Clinical trial results:
Randomised Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of an uninterrupted periproCedUral antIcoagulation sTrategy (The RE-CIRCUIT Trial)

Summary

EudraCT number	2014-003890-40
Trial protocol	IT ES NL DE BE GB FR
Global end of trial date	14 November 2016

Results information

Result version number	v1 (current)
This version publication date	11 November 2017
First version publication date	11 November 2017

Trial information

Trial identification

Sponsor protocol code	1160.204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02348723
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, +1 8002430127, clintriage.rdg@boehringer-ingelheim.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	16 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2016
Global end of trial reached?	Yes
Global end of trial date	14 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to assess the safety of an uninterrupted dabigatran etexilate periprocedural anticoagulant regimen compared with an uninterrupted periprocedural warfarin regimen in non-valvular atrial fibrillation (NVAF) patients undergoing ablation of AF in a PROBE (prospective, randomised, open label, blinded endpoint) active-controlled trial.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study.
All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 47
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Italy: 61
Country: Number of subjects enrolled	Japan: 115
Country: Number of subjects enrolled	Netherlands: 78
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United Kingdom: 71
Country: Number of subjects enrolled	United States: 116
Worldwide total number of subjects	704
EEA total number of subjects	361

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)	464
From 65 to 84 years	240
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were randomly assigned to dabigatran etexilate 150 mg twice daily or warfarin in a 1:1 ratio and remained on this treatment for the duration of the trial. 678 subjects were randomised and 676 were treated.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

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

Blinding implementation details:

Open-label trial; study had blinded endpoint adjudication

Arms

Are arms mutually exclusive?	Yes
Arm title	Dabigatran Etexilate 150 mg

Arm description:

Patients receiving Dabigatran Etexilate 150 mg capsule orally twice daily (BID); 1 capsule 150 mg twice daily (total daily dose 300 mg)

Arm type	Experimental
Investigational medicinal product name	Pradaxa®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule 150 mg twice daily (total daily dose 300 mg)

Arm title	Warfarin

Arm description:

Patients receiving Warfarin tablet orally; 1, 3, and 5 mg (dose adjusted to International normalized ratio (INR) target range)

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

Dosage and administration details:

1, 3, and 5 mg (dose adjusted to International normalized ratio (INR) target range

Number of subjects in period 1[1]	Dabigatran Etexilate 150 mg	Warfarin
Started	338	338
Completed	310	312
Not completed	28	26
Non-compliant with Protocol	1	-
Reason other than specified	1	1
Adverse event, non-fatal	3	1
No ablation	21	20
Consent withdrawn by subject	1	3
Lost to follow-up	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Dabigatran Etexilate 150 mg
Reporting group description:	
Patients receiving Dabigatran Etexilate 150 mg capsule orally twice daily (BID); 1 capsule 150 mg twice daily (total daily dose 300 mg)	
Reporting group title	Warfarin
Reporting group description:	
Patients receiving Warfarin tablet orally; 1, 3, and 5 mg (dose adjusted to International normalized ratio (INR) target range)	

Reporting group values	Dabigatran Etexilate 150 mg	Warfarin	Total
Number of subjects	338	338	676
Age categorical Units: Subjects			

Age Continuous			
Treated set (TS): The treated set (TS) included all patients who were randomised and subsequently treated with at least 1 tablet/capsule.			
Units: years			
arithmetic mean	59.2	59.4	
standard deviation	± 10.33	± 10.29	-
Gender, Male/Female			
Treated set (TS): The treated set (TS) included all patients who were randomised and subsequently treated with at least 1 tablet/capsule.			
Units: Subjects			
Female	93	81	174
Male	245	257	502

End points

End points reporting groups

Reporting group title	Dabigatran Etexilate 150 mg
Reporting group description:	
Patients receiving Dabigatran Etexilate 150 mg capsule orally twice daily (BID); 1 capsule 150 mg twice daily (total daily dose 300 mg)	
Reporting group title	Warfarin
Reporting group description:	
Patients receiving Warfarin tablet orally; 1, 3, and 5 mg (dose adjusted to International normalized ratio (INR) target range)	

Primary: Incidence of major bleeding events (MBEs), as defined by the International Society on Thrombosis and Haemostasis (ISTH)

End point title	Incidence of major bleeding events (MBEs), as defined by the International Society on Thrombosis and Haemostasis (ISTH)
End point description:	
Major bleeds were defined according to the ISTH definition of a major bleed, as follows • Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or • Bleeding associated with a reduction in haemoglobin of at least 2 g/dL (1.24 mmol/L), or leading to transfusion of 2 or more units of blood or packed cells. and/or • Fatal bleed Point estimates for the incidence of ISTH MBEs and their 2-sided 95% confidence intervals (CI), based on the normal approximation of independent binomial distribution without stratification, are presented. These are based on adjudicated data (blinded evaluation). The ablation set (AS) was the primary analysis set and included all patients in the TS who started the ablation procedure.	
End point type	Primary
End point timeframe:	
during and up to 2 months post-ablation	

End point values	Dabigatran Etexilate 150 mg	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317[1]	318[2]		
Units: percentage of participants				
number (confidence interval 95%)	1.6 (0.2 to 2.9)	6.9 (4.1 to 9.7)		

Notes:

[1] - AS

[2] - AS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The risk difference between dabigatran etexilate vs. warfarin, its 2-sided 95% CI, and corresponding p-value are presented.	
Comparison groups	Dabigatran Etexilate 150 mg v Warfarin
Number of subjects included in analysis	635

Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0009
Method	Chi-squared
Parameter estimate	Risk Difference (RD) %
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	-2.2

Secondary: Incidence of the composite of stroke, systemic embolism, or transient ischemic attack (TIA)

End point title	Incidence of the composite of stroke, systemic embolism, or transient ischemic attack (TIA)

End point description:

Stroke was defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction. Systemic embolism was defined as an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts) and was to be documented by angiography, surgery, scintigraphy or autopsy. Transient ischemic attack was defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction. Percentage of patients with composite of stroke, systemic embolism, or transient ischemic attack (TIA) is presented.
These are based on adjudicated data (blinded evaluation)

End point type	Secondary

End point timeframe:

during and up to 2 months post-ablation

End point values	Dabigatran Etexilate 150 mg	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317[3]	318[4]		
Units: percentage of participants				
number (not applicable)	0.0	0.3		

Notes:

[3] - AS

[4] - AS

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Minor bleeding events

End point title	Incidence of Minor bleeding events

End point description:

Minor bleeds were clinical bleeds that did not fulfil the criteria for major bleeds. Percentage of patients with Minor bleeding events are presented.
These are based on adjudicated data (blinded evaluation)

End point type	Secondary

End point timeframe:

during and up to 2 months post-ablation

End point values	Dabigatran Etexilate 150 mg	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317[5]	318[6]		
Units: percentage of participants				
number (not applicable)	18.6	17.0		

Notes:

[5] - AS

[6] - AS

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of ISTH MBE, stroke, systemic embolism, or TIA (composite endpoint combining safety and efficacy

End point title	Incidence of ISTH MBE, stroke, systemic embolism, or TIA (composite endpoint combining safety and efficacy

End point description:

Percentage of patients with ISTH MBE, stroke, systemic embolism, or TIA (composite endpoint combining safety and efficacy) are presented.
These are based on adjudicated data (blinded evaluation).

End point type	Secondary

End point timeframe:

during and up to 2 months post-ablation

End point values	Dabigatran Etexilate 150 mg	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317[7]	318[8]		
Units: percentage of participants				
number (not applicable)	1.6	7.2		

Notes:

[7] - AS

[8] - AS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse events which occurred after the first dose of trial medication up to 6 days after the last dose of trial medication; up to 225 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Dabigatran Etexilate 150 mg

Reporting group description:

Patients receiving Dabigatran Etexilate 150 mg capsule orally twice daily (BID); 1 capsule 150 mg twice daily (total daily dose 300 mg)

Reporting group title	Warfarin

Reporting group description:

Patients receiving Warfarin tablet orally; 1, 3, and 5 mg (dose adjusted to International normalized ratio (INR) target range)

Serious adverse events	Dabigatran Etexilate 150 mg	Warfarin	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 338 (18.64%)	75 / 338 (22.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 338 (0.00%)	6 / 338 (1.78%)	
occurrences causally related to treatment / all	0 / 0	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system neoplasm			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 338 (0.30%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyp			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
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			
Cardiac function disturbance postoperative			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac procedure complication			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Craniocerebral injury			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site haemorrhage			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 338 (0.00%)	4 / 338 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm ruptured			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Bleeding time prolonged			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 338 (1.78%)	13 / 338 (3.85%)	
occurrences causally related to treatment / all	0 / 6	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	20 / 338 (5.92%)	19 / 338 (5.62%)	
occurrences causally related to treatment / all	0 / 26	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	2 / 338 (0.59%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	2 / 338 (0.59%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 338 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	3 / 338 (0.89%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 338 (0.30%)	4 / 338 (1.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 338 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	2 / 338 (0.59%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
subjects affected / exposed	1 / 338 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	2 / 338 (0.59%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			

subjects affected / exposed	2 / 338 (0.59%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	3 / 338 (0.89%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
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 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
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 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			

subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral nerve paresis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phrenic nerve paralysis			
subjects affected / exposed	1 / 338 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			

subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal pain			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 338 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 338 (0.59%)	0 / 338 (0.00%)	

occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Diabetic ketoacidosis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 338 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 338 (0.30%)	0 / 338 (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	1 / 338 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Dabigatran Etexilate 150 mg	Warfarin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 338 (20.12%)	65 / 338 (19.23%)	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	40 / 338 (11.83%)	38 / 338 (11.24%)	
occurrences (all)	52	64	
Palpitations			
subjects affected / exposed	16 / 338 (4.73%)	19 / 338 (5.62%)	
occurrences (all)	24	21	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	18 / 338 (5.33%)	14 / 338 (4.14%)	
occurrences (all)	18	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2015	Changes introduced by the revision included the following: 1] The use of the dabigatran reversal agent was introduced for the management of haemorrhagic complications and emergency surgery. 2] The collection of information regarding use of the reversal agent was specified. 3] Clarification was provided that assessments of Visit 3 were to be performed before the start of the ablation procedure 4] The exclusion criterion regarding left atrium size was modified. 5] Clarification was provided that a baseline INR measurement was to be performed in patients randomised to warfarin. 6] Retrospective central assessment of trans-oesophageal echocardiography was removed from the trial procedures. 7] For the definition of the endpoint stroke, wording was added that had been omitted in the Clinical trial protocol. 8] Clarification was provided that a baseline INR measurement was to be performed in patients randomised to warfarin. 9] Clarification was provided on how CrCl was to be calculated based on the availability of weight.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported