline and at weeks 24, 48, 96, 144 and end of study visit (median time on study was 19.4 months).

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	615[6]	585[7]		
Units: Z score				
least squares mean (confidence interval 95%)	0.1098 (0.0511 to 0.1686)	0.0873 (0.0273 to 0.1472)		

Notes:

[6] - Cognitive function assessments after an on-study stroke event were excluded from the analysis.

[7] - Cognitive function assessments after an on-study stroke event were excluded from the analysis.

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

A repeated measures mixed-effect linear model was used to estimate treatment difference (placebo - evolocumab) in change from baseline and associated 95% confidence intervals (CI). The model included stratification factors for Study 20110118 (final screening LDL-C and geographical region), age, education level, baseline PAL total errors adjusted Z score, treatment group, visit, and treatment by visit interaction.

Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	1200
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment Difference
Point estimate	0.0226
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0422
upper limit	0.0873
Variability estimate	Standard error of the mean
Dispersion value	0.033

Secondary: Mean Change from Baseline in Reaction Time (RTI) Median 5-choice Reaction Time Z score

End point title	Mean Change from Baseline in Reaction Time (RTI) Median 5-choice Reaction Time Z score

End point description:

Assessments were performed with the CANTAB, a language-independent battery of computerized tests that is used to assess cognitive function. The Reaction Time (RTI) test assessed the cognitive domain of psychomotor speed (detecting and responding to a stimulus). Participants held down a button until a spot appeared in 1 of 5 circles on the screen. As soon as possible after the spot flashed up, the patient lifted their finger from the button and touched the circle in which the spot appeared. The RTI median 5-choice reaction time was the median duration between the onset of the stimulus and the release of the button. Z score represents the standardized measure of how far an individual participant deviates from the study cohort average at baseline. A higher Z score reflects better performance. The mean change from baseline averaged across all the visits is reported.

End point type	Secondary

End point timeframe:

Assessments were conducted at Baseline and at weeks 24, 48, 96, 144 and end of study visit (median time on study was 19.4 months).

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	611[8]	584[9]		
Units: Z score				
least squares mean (confidence interval 95%)	0.0153 (-0.0529 to 0.0834)	-0.0575 (-0.1270 to 0.0121)		

Notes:

[8] - Cognitive function assessments after an on-study stroke event were excluded from the analysis.

[9] - Cognitive function assessments after an on-study stroke event were excluded from the analysis.

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

A repeated measures mixed-effect linear model was used to estimate treatment difference (placebo - evolocumab) in change from baseline and associated 95% confidence intervals (CI). The model included stratification factors for Study 20110118 (final screening LDL-C and geographical region), age, education level, baseline RTI median 5-choice reaction time Z score, treatment group, visit, and treatment by visit interaction.

Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	1195
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment Difference
Point estimate	0.0727
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0022
upper limit	0.1477
Variability estimate	Standard error of the mean
Dispersion value	0.0382

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug to the end of study. The median duration of follow-up was 19.4 months.

Adverse event reporting additional description:

Although there was no separate safety data collection, recording or reporting planned in this study, an ad-hoc analysis of safety data collected in Study 20110118 was conducted for subjects in this Study and is reported here. Deaths by any cause were collected as adjudicated efficacy endpoints and reported as a secondary endpoint in Study 20110118.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Evolocumab

Reporting group description:

Participants received evolocumab 140 mg Q2W or 420 mg QM subcutaneous injections according to their own preference. Participants continued with their background statin therapy during the course of the study.

Reporting group title	Placebo

Reporting group description:

Participants received placebo subcutaneous injections either once every 2 weeks (Q2W) or once a month (QM) according to their own preference. Participants continued with their background statin therapy during the course of the study.

Serious adverse events	Evolocumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	212 / 983 (21.57%)	204 / 990 (20.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign pancreatic neoplasm			

subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma stage III			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer stage 0			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip and/or oral cavity cancer stage III			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	2 / 983 (0.20%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma metastatic			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 983 (0.10%)	4 / 990 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage III			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma benign			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoproliferative disorder			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer metastatic			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			

subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	1 / 983 (0.10%)	4 / 990 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
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	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	7 / 983 (0.71%)	5 / 990 (0.51%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 983 (0.31%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leriche syndrome			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	2 / 983 (0.20%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	10 / 983 (1.02%)	5 / 990 (0.51%)	
occurrences causally related to treatment / all	0 / 12	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			

subjects affected / exposed	2 / 983 (0.20%)	4 / 990 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	6 / 983 (0.61%)	4 / 990 (0.40%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery stenosis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 983 (0.10%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Fracture treatment			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric banding reversal			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 983 (0.20%)	4 / 990 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	6 / 983 (0.61%)	12 / 990 (1.21%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue inflammation			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 983 (0.10%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 983 (0.10%)	3 / 990 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma-chronic obstructive pulmonary disease overlap syndrome			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (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	4 / 983 (0.41%)	5 / 990 (0.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
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 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			

Device malfunction			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriogram coronary			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 983 (0.00%)	3 / 990 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Liver function test abnormal			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial necrosis marker increased			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid function test abnormal			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial bypass occlusion			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery restenosis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dislocation of sternum			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye injury			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (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	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial reocclusion			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery restenosis			

subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoconiosis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis chemical			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post concussion syndrome			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural constipation			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural swelling			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Intracranial lipoma			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	15 / 983 (1.53%)	16 / 990 (1.62%)	
occurrences causally related to treatment / all	0 / 18	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina unstable			
subjects affected / exposed	11 / 983 (1.12%)	15 / 990 (1.52%)	
occurrences causally related to treatment / all	0 / 14	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	13 / 983 (1.32%)	7 / 990 (0.71%)	
occurrences causally related to treatment / all	0 / 19	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 983 (0.00%)	3 / 990 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			

subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 983 (0.10%)	4 / 990 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	2 / 983 (0.20%)	4 / 990 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	4 / 983 (0.41%)	5 / 990 (0.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	2 / 983 (0.20%)	3 / 990 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dressler's syndrome			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart alternation			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve stenosis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	3 / 983 (0.31%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			

subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
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	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 983 (0.10%)	3 / 990 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Arachnoid cyst			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery disease			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	6 / 983 (0.61%)	5 / 990 (0.51%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical myelopathy			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 983 (0.00%)	3 / 990 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meralgia paraesthetica			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinsonism			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (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	3 / 983 (0.31%)	4 / 990 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 983 (0.20%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 983 (0.20%)	6 / 990 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spleen disorder			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 983 (0.10%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strabismus			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 983 (0.20%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	2 / 983 (0.20%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coeliac artery stenosis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric disorder			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			

subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 983 (0.20%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 983 (0.10%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	3 / 983 (0.31%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery stenosis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cyst			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux gastritis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis obstructive			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			

subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermal cyst			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	1 / 983 (0.10%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema nummular			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperhidrosis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	2 / 983 (0.20%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	2 / 983 (0.20%)	6 / 990 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urethral			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 983 (0.20%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
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	0 / 983 (0.00%)	5 / 990 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exostosis			

subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	2 / 983 (0.20%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 983 (0.10%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia intercostal			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	3 / 983 (0.31%)	3 / 990 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			

subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendiceal abscess			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burkholderia cepacia complex infection			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 983 (0.10%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			

subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	1 / 983 (0.10%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	3 / 983 (0.31%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 983 (1.02%)	7 / 990 (0.71%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 983 (0.20%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 983 (0.00%)	4 / 990 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 983 (0.00%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 983 (0.20%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	2 / 983 (0.20%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 983 (0.00%)	1 / 990 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 983 (0.10%)	2 / 990 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 983 (0.10%)	0 / 990 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Evolocumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	272 / 983 (27.67%)	257 / 990 (25.96%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	61 / 983 (6.21%)	66 / 990 (6.67%)	
occurrences (all)	62	75	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	58 / 983 (5.90%)	36 / 990 (3.64%)	
occurrences (all)	62	39	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	101 / 983 (10.27%)	74 / 990 (7.47%)	
occurrences (all)	133	85	
Upper respiratory tract infection			
subjects affected / exposed	53 / 983 (5.39%)	63 / 990 (6.36%)	
occurrences (all)	61	70	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	45 / 983 (4.58%)	59 / 990 (5.96%)	
occurrences (all)	48	65	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported