Clinical trial results:
An OPen-label, Randomized, Controlled, Multicenter Study ExplorIng TwO TreatmeNt StratEgiEs of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention

Summary

EudraCT number	2012-001491-11
Trial protocol	DE BE GB SE IT NL DK PL BG CZ
Global end of trial date	28 July 2016

Results information

Result version number	v1 (current)
This version publication date	16 July 2017
First version publication date	16 July 2017

Trial information

Trial identification

Sponsor protocol code	RIVAROXAFL3003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01830543
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Scientific Affairs, LLC
Sponsor organisation address	1125 Trenton-Harbourton Road, Titusville, NJ , United States, 08560
Public contact	Clinical Registry group, Janssen Scientific Affairs, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry group, Janssen Scientific Affairs, 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	28 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the safety of 2 rivaroxaban treatment strategies and a dose-adjusted vitamin K antagonist (VKA) treatment strategy after percutaneous coronary intervention (PCI) (with stent placement) in subjects with paroxysmal, persistent, or permanent non-valvular atrial fibrillation (AF), based on the composite of Thrombolysis in Myocardial Infarction (TIMI) major bleeding, minor bleeding, and bleeding requiring medical attention events (known collectively as clinically significant bleeding) after 12 months of therapy.

Protection of trial subjects:

Safety was evaluated throughout the study and included monitoring of clinical events (cardiovascular (CV) death, myocardial infarction (MI), stroke, bleeding events, and stent thrombosis) and adverse events (AEs), and performing clinical laboratory tests (hematology, serum chemistry, and international normalized ratio [INR]) bleeding event assessment and classification.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 (GCPs) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 May 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	Argentina: 82
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Belgium: 52
Country: Number of subjects enrolled	Brazil: 41
Country: Number of subjects enrolled	Bulgaria: 221
Country: Number of subjects enrolled	Canada: 66
Country: Number of subjects enrolled	Chile: 18
Country: Number of subjects enrolled	Czech Republic: 40
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	France: 84
Country: Number of subjects enrolled	Germany: 295
Country: Number of subjects enrolled	Italy: 72
Country: Number of subjects enrolled	Malaysia: 11
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Netherlands: 68

Country: Number of subjects enrolled	Poland: 218
Country: Number of subjects enrolled	Korea, Republic of: 39
Country: Number of subjects enrolled	Romania: 50
Country: Number of subjects enrolled	Russian Federation: 265
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Sweden: 47
Country: Number of subjects enrolled	Taiwan: 25
Country: Number of subjects enrolled	Turkey: 43
Country: Number of subjects enrolled	Ukraine: 60
Country: Number of subjects enrolled	United Kingdom: 131
Country: Number of subjects enrolled	United States: 151
Worldwide total number of subjects	2124
EEA total number of subjects	1290

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)	559
From 65 to 84 years	1479
85 years and over	86

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 2,124 subjects were randomized out of which 2,099 received at least 1 dose of study agent and 1,599 completed the treatment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rivaroxaban 15 milligram (mg)

Arm description:

Subjects received rivaroxaban 15 mg or 10 mg (for subjects with moderate renal impairment [creatinine clearance (CrCl): 30 to less than (<) 50 milliliter per minute (mL/min)]) once daily plus background therapy with clopidogrel 75 mg once daily or alternate P2Y12 inhibitor (prasugrel 10 mg per day or ticagrelor 90 mg twice daily) for 12 months.

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

Dosage and administration details:

Subjects received rivaroxaban 15 mg tablet (or 10 mg for subjects with moderate renal impairment [CrCl: 30 to <50 mL/min]) once daily for 12 months.

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

Dosage and administration details:

Subjects received clopidogrel 75 mg tablet daily as background therapy for 12 months.

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

Dosage and administration details:

Subjects received prasugrel 10 mg tablet per day as background therapy for 12 months.

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

Dosage and administration details:

Subjects received ticagrelor 90 mg tablet twice daily as background therapy for 12 months.

Arm title	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)

Arm description:

Subjects received rivaroxaban 2.5 mg twice daily plus background dual antiplatelet therapy (DAPT) with low dose acetylsalicylic acid (ASA) 75 to 100 mg per day and clopidogrel 75 mg once daily (or alternate P2Y12 inhibitor [prasugrel or ticagrelor]) for an intended DAPT duration of 1, 6, or 12 months. Only subjects with an intended DAPT duration of 1 or 6-month transitioned to receive rivaroxaban 15 mg or 10 mg (for subjects with moderate renal impairment) once daily plus background single antiplatelet therapy with low dose ASA for the rest of the period up to Month 12.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban 2.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received rivaroxaban 2.5 mg tablet twice daily for 1, 6 or 12 months.

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

Dosage and administration details:

Subjects received clopidogrel 75 mg tablet daily as background therapy for 1, 6 or 12 months.

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

Dosage and administration details:

Subjects received prasugrel 10 mg tablet per day as background therapy for 1, 6 or 12 months.

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

Dosage and administration details:

Subjects received ticagrelor 90 mg tablet twice daily as background therapy for 1, 6 or 12 months.

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

Dosage and administration details:

Subjects received low-dose of acetyl salicylic acid 75 to 100 mg tablet daily for 1, 6 or 12 months.

Investigational medicinal product name	Rivaroxaban 15 mg
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with an intended DAPT duration of 1 or 6-month transitioned to receive rivaroxaban 15 mg once daily plus background single antiplatelet therapy with low dose ASA for the rest of the period up to Month 12.

Investigational medicinal product name	Rivaroxaban 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with an intended DAPT duration of 1 or 6-month transitioned to receive rivaroxaban 10 mg (for subjects with moderate renal impairment) once daily plus background single antiplatelet therapy with low dose ASA for the rest of the period up to Month 12.

Arm title	Vitamin K antagonist (VKA)

Arm description:

Subjects received dose adjusted (to a target of international normalized ratio [INR] 2.0 to 3.0 [or target INR 2.0 to 2.5]) vitamin K antagonist (VKA) [eg, warfarin, acenocoumarol; assigned by the investigator according to approved formulations) once daily plus background DAPT (clopidogrel 75 mg [or alternate P2Y12 inhibitor (prasugrel or ticagrelor)] plus low dose ASA [75 to 100 mg] daily) for an intended DAPT duration of 1, 6, or 12 months. Only subjects with an intended DAPT duration of 1 or 6-month transitioned to receive dose adjusted VKA plus background single antiplatelet therapy with low dose ASA for the rest of the period up to Month 12.

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

Dosage and administration details:

Subjects recieved a single oral dose of warfarin adjusted (to a target of [INR] 2.0 to 3.0 [or target INR 2.0 to 2.5]) once daily for 1, 6 or 12 months.

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

Dosage and administration details:

Subjects recieved a single oral dose of acenocoumarol adjusted (to a target of [INR] 2.0 to 3.0 [or target INR 2.0 to 2.5]) once daily for 1, 6 or 12 months.

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

Dosage and administration details:

Subjects received clopidogrel 75 mg tablet daily as background therapy for 1, 6 or 12 months.

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

Dosage and administration details:

Subjects received ticagrelor 90 mg tablet twice daily as background therapy for 1, 6 or 12 months.

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

Dosage and administration details:

Subjects received prasugrel 10 mg tablet per day as background therapy for 1, 6 or 12 months.

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

Dosage and administration details:

Subjects received low-dose of acetyl salicylic acid 75 to 100 mg tablet daily for 1, 6 or 12 months.

Number of subjects in period 1	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)
Started	709	709	706
Treated	696	706	697
Completed	550	557	492
Not completed	159	152	214
Consent withdrawn by subject	3	3	3
Physician decision	11	5	12
Subject Decision	19	21	57
Death	20	22	22
Adverse event	91	77	76
Unspecified	12	17	37
Protocol deviation	3	7	7

Baseline characteristics

Reporting groups	
Reporting group title	Rivaroxaban 15 milligram (mg)
Reporting group description:	
Subjects received rivaroxaban 15 mg or 10 mg (for subjects with moderate renal impairment [creatinine clearance (CrCl): 30 to less than (<) 50 milliliter per minute (mL/min)]) once daily plus background therapy with clopidogrel 75 mg once daily or alternate P2Y12 inhibitor (prasugrel 10 mg per day or ticagrelor 90 mg twice daily) for 12 months.	
Reporting group title	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)
Reporting group description:	
Subjects received rivaroxaban 2.5 mg twice daily plus background dual antiplatelet therapy (DAPT) with low dose acetylsalicylic acid (ASA) 75 to 100 mg per day and clopidogrel 75 mg once daily (or alternate P2Y12 inhibitor [prasugrel or ticagrelor]) for an intended DAPT duration of 1, 6, or 12 months. Only subjects with an intended DAPT duration of 1 or 6-month transitioned to receive rivaroxaban 15 mg or 10 mg (for subjects with moderate renal impairment) once daily plus background single antiplatelet therapy with low dose ASA for the rest of the period up to Month 12.	
Reporting group title	Vitamin K antagonist (VKA)
Reporting group description:	
Subjects received dose adjusted (to a target of international normalized ratio [INR] 2.0 to 3.0 [or target INR 2.0 to 2.5]) vitamin K antagonist (VKA) [eg, warfarin, acenocoumarol; assigned by the investigator according to approved formulations) once daily plus background DAPT (clopidogrel 75 mg [or alternate P2Y12 inhibitor (prasugrel or ticagrelor)] plus low dose ASA [75 to 100 mg] daily) for an intended DAPT duration of 1, 6, or 12 months. Only subjects with an intended DAPT duration of 1 or 6-month transitioned to receive dose adjusted VKA plus background single antiplatelet therapy with low dose ASA for the rest of the period up to Month 12.	

Reporting group values	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)
Number of subjects	709	709	706
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	186	193	180
From 65 to 84 years	489	488	502
85 years and over	34	28	24
Title for AgeContinuous Units: years			
arithmetic mean	70.4	70	69.9
standard deviation	± 9.12	± 9.11	± 8.67
Title for Gender Units: subjects			
Female	181	174	188
Male	528	535	518

Reporting group values	Total		
Number of subjects	2124		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	559		

From 65 to 84 years	1479		
85 years and over	86		

Title for AgeContinuous Units: years arithmetic mean standard deviation	- -		
Title for Gender Units: subjects			
Female	543		
Male	1581		

End points

End points reporting groups

Reporting group title	Rivaroxaban 15 milligram (mg)
Reporting group description:	
Subjects received rivaroxaban 15 mg or 10 mg (for subjects with moderate renal impairment [creatinine clearance (CrCl): 30 to less than (<) 50 milliliter per minute (mL/min)]) once daily plus background therapy with clopidogrel 75 mg once daily or alternate P2Y12 inhibitor (prasugrel 10 mg per day or ticagrelor 90 mg twice daily) for 12 months.	
Reporting group title	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)
Reporting group description:	
Subjects received rivaroxaban 2.5 mg twice daily plus background dual antiplatelet therapy (DAPT) with low dose acetylsalicylic acid (ASA) 75 to 100 mg per day and clopidogrel 75 mg once daily (or alternate P2Y12 inhibitor [prasugrel or ticagrelor]) for an intended DAPT duration of 1, 6, or 12 months. Only subjects with an intended DAPT duration of 1 or 6-month transitioned to receive rivaroxaban 15 mg or 10 mg (for subjects with moderate renal impairment) once daily plus background single antiplatelet therapy with low dose ASA for the rest of the period up to Month 12.	
Reporting group title	Vitamin K antagonist (VKA)
Reporting group description:	
Subjects received dose adjusted (to a target of international normalized ratio [INR] 2.0 to 3.0 [or target INR 2.0 to 2.5]) vitamin K antagonist (VKA) [eg, warfarin, acenocoumarol; assigned by the investigator according to approved formulations) once daily plus background DAPT (clopidogrel 75 mg [or alternate P2Y12 inhibitor (prasugrel or ticagrelor)] plus low dose ASA [75 to 100 mg] daily) for an intended DAPT duration of 1, 6, or 12 months. Only subjects with an intended DAPT duration of 1 or 6-month transitioned to receive dose adjusted VKA plus background single antiplatelet therapy with low dose ASA for the rest of the period up to Month 12.	

Primary: Percentage of Subjects With Clinically Significant Bleeding

End point title	Percentage of Subjects With Clinically Significant Bleeding
End point description:	
Clinically significant bleeding is a composite of TIMI major bleeding, minor bleeding, and BRMA. TIMI major bleeding is defined as any symptomatic intracranial hemorrhage, clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of greater than or equal to (>=) 5 g/dL (or when the hemoglobin concentration is not available, an absolute drop in hematocrit of >=15 percent). TIMI minor bleeding event is defined as any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin concentration of 3 to less than (<)5 g/dL (or, when hemoglobin concentration is not available, a fall in hematocrit of 9 percent to <15 percent). A BRMA event is defined as any bleeding event that requires medical treatment, surgical treatment, or laboratory evaluation, and does not meet criteria for a major or minor bleeding event. The Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Up to Month 12	

End point values	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	696	706	697	
Units: percentage of subjects				
number (not applicable)	15.7	16.6	24	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rivaroxaban 15 milligram (mg) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1393
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.76

Statistical analysis title	Statistical Analysis 2
Comparison groups	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1403
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.8

Secondary: Percentage of Subjects With Thrombolysis in Myocardial Infarction (TIMI) Major Bleeding

End point title	Percentage of Subjects With Thrombolysis in Myocardial Infarction (TIMI) Major Bleeding

End point description:

TIMI major bleeding is defined as any symptomatic intracranial hemorrhage, Clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of greater than or equal to (>=5) grams per deciliter (g/dL) (or when the hemoglobin concentration is not available, an absolute drop in hematocrit of >=15 percent). The Safety Analysis Set is defined as all randomized subjects who

received at least 1 dose of study drug. Here, 'n' signifies number of subjects analyzed at specific time-point in this endpoint and '99999' signifies that no data was analysed in this endpoint for the specified arm as the analysis at end of DAPT-1, 6 and 12 month conducted only in subjects who received DAPT as part of therapy.

End point type	Secondary
End point timeframe:	
Up to Month 12 and end of DAPT-Month 1, 6 and 12	

End point values	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	696	706	697	
Units: Percentage of subjects				
number (not applicable)				
Up to Month 12 (n= 696, 706, 697)	2	1.7	2.9	
End of DAPT-1 Month (n= 0, 108,113)	99999	0.9	4.4	
End of DAPT-6 Month (n= 0, 248,243)	99999	2.8	3.7	
End of DAPT-12 Month (n= 0,350,341)	99999	1.1	1.8	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Rivaroxaban 15 milligram (mg) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1393
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.234
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.31

Statistical analysis title	Statistical analysis 2
Comparison groups	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD) v Vitamin K antagonist (VKA)

Number of subjects included in analysis	1403
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.114
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.16

Secondary: Percentage of Subjects With Thrombolysis in Myocardial Infarction (TIMI) Minor Bleeding

End point title	Percentage of Subjects With Thrombolysis in Myocardial Infarction (TIMI) Minor Bleeding

End point description:

TIMI minor bleeding event is defined as any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin concentration of 3 to less than <5 g/dL (or, when hemoglobin concentration is not available, a fall in hematocrit of 9 percent to (<)15 percent). The Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of study drug. Here 'n' signifies number of subjects analyzed at specific time-point in this endpoint and '99999' signifies that no data was analysed in this endpoint for the specified arm as the analysis at end of DAPT-1, 6 and 12 month conducted only in subjects who received DAPT as part of therapy.

End point type	Secondary

End point timeframe:

Up to Month 12 and end of DAPT-Month 1, 6 and 12

End point values	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	696	706	697	
Units: Percentage of subjects				
number (not applicable)				
Up to Month 12 (n= 696, 706, 697)	1	1	1.9	
End of DAPT-1 Month (n= 0, 108, 113)	99999	0.9	1.8	
End of DAPT-6 Month (n= 0, 248, 243)	99999	0.4	2.5	
End of DAPT-12 Month (n= 0, 350, 341)	99999	1.4	1.5	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Rivaroxaban 15 milligram (mg) v Vitamin K antagonist (VKA)

Number of subjects included in analysis	1393
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.144
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.28

Statistical analysis title	Statistical analysis 2
Comparison groups	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1403
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.134
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.26

Secondary: Percentage of Subjects With Bleeding Requiring Medical Attention (BRMA)

End point title	Percentage of Subjects With Bleeding Requiring Medical Attention (BRMA)

End point description:

A BRMA event is defined as any bleeding event that requires medical treatment, surgical treatment, or laboratory evaluation, and does not meet criteria for a major or minor bleeding event. The Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of study drug. Here 'n' signifies number of subjects analyzed at specific time-point in this endpoint and '99999' signifies that no data was analysed in this endpoint for the specified arm as the analysis at end of DAPT-1, 6 and 12 month conducted only in subjects who received DAPT as part of therapy.

End point type	Secondary

End point timeframe:

Up to Month 12 and end of DAPT-Month 1, 6 and 12

End point values	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	696	706	697	
Units: percentage of subjects				
number (not applicable)				
Up to Month 12 (n= 696, 706, 697)	13.4	14.4	19.9	
End of DAPT-1 Month (n= 0, 108, 113)	99999	16.7	18.6	
End of DAPT-6 Month (n= 0, 248, 243)	99999	12.9	23	
End of DAPT-12 Month (n= 0, 350, 341)	99999	14.9	18.2	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Rivaroxaban 15 milligram (mg) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1393
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.8

Statistical analysis title	Statistical analysis 2
Comparison groups	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1403
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.86

Secondary: Percentage of Subjects With Composite of Adverse Cardiovascular Events (Cardiovascular Death, Myocardial Infarction (MI) and Stroke)

End point title	Percentage of Subjects With Composite of Adverse Cardiovascular Events (Cardiovascular Death, Myocardial Infarction (MI) and Stroke)

End point description:

Percentage of subjects who experienced adverse cardiovascular events (Cardiovascular Death, Myocardial Infarction (MI) and Stroke) collectively, were assessed. The Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of study drug. Here 'N' signifies number of subjects who were evaluable for this outcome measure, 'n' signifies number of subjects analyzed at specific time-point in this endpoint. Here '99999' signifies that no data was analysed in this endpoint for the specified arm as the analysis at end of DAPT-1, 6 and 12 month conducted only in subjects who received DAPT as part of therapy.

End point type	Secondary

End point timeframe:

Up to Month 12 and end of DAPT-month 1, 6 and 12

End point values	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	694	704	695	
Units: Percentage of subjects				
number (not applicable)				
Up to Month 12 (n= 694, 704, 695)	5.9	5.1	5.2	
End of DAPT-1 Month (n= 0, 108, 112)	99999	5.6	4.5	
End of DAPT-6 Month (n= 0, 248, 243)	99999	6.5	3.7	
End of DAPT-12 Month (n= 0, 348, 340)	99999	4	6.5	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Rivaroxaban 15 milligram (mg) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1389
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.75
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.68

Statistical analysis title	Statistical analysis 2
Comparison groups	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1399
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.765
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.48

Secondary: Percentage of Subjects With Cardiovascular Death

End point title	Percentage of Subjects With Cardiovascular Death

End point description:

The percentage of subjects with the first occurrence of cardiovascular death were evaluated. The Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of study drug.Here 'N' signifies number of subjects who were evaluable for this outcome measure, 'n' signifies number of subjects analyzed at specific time-point in this endpoint and '99999' signifies that no data was analysed in this endpoint for the specified category as the analysis at end of DAPT-1, 6 and 12 month conducted only in subjects who received DAPT as part of therapy.

End point type	Secondary

End point timeframe:

Up to Month 12 and end of DAPT-month 1, 6 and 12

End point values	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	694	704	695	
Units: percentage of subjects				
number (not applicable)				
Up to Month 12 (n= 694, 704, 695)	2.2	2	1.6	
End of DAPT-1 Month (n= 0, 108, 112)	99999	1.9	1.8	

End of DAPT-6 Month (n= 0, 248, 243)	99999	2.4	1.6	
End of DAPT-12 Month (n= 0, 348, 340)	99999	1.7	1.5	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Rivaroxaban 15 milligram (mg) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1389
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.523
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.8

Statistical analysis title	Statistical analysis 2
Comparison groups	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1399
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.664
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	2.62

Secondary: Percentage of Subjects With Myocardial Infarction

End point title	Percentage of Subjects With Myocardial Infarction

End point description:

The percentage of subjects with the first occurrence of the myocardial infarction were evaluated. The Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of study drug. Here 'N' signifies number of subjects who were evaluable for this outcome measure, 'n' signifies number of subjects analyzed at specific time-point in this endpoint and '99999' signifies that no data was analysed in this endpoint for the specified category as the analysis at end of DAPT-1, 6 and 12 month conducted only in subjects who received DAPT as part of therapy.

End point type	Secondary
End point timeframe:	
Up to Month 12 and end of DAPT-Month 1, 6 and 12	

End point values	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	694	704	695	
Units: percentage of subjects				
number (not applicable)				
Up to Month 12 (n= 694, 704, 695)	2.7	2.4	3	
End of DAPT-1 Month (n= 0, 108, 112)	99999	2.8	0.9	
End of DAPT-6 Month (n= 0, 248, 243)	99999	2.8	2.5	
End of DAPT-12 Month (n= 0, 348, 340)	99999	2	4.1	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Rivaroxaban 15 milligram (mg) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1389
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.625
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.59

Statistical analysis title	Statistical analysis 2
Comparison groups	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD) v Vitamin K antagonist (VKA)

Number of subjects included in analysis	1399
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.374
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.42

Secondary: Percentage of Subjects With Stroke

End point title	Percentage of Subjects With Stroke

End point description:

The percentage of subjects with the first occurrence of stroke were evaluated. The Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of study drug.Here 'N' signifies number of subjects who were evaluable for this outcome measure, 'n' signifies number of subjects analyzed at specific time-point in this endpoint and '99999' signifies that no data was analysed in this endpoint for the specified category as the analysis at end of DAPT-1, 6 and 12 month conducted only in subjects who received DAPT as part of therapy.

End point type	Secondary

End point timeframe:

Up to Month 12 and end of DAPT-Month 1, 6 and 12

End point values	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	694	704	695	
Units: percentage of subjects				
number (not applicable)				
Up to Month 12 (n= 694, 704, 695)	1.2	1.4	1	
End of DAPT-1 Month (n= 0, 108, 112)	99999	1.9	2.7	
End of DAPT-6 Month (n= 0, 248, 243)	99999	2.4	0	
End of DAPT-12 Month (n= 0, 348, 340)	99999	0.6	1.2	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Rivaroxaban 15 milligram (mg) v Vitamin K antagonist (VKA)

Number of subjects included in analysis	1389
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.891
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	2.96

Statistical analysis title	Statistical analysis 2
Comparison groups	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1399
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.53
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	3.58

Secondary: Percentage of Subjects With Stent Thrombosis

End point title	Percentage of Subjects With Stent Thrombosis

End point description:

The percentage of subjects with the first occurrence of the stent thrombosis were evaluated. The Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of study drug. Here 'N' signifies number of subjects who were evaluable for this outcome measure, 'n' signifies number of subjects analyzed at specific time-point in this outcome measureand '99999' signifies that no data was analysed in this endpoint for the specified category as the analysis at end of DAPT-1, 6 and 12 month conducted only in subjects who received DAPT as part of therapy.

End point type	Secondary

End point timeframe:

Up to Month 12 and end of DAPT-month 1, 6 and 12

End point values	Rivaroxaban 15 milligram (mg)	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD)	Vitamin K antagonist (VKA)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	694	704	695	
Units: percentage of subjects				
number (not applicable)				
Up to Month 12 (n= 694, 704, 695)	0.7	0.9	0.6	
End of DAPT-1 Month (n= 0, 108, 112)	99999	1.9	0.9	
End of DAPT-6 Month (n= 0, 248, 243)	99999	1.6	0.4	
End of DAPT-12 Month (n= 0, 348, 340)	99999	0	0.6	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Rivaroxaban 15 milligram (mg) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1389
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.79
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	4.45

Statistical analysis title	Statistical analysis 2
Comparison groups	Rivaroxaban 2.5 mg Twice Daily (BID)/15 mg Once Daily(QD) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1399
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.574
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	5.09

Adverse events

Adverse events information

Timeframe for reporting adverse events:

t7g6f8Up to 12 months

Adverse event reporting additional description:

The Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Rivaroxaban 15 mg

Reporting group description:

Subjects received rivaroxaban 15 mg or 10 mg (for subjects with moderate renal impairment [creatinine clearance (CrCl): 30 to less than (<) 50 milliliter per minute (mL/min)]) once daily plus background therapy with clopidogrel 75 mg once daily or alternate P2Y12 inhibitor (prasugrel 10 mg per day or ticagrelor 90 mg twice daily) for 12 months.

Reporting group title	Rivaroxaban 2.5 mg BID/15 mg

Reporting group description:

Subjects received rivaroxaban 2.5 mg twice daily plus background dual antiplatelet therapy (DAPT) with low dose acetylsalicylic acid (ASA) 75 to 100 mg per day and clopidogrel 75 mg once daily (or alternate P2Y12 inhibitor [prasugrel or ticagrelor]) for an intended DAPT duration of 1, 6, or 12 months. Only subjects with an intended DAPT duration of 1 or 6 month transitioned to receive rivaroxaban 15 mg or 10 mg (for subjects with moderate renal impairment) once daily plus background single antiplatelet therapy with low dose ASA for the rest of the period up to Month 12.

Reporting group title	vitamin K antagonist (VKA)

Reporting group description:

Subjects received dose adjusted (to a target of international normalized ratio [INR] 2.0 to 3.0 [or target INR 2.0 to 2.5]) vitamin K antagonist (VKA) [eg, warfarin, acenocoumarol; assigned by the investigator according to approved formulations) once daily plus background DAPT (clopidogrel 75 mg [or alternate P2Y12 inhibitor (prasugrel or ticagrelor)] plus low dose ASA [75 to 100 mg] daily) for an intended DAPT duration of 1, 6, or 12 months. Only subjects with an intended DAPT duration of 1 or 6 month transitioned to receive dose adjusted VKA plus background single antiplatelet therapy with low dose ASA for the rest of the period up to Month 12.

Serious adverse events	Rivaroxaban 15 mg	Rivaroxaban 2.5 mg BID/15 mg	vitamin K antagonist (VKA)
Total subjects affected by serious adverse events			
subjects affected / exposed	237 / 696 (34.05%)	225 / 706 (31.87%)	271 / 697 (38.88%)
number of deaths (all causes)	19	21	18
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal Neoplasm			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ameloblastoma			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal Cell Carcinoma			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Cancer			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Cancer Recurrent			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Neoplasm			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's Disease			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain Neoplasm Malignant			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer Stage I			

subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial Carcinoma			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cholangiocarcinoma			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon Cancer			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon Neoplasm			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal Adenocarcinoma			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse Large B-Cell Lymphoma			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder Cancer Metastatic			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Stromal Tumour			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular Carcinoma			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Neoplasm Malignant			
subjects affected / exposed	1 / 696 (0.14%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Meningioma			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to Liver			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cancer			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary Tumour Benign			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Cancer			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Neoplasm			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Cell Carcinoma			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Neoplasm			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Cell Lung Cancer Metastatic			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous Cell Carcinoma			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic Aneurysm			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Aortic Stenosis			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial Stenosis			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Arteriovenous Fistula			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory Collapse			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep Vein Thrombosis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity Necrosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral Artery Occlusion			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			

subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	2 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	3 / 696 (0.43%)	2 / 706 (0.28%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive Crisis			
subjects affected / exposed	1 / 696 (0.14%)	3 / 706 (0.42%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent Claudication			
subjects affected / exposed	1 / 696 (0.14%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocele			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Hypertension			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Arterial Occlusive Disease			

subjects affected / exposed	4 / 696 (0.57%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Thrombosis			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peripheral Embolism			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Ischaemia			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Vascular Disorder			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock Haemorrhagic			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous Occlusion			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous Thrombosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Angioplasty			

subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic Valve Replacement			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Ablation			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Pacemaker Insertion			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Resynchronisation Therapy			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardioversion			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Arterial Stent Insertion			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Bypass			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hospitalisation			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileostomy Closure			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implantable Defibrillator Insertion			
subjects affected / exposed	1 / 696 (0.14%)	2 / 706 (0.28%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee Arthroplasty			
subjects affected / exposed	1 / 696 (0.14%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral Valve Repair			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Percutaneous Coronary Intervention			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Sympathetic Nerve Ablation			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth Extraction			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter Site Swelling			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest Discomfort			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest Pain			
subjects affected / exposed	8 / 696 (1.15%)	4 / 706 (0.57%)	9 / 697 (1.29%)
occurrences causally related to treatment / all	0 / 8	0 / 4	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 696 (0.29%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Device Failure			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Intolerance			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Resistance			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Withdrawal Syndrome			

subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait Disturbance			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical Device Complication			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-Organ Failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema Peripheral			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Cardiac Death			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Sudden Death			
subjects affected / exposed	2 / 696 (0.29%)	1 / 706 (0.14%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 3
Ulcer Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Stent Occlusion			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Stent Restenosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Stent Thrombosis			
subjects affected / exposed	1 / 696 (0.14%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Vessel Puncture Site Haematoma			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic Shock			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical Polyp			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	2 / 696 (0.29%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute Respiratory Failure			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis Chronic			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumopathy			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	2 / 696 (0.29%)	2 / 706 (0.28%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			

subjects affected / exposed	6 / 696 (0.86%)	6 / 706 (0.85%)	10 / 697 (1.43%)
occurrences causally related to treatment / all	0 / 7	0 / 7	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea Exertional			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea at Rest			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	5 / 696 (0.72%)	5 / 706 (0.71%)	5 / 697 (0.72%)
occurrences causally related to treatment / all	6 / 6	5 / 5	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	2 / 696 (0.29%)	2 / 706 (0.28%)	4 / 697 (0.57%)
occurrences causally related to treatment / all	2 / 3	2 / 2	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial Lung Disease			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung Disorder			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			

subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Congestion			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Hypertension			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Mass			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Oedema			
subjects affected / exposed	2 / 696 (0.29%)	1 / 706 (0.14%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Distress			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sleep Apnoea Syndrome			

subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety Disorder			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional State			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Biopsy Prostate			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Stress Test			

subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection Fraction Decreased			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram Ambulatory Abnormal			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin Decreased			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International Normalised Ratio Increased			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	4 / 697 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipids Increased			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Compression Fracture			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Concussion			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Restenosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral Injury			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Fall			
subjects affected / exposed	1 / 696 (0.14%)	2 / 706 (0.28%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral Neck Fracture			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip Fracture			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Incisional Hernia			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Limb Fracture			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle Rupture			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	5 / 696 (0.72%)	6 / 706 (0.85%)	7 / 697 (1.00%)
occurrences causally related to treatment / all	1 / 5	5 / 6	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax Traumatic			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Complication			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Haematoma			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Haemorrhage			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis Fracture			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius Fracture			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road Traffic Accident			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural Haematoma			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Subdural Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to Various Agents			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Fracture			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Haematoma			

subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Limb Fracture			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Pseudoaneurysm			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Dehiscence			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	3 / 696 (0.43%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	5 / 696 (0.72%)	5 / 706 (0.71%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina Pectoris			
subjects affected / exposed	7 / 696 (1.01%)	13 / 706 (1.84%)	15 / 697 (2.15%)
occurrences causally related to treatment / all	0 / 9	0 / 16	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			
subjects affected / exposed	16 / 696 (2.30%)	12 / 706 (1.70%)	23 / 697 (3.30%)
occurrences causally related to treatment / all	1 / 17	0 / 13	0 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			

subjects affected / exposed	13 / 696 (1.87%)	21 / 706 (2.97%)	23 / 697 (3.30%)
occurrences causally related to treatment / all	0 / 17	0 / 24	0 / 30
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Flutter			
subjects affected / exposed	0 / 696 (0.00%)	5 / 706 (0.71%)	4 / 697 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Tachycardia			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Thrombosis			
subjects affected / exposed	4 / 696 (0.57%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	2 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block Complete			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradyarrhythmia			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	2 / 696 (0.29%)	1 / 706 (0.14%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Arrest			

subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac Disorder			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 696 (3.02%)	16 / 706 (2.27%)	31 / 697 (4.45%)
occurrences causally related to treatment / all	0 / 25	0 / 21	0 / 32
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 1
Cardiac Failure Acute			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 696 (0.43%)	3 / 706 (0.42%)	4 / 697 (0.57%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac Failure Chronic			
subjects affected / exposed	3 / 696 (0.43%)	1 / 706 (0.14%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac Failure Congestive			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 696 (1.01%)	4 / 706 (0.57%)	11 / 697 (1.58%)
occurrences causally related to treatment / all	0 / 9	0 / 5	1 / 11
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiac Pseudoaneurysm			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic Shock			

subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular Disorder			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	3 / 696 (0.43%)	5 / 706 (0.71%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary Artery Stenosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Thrombosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dressler's Syndrome			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Cardiomyopathy			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Ventricular Dysfunction			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Ventricular Failure			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Myocardial Ischaemia			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial Effusion			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial Haemorrhage			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Bradycardia			

subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Node Dysfunction			
subjects affected / exposed	4 / 696 (0.57%)	1 / 706 (0.14%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular Tachycardia			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia Induced Cardiomyopathy			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Arrhythmia			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Extrasystoles			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Fibrillation			
subjects affected / exposed	2 / 696 (0.29%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Tachycardia			

subjects affected / exposed	3 / 696 (0.43%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid Artery Stenosis			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	4 / 697 (0.57%)
occurrences causally related to treatment / all	0 / 0	2 / 4	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 1	3 / 3
Cerebral Infarction			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Ischaemia			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	2 / 696 (0.29%)	4 / 706 (0.57%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dizziness Postural			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Stroke			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Hemianopia			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intercostal Neuralgia			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intracranial Haematoma			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	5 / 696 (0.72%)	2 / 706 (0.28%)	4 / 697 (0.57%)
occurrences causally related to treatment / all	1 / 6	1 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Lacunar Infarction			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's Disease			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 696 (0.14%)	4 / 706 (0.57%)	8 / 697 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension Headache			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viith Nerve Paralysis			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 696 (0.72%)	4 / 706 (0.57%)	4 / 697 (0.57%)
occurrences causally related to treatment / all	4 / 5	2 / 4	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Anaemia			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypergammaglobulinaemia			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypochromic Anaemia			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microcytic Anaemia			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Deafness Neurosensory			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Age-Related Macular Degeneration			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	3 / 696 (0.43%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Lower			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute Abdomen			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Fistula			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Barrett's Oesophagus			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Change of Bowel Habit			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis Microscopic			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's Disease			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Ulcer			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastric Mucosa Erythema			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 696 (0.14%)	3 / 706 (0.42%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	1 / 2	2 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastritis			
subjects affected / exposed	2 / 696 (0.29%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis Erosive			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis Haemorrhagic			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenitis Haemorrhagic			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 696 (1.01%)	7 / 706 (0.99%)	9 / 697 (1.29%)
occurrences causally related to treatment / all	7 / 7	6 / 7	7 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Ulcer			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus Hernia			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired Gastric Emptying			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	3 / 696 (0.43%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Haemorrhage			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Ischaemia			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-Abdominal Haematoma			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss Syndrome			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	4 / 697 (0.57%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Chronic			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Haemorrhage			
subjects affected / exposed	4 / 696 (0.57%)	2 / 706 (0.28%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	3 / 4	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	2 / 696 (0.29%)	1 / 706 (0.14%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	2 / 2	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile Duct Stone			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Chronic			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Cyst			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis Acute			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis Toxic			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular Injury			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic Foot			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurodermatitis			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Necrosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Ulcer			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute Kidney Injury			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 696 (0.29%)	2 / 706 (0.28%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Bladder Tamponade			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Ureteric			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Urethral			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Urinary			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	5 / 696 (0.72%)	3 / 706 (0.42%)	4 / 697 (0.57%)
occurrences causally related to treatment / all	5 / 5	3 / 3	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage Urinary Tract			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Prerenal Failure			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Artery Stenosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	2 / 696 (0.29%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral Haemorrhage			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral Stenosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Retention			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back Pain			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty Arthritis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Effusion			

subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Disorder			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck Pain			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in Extremity			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			

subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rheumatic Disorder			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Column Stenosis			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Disorder			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Osteoarthritis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Pain			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal Wall Abscess			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess Limb			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis Bacterial			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Sepsis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bronchitis			
subjects affected / exposed	3 / 696 (0.43%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis Bacterial			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis Viral			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 696 (0.00%)	2 / 706 (0.28%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Infection			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma Infection			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes Zoster			

subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected Skin Ulcer			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective Exacerbation of Chronic Obstructive Airways Disease			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Discitis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver Abscess			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised Infection			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			

subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periodontitis			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	12 / 696 (1.72%)	12 / 706 (1.70%)	14 / 697 (2.01%)
occurrences causally related to treatment / all	0 / 13	0 / 13	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Tract Infection			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal Abscess			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tracheitis			

subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	2 / 696 (0.29%)	2 / 706 (0.28%)	3 / 697 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 696 (0.00%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 696 (0.14%)	1 / 706 (0.14%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes Mellitus			
subjects affected / exposed	2 / 696 (0.29%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic Metabolic Decompensation			

subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	2 / 697 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 696 (0.00%)	0 / 706 (0.00%)	1 / 697 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic Disorder			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 Diabetes Mellitus			
subjects affected / exposed	1 / 696 (0.14%)	0 / 706 (0.00%)	0 / 697 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Rivaroxaban 15 mg	Rivaroxaban 2.5 mg BID/15 mg	vitamin K antagonist (VKA)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	174 / 696 (25.00%)	210 / 706 (29.75%)	234 / 697 (33.57%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	13 / 696 (1.87%)	35 / 706 (4.96%)	25 / 697 (3.59%)
occurrences (all)	17	47	32
Subcutaneous Haematoma			

subjects affected / exposed	2 / 696 (0.29%)	10 / 706 (1.42%)	14 / 697 (2.01%)
occurrences (all)	9	13	15
Vascular disorders			
Haematoma			
subjects affected / exposed	21 / 696 (3.02%)	31 / 706 (4.39%)	61 / 697 (8.75%)
occurrences (all)	21	40	85
Hypertension			
subjects affected / exposed	17 / 696 (2.44%)	2 / 706 (0.28%)	7 / 697 (1.00%)
occurrences (all)	17	2	7
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	13 / 696 (1.87%)	18 / 706 (2.55%)	12 / 697 (1.72%)
occurrences (all)	15	22	14
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 696 (1.15%)	7 / 706 (0.99%)	15 / 697 (2.15%)
occurrences (all)	8	7	16
General disorders and administration site conditions			
Oedema Peripheral			
subjects affected / exposed	14 / 696 (2.01%)	12 / 706 (1.70%)	18 / 697 (2.58%)
occurrences (all)	14	13	18
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 696 (1.72%)	18 / 706 (2.55%)	11 / 697 (1.58%)
occurrences (all)	13	19	11
Gingival Bleeding			
subjects affected / exposed	17 / 696 (2.44%)	16 / 706 (2.27%)	18 / 697 (2.58%)
occurrences (all)	19	20	20
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	27 / 696 (3.88%)	21 / 706 (2.97%)	18 / 697 (2.58%)
occurrences (all)	31	23	21
Epistaxis			
subjects affected / exposed	67 / 696 (9.63%)	59 / 706 (8.36%)	82 / 697 (11.76%)
occurrences (all)	82	79	108
Skin and subcutaneous tissue disorders			

Ecchymosis subjects affected / exposed occurrences (all)	4 / 696 (0.57%) 5	16 / 706 (2.27%) 21	15 / 697 (2.15%) 17
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	18 / 696 (2.59%) 21	14 / 706 (1.98%) 21	14 / 697 (2.01%) 14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2012	Included modifications to inclusion and exclusion criteria; Increased the time window allowed for administration of first dose of study agent; modified the schedule for monitoring the international normalized ratio (INR) in subjects randomized to vitamin K antagonist (VKA) treatment in the dual antiplatelet therapy (DAPT) period; defined which creatinine laboratory test result was used to establish whether the rivaroxaban dose should be reduced for subjects with moderate renal impairment; and added collection of blood samples for exploratory pharmacokinetic and pharmacodynamic testing at selected study sites.
10 August 2012	Included a change to the concomitant medications to agree with current prescribing information for clopidogrel that recommended avoiding concomitant administration with omeprazole or esomeprazole.
12 December 2012	Included addition of a third treatment strategy group based on results from the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting (WOEST) trial that was presented at 2012 European Society of Cardiology meeting; This new data suggested that dual therapy with warfarin plus clopidogrel caused less bleeding and lower rates of mortality than standard triple therapy with warfarin, clopidogrel, and acetylsalicylic acid (ASA) in patients undergoing percutaneous coronary intervention (PCI) who required anticoagulation; a third treatment strategy group with rivaroxaban plus clopidogrel administered for 12 months was added, the vitamin K antagonist (VKA) treatment strategy was changed to VKA for 12 months plus dual antiplatelet therapy (DAPT) followed by ASA, and changed the once-daily dose of rivaroxaban to 15 mg, and an alternative to clopidogrel, P2Y12 inhibitors (prasugrel or ticagrelor) were allowed.
11 October 2013	Included simplification of the timing of the first dose so that all treatment strategy groups had the first dose based only on time of sheath removal; Additional clarifications were made related to performing international normalized ratio (INR) tests in all subjects and only in those subjects randomized to VKA treatment strategy; Additional clarifications were made related to performing INR tests in all subjects and only in those subjects randomized to vitamin K antagonist (VKA) treatment strategy; The reporting of safety endpoint events of myocardial infarction (MI) and stent thrombosis was clarified; these events were not to be reported as serious adverse events (SAEs), rather, they would be captured as safety endpoint events in the CRF within 24 hours after the investigational staff's knowledge of the event.

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.

First the stratification to either 1, 6 or 12 months of DAPT was based upon clinician choice and was not randomized. Secondly there was not sufficient power to definitively assess efficacy due to the modest number of adverse CV events.

Notes: