Clinical trial results:
A Randomized, Double-blind, Double-dummy, Active-controlled, Parallel-group, Multicenter Study to Compare the Safety of Rivaroxaban versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Subjects with Acute Coronary Syndrome

Summary

EudraCT number	2014-004266-26
Trial protocol	BE SE CZ NL HU ES IT BG DK
Global end of trial date	14 October 2016

Results information

Result version number	v1 (current)
This version publication date	27 October 2017
First version publication date	27 October 2017

Trial information

Trial identification

Sponsor protocol code	RIVAROXACS2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02293395
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Highway 202 S, Raritan, NJ, United States, 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to estimate the bleeding risk with rivaroxaban, compared with acetyl salicylic acid (ASA), in addition to a single antiplatelet P2Y12 inhibitor agent (clopidogrel or ticagrelor), in subjects with a recent acute coronary syndrome (ACS) (including ST-segment elevation myocardial infarction [STEMI] and non-ST-segment elevation acute coronary syndrome [NSTE-ACS]).

Protection of trial subjects:

The safety evaluations included bleeding events, other adverse events, and clinical laboratory tests (hematology and clinical chemistry) that were relevant and clinically meaningful to a serious adverse event (SAE) or endpoint event. Safety data obtained during the study were reviewed on a routine basis by an unblinded, independent data monitoring committee (IDMC). This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 131
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Belgium: 89
Country: Number of subjects enrolled	Bulgaria: 161
Country: Number of subjects enrolled	Brazil: 162
Country: Number of subjects enrolled	Canada: 84
Country: Number of subjects enrolled	Czech Republic: 71
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Spain: 122
Country: Number of subjects enrolled	France: 57
Country: Number of subjects enrolled	Hungary: 201
Country: Number of subjects enrolled	Italy: 134
Country: Number of subjects enrolled	Japan: 59
Country: Number of subjects enrolled	Korea, Republic of: 54
Country: Number of subjects enrolled	Netherlands: 134
Country: Number of subjects enrolled	Poland: 333
Country: Number of subjects enrolled	Russian Federation: 481

Country: Number of subjects enrolled	Sweden: 79
Country: Number of subjects enrolled	Turkey: 200
Country: Number of subjects enrolled	Ukraine: 266
Country: Number of subjects enrolled	United States: 181
Worldwide total number of subjects	3037
EEA total number of subjects	1384

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)	1776
From 65 to 84 years	1250
85 years and over	11

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 3,145 subjects were screened for eligibility, of these 108 subjects were screening failures and the remaining 3,037 subjects were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rivaroxaban 2.5 mg Twice Daily (BID)

Arm description:

Subjects received oral dose of 2.5 milligram (mg) rivaroxaban BID and Acetylsalicylic acid (ASA) placebo once daily (OD) along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY59-7939
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received oral dose of 2.5 mg rivaroxaban BID for a minimum of 180 days, and up to 360 days of treatment.

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

Dosage and administration details:

Subjects received oral dose of placebo matching to 100 mg ASA OD along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

Arm title	Acetylsalicylic acid 100 mg Once Daily (OD)

Arm description:

Subjects received oral dose of 100 mg ASA OD and rivaroxaban placebo BID along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

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

Dosage and administration details:

Subjects received oral dose of placebo matching to 2.5 mg rivaroxaban BID along with either clopidogrel

75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

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

Dosage and administration details:

Subjects received oral dose of 100 mg ASA OD for a minimum of 180 days, and up to 360 days of treatment.

Number of subjects in period 1	Rivaroxaban 2.5 mg Twice Daily (BID)	Acetylsalicylic acid 100 mg Once Daily (OD)
Started	1519	1518
Treated	1510	1506 [1]
Completed	1510	1511
Not completed	9	7
Consent withdrawn by subject	8	7
Lost to follow-up	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: To provide more clarification for the subjects who were treated and to justify safety analysis population, we have created a milestone in subject disposition as "Treated".

Baseline characteristics

Reporting groups	
Reporting group title	Rivaroxaban 2.5 mg Twice Daily (BID)
Reporting group description:	
Subjects received oral dose of 2.5 milligram (mg) rivaroxaban BID and Acetylsalicylic acid (ASA) placebo once daily (OD) along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.	
Reporting group title	Acetylsalicylic acid 100 mg Once Daily (OD)
Reporting group description:	
Subjects received oral dose of 100 mg ASA OD and rivaroxaban placebo BID along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.	

Reporting group values	Rivaroxaban 2.5 mg Twice Daily (BID)	Acetylsalicylic acid 100 mg Once Daily (OD)	Total
Number of subjects	1519	1518	3037
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	887	889	1776
From 65 to 84 years	627	623	1250
85 years and over	5	6	11
Title for AgeContinuous Units: years			
arithmetic mean	62.7	62.9	
standard deviation	± 9.14	± 8.82	-
Title for Gender Units: subjects			
Female	385	377	762
Male	1134	1141	2275

End points

End points reporting groups

Reporting group title	Rivaroxaban 2.5 mg Twice Daily (BID)

Reporting group description:

Subjects received oral dose of 2.5 milligram (mg) rivaroxaban BID and Acetylsalicylic acid (ASA) placebo once daily (OD) along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

Reporting group title	Acetylsalicylic acid 100 mg Once Daily (OD)

Reporting group description:

Subjects received oral dose of 100 mg ASA OD and rivaroxaban placebo BID along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

Primary: Number of Subjects with non Coronary Artery Bypass Graft-Related (non CABG-related) Thrombolysis in Myocardial Infarction (TIMI) Clinically Significant Bleeding Events

End point title	Number of Subjects with non Coronary Artery Bypass Graft-Related (non CABG-related) Thrombolysis in Myocardial Infarction (TIMI) Clinically Significant Bleeding Events

End point description:

Non CABG-related TIMI clinically significant bleeding events are sum of non CABG-related TIMI major bleeding events, TIMI minor bleeding events and TIMI bleeding events requiring medical attention. Major: any symptomatic intracranial bleeding: clinically overt signs of hemorrhage with hemoglobin (Hb) drop of greater than or equal to (>=)5 gram per deciliter (g/dl) (or absolute drop in hematocrit of >=15%) and fatal bleeding (results in death within 7 days); Minor: clinically overt sign of hemorrhage with Hb drop of 3 - <5 g/dl (or drop in hematocrit of 9 - <15%); requiring medical attention: bleeding event that required medical, surgical treatment/laboratory evaluation and did not meet criteria for major/minor bleeding event. Population analyzed included all randomized subjects who had received at least one dose of study drug and had events between randomization and last dose of study drug +2 days or untreated subjects who had events between randomization to 2 days thereafter.

End point type	Primary

End point timeframe:

From start of study treatment until follow-up (up to 390 days)

End point values	Rivaroxaban 2.5 mg Twice Daily (BID)	Acetylsalicylic acid 100 mg Once Daily (OD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1519	1518		
Units: subjects	80	74		

Statistical analyses

Statistical analysis title	Non CABG-related TIMI
Comparison groups	Rivaroxaban 2.5 mg Twice Daily (BID) v Acetylsalicylic acid 100 mg Once Daily (OD)

Number of subjects included in analysis	3037
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.584
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.5

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 390 days

Adverse event reporting additional description:

Population analyzed included all randomized subjects who had received at least one dose of study drug and had events between randomization and last dose of study drug +2 days.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Acetylsalicylic acid 100 mg Once Daily (OD)

Reporting group description:

Subjects received oral dose of 100 mg ASA OD and rivaroxaban placebo BID along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

Reporting group title	Rivaroxaban 2.5 mg Twice Daily (BID)

Reporting group description:

Subjects received oral dose of 2.5 mg rivaroxaban BID and ASA placebo OD along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

Serious adverse events	Acetylsalicylic acid 100 mg Once Daily (OD)	Rivaroxaban 2.5 mg Twice Daily (BID)	
Total subjects affected by serious adverse events			
subjects affected / exposed	138 / 1506 (9.16%)	125 / 1510 (8.28%)	
number of deaths (all causes)	9	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain Neoplasm			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix Carcinoma Recurrent			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon Cancer Recurrent			

subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
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 / 1506 (0.00%)	1 / 1510 (0.07%)	
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 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular Carcinoma			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Cancer			
subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Neoplasm Malignant			
subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Carcinoma			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate Cancer			
subjects affected / exposed	1 / 1506 (0.07%)	2 / 1510 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Adenocarcinoma			

subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal Neoplasm			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary Gland Cancer Recurrent			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Cancer			
subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Neoplasm			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Aneurysm			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			

subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachiocephalic Arteriosclerosis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	2 / 1506 (0.13%)	5 / 1510 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
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	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Aneurysm			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Occlusion			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Stenosis			

subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian Artery Stenosis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Occlusion			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Inguinal Hernia Repair			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Neoplasm Surgery			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenectomy			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (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			
Chest Pain			
subjects affected / exposed	2 / 1506 (0.13%)	2 / 1510 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Implant Site Ulcer			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (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	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent-Graft Endoleak			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Stent Restenosis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Stent Stenosis			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			

subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Respiratory Failure			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	3 / 1506 (0.20%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 1506 (0.27%)	4 / 1510 (0.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
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	4 / 1506 (0.27%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Mass			

subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (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	3 / 1506 (0.20%)	3 / 1510 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol Withdrawal Syndrome			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic Attack			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Cardiac Stress Test Abnormal			
subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (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 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Enzyme Increased			

subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Function Test Increased			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinoscopy			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight Decreased			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol Poisoning			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Restenosis			
subjects affected / exposed	3 / 1506 (0.20%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand Fracture			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat Illness			

subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Dislocation			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament Sprain			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Limb Fracture			
subjects affected / exposed	2 / 1506 (0.13%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius Fracture			

subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Fracture			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna Fracture			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Access Site Pain			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Graft Occlusion			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Pseudoaneurysm			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Left Ventricular Failure			
subjects affected / exposed	0 / 1506 (0.00%)	3 / 1510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			

subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	5 / 1506 (0.33%)	5 / 1510 (0.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Valve Stenosis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
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	7 / 1506 (0.46%)	3 / 1510 (0.20%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial Flutter			
subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Second Degree			
subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	7 / 1506 (0.46%)	9 / 1510 (0.60%)	
occurrences causally related to treatment / all	0 / 9	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Acute			

subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Chronic			
subjects affected / exposed	0 / 1506 (0.00%)	3 / 1510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 1506 (0.07%)	2 / 1510 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Ventricular Thrombosis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular Insufficiency			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	0 / 1506 (0.00%)	2 / 1510 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Stenosis			
subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac Thrombus			
subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral Valve Incompetence			

subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Fibrosis			
subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
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 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericarditis			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuropericarditis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
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	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Arrest			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Extrasystoles			

subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (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			
Carotid Artery Stenosis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial Paralysis			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial Aneurysm			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 1506 (0.20%)	2 / 1510 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral Artery Stenosis			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo Positional			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Gastritis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis Ulcerative			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum Intestinal			

subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive Oesophagitis			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Necrosis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatitis Acute			
subjects affected / exposed	2 / 1506 (0.13%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Chronic			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			

subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (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	1 / 1506 (0.07%)	2 / 1510 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
subjects affected / exposed	5 / 1506 (0.33%)	3 / 1510 (0.20%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 1506 (0.07%)	3 / 1510 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-Induced Liver Injury			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	2 / 1506 (0.13%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nephrolithiasis			
subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy Toxic			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Artery Stenosis			

subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (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 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	0 / 1506 (0.00%)	2 / 1510 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Obstruction			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Disorder			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Protrusion			
subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligamentitis			

subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Discomfort			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rapidly Progressive Osteoarthritis			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (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 / 1506 (0.07%)	0 / 1510 (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 / 1506 (0.07%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 1506 (0.07%)	1 / 1510 (0.07%)	
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 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Infection			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
H1n1 Influenza			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Herpes Zoster			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious Pleural Effusion			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective Exacerbation of Chronic Obstructive Airways Disease			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 1506 (0.00%)	2 / 1510 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 1506 (0.33%)	7 / 1510 (0.46%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postoperative Wound Infection			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Chronic			
subjects affected / exposed	1 / 1506 (0.07%)	2 / 1510 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Infection			
subjects affected / exposed	0 / 1506 (0.00%)	1 / 1510 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			

subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	2 / 1506 (0.13%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 1506 (0.07%)	0 / 1510 (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: 1 %

Non-serious adverse events	Acetylsalicylic acid 100 mg Once Daily (OD)	Rivaroxaban 2.5 mg Twice Daily (BID)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 1506 (5.58%)	81 / 1510 (5.36%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 1506 (1.46%)	23 / 1510 (1.52%)	
occurrences (all)	24	24	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	19 / 1506 (1.26%)	11 / 1510 (0.73%)	
occurrences (all)	21	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 1506 (0.93%)	16 / 1510 (1.06%)	
occurrences (all)	14	16	

Dyspnoea subjects affected / exposed occurrences (all)	39 / 1506 (2.59%) 39	33 / 1510 (2.19%) 34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2014	The following changes were made in this amendment: modified a number of the inclusion criteria to simplify enrollment of subjects into the study; changes were made to clarify: the definition of the primary endpoint as it related to TIMI clinically significant bleeding events, stratification, the composition and conduct of the committees, the data to be used in the analyses, and the planned interim analysis; changes were made to ensure the evaluation of the cytochrome P450 2C19 genotype in all subjects regardless of P2Y12 inhibitor choice and to modify the timing of parenteral anticoagulants during the index hospitalization to the first dose of the study agent for consistency with the guidelines and previous studies conducted in the acute coronary syndrome (ACS) population.
21 April 2015	The following changes were made in this amendment: eligibility criteria was revised and it allowed for the inclusion of subjects with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) with positive biomarkers of myocardial necrosis without transient electrocardiogram (ECG) changes if there was a culprit lesion on coronary angiography demonstrating that a recent, active intracoronary atherothrombosis was identified; additionally, subjects with unstable angina without elevated cardiac biomarkers were eligible for enrollment based on ECG changes, a revascularization procedure, or an elevated TIMI risk score; furthermore, the adverse event reporting section was updated to exclude events that were suggestive of and reported as endpoint events from serious adverse event reporting and unblinding procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study population was homogenous with limited participation of non-Caucasian subjects. Randomization was not performed for use of P2Y12 inhibitor; strata comparisons between bleeding and efficacy endpoints are confounded and were not planned.

Notes: