Clinical trial results:
A prospective, randomized, open-label, parallel-group, active-controlled, multicenter study exploring the efficacy and safety of once-daily oral rivaroxaban (BAY59-7939) compared with that of dose-adjusted oral vitamin K antagonist (VKA) for the prevention of stroke and non-central nervous system systemic embolism in subjects with non-valvular atrial fibrillation scheduled for cardioversion

Summary

EudraCT number	2011-002234-39
Trial protocol	FI PT ES NL DE GR BE GB IT DK
Global end of trial date	24 January 2014

Results information

Result version number	v2
This version publication date	24 July 2016
First version publication date	26 April 2015
Version creation reason	• Correction of full data set control of data entry

Trial information

Trial identification

Sponsor protocol code	BAY59-7939/15693

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01674647
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, D-51368, Germany,
Public contact	Clinical Trials Contact, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Clinical Trials Contact, Bayer AG, clinical-trials-contact@bayer.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	11 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy and safety objectives were to explore the efficacy of rivaroxaban compared with that of dose-adjusted VKA in the prevention of the events with regard to the combined efficacy endpoint of all stroke or transient ischemic attack (TIA), non-central nervous system (CNS) systemic embolism, myocardial infarction (MI), and cardiovascular death in subjects with atrial fibrillation (AF) scheduled for cardioversion; and to explore the safety of rivaroxaban compared with dose-adjusted VKA with regard to the safety endpoint of major bleeding events in subjects with AF scheduled for cardioversion.

Protection of trial subjects:

All clinical work conducted in this study was subjected to the rules of Good Clinical Practice and under the guidelines of Declaration of Helsinki. Participating subjects or their legally authorized representative signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2012
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	Portugal: 62
Country: Number of subjects enrolled	Spain: 84
Country: Number of subjects enrolled	United Kingdom: 117
Country: Number of subjects enrolled	Netherlands: 82
Country: Number of subjects enrolled	Belgium: 108
Country: Number of subjects enrolled	Denmark: 160
Country: Number of subjects enrolled	Finland: 84
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Germany: 120
Country: Number of subjects enrolled	Greece: 23
Country: Number of subjects enrolled	Italy: 156
Country: Number of subjects enrolled	United States: 290
Country: Number of subjects enrolled	South Africa: 93

Country: Number of subjects enrolled	Singapore: 20
Country: Number of subjects enrolled	Canada: 74
Country: Number of subjects enrolled	China: 65
Worldwide total number of subjects	1584
EEA total number of subjects	1042

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)	696
From 65 to 84 years	858
85 years and over	30

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 141 centers (involving 144 investigators) in Europe, South Africa, North America, and Asia Pacific.

Pre-assignment

Screening details:

Overall, 1584 subjects were screened and 80 subjects did not complete or pass screening. 1504 subjects were randomized; 1002 were assigned to rivaroxaban and 502 to Vitamin K antagonist (VKA).

Pre-assignment period milestones

Number of subjects started	1584
Number of subjects completed	1504

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 7
Reason: Number of subjects	Screening failure: 71
Reason: Number of subjects	Adverse event: 2

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Rivaroxaban (Xarelto; BAY59-7939)

Arm description:

Subjects randomized to treatment with rivaroxaban received rivaroxaban 20 milligram (mg) orally once daily. Subjects with moderate renal impairment [i.e., Creatinine clearance (CrCl) of 30 to 49 milliliter per minute (mL/min), inclusive] at screening received the adjusted dose of 15 mg once daily. The duration of the treatment period for a given subject depended on the cardioversion strategy. For subjects in the Direct Cardioversion Strategy, the cardioversion procedure was performed within 1-5 days after randomization. Rivaroxaban was given for 1-5 days before planned direct cardioversion and for 42 days thereafter. Subjects in the Delayed Cardioversion Strategy received rivaroxaban for 21 (+4) to 56 (+4) days prior to cardioversion and for 42 days thereafter.

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

Dosage and administration details:

Rivaroxaban 20 mg orally once daily; subjects with moderate renal impairment [i.e., CrCl of 30 to 49 mL/min, inclusive] received the adjusted dose of 15 mg orally once daily.

Arm title	Vitamin K antagonist (VKA)

Arm description:

Subjects assigned to treatment with VKA received VKA orally once daily titrated to a target INR of 2.5 (range 2.0-3.0, inclusive). The specific VKA was assigned by the investigator according to the local standard of practice. For subjects randomized to receive VKA, the investigator assessed if a parenteral

anticoagulant drug, particularly prior to cardioversion, was needed as bridging therapy with VKA as standard of care (until target INR was achieved). The duration depended on the cardioversion strategy. For subjects in the Direct Cardioversion Strategy, the cardioversion procedure was performed within 1-5 days after randomization. VKA was given for 1-5 days before cardioversion and for 42 days thereafter. Subjects in the Delayed Cardioversion Strategy received VKA for 21 (+4) to 56 (+4) days before cardioversion and for 42 days thereafter.

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

Dosage and administration details:

Subjects assigned to treatment with VKA received VKA orally once daily titrated to a target INR of 2.5 (range 2.0-3.0, inclusive). The specific VKA (eg, warfarin) was assigned by the investigator according to the local standard of practice.

Number of subjects in period 1[1]	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)
Started	1002	502
subjects received treatment	988	499
Completed	846	400
Not completed	156	102
Consent withdrawn by subject	19	16
Physician decision	3	1
Logistical difficulties	5	8
Treatment failure	-	14
Protocol violation	56	36
Death	4	1
Switching to other therapy	5	2
Non-compliance with study drug	3	-
Adverse event	60	22
Efficacy outcome reached	-	1
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: Due to screen failure, not all enrolled subjects were randomized and treated with study drugs.

Period 2

Period 2 title	30-day safety follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	No
Arm title	Rivaroxaban (Xarelto; BAY59-7939)

Arm description:

After the 42 day treatment period subsequent to cardioversion, the investigator assessed whether or not long-term anticoagulation was warranted and treated the subject according to standard of care. The subject then entered the 30-day follow-up period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Vitamin K antagonist (VKA)

Arm description:

After the 42 day treatment period subsequent to cardioversion, the investigator assessed whether or not long-term anticoagulation was warranted and treated the subject according to standard of care. The subject then entered the 30-day follow-up period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)
Started	982	487
Completed	924	446
Not completed	58	41
Consent withdrawn by subject	7	8
Logistical difficulties	1	3
Protocol violation	39	22
Death	3	2
Non-compliance with study drug	-	1
Lost to follow-up	8	5

Baseline characteristics

Reporting groups	
Reporting group title	Rivaroxaban (Xarelto; BAY59-7939)

Reporting group description:

Subjects randomized to treatment with rivaroxaban received rivaroxaban 20 milligram (mg) orally once daily. Subjects with moderate renal impairment [i.e., Creatinine clearance (CrCl) of 30 to 49 milliliter per minute (mL/min), inclusive] at screening received the adjusted dose of 15 mg once daily. The duration of the treatment period for a given subject depended on the cardioversion strategy. For subjects in the Direct Cardioversion Strategy, the cardioversion procedure was performed within 1-5 days after randomization. Rivaroxaban was given for 1-5 days before planned direct cardioversion and for 42 days thereafter. Subjects in the Delayed Cardioversion Strategy received rivaroxaban for 21 (+4) to 56 (+4) days prior to cardioversion and for 42 days thereafter.

Reporting group title	Vitamin K antagonist (VKA)

Reporting group description:

Subjects assigned to treatment with VKA received VKA orally once daily titrated to a target INR of 2.5 (range 2.0-3.0, inclusive). The specific VKA was assigned by the investigator according to the local standard of practice. For subjects randomized to receive VKA, the investigator assessed if a parenteral anticoagulant drug, particularly prior to cardioversion, was needed as bridging therapy with VKA as standard of care (until target INR was achieved). The duration depended on the cardioversion strategy. For subjects in the Direct Cardioversion Strategy, the cardioversion procedure was performed within 1-5 days after randomization. VKA was given for 1-5 days before cardioversion and for 42 days thereafter. Subjects in the Delayed Cardioversion Strategy received VKA for 21 (+4) to 56 (+4) days before cardioversion and for 42 days thereafter.

Reporting group values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)	Total
Number of subjects	1002	502	1504
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	64.9	64.7	
standard deviation	± 10.6	± 10.5	-
Gender categorical			
Units: Subjects			
Female	275	135	410
Male	727	367	1094
CHADS 2 score			
Predicts clinical risk of stroke and thromboembolism in atrial fibrillation incorporating these risk factors: Congestive heart failure, Hypertension, Age [greater than or equal to (>=)75 years], Diabetes mellitus, Stroke/transient ischemic attack. Total score ranged from 0 to 6, with "0"= low risk, "1"= moderate risk and ">=2"= high risk.			
Units: units on scale			
arithmetic mean	1.3	1.4	
standard deviation	± 1.1	± 1.1	-
CHA 2 DS 2 VASc score			
Predicts clinical risk of stroke and thromboembolism in atrial fibrillation incorporating these risk factors: Congestive heart failure/left ventricular dysfunction, Hypertension, Age >= 75 years, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism, Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), Age 65 - 74 years, Sex category (i.e., female). Total score ranged from 0 to 8, with "0" (or 1 if female only)= Low risk ; "1" (except for female gender alone)= moderate risk and ">=2"=high risk.			
Units: units on scale			

arithmetic mean	2.3	2.3	
standard deviation	± 1.6	± 1.6	-

End points

End points reporting groups

Reporting group title	Rivaroxaban (Xarelto; BAY59-7939)

Reporting group description:

Subjects randomized to treatment with rivaroxaban received rivaroxaban 20 milligram (mg) orally once daily. Subjects with moderate renal impairment [i.e., Creatinine clearance (CrCl) of 30 to 49 milliliter per minute (mL/min), inclusive] at screening received the adjusted dose of 15 mg once daily. The duration of the treatment period for a given subject depended on the cardioversion strategy. For subjects in the Direct Cardioversion Strategy, the cardioversion procedure was performed within 1-5 days after randomization. Rivaroxaban was given for 1-5 days before planned direct cardioversion and for 42 days thereafter. Subjects in the Delayed Cardioversion Strategy received rivaroxaban for 21 (+4) to 56 (+4) days prior to cardioversion and for 42 days thereafter.

Reporting group title	Vitamin K antagonist (VKA)

Reporting group description:

Subjects assigned to treatment with VKA received VKA orally once daily titrated to a target INR of 2.5 (range 2.0-3.0, inclusive). The specific VKA was assigned by the investigator according to the local standard of practice. For subjects randomized to receive VKA, the investigator assessed if a parenteral anticoagulant drug, particularly prior to cardioversion, was needed as bridging therapy with VKA as standard of care (until target INR was achieved). The duration depended on the cardioversion strategy. For subjects in the Direct Cardioversion Strategy, the cardioversion procedure was performed within 1-5 days after randomization. VKA was given for 1-5 days before cardioversion and for 42 days thereafter. Subjects in the Delayed Cardioversion Strategy received VKA for 21 (+4) to 56 (+4) days before cardioversion and for 42 days thereafter.

Reporting group title	Rivaroxaban (Xarelto; BAY59-7939)

Reporting group description:

After the 42 day treatment period subsequent to cardioversion, the investigator assessed whether or not long-term anticoagulation was warranted and treated the subject according to standard of care. The subject then entered the 30-day follow-up period.

Reporting group title	Vitamin K antagonist (VKA)

Reporting group description:

After the 42 day treatment period subsequent to cardioversion, the investigator assessed whether or not long-term anticoagulation was warranted and treated the subject according to standard of care. The subject then entered the 30-day follow-up period.

Subject analysis set title	Intention-to-treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized unique subjects. Subjects were analyzed as randomized.

Subject analysis set title	modified ITT (mITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects in the ITT population in whom a left atrial/left atrial appendage (LA/LAA) thrombus was not diagnosed during a transesophageal echocardiogram (TEE) performed before the first planned cardioversion in the study. Subjects were analyzed as randomized. A total of 34 subjects were excluded from the ITT population based upon confirmation of LA/LAA thrombus; thus, the mITT population comprised 1470 subjects, including 978 subjects randomized to rivaroxaban and 492 subjects randomized to VKA.

Subject analysis set title	Safety analysis set (SAF) population
Subject analysis set type	Safety analysis

Subject analysis set description:

SAF population included all randomized subjects who received at least 1 dose of study medication after randomization during the treatment period. Subjects were analyzed as treated. The SAF population comprised 1487 subjects, including 988 subjects randomized to rivaroxaban and 499 subjects randomized to VKA.

Primary: Number of subjects with composite of the following events, adjudicated centrally: stroke, transient ischemic attack, non-central nervous system systemic embolism, myocardial infarction and cardiovascular death

End point title	Number of subjects with composite of the following events, adjudicated centrally: stroke, transient ischemic attack, non-central nervous system systemic embolism, myocardial infarction and cardiovascular death

End point description:

Stroke, TIA, Non-CNS Embolism, MI and cardiovascular death were adjudicated and confirmed by Clinical Endpoints Committee (CEC). Stroke included hemorrhagic and ischemic infarction. TIA including information if with or without matching lesion. Non CNS systemic embolism included emboli in peripheral arterial of the upper and lower extremities, ocular and retinal (pulmonary embolism and MI were excluded from the category). MI was assessed based on either cardiac biomarkers, new abnormal Q waves appeared on electrocardiogram for >= 2 leads, or autopsy confirmation. Cardiovascular death included death in subjects with non-valvular atrial fibrillation (AF). Number of subjects with composite events were reported.

End point type	Primary

End point timeframe:

From randomization to the date of last dose of study drug +2 days for subjects who completed planned treatment or the earlier date [last planned dose, follow-up visit at the end of 30-day follow-up period] for subjects who prematurely stopped treatment

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	978[1]	492[2]		
Units: subjects	5	5		

Notes:

[1] - The primary population for the efficacy analysis was the mITT population.

[2] - The primary population for the efficacy analysis was the mITT population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

No statistical test performed; Descriptive comparison of crude estimates of the cumulative incidence and estimation of risk ratio, all with 95% confidence intervals.

Comparison groups	Rivaroxaban (Xarelto; BAY59-7939) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1470
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Risk ratio (RR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.73

Notes:

[3] - Crude estimate of the cumulative incidence for rivaroxaban (Xarelto, BAY59-7939): 0.51% (0.20% - 1.17%). Crude estimate of the cumulative incidence for Vitamin K antagonist (VKA): 1.02% (0.40% - 2.34%).

Primary: Number of Subjects with Major Bleedings as per Central Adjudication

End point title	Number of Subjects with Major Bleedings as per Central Adjudication

End point description:

Bleeding events were adjudicated and confirmed by CEC blinded to treatment. The CEC categorized the bleeding events as major or non-major. The bleeding events were defined per the International Society on Thrombosis and Hemostasis (ISTH) criteria. Major bleeding was clinically overt bleeding associated with a fall in hemoglobin of 2 gram per deciliter (g/dL) or higher, leading to a transfusion of 2 or more units of packed red blood cells or whole blood, occurring in a critical site or contributing to death. Number of subjects with confirmed adjudicated bleeding events occurring in greater than (>)1 total subjects were reported.

End point type	Primary

End point timeframe:

From randomization up to the date of the last dose of study drug + 2 days

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	988[4]	499[5]		
Units: subjects	6	4		

Notes:

[4] - SAF population included all randomized subjects who received at least 1 dose of study medication.

[5] - SAF population included all randomized subjects who received at least 1 dose of study medication.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

No test performed; Descriptive comparison of crude estimates of the cumulative incidence and estimation of risk ratio, all with 95% confidence intervals

Comparison groups	Rivaroxaban (Xarelto; BAY59-7939) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1487
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Risk ratio (RR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	2.67

Notes:

[6] - Crude estimate of the cumulative incidence for rivaroxaban (Xarelto, BAY59-7939): 0.61% (0.26% - 1.27%). Crude estimate of the cumulative incidence for Vitamin K antagonist (VKA): 0.80% (0.27% - 2.00%).

Secondary: Number of Subjects with Composite of Strokes and Non-central Nervous System Systemic Embolisms

End point title	Number of Subjects with Composite of Strokes and Non-central Nervous System Systemic Embolisms

End point description:

Stroke and Non-CNS Embolism were adjudicated and confirmed by CEC. Stroke included hemorrhagic and ischemic infarction. Non CNS systemic embolism included emboli in peripheral arterial of the upper and lower extremities, ocular and retinal (pulmonary embolism and MI were excluded from the category). Number of subjects with composite events were reported.

End point type	Secondary

End point timeframe:

From randomization to the date of last dose of study drug +2 days for subjects who completed planned treatment or the earlier date [last planned dose, follow-up visit at the end of 30-day follow-up period] for subjects who prematurely stopped treatment

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	978[7]	492[8]		
Units: subjects	2	3		

Notes:

[7] - The primary population for the efficacy analysis was the mITT population.

[8] - The primary population for the efficacy analysis was the mITT population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

No statistical test performed; Descriptive comparison of crude estimates of the cumulative incidence and estimation of risk ratio, all with 95% confidence intervals.

Comparison groups	Rivaroxaban (Xarelto; BAY59-7939) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1470
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Risk ratio (RR)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	2

Notes:

[9] - Crude estimate of the cumulative incidence for rivaroxaban (Xarelto, BAY59-7939): 0.20% (0.04% - 0.71%). Crude estimate of the cumulative incidence for Vitamin K antagonist (VKA): 0.61% (0.17% - 1.72%).

Secondary: Number of subjects with Composite of Strokes, Transient Ischemic Attacks, Non-central Nervous System Systemic Embolisms, Myocardial Infarctions and All-cause Mortality

End point title	Number of subjects with Composite of Strokes, Transient Ischemic Attacks, Non-central Nervous System Systemic Embolisms, Myocardial Infarctions and All-cause Mortality

End point description:

Stroke, TIA, Non- CNS systemic embolism, MI and all-cause mortality were adjudicated and confirmed by CEC. Stroke included hemorrhagic and ischemic infarction. TIA including information if with or without matching lesion. Non CNS systemic embolism included emboli in peripheral arterial of the upper and lower extremities, ocular and retinal (pulmonary embolism and MI were excluded from the

category). MI was assessed based on either cardiac biomarkers, new abnormal Q waves appeared on electrocardiogram for >= 2 leads, or autopsy confirmation. All-cause mortality included vascular death and non-vascular death. Number of subjects with composite events were reported.

End point type	Secondary

End point timeframe:

From randomization to the date of last dose of study drug +2 days for subjects who completed planned treatment or the earlier date [last planned dose, follow-up visit at the end of 30-day follow-up period] for subjects who prematurely stopped treatment

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	978[10]	492[11]		
Units: subjects	6	6		

Notes:

[10] - The primary population for the efficacy analysis was the mITT population.

[11] - The primary population for the efficacy analysis was the mITT population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

No statistical test performed; Descriptive comparison of crude estimates of the cumulative incidence and estimation of risk ratio, all with 95% confidence intervals

Comparison groups	Rivaroxaban (Xarelto; BAY59-7939) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1470
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	Risk ratio (RR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	1.55

Notes:

[12] - Crude estimate of the cumulative incidence for rivaroxaban (Xarelto, BAY59-7939): 0.61% (0.27% - 1.29%). Crude estimate of the cumulative incidence for Vitamin K antagonist (VKA): 1.22% (0.53% - 2.51%).

Secondary: Number of subjects with Strokes

End point title	Number of subjects with Strokes

End point description:

All events were adjudicated and confirmed by a CEC blinded to treatment. Stroke included hemorrhagic (Stroke with local collections of intraparenchymal blood. Subarachnoid hemorrhage, subdural hemorrhage, and epidural hemorrhage were excluded), ischemic infarction (Stroke without focal collection of intracranial blood) and unknown (No imaging data and anatomic findings were available). Number of subjects with strokes were reported.

End point type	Secondary

End point timeframe:

From randomization to the date of last dose of study drug +2 days for subjects who completed planned treatment or the earlier date [last planned dose, follow-up visit at the end of 30-day follow-up period]

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	978[13]	492[14]		
Units: subjects	2	2		

Notes:

[13] - The primary population for the efficacy analysis was the mITT population.

[14] - The primary population for the efficacy analysis was the mITT population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Transient Ischemic Attacks

End point title	Number of subjects with Transient Ischemic Attacks

End point description:

All events were adjudicated and confirmed by a CEC blinded to treatment. Number of subjects with TIA were reported.

End point type	Secondary

End point timeframe:

From randomization to the date of last dose of study drug +2 days for subjects who completed planned treatment or the earlier date [last planned dose, follow-up visit at the end of 30-day follow-up period] for subjects who prematurely stopped treatment

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	978[15]	492[16]		
Units: subjects	0	0		

Notes:

[15] - The primary population for the efficacy analysis was the mITT population.

[16] - The primary population for the efficacy analysis was the mITT population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Non-Central Nervous System Systemic Embolisms

End point title	Number of subjects with Non-Central Nervous System Systemic Embolisms

End point description:

All events were adjudicated and confirmed by a CEC blinded to treatment. Non CNS systemic embolism included emboli in peripheral arterial of the upper and lower extremities, ocular and retinal (pulmonary embolism and MI were excluded from the category). Number of subjects with non-CNS embolism were reported.

End point type	Secondary

End point timeframe:

From randomization to the date of last dose of study drug +2 days for subjects who completed planned treatment or the earlier date [last planned dose, follow-up visit at the end of 30-day follow-up period] for subjects who prematurely stopped treatment

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	978[17]	492[18]		
Units: subjects	0	1		

Notes:

[17] - The primary population for the efficacy analysis was the mITT population.

[18] - The primary population for the efficacy analysis was the mITT population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Myocardial Infarctions

End point title	Number of subjects with Myocardial Infarctions

End point description:

All events were adjudicated and confirmed by a CEC blinded to treatment. MI was assessed based on either cardiac biomarkers, new abnormal Q waves appeared on electrocardiogram for >= 2 leads, or autopsy confirmation. Number of subjects with MI were reported.

End point type	Secondary

End point timeframe:

From randomization to the date of last dose of study drug +2 days for subjects who completed planned treatment or the earlier date [last planned dose, follow-up visit at the end of 30-day follow-up period] for subjects who prematurely stopped treatment

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	978[19]	492[20]		
Units: subjects	1	1		

Notes:

[19] - The primary population for the efficacy analysis was the mITT population.

[20] - The primary population for the efficacy analysis was the mITT population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Cardiovascular Deaths

End point title	Number of subjects with Cardiovascular Deaths

End point description:

All events were adjudicated and confirmed by a CEC blinded to treatment. Any death that was not clearly non-vascular (e.g., deaths due to spontaneous bleeding, myocardial infarction, stroke, cardiac failure, and arrhythmia). Number of subjects with cardiovascular deaths were reported.

End point type	Secondary

End point timeframe:

From randomization to the date of last dose of study drug +2 days for subjects who completed planned treatment or the earlier date [last planned dose, follow-up visit at the end of 30-day follow-up period] for subjects who prematurely stopped treatment

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	978[21]	492[22]		
Units: subjects	4	2		

Notes:

[21] - The primary population for the efficacy analysis was the mITT population.

[22] - The primary population for the efficacy analysis was the mITT population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

No statistical test performed; Descriptive comparison of crude estimates of the cumulative incidence and estimation of risk ratio, all with 95% confidence intervals.

Comparison groups	Rivaroxaban (Xarelto; BAY59-7939) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1470
Analysis specification	Pre-specified
Analysis type	other[23]
Parameter estimate	Risk ratio (RR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	5.47

Notes:

[23] - Crude estimate of the cumulative incidence for rivaroxaban (Xarelto, BAY59-7939): 0.41% (0.14% - 1.02%). Crude estimate of the cumulative incidence for Vitamin K antagonist (VKA): 0.41% (0.07% - 1.41%).

Secondary: Number of subjects with All-cause Mortality

End point title	Number of subjects with All-cause Mortality

End point description:

All events were adjudicated and confirmed by a CEC blinded to treatment. All-cause mortality included vascular death and non-vascular death. Number of subjects with all-cause mortality were reported.

End point type	Secondary

End point timeframe:

From randomization to the date of last dose of study drug +2 days for subjects who completed planned treatment or the earlier date [last planned dose, follow-up visit at the end of 30-day follow-up period] for subjects who prematurely stopped treatment

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	978[24]	492[25]		
Units: subjects	5	3		

Notes:

[24] - The primary population for the efficacy analysis was the mITT population.

[25] - The primary population for the efficacy analysis was the mITT population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

No statistical test performed; Descriptive comparison of crude estimates of the cumulative incidence and estimation of risk ratio, all with 95% confidence intervals.

Comparison groups	Rivaroxaban (Xarelto; BAY59-7939) v Vitamin K antagonist (VKA)
Number of subjects included in analysis	1470
Analysis specification	Pre-specified
Analysis type	other[26]
Parameter estimate	Risk ratio (RR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	3.49

Notes:

[26] - Crude estimate of the cumulative incidence for rivaroxaban (Xarelto, BAY59-7939): 0.51% (0.20% - 1.17%). Crude estimate of the cumulative incidence for Vitamin K antagonist (VKA): 0.61% (0.17% - 1.72%).

Secondary: Number of subjects with Composite of Major and Non-major Bleeding Events

End point title	Number of subjects with Composite of Major and Non-major Bleeding Events

End point description:

All events were adjudicated and confirmed by a CEC blinded to treatment. The CEC categorized the bleeding events as major or non-major. The bleeding events were defined per the ISTH criteria. Clinically relevant bleeding included major bleeding (overt bleeding associated with 2 g/dL or greater fall in hemoglobin, leading to a transfusion of 2 or more units of packed red blood cells or whole blood, occurring in a critical site or contributing to death) and non-major bleeding associated with medical intervention, unscheduled physician contact, (temporary) cessation of study treatment, discomfort for the participants such as pain, or impairment of activities of daily life. Number of subjects with clinically relevant major and non-major bleeding events were reported.

End point type	Secondary

End point timeframe:

From randomization up to the date of the last dose of study drug + 2 days

End point values	Rivaroxaban (Xarelto; BAY59-7939)	Vitamin K antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	988[27]	499[28]		
Units: subjects	33	14		

Notes:

[27] - SAF population included all randomized subjects who received at least 1 dose of study medication.

[28] - SAF population included all randomized subjects who received at least 1 dose of study medication.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of study drug to date of last study drug + 2 days

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Vitamin K Antagonist (VKA)

Reporting group description:

Subjects assigned to treatment with VKA received VKA orally once daily titrated to a target INR of 2.5 (range 2.0-3.0, inclusive). The specific VKA was assigned by the investigator according to the local standard of practice. For subjects randomized to receive VKA, the investigator assessed if a parenteral anticoagulant drug, particularly prior to cardioversion, was needed as bridging therapy with VKA as standard of care (until target INR was achieved). The duration depended on the cardioversion strategy. For subjects in the Direct Cardioversion Strategy, the cardioversion procedure was performed within 1-5 days after randomization. VKA was given for 1-5 days before cardioversion and for 42 days thereafter. Subjects in the Delayed Cardioversion Strategy received VKA for 21 (+4) to 56 (+4) days before cardioversion and for 42 days thereafter.

Reporting group title	Rivaroxaban (Xarelto; BAY59-7939)

Reporting group description:

Subjects randomized to treatment with rivaroxaban received rivaroxaban 20 milligram (mg) orally... more once daily. Subjects with moderate renal impairment [i.e., Creatinine clearance (CrCl) of 30 to 49 milliliter per minute (mL/min), inclusive] at screening received the adjusted dose of 15 mg once daily. The duration of the treatment period for a given subject depended on the cardioversion strategy. For subjects in the Direct Cardioversion Strategy, the cardioversion procedure was performed within 1-5 days after randomization. Rivaroxaban was given for 1-5 days before planned direct cardioversion and for 42 days thereafter. Subjects in the Delayed Cardioversion Strategy received rivaroxaban for 21 (+4) to 56 (+4) days prior to cardioversion and for 42 days thereafter.

Serious adverse events	Vitamin K Antagonist (VKA)	Rivaroxaban (Xarelto; BAY59-7939)	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 499 (7.62%)	93 / 988 (9.41%)	
number of deaths (all causes)	3	8	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			

subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 499 (0.00%)	2 / 988 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bladder catheterisation			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ablation			
subjects affected / exposed	1 / 499 (0.20%)	3 / 988 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implantable defibrillator insertion			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plastic surgery			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder arthroplasty			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
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			
Chest discomfort			
subjects affected / exposed	1 / 499 (0.20%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 499 (0.00%)	5 / 988 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site reaction			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
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 / 499 (0.00%)	1 / 988 (0.10%)	
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 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 499 (0.20%)	4 / 988 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
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 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			

subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Arteriogram coronary			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
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			
Subdural haematoma			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 499 (0.00%)	2 / 988 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
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	4 / 499 (0.80%)	8 / 988 (0.81%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 499 (0.20%)	4 / 988 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	3 / 499 (0.60%)	4 / 988 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	3 / 499 (0.60%)	3 / 988 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 499 (0.00%)	3 / 988 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 499 (0.40%)	8 / 988 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 499 (0.40%)	10 / 988 (1.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (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	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			

subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
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	0 / 499 (0.00%)	3 / 988 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhythm idioventricular			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	2 / 499 (0.40%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	2 / 499 (0.40%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia induced cardiomyopathy			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
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	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Presyncope			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 499 (0.00%)	2 / 988 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamus haemorrhage			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Blindness transient			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (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 pain			
subjects affected / exposed	0 / 499 (0.00%)	4 / 988 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
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 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 499 (0.20%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nausea			
subjects affected / exposed	0 / 499 (0.00%)	2 / 988 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			

subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 499 (0.00%)	2 / 988 (0.20%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 499 (0.40%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vomiting			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 499 (0.40%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital haemorrhage			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (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			
Bronchitis			
subjects affected / exposed	1 / 499 (0.20%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 499 (0.20%)	2 / 988 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 499 (0.60%)	2 / 988 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomembranous colitis			

subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 499 (0.20%)	0 / 988 (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			
Hyponatraemia			
subjects affected / exposed	0 / 499 (0.00%)	1 / 988 (0.10%)	
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: 1 %

Non-serious adverse events	Vitamin K Antagonist (VKA)	Rivaroxaban (Xarelto; BAY59-7939)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 499 (25.25%)	272 / 988 (27.53%)	
Investigations			
International normalised ratio increased			
subjects affected / exposed	9 / 499 (1.80%)	1 / 988 (0.10%)	
occurrences (all)	10	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 499 (1.00%)	3 / 988 (0.30%)	
occurrences (all)	5	5	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 499 (0.80%)	22 / 988 (2.23%)	
occurrences (all)	4	22	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	7 / 499 (1.40%)	2 / 988 (0.20%)	
occurrences (all)	7	2	
Atrial thrombosis			

subjects affected / exposed	6 / 499 (1.20%)	16 / 988 (1.62%)	
occurrences (all)	6	16	
Atrioventricular block first degree			
subjects affected / exposed	25 / 499 (5.01%)	40 / 988 (4.05%)	
occurrences (all)	25	40	
Bradycardia			
subjects affected / exposed	13 / 499 (2.61%)	30 / 988 (3.04%)	
occurrences (all)	15	30	
Sinus bradycardia			
subjects affected / exposed	12 / 499 (2.40%)	25 / 988 (2.53%)	
occurrences (all)	12	25	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 499 (1.80%)	25 / 988 (2.53%)	
occurrences (all)	9	28	
Headache			
subjects affected / exposed	7 / 499 (1.40%)	25 / 988 (2.53%)	
occurrences (all)	7	25	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 499 (1.80%)	14 / 988 (1.42%)	
occurrences (all)	9	15	
Oedema peripheral			
subjects affected / exposed	5 / 499 (1.00%)	20 / 988 (2.02%)	
occurrences (all)	5	20	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 499 (0.60%)	10 / 988 (1.01%)	
occurrences (all)	3	11	
Diarrhoea			
subjects affected / exposed	3 / 499 (0.60%)	18 / 988 (1.82%)	
occurrences (all)	3	18	
Nausea			
subjects affected / exposed	1 / 499 (0.20%)	17 / 988 (1.72%)	
occurrences (all)	1	17	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 499 (0.60%)	13 / 988 (1.32%)	
occurrences (all)	3	13	
Dyspnoea			
subjects affected / exposed	12 / 499 (2.40%)	16 / 988 (1.62%)	
occurrences (all)	12	18	
Epistaxis			
subjects affected / exposed	9 / 499 (1.80%)	30 / 988 (3.04%)	
occurrences (all)	9	36	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 499 (1.00%)	12 / 988 (1.21%)	
occurrences (all)	5	12	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 499 (1.00%)	12 / 988 (1.21%)	
occurrences (all)	6	12	
Influenza			
subjects affected / exposed	5 / 499 (1.00%)	3 / 988 (0.30%)	
occurrences (all)	5	3	
Urinary tract infection			
subjects affected / exposed	5 / 499 (1.00%)	7 / 988 (0.71%)	
occurrences (all)	5	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25182247

http://www.ncbi.nlm.nih.gov/pubmed/24944325