Clinical trial results:
A Phase 4 Trial to Assess the Effectiveness of Apixaban Compared With Usual Care Anticoagulation in Subjects With Nonvalvular Atrial Fibrillation Undergoing Cardioversion

Summary

EudraCT number	2014-001231-36
Trial protocol	DK ES BE SE DE
Global end of trial date	08 February 2017

Results information

Result version number	v1 (current)
This version publication date	02 February 2018
First version publication date	02 February 2018

Trial information

Trial identification

Sponsor protocol code	B0661025/CV185-267

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02100228
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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	07 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the occurrence of clinical endpoints in nonvalvular atrial fibrillation subjects (i.e., without rheumatic mitral valve disease, a prosthetic heart valve, or valve repair) indicated for cardioversion and treated with apixaban or usual care (parenteral heparin and/or oral anticoagulation with vitamin K antagonist, excluding other novel oral anticoagulant).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 135
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	Denmark: 70
Country: Number of subjects enrolled	Germany: 320
Country: Number of subjects enrolled	Israel: 295
Country: Number of subjects enrolled	Italy: 55
Country: Number of subjects enrolled	Japan: 49
Country: Number of subjects enrolled	Korea, Republic of: 102
Country: Number of subjects enrolled	Romania: 79
Country: Number of subjects enrolled	Spain: 57
Country: Number of subjects enrolled	Sweden: 84
Country: Number of subjects enrolled	United States: 216
Worldwide total number of subjects	1500
EEA total number of subjects	800

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)	679
From 65 to 84 years	774
85 years and over	47

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Fifteen hundred subjects were enrolled at 134 centers. The study was conducted from 14 July 2014 to 08 Feb 2017.

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	Apixaban

Arm description:

Subjects with non-valvular atrial fibrillation undergoing cardioversion, received Apixaban orally for 30 days after cardioversion or 90 days after randomization if cardioversion was not performed. The dosing of Apixaban was based on investigator's judgement as per local label for the prevention of stroke and systemic embolism in subjects.

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

Dosage and administration details:

Subjects were administered orally with 2.5 or 5 milligram (mg) of Apixaban twice daily for 30 days following cardioversion or 90 days post randomization if cardioversion was not performed within that timeframe.

Arm title	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)

Arm description:

Subjects with non-valvular atrial fibrillation undergoing cardioversion, received parenteral heparin and/or oral Vitamin K antagonist as usual care, orally for 30 days after cardioversion or 90 days after randomization if cardioversion was not performed. The dosing of the parenteral heparin and Vitamin K antagonist was based on individual subject's sensitivity to the drug according to the investigators usual practice.

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

Dosage and administration details:

Subjects were administered orally with Vitamin K (dosing was based on individual subject's sensitivity to the drug according to the investigators usual practice) for 30 days following cardioversion or 90 days post randomization if cardioversion was not performed within that timeframe.

Investigational medicinal product name	Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection

Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered intravenously with Heparin (dosing was based on individual subject's sensitivity to the drug according to the investigators usual practice) for 30 days following cardioversion or 90 days post randomization if cardioversion was not performed within that timeframe.

Number of subjects in period 1	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)
Started	753	747
Completed	678	657
Not completed	75	90
Adverse event, serious fatal	1	1
Inclusion/Exclusion criteria not met	12	16
Consent withdrawn by subject	27	37
Adverse event, non-fatal	16	12
Non-compliance	-	3
Unspecified	19	19
Lost to follow-up	-	1
Administrative reason	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Apixaban
Reporting group description:	
Subjects with non-valvular atrial fibrillation undergoing cardioversion, received Apixaban orally for 30 days after cardioversion or 90 days after randomization if cardioversion was not performed. The dosing of Apixaban was based on investigator's judgement as per local label for the prevention of stroke and systemic embolism in subjects.	
Reporting group title	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)
Reporting group description:	
Subjects with non-valvular atrial fibrillation undergoing cardioversion, received parenteral heparin and/or oral Vitamin K antagonist as usual care, orally for 30 days after cardioversion or 90 days after randomization if cardioversion was not performed. The dosing of the parenteral heparin and Vitamin K antagonist was based on individual subject's sensitivity to the drug according to the investigators usual practice.	

Reporting group values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)	Total
Number of subjects	753	747	1500
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	342	337	679
From 65-84 years	388	386	774
85 years and over	23	24	47
Age Continuous Units: years			
arithmetic mean	64.7	64.5	
standard deviation	± 12.19	± 12.76	-
Gender, Male/Female Units: Subjects			
Female	248	250	498
Male	505	497	1002
Race/Ethnicity, Customized Units: Subjects			
Race: White	654	648	1302
Race: Black or African American	21	20	41
Race: Asian	78	76	154
Race: Other	0	3	3
Race/Ethnicity, Customized Units: Subjects			
Ethnicity: Hispanic or Latino	8	9	17
Ethnicity: Not Hispanic or Latino	100	99	199

Ethnicity: Unknown or Not Reported	645	639	1284

End points

End points reporting groups

Reporting group title	Apixaban

Reporting group description:

Subjects with non-valvular atrial fibrillation undergoing cardioversion, received Apixaban orally for 30 days after cardioversion or 90 days after randomization if cardioversion was not performed. The dosing of Apixaban was based on investigator's judgement as per local label for the prevention of stroke and systemic embolism in subjects.

Reporting group title	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)

Reporting group description:

Subjects with non-valvular atrial fibrillation undergoing cardioversion, received parenteral heparin and/or oral Vitamin K antagonist as usual care, orally for 30 days after cardioversion or 90 days after randomization if cardioversion was not performed. The dosing of the parenteral heparin and Vitamin K antagonist was based on individual subject's sensitivity to the drug according to the investigators usual practice.

Primary: Number of Subjects With Acute Stroke Event

End point title	Number of Subjects With Acute Stroke Event

End point description:

An acute stroke was defined as a new, important neurological insufficiency of rapid onset that lasted for at least 24 hours and that was not due to a readily identifiable non-vascular cause (like brain tumor or trauma). Full analysis set included all randomized subjects.

End point type	Primary

End point timeframe:

Baseline up to 30 days post cardio version (or up to 90 days after randomization, if cardio version was not performed within that time frame)

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	753	747		
Units: subjects	0	6		

Statistical analyses

Statistical analysis title	Comparison of Apixaban and Usual Care

Statistical analysis description:

This was a descriptive study, and there was no formal pre-defined hypothesis testing.

Comparison groups	Apixaban v Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)

Number of subjects included in analysis	1500
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0151
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.6425

Notes:

[1] - Display exact confidence limits for relative risk and Fisher's exact test for comparisons of two proportions.

Primary: Number of Subjects With Systemic Embolism Event

End point title	Number of Subjects With Systemic Embolism Event[2]

End point description:

Systemic embolism occurred in subject when there was a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries), which was supported by evidence of embolism from surgical specimens, autopsy, angiography, or other objective testing. Full analysis set included all randomized subjects.

End point type	Primary

End point timeframe:

Baseline up to 30 days post cardioversion (or up to 90 days after randomization, if cardioversion was not performed within that time frame)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was done for this endpoint since there were no subjects with systemic embolism event.

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	753	747		
Units: subjects				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Major Bleeding Event

End point title	Number of Subjects With Major Bleeding Event

End point description:

Major bleeding was defined as clinically evident bleeding that was accompanied by one or more of the following: a decrease in hemoglobin of 2 gram per deciliter or more, a transfusion of 2 or more units of packed red blood cells, bleeding that was fatal or bleeding that occurred in at least one of the following

critical sites: intracranial, intra-spinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed was not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal. Full analysis set included all randomized subjects.

End point type	Primary

End point timeframe:

Baseline up to 30 days post cardioversion (or up to 90 days after randomization, if cardioversion was not performed within that time frame)

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	735	721		
Units: subjects				
number (not applicable)	3	6		

Statistical analyses

Statistical analysis title	Comparison of Apixaban and Usual Care

Statistical analysis description:

This was a descriptive study, and there was no formal pre-defined hypothesis testing.

Comparison groups	Apixaban v Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)
Number of subjects included in analysis	1456
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.3378
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.4905
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1046
upper limit	2.0678

Notes:

[3] - Display exact confidence limits for relative risk and Fisher's exact test for comparisons of two proportions.

Primary: Number of Subjects With Clinically Relevant Non-Major Bleeding Events

End point title	Number of Subjects With Clinically Relevant Non-Major Bleeding Events

End point description:

Clinically relevant non-major bleeding was defined as the clinically evident bleeding consisted of any bleeding that compromised hemodynamics, led to hospitalization, subcutaneous hematoma larger than 25/100 centimeter square if there was a traumatic cause, intramuscular hematoma, epistaxis, gingival bleeding, hematuria, macroscopic gastrointestinal hemorrhage with at least one episode of melena or hematemesis, rectal blood loss, hemoptysis or any other bleeding type with clinical consequences for a subject, such as medical intervention, the need for unscheduled contact with a physician, temporary

cessation of a study drug, or associated with pain or impairment of activities of daily life. Full analysis set included all randomized subjects.

End point type	Primary

End point timeframe:

Baseline up to 30 days post cardioversion (or up to 90 days after randomization, if cardioversion was not performed within that time frame)

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	735	721		
Units: subjects				
number (not applicable)	11	13		

Statistical analyses

Statistical analysis title	Comparison of Apixaban and Usual Care

Statistical analysis description:

This was a descriptive study, and there was no formal pre-defined hypothesis testing.

Comparison groups	Apixaban v Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)
Number of subjects included in analysis	1456
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.6851
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3433
upper limit	1.8916

Notes:

[4] - Display exact confidence limits for relative risk and Fisher's exact test for comparisons of two proportions.

Primary: Number of Subjects With All Cause Death

End point title	Number of Subjects With All Cause Death

End point description:

Full analysis set included all randomized subjects.

End point type	Primary

End point timeframe:

Baseline up to 30 days post cardioversion (or up to 90 days after randomization, if cardioversion was not performed within that time frame)

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	753	747		
Units: subjects				
number (not applicable)	2	1		

Statistical analyses

Statistical analysis title	Comparison of Apixaban and Usual Care

Statistical analysis description:

This was a descriptive study, and there was no formal pre-defined hypothesis testing.

Comparison groups	Apixaban v Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)
Number of subjects included in analysis	1500
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	> 0.9999
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.9841
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1866
upper limit	53.9968

Notes:

[5] - Display exact confidence limits for relative risk and Fisher's exact test for comparisons of two proportions.

Secondary: Time to First Attempt of Cardioversion

End point title	Time to First Attempt of Cardioversion

End point description:

Cardioversion was an effective method of converting an abnormally fast heart rate (tachycardia) or other cardiac arrhythmia to normal rhythm using electricity or drugs. First attempt of cardioversion was defined as the first time the subject was admitted for the cardioversion procedure. Full analysis set included all randomized subjects. Here "N" signifies number of subjects evaluable for the specified outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Day of first attempt of cardioversion procedure (Visit 2, up to 130 days)

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	510	511		
Units: days				
median (full range (min-max))	2.0 (1 to 93)	2.0 (1 to 126)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Different Type of Cardioversion Events

End point title	Number of Subjects With Different Type of Cardioversion Events

End point description:

Cardioversion was an effective method of converting an abnormally fast heart rate (tachycardia) or other cardiac arrhythmia to normal rhythm using different type of cardioversion events i.e. electrical and pharmacologic. Electrical cardioversion was a procedure in which an electric current was used to reset the heart's rhythm back to its regular pattern (normal sinus rhythm). Pharmacologic cardioversion, also called chemical cardioversion, used antiarrhythmia medication instead of an electrical shock. Full analysis set included all randomized subjects. Here "N" signifies number of subjects evaluable for the specified outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Day of first attempt of cardioversion procedure (Visit 2, up to 130 days)

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	496	494		
Units: subjects				
Electrical	461	464		
Pharmacologic	35	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Cardioversion Attempt of Subjects

End point title	Number of Cardioversion Attempt of Subjects

End point description:

Cardioversion attempts were defined as the number of times the subject was admitted to hospital for

the cardioversion procedure and not the number of attempts during a single hospital admission. Full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to Day of first attempt of cardioversion procedure (Visit 2, up to 130 days)

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	753	747		
Units: subjects				
No Cardioversion Attempt	234	224		
1 Cardioversion Attempt	488	496		
More than 2 Cardioversion Attempts	31	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Their Rhythm Status

End point title	Number of Subjects With Their Rhythm Status

End point description:

Rhythm status was further distinguished into sinus rhythm, atrial fibrillation and atrial flutter. Sinus rhythm was defined as a normal heartbeat. Atrial fibrillation was an irregular heartbeat (arrhythmia) that can lead to blood clots, stroke, heart failure and other heart-related complications and atrial flutter was a common abnormal heart rhythm that was usually associated with a fast heart rate (100 or more heart beats per minute). Safety data set included all treated subjects (randomized subjects who received at least one dose of study drug). Here "N" signifies number of subjects evaluable for the specified outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Day of first attempt of cardioversion procedure (Visit 2, up to 130 days)

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	719	712		
Units: subjects				
Normal Sinus	1	2		
Atrial Fibrillation	715	704		
Atrial Flutter	3	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospital Stay of Subjects

End point title	Duration of Hospital Stay of Subjects

End point description:

Duration of hospital stay was defined as the number of hours from hospital admission to hospital discharge followed by early cardioversion. Full analysis set included all randomized subjects. Here "N" signifies number of subjects evaluable for the specified outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Day of first attempt of cardioversion procedure (Visit 2, up to 130 days)

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	346		
Units: hours				
median (full range (min-max))	45.36 (0.4 to 747.0)	49.47 (0.6 to 709.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Used Image Guidance Approach

End point title	Number of Subjects Who Used Image Guidance Approach

End point description:

An image-guided approach helped cardioversion earlier than the conventional minimum of 3 weeks of anticoagulation that would normally be required prior to cardioversion. Transesophageal echocardiography (TEE or TOE) and computed tomography (CT) were 2 image-guided approaches that were used in this study. Full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to Day of first attempt of cardioversion procedure (Visit 2, up to 130 days)

End point values	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	753	747		
Units: subjects	383	399		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to 30 days after cardioversion or 90 days after randomization, if cardioversion was not performed

Adverse event reporting additional description:

Same event may appear as adverse event (AE) and serious adverse event (SAE), what is presented are distinct events. Event may be categorized as serious in 1 subject and as non-serious in another subject or 1 subject may have experienced both serious and non-serious event during study. Safety data set included all treated subjects.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Apixaban

Reporting group description:

Subjects with non-valvular atrial fibrillation undergoing cardioversion, received Apixaban orally for 30 days after cardioversion or 90 days after randomization if cardioversion was not performed. The dosing of Apixaban was based on investigator's judgement as per local label for the prevention of stroke and systemic embolism in subjects.

Reporting group title	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)

Reporting group description:

Subjects with non-valvular atrial fibrillation undergoing cardioversion, received parenteral heparin and/or oral Vitamin K antagonist as usual care, orally for 30 days after cardioversion or 90 days after randomization if cardioversion was not performed. The dosing of the parenteral heparin and Vitamin K antagonist was based on individual subject's sensitivity to the drug according to the investigators usual practice.

Serious adverse events	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)	
Total subjects affected by serious adverse events			
subjects affected / exposed	100 / 735 (13.61%)	112 / 721 (15.53%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE LEUKAEMIA			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADENOCARCINOMA			

subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST CANCER			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOMETRIAL CANCER			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO BONE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATE CANCER			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
ARTERIAL HAEMORRHAGE			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTERIOVENOUS FISTULA			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA			

subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 735 (0.00%)	2 / 721 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERNIA			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL HAEMORRHAGE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			

subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	3 / 735 (0.41%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
VAGINAL HAEMORRHAGE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	1 / 735 (0.14%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATELECTASIS			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			

subjects affected / exposed	3 / 735 (0.41%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MEDIASTINAL CYST			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MEDIASTINAL HAEMATOMA			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	2 / 735 (0.27%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY CONGESTION			
subjects affected / exposed	3 / 735 (0.41%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY HYPERTENSION			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY OEDEMA			

subjects affected / exposed	1 / 735 (0.14%)	2 / 721 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY SARCOIDOSIS			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
COMPUTERISED TOMOGRAM CORONARY ARTERY ABNORMAL			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FUNCTIONAL RESIDUAL CAPACITY DECREASED			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ENZYME INCREASED			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERNATIONAL NORMALISED RATIO ABNORMAL			

subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ARTERIAL BYPASS THROMBOSIS			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EYE INJURY			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	2 / 735 (0.27%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAD INJURY			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVERDOSE			

subjects affected / exposed	0 / 735 (0.00%)	3 / 721 (0.42%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC INTRACRANIAL HAEMORRHAGE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR PSEUDOANEURYSM			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
ADENOMATOUS POLYPOSIS COLI			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTROPHIC CARDIOMYOPATHY			
subjects affected / exposed	1 / 735 (0.14%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	2 / 735 (0.27%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

ANGINA PECTORIS			
subjects affected / exposed	2 / 735 (0.27%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTERIOSCLEROSIS CORONARY ARTERY			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	27 / 735 (3.67%)	40 / 721 (5.55%)	
occurrences causally related to treatment / all	0 / 30	0 / 48	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	3 / 735 (0.41%)	6 / 721 (0.83%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL THROMBOSIS			
subjects affected / exposed	0 / 735 (0.00%)	3 / 721 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR DISSOCIATION			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYCARDIA			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			

subjects affected / exposed	5 / 735 (0.68%)	7 / 721 (0.97%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE ACUTE			
subjects affected / exposed	1 / 735 (0.14%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	9 / 735 (1.22%)	7 / 721 (0.97%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIOGENIC SHOCK			
subjects affected / exposed	2 / 735 (0.27%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONGESTIVE CARDIOMYOPATHY			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	2 / 735 (0.27%)	6 / 721 (0.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY STENOSIS			
subjects affected / exposed	1 / 735 (0.14%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC CARDIOMYOPATHY			

subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MITRAL VALVE INCOMPETENCE			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MITRAL VALVE PROLAPSE			
subjects affected / exposed	0 / 735 (0.00%)	3 / 721 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PALPITATIONS			
subjects affected / exposed	1 / 735 (0.14%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDITIS CONSTRICTIVE			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS ARREST			
subjects affected / exposed	2 / 735 (0.27%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS NODE DYSFUNCTION			

subjects affected / exposed	2 / 735 (0.27%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYARRHYTHMIA			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA INDUCED CARDIOMYOPATHY			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRICUSPID VALVE INCOMPETENCE			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
BRAIN INJURY			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL INFARCTION			
subjects affected / exposed	1 / 735 (0.14%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			

subjects affected / exposed	1 / 735 (0.14%)	3 / 721 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEMENTIA			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRESYNCOPE			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	0 / 735 (0.00%)	2 / 721 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 735 (0.00%)	2 / 721 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
HAEMORRHAGIC ANAEMIA			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL HERNIA INCARCERATED			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	2 / 735 (0.27%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	2 / 735 (0.27%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATEMESIS			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOCHEZIA			

subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE PERFORATION			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
MELAENA			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MESENTERIC PANNICULITIS			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMATOUS PANCREATITIS			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGITIS			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PEPTIC ULCER			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PEPTIC ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			

subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CONGESTION			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DECUBITUS ULCER			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC FOOT			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PETECHIAE			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBCUTANEOUS EMPHYSEMA			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 735 (0.14%)	5 / 721 (0.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATURIA			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTRENAL FAILURE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL HAEMORRHAGE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
ADRENAL HAEMORRHAGE			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXIC NODULAR GOITRE			
subjects affected / exposed	2 / 735 (0.27%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
FLANK PAIN			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABSCESS LIMB			

subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	2 / 735 (0.27%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	1 / 735 (0.14%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL SEPSIS			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			

subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	3 / 735 (0.41%)	5 / 721 (0.69%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	1 / 735 (0.14%)	0 / 721 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 735 (0.14%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 735 (0.14%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	0 / 735 (0.00%)	1 / 721 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Apixaban	Parenteral heparin/Oral Vitamin K Antagonist (Usual Care)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 735 (9.52%)	101 / 721 (14.01%)	
Investigations			
INTERNATIONAL NORMALISED RATIO ABNORMAL			
subjects affected / exposed	0 / 735 (0.00%)	19 / 721 (2.64%)	
occurrences (all)	0	41	
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	0 / 735 (0.00%)	27 / 721 (3.74%)	
occurrences (all)	0	30	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	43 / 735 (5.85%)	46 / 721 (6.38%)	
occurrences (all)	43	48	
ATRIAL THROMBOSIS			
subjects affected / exposed	17 / 735 (2.31%)	13 / 721 (1.80%)	
occurrences (all)	17	13	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	15 / 735 (2.04%)	8 / 721 (1.11%)	
occurrences (all)	15	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2016	Simultaneous treatment with both aspirin and a thienopyridine (eg, clopidogrel, ticlopidine, prasugrel) or simultaneous treatment with both aspirin and ticagrelor.

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.

The prioritization of outcome measures is not mentioned in the study documents (Statistical Analysis Plan and Protocol). The prioritization of outcome measures is based on team's discretion.

Notes: