



Clinical trial results:

PROSPECTIVE, RANDOMIZED TRIAL OF TICAGRELOR VERSUS PRASUGREL IN PATIENTS WITH ACUTE CORONARY SYNDROME

Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment – ISAR-REACT 5

Summary

EudraCT number	2013-002272-40
Trial protocol	DE IT
Global end of trial date	20 September 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	GE-IDE-No.00113
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01944800
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Deutsches Herzzentrum München, Klinik an der Technischen Universität München
Sponsor organisation address	Lazarettstr. 36, Munich, Germany, 80636
Public contact	ISARResearch Center, Deutsches Herzzentrum München, +49 8912184578, kastrati@dhm.mhn.de
Scientific contact	ISARResearch Center, Deutsches Herzzentrum München, +49 8912184578, kastrati@dhm.mhn.de

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	15 September 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to test the hypothesis that ticagrelor is superior to prasugrel regarding the composite of death, myocardial infarction or stroke at 12 months after randomisation.

Protection of trial subjects:

Not applicable.

Background therapy:

All patients will receive a loading dose of 150-500 mg of chewed or i.v. ASA (if they have not received it within the last 12 hours). Afterwards, all patients will receive an oral maintenance dose of 75-150 mg/day ASA for the duration of the study. Exploratory analyses of the PLATO trial suggest a possible association of ticagrelor with ASA dose such that reduced efficacy was observed with ticagrelor with increasing ASA doses. Therefore, the recommended chronic daily ASA dose to accompany ticagrelor is 75-150 mg.

Other cardiac medications (e.g. β -blockers, ACE-inhibitors, statins etc.) will be given according to the judgement of patient's physician, current practice guidelines and the summary of medical product characteristics.

Evidence for comparator:

Although both drugs provided superior efficacy compared to clopidogrel in the pivotal randomized trials, ACS patients continue to have an excess risk of ischemic events. Moreover, both drugs were shown to increase bleeding. Due to different ACS populations and conditions investigated the relative merits of prasugrel and ticagrelor in the treatment of ACS patients with planned invasive strategy cannot be reliably estimated from independent trials alone. To date, no direct head-to-head comparison of the two new P2Y₁₂ receptor antagonists prasugrel and ticagrelor in terms of clinical outcome exists. The hypothesis to be tested will therefore be that ticagrelor is superior to prasugrel in terms of clinical outcomes. This will be achieved by means of a randomized, open label, multicentre trial. The primary endpoint will be the composite of death, myocardial infarction or stroke at 12 months after randomisation.

Actual start date of recruitment	01 September 2013
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	Germany: 3328
Country: Number of subjects enrolled	Italy: 690
Worldwide total number of subjects	4018
EEA total number of subjects	4018

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)	1968
From 65 to 84 years	1908
85 years and over	142

Subject disposition

Recruitment

Recruitment details:

The recruitment for the trial started in Sep 2013.

Pre-assignment

Screening details:

For inclusion the patients had to fulfil the following criteria:

1. Hospitalization for an acute coronary syndrome (unstable angina pectoris, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction) with planned invasive strategy
2. age ≥ 18 years
3. Written informed consent

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ticagrelor
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Brilique
Investigational medicinal product code	
Other name	Ticagrelor
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Both study medications, ticagrelor and prasugrel, are for oral use. They can be administered with or without food. Therapy with ticagrelor should be started with a loading dose of 180 mg (2 tablets of 90 mg) and continued with a maintenance dose of 90 mg twice daily. Maintenance doses should be taken in the morning and in the evening, at approximately 12-hour intervals.

Arm title	Prasugrel
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Efient
Investigational medicinal product code	
Other name	Prasugrel
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Both study medications, ticagrelor and prasugrel, are for oral use. They can be administered with or without food. Therapy with prasugrel should be started with a loading dose of 60 mg (6 tablets of 10 mg) and continued with a maintenance dose of 10 mg once per day. A reduced maintenance dose of 5 mg daily is recommended in patients at the age of 75 years or older or with a body weight of less than 60 kg.

Number of subjects in period 1	Ticagrelor	Prasugrel
Started	2012	2006
Completed	2012	2006

Period 2

Period 2 title	1-year Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ticagrelor
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Brilique
Investigational medicinal product code	
Other name	Ticagrelor
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Both study medications, ticagrelor and prasugrel, are for oral use. They can be administered with or without food. Therapy with ticagrelor should be started with a loading dose of 180 mg (2 tablets of 90 mg) and continued with a maintenance dose of 90 mg twice daily. Maintenance doses should be taken in the morning and in the evening, at approximately 12-hour intervals.

Arm title	Prasugrel
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Efient
Investigational medicinal product code	
Other name	Prasugrel
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Both study medications, ticagrelor and prasugrel, are for oral use. They can be administered with or without food. Therapy with prasugrel should be started with a loading dose of 60 mg (6 tablets of 10 mg) and continued with a maintenance dose of 10 mg once per day. A reduced maintenance dose of 5 mg daily is recommended in patients at the age of 75 years or older or with a body weight of less than 60 kg.

Number of subjects in period 2	Ticagrelor	Prasugrel
Started	2012	2006
Completed	1971	1957
Not completed	41	49
Consent withdrawn by subject	22	31
Lost to follow-up	19	18

Period 3

Period 3 title	3-year Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ticagrelor
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Brilique
Investigational medicinal product code	
Other name	Ticagrelor
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Both study medications, ticagrelor and prasugrel, are for oral use. They can be administered with or without food. Therapy with ticagrelor should be started with a loading dose of 180 mg (2 tablets of 90 mg) and continued with a maintenance dose of 90 mg twice daily. Maintenance doses should be taken in the morning and in the evening, at approximately 12-hour intervals.

Arm title	Prasugrel
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Efient
Investigational medicinal product code	
Other name	Prasugrel
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Both study medications, ticagrelor and prasugrel, are for oral use. They can be administered with or without food. Therapy with prasugrel should be started with a loading dose of 60 mg (6 tablets of 10 mg) and continued with a maintenance dose of 10 mg once per day. A reduced maintenance dose of 5 mg daily is recommended in patients at the age of 75 years or older or with a body weight of less than 60 kg.

Number of subjects in period 3	Ticagrelor	Prasugrel
Started	1971	1957
Completed	1921	1906
Not completed	50	51
Consent withdrawn by subject	3	1
Lost to follow-up	47	50

Baseline characteristics

Reporting groups

Reporting group title	Ticagrelor
Reporting group description: -	
Reporting group title	Prasugrel
Reporting group description: -	

Reporting group values	Ticagrelor	Prasugrel	Total
Number of subjects	2012	2006	4018
Age categorical Units: Subjects			
Adults (18-64 years)	976	992	1968
From 65-84 years	966	942	1908
85 years and over	70	72	142
Age continuous Units: years			
median	64.5	64.6	-
standard deviation	± 12.0	± 12.1	-
Gender categorical Units: Subjects			
Female	478	478	956
Male	1534	1528	3062
Diabetes Units: Subjects			
Diabetes yes	463	429	892
Diabetes no	1548	1576	3124
Not recorded	1	1	2
Use of insulin for diabetes Units: Subjects			
Use of insulin for diabetes yes	143	137	280
se of insulin for diabetes no	1868	1868	3736
Not recorded	1	1	2
Current smoker Units: Subjects			
Current smoker yes	682	667	1349
Current smoker no	1320	1332	2652
Not recorded	10	7	17
Arterial hypertension Units: Subjects			
Arterial hypertension yes	1432	1384	2816
Arterial hypertension no	576	619	1195
Not recorded	4	3	7
Hypercholesterolemia Units: Subjects			
Hypercholesterolemia yes	1178	1163	2341
Hypercholesterianemia no	829	840	1669
Not recorded	5	3	8

Myocardial Infarction Units: Subjects			
Myocardial infarction yes	311	320	631
Myocardial infarction no	1699	1685	3384
Not recorded	2	1	3
PCI Units: Subjects			
PCI yes	453	463	916
PCI no	1558	1541	3099
Not recorded	1	2	3
Aortocoronary bypass surgery Units: Subjects			
Aortocoronary bypass surgery yes	115	130	245
Aortocoronary bypass surgery no	1896	1875	3771
Not recorded	1	1	2
Cardiogenic shock Units: Subjects			
Cardiogenic shock yes	31	34	65
Cardiogenic shock no	1981	1972	3953
Weight < 60 kg Units: Subjects			
Weight < 60 kg yes	108	94	202
Weight < 60 kg no	1895	1894	3789
Not recorded	9	18	27
Diagnosis at admission Units: Subjects			
Unstable angina	249	261	510
NSTEMI	930	925	1855
STEMI	833	820	1653
Coronary angiography Units: Subjects			
Coronary angiography yes	2003	2001	4004
Coronary angiography no	9	5	14
Treatment strategy Units: Subjects			
PCI	1676	1701	3377
CABG	47	36	83
Conservative therapy	285	268	553
Other	1	0	1
Not recorded	3	1	4
Blood pressure systolic Units: mmHg			
median	144	143	
standard deviation	± 25	± 24	-
Blood pressure diastolic Units: mmHg			
median	82	82	
standard deviation	± 15	± 14	-
Heart rate Units: beats/min			
median	77	76	

standard deviation	± 16	± 16	-
BMI			
Units: kg/m2			
median	27.8	27.8	
standard deviation	± 4.6	± 4.4	-
Creatinine level			
Units: µmol/L			
median	88	88	
standard deviation	± 27	± 31	-

End points

End points reporting groups

Reporting group title	Ticagrelor
Reporting group description: -	
Reporting group title	Prasugrel
Reporting group description: -	
Reporting group title	Ticagrelor
Reporting group description: -	
Reporting group title	Prasugrel
Reporting group description: -	
Reporting group title	Ticagrelor
Reporting group description: -	
Reporting group title	Prasugrel
Reporting group description: -	

Primary: Composite of death, myocardial infarction, stroke

End point title	Composite of death, myocardial infarction, stroke
End point description:	
End point type	Primary
End point timeframe:	
1 year after randomization	

End point values	Ticagrelor	Prasugrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2012	2006		
Units: Patients	184	137		

Statistical analyses

Statistical analysis title	Endpoint analysis
Statistical analysis description:	
ITT	
Comparison groups	Ticagrelor v Prasugrel
Number of subjects included in analysis	4018
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	1.7

Secondary: Death

End point title	Death
End point description:	
End point type	Secondary
End point timeframe:	
1 year after randomization	

End point values	Ticagrelor	Prasugrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2012	2006		
Units: Events				
From any cause	90	73		

Statistical analyses

Statistical analysis title	Endpoint analysis
Statistical analysis description:	
ITT	
Comparison groups	Ticagrelor v Prasugrel
Number of subjects included in analysis	4018
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.68

Secondary: Myocardial infarction

End point title	Myocardial infarction
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End point description:

End point type	Secondary
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End point timeframe:

1 year after randomization

End point values	Ticagrelor	Prasugrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2012	2006		
Units: Events				
Myocardial infarction	96	60		

Statistical analyses

Statistical analysis title	Endpoint analysis
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Statistical analysis description:

ITT

Comparison groups	Ticagrelor v Prasugrel
Number of subjects included in analysis	4018
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	2.25

Secondary: Stroke

End point title	Stroke
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End point description:

End point type	Secondary
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End point timeframe:

1 year after randomization

End point values	Ticagrelor	Prasugrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2012	2006		
Units: Subjects	22	19		

Statistical analyses

Statistical analysis title	Endpoint analysis
Statistical analysis description:	
ITT	
Comparison groups	Ticagrelor v Prasugrel
Number of subjects included in analysis	4018
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	2.15

Secondary: Definite or probable stent thrombosis

End point title	Definite or probable stent thrombosis
End point description:	
End point type	Secondary
End point timeframe:	
1 year after randomization	

End point values	Ticagrelor	Prasugrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2012	2006		
Units: Subjects	26	20		

Statistical analyses

Statistical analysis title	Endpoint analysis
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Statistical analysis description:

ITT

Comparison groups	Ticagrelor v Prasugrel
Number of subjects included in analysis	4018
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2.33

Secondary: Safety endpoint (Bleeding BARC type 3, 4 or 5)

End point title	Safety endpoint (Bleeding BARC type 3, 4 or 5)
End point description:	
End point type	Secondary
End point timeframe:	
1 year after randomization	

End point values	Ticagrelor	Prasugrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1989	1773		
Units: Subjects	95	80		

Statistical analyses

Statistical analysis title	Endpoint analysis
Statistical analysis description:	
modified ITT (all patients who received at least one dose of the randomly assigned trial drug and were assessed for bleeding events up to 7 days after discontinuation of the trial drug)	
Comparison groups	Ticagrelor v Prasugrel
Number of subjects included in analysis	3762
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.51

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

During the one year follow-up period all SAEs were reported, after the one year follow-up period until the 3 year follow-up only fatal and lifethreatening events were reported.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25
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Reporting groups

Reporting group title	Ticagrelor
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Reporting group description:

For SAE evaluation the ITT population was taken.

In the Ticagrelor group 1180 non-serious adverse events occurred. A detailed analysis of non-serious adverse events was not performed.

Reporting group title	Prasugrel
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Reporting group description:

For SAE evaluation the ITT population was taken.

In the Prasugrel group 1102 non-serious adverse events occurred. A detailed analysis of non-serious adverse events was not performed.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: A detailed analysis of non-serious adverse events was not performed.

Serious adverse events	Ticagrelor	Prasugrel	
Total subjects affected by serious adverse events			
subjects affected / exposed	778 / 2012 (38.67%)	757 / 2006 (37.74%)	
number of deaths (all causes)	147	136	
number of deaths resulting from adverse events	147	136	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma gastric			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal cancer			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendix cancer			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 2012 (0.10%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchial carcinoma			
subjects affected / exposed	3 / 2012 (0.15%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac myxoma			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon cancer			
subjects affected / exposed	3 / 2012 (0.15%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Colorectal cancer			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endometrial cancer metastatic			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Extranodal marginal zone B-cell lymphoma (MALT type)			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric cancer			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Glioblastoma			

subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Glioblastoma multiforme			
subjects affected / exposed	4 / 2012 (0.20%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intraductal papillary-mucinous carcinoma of pancreas			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	6 / 2012 (0.30%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 1	
Lymphoma			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Malignant melanoma			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
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	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 2012 (0.05%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	4 / 2012 (0.20%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Rectal adenocarcinoma			
subjects affected / exposed	3 / 2012 (0.15%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer	Additional description: Related event associated with bleeding		
subjects affected / exposed	4 / 2012 (0.20%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer recurrent			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testis cancer			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transitional cell carcinoma			

subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	2 / 2012 (0.10%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic dissection			
subjects affected / exposed	5 / 2012 (0.25%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic occlusion			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortitis			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Artery dissection			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	3 / 2012 (0.15%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coeliac artery occlusion			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (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	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distributive shock			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giant cell arteritis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	2 / 2012 (0.10%)	6 / 2006 (0.30%)	
occurrences causally related to treatment / all	2 / 3	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	9 / 2012 (0.45%)	10 / 2006 (0.50%)	
occurrences causally related to treatment / all	0 / 11	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis	Additional description: Related event associated with bleeding		
subjects affected / exposed	18 / 2012 (0.89%)	29 / 2006 (1.45%)	
occurrences causally related to treatment / all	0 / 18	1 / 38	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	6 / 2012 (0.30%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			

subjects affected / exposed	0 / 2012 (0.00%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leriche syndrome			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penetrating aortic ulcer			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
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	16 / 2012 (0.80%)	10 / 2006 (0.50%)	
occurrences causally related to treatment / all	0 / 20	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral artery occlusion			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery restenosis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			

subjects affected / exposed	4 / 2012 (0.20%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	4 / 2012 (0.20%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	2 / 4	3 / 4	
deaths causally related to treatment / all	1 / 2	1 / 1	
Skin ulcer			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery stenosis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subgaleal haematoma			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft stenosis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Alcohol detoxification			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve replacement			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker replacement			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colectomy			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery bypass			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Finger amputation			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb operation			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctectomy			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain	Additional description: Related due to dyspnoea		
subjects affected / exposed	63 / 2012 (3.13%)	46 / 2006 (2.29%)	
occurrences causally related to treatment / all	1 / 74	0 / 50	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	20 / 2012 (0.99%)	31 / 2006 (1.55%)	
occurrences causally related to treatment / all	0 / 20	0 / 31	
deaths causally related to treatment / all	0 / 20	0 / 31	
Fatigue			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia incarcerated			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	3 / 2012 (0.15%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site haematoma			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site haemorrhage			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	4 / 2012 (0.20%)	5 / 2006 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 4	0 / 5	
Pain			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (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 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	7 / 2012 (0.35%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	7 / 7	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilic granulomatosis with polyangiitis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heavy menstrual bleeding			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vaginal haemorrhage			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive airways disease exacerbated			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	9 / 2012 (0.45%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 0	
Dyspnoea			

subjects affected / exposed	23 / 2012 (1.14%)	16 / 2006 (0.80%)
occurrences causally related to treatment / all	9 / 24	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0
Emphysema		
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Epistaxis		
subjects affected / exposed	3 / 2012 (0.15%)	3 / 2006 (0.15%)
occurrences causally related to treatment / all	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Haemoptysis		
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)
occurrences causally related to treatment / all	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemothorax		
subjects affected / exposed	1 / 2012 (0.05%)	4 / 2006 (0.20%)
occurrences causally related to treatment / all	1 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Nasal septum deviation		
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)
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	3 / 2012 (0.15%)	3 / 2006 (0.15%)
occurrences causally related to treatment / all	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Pleural mass		
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)
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 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	4 / 2012 (0.20%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pneumothorax			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
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	11 / 2012 (0.55%)	8 / 2006 (0.40%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary fibrosis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	19 / 2012 (0.94%)	13 / 2006 (0.65%)	
occurrences causally related to treatment / all	0 / 20	0 / 13	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory distress			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 2012 (0.05%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchopathia osteoplastica			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord thickening			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 2012 (0.10%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 2012 (0.05%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	2 / 2012 (0.10%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somatic symptom disorder			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (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 capturing issue			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prosthetic cardiac valve malfunction			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (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	2 / 2012 (0.10%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst ruptured	Additional description: Associated with bleeding		
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haematoma			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac cirrhosis			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	5 / 2012 (0.25%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Arteriogram coronary normal			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine increased			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood electrolytes decreased			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose abnormal			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigation abnormal			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (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	5 / 2012 (0.25%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress echocardiogram abnormal			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia postoperative			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delayed recovery from anaesthesia			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat stroke			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraoperative haemorrhage	Additional description: Intraoperative haemorrhage		
subjects affected / exposed	4 / 2012 (0.20%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	4 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb fracture			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprocedural myocardial infarction			
subjects affected / exposed	6 / 2012 (0.30%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			

subjects affected / exposed	2 / 2012 (0.10%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural myocardial infarction			
subjects affected / exposed	4 / 2012 (0.20%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postoperative renal failure			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture	Additional description: Associated with bleeding		

subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt stenosis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Subdural haematoma			
subjects affected / exposed	3 / 2012 (0.15%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 2012 (0.00%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemorrhage			

subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site haematoma			
subjects affected / exposed	9 / 2012 (0.45%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	8 / 9	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site haemorrhage			
subjects affected / exposed	7 / 2012 (0.35%)	7 / 2006 (0.35%)	
occurrences causally related to treatment / all	7 / 7	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	4 / 2012 (0.20%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	1 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricle rupture			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (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			
Atrial septal defect			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
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	3 / 2012 (0.15%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	67 / 2012 (3.33%)	45 / 2006 (2.24%)	
occurrences causally related to treatment / all	0 / 72	0 / 49	
deaths causally related to treatment / all	0 / 2	0 / 3	
Angina pectoris			
subjects affected / exposed	60 / 2012 (2.98%)	76 / 2006 (3.79%)	
occurrences causally related to treatment / all	0 / 70	0 / 81	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	61 / 2012 (3.03%)	50 / 2006 (2.49%)	
occurrences causally related to treatment / all	0 / 68	0 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	2 / 2012 (0.10%)	11 / 2006 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia			
subjects affected / exposed	5 / 2012 (0.25%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriospasm coronary			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	31 / 2012 (1.54%)	30 / 2006 (1.50%)	
occurrences causally related to treatment / all	0 / 36	0 / 32	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	5 / 2012 (0.25%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 2012 (0.00%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	17 / 2012 (0.84%)	6 / 2006 (0.30%)	
occurrences causally related to treatment / all	3 / 17	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 2012 (0.05%)	6 / 2006 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block third degree			

subjects affected / exposed	3 / 2012 (0.15%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	6 / 2012 (0.30%)	7 / 2006 (0.35%)	
occurrences causally related to treatment / all	5 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac aneurysm			
subjects affected / exposed	3 / 2012 (0.15%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest	Additional description: Related event due to bradycardia		
subjects affected / exposed	6 / 2012 (0.30%)	10 / 2006 (0.50%)	
occurrences causally related to treatment / all	1 / 6	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac death			
subjects affected / exposed	4 / 2012 (0.20%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
Cardiac failure			
subjects affected / exposed	38 / 2012 (1.89%)	34 / 2006 (1.69%)	
occurrences causally related to treatment / all	0 / 41	0 / 49	
deaths causally related to treatment / all	0 / 9	0 / 7	
Cardiac failure acute			
subjects affected / exposed	7 / 2012 (0.35%)	5 / 2006 (0.25%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 3	
Cardiac failure congestive			

subjects affected / exposed	4 / 2012 (0.20%)	5 / 2006 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 3	
Cardiac tamponade			
subjects affected / exposed	2 / 2012 (0.10%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiogenic shock			
subjects affected / exposed	20 / 2012 (0.99%)	19 / 2006 (0.95%)	
occurrences causally related to treatment / all	0 / 20	0 / 20	
deaths causally related to treatment / all	0 / 12	0 / 12	
Cardiomyopathy			
subjects affected / exposed	1 / 2012 (0.05%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 2012 (0.00%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiorenal syndrome			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	32 / 2012 (1.59%)	21 / 2006 (1.05%)	
occurrences causally related to treatment / all	0 / 32	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery dissection			

subjects affected / exposed	4 / 2012 (0.20%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery occlusion			
subjects affected / exposed	2 / 2012 (0.10%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery perforation			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery restenosis			
subjects affected / exposed	19 / 2012 (0.94%)	24 / 2006 (1.20%)	
occurrences causally related to treatment / all	0 / 20	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	42 / 2012 (2.09%)	57 / 2006 (2.84%)	
occurrences causally related to treatment / all	0 / 43	0 / 58	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dressler's syndrome			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interventricular septum rupture			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intracardiac thrombus			

subjects affected / exposed	5 / 2012 (0.25%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	5 / 2012 (0.25%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	4 / 2012 (0.20%)	8 / 2006 (0.40%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	19 / 2012 (0.94%)	17 / 2006 (0.85%)	
occurrences causally related to treatment / all	0 / 19	0 / 18	
deaths causally related to treatment / all	0 / 7	0 / 3	
Myocardial ischaemia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial rupture			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myopericarditis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal arrhythmia			

subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal rhythm			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	2 / 2012 (0.10%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	7 / 2012 (0.35%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	6 / 7	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	2 / 2012 (0.10%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuropericarditis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postinfarction angina			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	4 / 2012 (0.20%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Rhythm idioventricular			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right heart failure			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Right ventricular failure			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	3 / 2012 (0.15%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinuatrial block			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrhythmia			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			

subjects affected / exposed	4 / 2012 (0.20%)	5 / 2006 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 4	0 / 5	
Supraventricular tachycardia			
subjects affected / exposed	3 / 2012 (0.15%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 2012 (0.10%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	16 / 2012 (0.80%)	9 / 2006 (0.45%)	
occurrences causally related to treatment / all	0 / 16	0 / 9	
deaths causally related to treatment / all	0 / 3	0 / 1	
Torsade de pointes			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular bigeminy			

subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular dysfunction			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	2 / 2012 (0.10%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	21 / 2012 (1.04%)	17 / 2006 (0.85%)	
occurrences causally related to treatment / all	0 / 21	0 / 18	
deaths causally related to treatment / all	0 / 2	0 / 2	
Ventricular flutter			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	20 / 2012 (0.99%)	14 / 2006 (0.70%)	
occurrences causally related to treatment / all	0 / 24	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bundle branch block left			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick node dysfunction			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Basal ganglia haemorrhage			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain hypoxia			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Brain injury			
subjects affected / exposed	7 / 2012 (0.35%)	5 / 2006 (0.25%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 3	
Brain stem ischaemia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
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	3 / 2012 (0.15%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	5 / 2012 (0.25%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	1 / 5	1 / 3	
deaths causally related to treatment / all	1 / 4	1 / 1	
Cerebral ischaemia			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	18 / 2012 (0.89%)	22 / 2006 (1.10%)	
occurrences causally related to treatment / all	0 / 20	0 / 22	
deaths causally related to treatment / all	0 / 3	0 / 2	
Cervical radiculopathy			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	3 / 2012 (0.15%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embololic stroke			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 2012 (0.00%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Global amnesia			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intensive care unit acquired weakness			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neurodegenerative disorder			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neurosarcoidosis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinsonism			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	3 / 2012 (0.15%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	16 / 2012 (0.80%)	5 / 2006 (0.25%)	
occurrences causally related to treatment / all	1 / 16	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	7 / 2012 (0.35%)	5 / 2006 (0.25%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasovagal attack			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 2012 (0.25%)	7 / 2006 (0.35%)	
occurrences causally related to treatment / all	3 / 5	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia macrocytic			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			

subjects affected / exposed	2 / 2012 (0.10%)	8 / 2006 (0.40%)	
occurrences causally related to treatment / all	2 / 2	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic diathesis			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperleukocytosis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
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	3 / 2012 (0.15%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIIth cranial nerve disorders			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden hearing loss			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Maculopathy	Additional description: Due to bleeding		
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
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	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal compartment syndrome			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 2012 (0.10%)	8 / 2006 (0.40%)	
occurrences causally related to treatment / all	0 / 2	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
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	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 2012 (0.15%)	5 / 2006 (0.25%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	3 / 2012 (0.15%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer	Additional description: Associated with bleeding		
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
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 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric ulcer			
subjects affected / exposed	3 / 2012 (0.15%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 2012 (0.10%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			

subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 2012 (0.15%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	20 / 2012 (0.99%)	19 / 2006 (0.95%)	
occurrences causally related to treatment / all	18 / 20	14 / 19	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ischaemia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heyde's syndrome			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (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 / 2012 (0.05%)	0 / 2006 (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 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Inguinal hernia			
subjects affected / exposed	2 / 2012 (0.10%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vascular occlusion			

subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	2 / 2012 (0.10%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Subileus			

subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ulcer			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prurigo			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	2 / 2012 (0.10%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	11 / 2012 (0.55%)	7 / 2006 (0.35%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute prerenal failure			
subjects affected / exposed	3 / 2012 (0.15%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute renal injury			
subjects affected / exposed	15 / 2012 (0.75%)	13 / 2006 (0.65%)	
occurrences causally related to treatment / all	0 / 16	0 / 13	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 2012 (0.10%)	6 / 2006 (0.30%)	
occurrences causally related to treatment / all	1 / 2	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Micturition disorder			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	10 / 2012 (0.50%)	5 / 2006 (0.25%)	
occurrences causally related to treatment / all	1 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal infarct			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (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 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral haemorrhage			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyrotoxic crisis			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Antisynthetase syndrome			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bursitis			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	2 / 2012 (0.10%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
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	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sacral pain			

subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess intestinal			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess oral			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	3 / 2012 (0.15%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteriuria			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon gangrene			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cystitis			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 2012 (0.00%)	6 / 2006 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis intestinal perforated			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 2012 (0.05%)	3 / 2006 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis clostridial			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder empyema			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			

subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 2012 (0.05%)	5 / 2006 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site infection			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Orchitis			

subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal abscess			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 2012 (0.10%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	69 / 2012 (3.43%)	47 / 2006 (2.34%)	
occurrences causally related to treatment / all	0 / 73	0 / 50	
deaths causally related to treatment / all	0 / 10	0 / 3	
Pulmonary sepsis			
subjects affected / exposed	1 / 2012 (0.05%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural pneumonia			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudoaneurysm infection			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	9 / 2012 (0.45%)	7 / 2006 (0.35%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 3	0 / 5	
Septic shock			
subjects affected / exposed	2 / 2012 (0.10%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 3	
Submandibular abscess			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (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	4 / 2012 (0.20%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	3 / 2012 (0.15%)	4 / 2006 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Vestibular neuronitis			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital infection male			
subjects affected / exposed	0 / 2012 (0.00%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 2012 (0.10%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	5 / 2012 (0.25%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic_ketoacidosis			
subjects affected / exposed	1 / 2012 (0.05%)	1 / 2006 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (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	2 / 2012 (0.10%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 2012 (0.00%)	2 / 2006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	1 / 2012 (0.05%)	0 / 2006 (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: 0 %

Non-serious adverse events	Ticagrelor	Prasugrel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2012 (0.00%)	0 / 2006 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2014	<p>Protocol V 2.0 dated May 2014 (versus Protocol V 1.1)</p> <ul style="list-style-type: none"> - Removal of Core lab - Secondary endpoints: Stent thrombosis according to ARC criteria (definite or probable) - Follow-up: time frame extended 30 (+10) days, 6 months (\pm 1 month), 12 months (\pm 1 month), long term outcome: 3-year (\pm 2 months) mortality (outpatient clinic, phone or letter) - Inclusion criteria: Pregnancy test removed - Exclusion criteria: Pregnancy test added, intracranial bleeding added - Study medication: Description adapted to SmPCs - Concomitant medication/ ASA/ Adjunct antithrombotic therapy: The initial dose of 150-500 mg was defined, if patients did not receive ASA within the past 12 hours. If a triple therapy is indicated, it is recommended to switch Ticagrelor or Prasugrel to Clopidogrel. - Laboratory: The heart enzymes should be taken at least twice and in case of a recurrent cardiac event. - Pharmacovigilance: <ul style="list-style-type: none"> o Information regarding documentation of (S)AEs and endpoints o Definition of adverse events o Other medically important events o The term life threatening was explained in detail - Sample size calculation - ICF: Procedure with patients with cardiogenic shock was added - Endpoint Definitions were updated.
16 December 2015	Interruption of recruitment 17 Dec 2015
19 July 2016	<p>Protocol V 4.0 dated 19 Jul 2016</p> <ul style="list-style-type: none"> - Added to Risk to benefit assessment: Therefore the risk of participating in this clinical trial for the patient is limited to the risk of randomization. - Primary endpoint: Description in more detail <ul style="list-style-type: none"> This endpoint consists of a time component and a status component. The former is measured in days between the date of randomization and <ul style="list-style-type: none"> • the date of the first event that occurs until (and including) the date of the final investigation after 12 months \pm 1 months, or • the date of the final investigation after 12 months \pm 1 months, if there was no event up to that point in time, or • the last follow-up date if there is no event up to that point in time and the 12 months \pm 1 months measurement is missing. The corresponding status takes the value 1 if an event occurred and 0, otherwise. The last point in the previous listing indicates how missing values are handled. - Secondary endpoint: added <ul style="list-style-type: none"> Death within 12 months after randomization Myocardial infarction within 12 months after randomization Stroke within 12 months after randomization - Safety Reporting: Description in more detail. After one year of follow-up, only adverse events that are fatal or life threatening have to be reported. - Hypothesis testing: updated - Statistics: <ul style="list-style-type: none"> Primary endpoint: Analysis updated Secondary endpoint: Analysis updated Analysis after 2000 patients adapted

17 October 2016	Restart of recruitment 15 Nov 2016, dated 17 Oct 2016
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 December 2015	Interruption of recruitment due to inspection findings (BfArM). Italian sites completed recruitment in Dec 2015.	15 November 2016

Notes:

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31475799>

<http://www.ncbi.nlm.nih.gov/pubmed/24371012>