Clinical trial results:
A Randomized, Open-label, Active-controlled Multi-center Study to Evaluate the Safety of Rivaroxaban and Vitamin K Antagonists in Subjects Undergoing Catheter Ablation for Atrial Fibrillation

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-001484-79
Trial protocol	DE GB BE
Global end of trial date	29 October 2014

Results information

Result version number	v1 (current)
This version publication date	09 March 2016
First version publication date	09 March 2016

Trial information

Trial identification

Sponsor protocol code	RIVAROXAFL3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01729871
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Scientific Affairs, LLC
Sponsor organisation address	Antwerpseweg 15-17, B-2340 Beerse, Belgium,
Public contact	Clinical Registry Group-JB BV, Janssen Research and Development, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group-JB BV, Janssen Research and Development, 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	29 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety of rivaroxaban and uninterrupted vitamin K antagonist (VKA) in adult subjects with nonvalvular atrial fibrillation (NVAF) who undergo catheter ablation as measured by post-procedure major bleeding events.

Protection of trial subjects:

The safety assessments included the incidence and severity of adverse events (AEs), bleeding and other events of special interest, clinical laboratory tests (hematology and serum chemistry), electrocardiogram (ECG) and vital signs measurement were assessed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 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	Belgium: 48
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	United Kingdom: 48
Country: Number of subjects enrolled	United States: 77
Worldwide total number of subjects	248
EEA total number of subjects	171

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)	158
From 65 to 84 years	89
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 22 February 2013 to 29 October 2014 in 37 sites of 5 countries.

Pre-assignment

Screening details:

Total 248 subjects were randomized out of which an equal number of subjects were randomized to the uninterrupted rivaroxaban (124 subjects) and uninterrupted VKA (124 subjects) treatment arms.

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

Arm description:

Rivaroxaban 20 milligram orally was taken once-daily preferably with the evening meal for 8-10 weeks.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY 59-7939 (JNJ-39039039)
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Rivaroxaban 20 milligram orally was taken once-daily preferably with the evening meal for 8-10 weeks.

Arm title	Vitamin K Antagonist (VKA)

Arm description:

Dose-adjusted vitamin K antagonist (VKA) to achieve a recommended International Normalized Ratio (INR) of 2.0 to 3.0

Arm type	Active comparator
Investigational medicinal product name	vitamin K antagonist (VKA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose-adjusted vitamin K antagonist (VKA) to achieve a recommended International Normalized Ratio (INR) of 2.0 to 3.0

Number of subjects in period 1	Rivaroxaban	Vitamin K Antagonist (VKA)
Started	124	124
Completed	112	101
Not completed	12	23
Physician decision	-	2
Consent withdrawn by subject	-	3
Other	4	8
Death	-	1
Adverse event	7	7
Noncompliance with study drug	-	1
Protocol deviation	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Rivaroxaban
Reporting group description:	
Rivaroxaban 20 milligram orally was taken once-daily preferably with the evening meal for 8-10 weeks.	
Reporting group title	Vitamin K Antagonist (VKA)
Reporting group description:	
Dose-adjusted vitamin K antagonist (VKA) to achieve a recommended International Normalized Ratio (INR) of 2.0 to 3.0	

Reporting group values	Rivaroxaban	Vitamin K Antagonist (VKA)	Total
Number of subjects	124	124	248
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	85	73	158
From 65 to 84 years	38	51	89
85 years and over	1	0	1
Title for AgeContinuous Units: years			
arithmetic mean	58.6	60.5	
standard deviation	± 9.86	± 10.51	-
Title for Gender Units: subjects			
Female	38	34	72
Male	86	90	176

End points

End points reporting groups

Reporting group title	Rivaroxaban

Reporting group description:

Rivaroxaban 20 milligram orally was taken once-daily preferably with the evening meal for 8-10 weeks.

Reporting group title	Vitamin K Antagonist (VKA)

Reporting group description:

Dose-adjusted vitamin K antagonist (VKA) to achieve a recommended International Normalized Ratio (INR) of 2.0 to 3.0

Subject analysis set title	Per-protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol analysis set included all randomized subjects who took at least 1 dose of study drug and underwent the catheter ablation procedure.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The overall treatment-emergent adverse event (TEAEs), serious adverse events, and adverse events leading to discontinuation are based on 244 participants who were randomized and received at least 1 dose of study drug.

Primary: Number of Subjects With Incidence of Post-Procedure Major Bleeding Events

End point title	Number of Subjects With Incidence of Post-Procedure Major Bleeding Events[1]

End point description:

Post-procedure major bleeding events include Thrombolysis in Myocardial Infarction (TIMI), International Society on Thrombosis and Haemostasis (ISTH) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) Severe/life threatening bleeding.

End point type	Primary

End point timeframe:

Up to 30 plus or minus (+-) 5 days after the catheter ablation procedure

Notes:

[1] - 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: Statistical analysis was not reported for this endpoint as inferential analysis was not performed as planned.

End point values	Rivaroxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114[2]	107[3]		
Units: Participants				
number (not applicable)				
TIMI Major Bleeding	0	0		
ISTH Major Bleeding	0	1		
GUSTO Severe/Life Threatening Bleeding	0	0		

Notes:

[2] - Per Protocol Analysis Set

[3] - Per Protocol Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Composite Endpoint of Myocardial Infarction (MI), Ischemic Stroke, Non-Central Nervous System (non-CNS) Systemic Embolism and Vascular Death

End point title	Number of Subjects With Composite Endpoint of Myocardial Infarction (MI), Ischemic Stroke, Non-Central Nervous System (non-CNS) Systemic Embolism and Vascular Death

End point description:

The composite endpoint include Myocardial Infarction (MI), Ischemic Stroke, Non-Central Nervous System (non-CNS) Systemic Embolism and Vascular Death.

End point type	Secondary

End point timeframe:

Up to 30 plus or minus (+-) 5 days after the catheter ablation procedure

End point values	Rivaroxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114[4]	107[5]		
Units: Participants				
number (not applicable)	0	2		

Notes:

[4] - Per Protocol Analysis Set

[5] - Per Protocol Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Myocardial Infarction (MI)

End point title	Number of Subjects With Myocardial Infarction (MI)

End point description:

The MI was defined as clinical symptoms consistent with myocardial ischemia and cardiac biomarker elevation greater than the site's upper limit of normal (ULN) or development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram (ECG) or autopsy confirmation, OR Creatine kinase-muscle and brain subunit [or creatine kinase (CK) in the absence of CK-MB] greater than (>) 3 or 5 or 10 x ULN for samples obtained within 24 hours of the procedure if the baseline values were normal or at least a 50 percent (%) increase over elevated baseline values that were stable or decreasing or development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram. Symptoms of cardiac ischemia were not required.

End point type	Secondary

End point timeframe:

Up to 30 plus or minus (+-) 5 days after the catheter ablation procedure

End point values	Rivaroxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114[6]	107[7]		
Units: Participants				
number (not applicable)	0	0		

Notes:

[6] - Per Protocol Analysis Set

[7] - Per Protocol Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Ischemic Stroke

End point title	Number of Subjects With Ischemic Stroke

End point description:

Stroke was defined as a new, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause that was not reversible within 24 hours and not due to a readily identifiable cause such as a tumor or seizure.

End point type	Secondary

End point timeframe:

Up to 30 plus or minus (+-) 5 days after the catheter ablation procedure

End point values	Rivaroxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114[8]	107[9]		
Units: Participants				
number (not applicable)	0	1		

Notes:

[8] - Per Protocol Analysis Set

[9] - Per Protocol Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Non-Central Nervous System (Non-CNS) Systemic Embolism

End point title	Number of Subjects With Non-Central Nervous System (Non-CNS) Systemic Embolism

End point description:

The Non-CNS systemic embolism was defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms, (example; trauma, atherosclerosis, instrumentation).

End point type	Secondary

End point timeframe:

Up to 30 plus or minus (+-) 5 days after the catheter ablation procedure

End point values	Rivaroxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114[10]	107[11]		
Units: Participants				
number (not applicable)	0	0		

Notes:

[10] - Per Protocol Analysis Set

[11] - Per Protocol Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Vascular Death

End point title	Number of Subjects With Vascular Death

End point description:

Any death that was not clearly non-vascular. Examples of vascular death included deaths due to bleeding, Myocardial Infarction (MI), stroke, heart failure and arrhythmias.

End point type	Secondary

End point timeframe:

Up to 30 plus or minus (+-) 5 days after the catheter ablation procedure

End point values	Rivaroxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114[12]	107[13]		
Units: Participants				
number (not applicable)	0	1		

Notes:

[12] - Per Protocol Analysis Set

[13] - Per Protocol Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Screeing up to week 8-10	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Rivaroxaban
Reporting group description: Rivaroxaban 20 milligram orally was taken once-daily preferably with the evening meal for 8-10 weeks	
Reporting group title	Vitamin K Antagonist (VKA)
Reporting group description: Dose-adjusted vitamin K antagonist (VKA) to achieve a recommended International Normalized Ratio (INR) of 2.0 to 3.0	

Serious adverse events	Rivaroxaban	Vitamin K Antagonist (VKA)	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 123 (13.82%)	20 / 121 (16.53%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Investigations			
International Normalised Ratio Increased			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Excoriation			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon Rupture			

subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Pseudoaneurysm			
subjects affected / exposed	2 / 123 (1.63%)	2 / 121 (1.65%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriovenous Fistula			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	3 / 123 (2.44%)	5 / 121 (4.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Tachycardia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 123 (1.63%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			

subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericarditis			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Arrest			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Tachycardia			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Atonic Seizures			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of Consciousness			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			

subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Puncture Site Haemorrhage			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 123 (1.63%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic Pain			

subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stenosis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid Overload			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
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: 0 %

Non-serious adverse events	Rivaroxaban	Vitamin K Antagonist (VKA)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 123 (64.23%)	66 / 121 (54.55%)	
Vascular disorders			
Aortic Calcification			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	9 / 123 (7.32%)	9 / 121 (7.44%)	
occurrences (all)	10	10	
Hypotension			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Catheter Site Haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Catheter Site Pain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Chest Discomfort			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Chest Pain			
subjects affected / exposed	3 / 123 (2.44%)	5 / 121 (4.13%)	
occurrences (all)	3	6	
Chills			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Discomfort			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Fatigue			

subjects affected / exposed	8 / 123 (6.50%)	2 / 121 (1.65%)	
occurrences (all)	8	3	
Local Swelling			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Medical Device Complication			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 123 (1.63%)	0 / 121 (0.00%)	
occurrences (all)	2	0	
Puncture Site Reaction			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	4 / 123 (3.25%)	4 / 121 (3.31%)	
occurrences (all)	4	4	
Vessel Puncture Site Haematoma			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Vessel Puncture Site Haemorrhage			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 123 (0.81%)	6 / 121 (4.96%)	
occurrences (all)	1	6	
Diaphragmatic Paralysis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Dysphonia			

subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			
subjects affected / exposed	1 / 123 (0.81%)	5 / 121 (4.13%)	
occurrences (all)	1	5	
Epistaxis			
subjects affected / exposed	2 / 123 (1.63%)	1 / 121 (0.83%)	
occurrences (all)	2	1	
Haemoptysis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Nasal Congestion			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences (all)	1	1	
Oropharyngeal Pain			
subjects affected / exposed	4 / 123 (3.25%)	3 / 121 (2.48%)	
occurrences (all)	4	3	
Productive Cough			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Investigations			
Bleeding Time Prolonged			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Blood Magnesium Decreased			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Ejection Fraction Decreased			

subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
International Normalised Ratio Increased			
subjects affected / exposed	0 / 123 (0.00%)	2 / 121 (1.65%)	
occurrences (all)	0	2	
Laboratory Test Abnormal			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Weight Increased			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 123 (0.81%)	2 / 121 (1.65%)	
occurrences (all)	1	2	
Excoriation			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Overdose			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Post Procedural Complication			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Post Procedural Haematoma			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Procedural Hypertension			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Procedural Nausea			

subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Procedural Pain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Vascular Pseudoaneurysm			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences (all)	1	1	
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	2 / 123 (1.63%)	0 / 121 (0.00%)	
occurrences (all)	2	0	
Arrhythmia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Arrhythmia Supraventricular			
subjects affected / exposed	2 / 123 (1.63%)	0 / 121 (0.00%)	
occurrences (all)	3	0	
Atrial Fibrillation			
subjects affected / exposed	10 / 123 (8.13%)	10 / 121 (8.26%)	
occurrences (all)	11	11	
Atrial Tachycardia			
subjects affected / exposed	1 / 123 (0.81%)	4 / 121 (3.31%)	
occurrences (all)	1	4	
Atrial Thrombosis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Cardiac Failure Congestive			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	3 / 123 (2.44%)	0 / 121 (0.00%)	
occurrences (all)	3	0	
Pericardial Effusion			
subjects affected / exposed	1 / 123 (0.81%)	2 / 121 (1.65%)	
occurrences (all)	1	2	

Pericarditis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Sinus Arrhythmia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Sinus Bradycardia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Supraventricular Tachycardia			
subjects affected / exposed	0 / 123 (0.00%)	2 / 121 (1.65%)	
occurrences (all)	0	2	
Ventricular Extrasystoles			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 123 (2.44%)	1 / 121 (0.83%)	
occurrences (all)	3	1	
Dizziness Exertional			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Dizziness Postural			
subjects affected / exposed	1 / 123 (0.81%)	2 / 121 (1.65%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	5 / 123 (4.07%)	4 / 121 (3.31%)	
occurrences (all)	5	4	
Hypoaesthesia			
subjects affected / exposed	3 / 123 (2.44%)	0 / 121 (0.00%)	
occurrences (all)	3	0	
Hypokinesia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Migraine			

subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	0 / 123 (0.00%)	2 / 121 (1.65%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
External Ear Inflammation			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Meniere's Disease			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 123 (0.00%)	2 / 121 (1.65%)	
occurrences (all)	0	2	
Eye disorders			
Eye Haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Retinal Vascular Occlusion			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Abdominal Pain			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences (all)	1	1	
Abdominal Pain Upper			
subjects affected / exposed	1 / 123 (0.81%)	3 / 121 (2.48%)	
occurrences (all)	1	3	
Constipation			

subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	3 / 123 (2.44%)	2 / 121 (1.65%)	
occurrences (all)	4	2	
Dry Mouth			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences (all)	1	1	
Epigastric Discomfort			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Eructation			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Frequent Bowel Movements			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Gingival Bleeding			
subjects affected / exposed	2 / 123 (1.63%)	0 / 121 (0.00%)	
occurrences (all)	2	0	
Gingival Inflammation			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Lip Disorder			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Mouth Haemorrhage			

subjects affected / exposed	2 / 123 (1.63%)	0 / 121 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	4 / 123 (3.25%)	3 / 121 (2.48%)	
occurrences (all)	4	3	
Oesophageal Irritation			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Stomatitis Haemorrhagic			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Ecchymosis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 123 (0.00%)	2 / 121 (1.65%)	
occurrences (all)	0	3	
Hyperhidrosis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Rash Generalised			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Sunburn			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			

subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	2 / 123 (1.63%)	0 / 121 (0.00%)	
occurrences (all)	2	0	
Renal Failure Acute			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Urinary Retention			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Back Pain			
subjects affected / exposed	6 / 123 (4.88%)	2 / 121 (1.65%)	
occurrences (all)	6	2	
Groin Pain			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences (all)	1	1	
Joint Swelling			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Muscle Spasms			
subjects affected / exposed	2 / 123 (1.63%)	0 / 121 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Musculoskeletal Discomfort			

subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal Stiffness			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Neck Pain			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences (all)	1	1	
Pain in Extremity			
subjects affected / exposed	2 / 123 (1.63%)	1 / 121 (0.83%)	
occurrences (all)	2	1	
Infections and infestations			
Acute Tonsillitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences (all)	1	1	
Cystitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Diverticulitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Ear Infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis Viral			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Herpes Zoster			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	4 / 123 (3.25%)	3 / 121 (2.48%)	
occurrences (all)	4	3	

Pulpitis Dental			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Respiratory Tract Infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Septic Shock			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	
occurrences (all)	1	1	
Tooth Abscess			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	
Urinary Tract Infection			
subjects affected / exposed	5 / 123 (4.07%)	1 / 121 (0.83%)	
occurrences (all)	5	1	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Gout			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2013	An addition was made to the inclusion criteria to indicate that suitability for anticoagulant should be defined by a CHADS 2 or CHA 2 DS 2 VASc score ≥1, uncontrolled hypertension was added to the list of conditions for which anticoagulant therapy would be contraindicated and Hepatic impairment, as an exclusion criteria for subjects, was defined as alanine aminotransferase (ALT) >5 x upper limits normal (ULN) or ALT >3 x ULN plus total bilirubin >2 x ULN, using laboratory values from the screening period.
31 May 2013	At the request of the Food and Drug Administration (FDA), rheumatic heart disease was added to the list of examples of conditions of cardiac valvular disease that does not meet the NVAF definition in the exclusion criteria. Changes were incorporated to clarify adverse event reporting requirements (all adverse events, serious or non-serious should be collected). Definitions of major bleeding and non-major bleeding were replaced with Thrombosis in Myocardial Infarction (TIMI) bleeding event for consistent classification of bleeding events by investigators. Definition of persistent NVAF was changed to remove the phrase <1 week. Rivaroxaban drug-drug interaction information was provided as an Attachment to the Protocol.
05 November 2013	Change was made to allow subjects who met 1 of 3 protocol specified conditions to have their catheter ablation procedure performed after 1 to 7 days of exposure to randomized study drug (instead of waiting for 4 to 5 weeks after receiving the first dose of randomized study drug to undergo the ablation procedure). In order to more closely represent the patient population in real-world clinical practice, subjects with long standing persistent (≥1 year) NVAF were no longer excluded from participation in the study. In order to more closely represent the patient population in real-world clinical practice, subjects scheduled for a repeat catheter ablation procedure for NVAF were no longer excluded from participation in the study. In order to more closely represent the patient population in real-world clinical practice, for subjects taking acetylsalicylic acid (ASA) > 100 mg per day at screening, an allowance was made for a one time dose adjustment (reduction) to ≤ 100 mg ASA starting at randomization. In order to reduce unnecessary procedures, subjects with a recent usual care physical examination (within 4 weeks prior to screening visit) were not required to have another physical examination at screening.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported