Clinical trial results:
An open-label, international, multicenter, interventional study exploring the efficacy of once-daily oral rivaroxaban (BAY 59 7939) for the treatment of left atrial/left atrial appendage thrombus in subjects with nonvalvular atrial fibrillation or atrial flutter

Summary

EudraCT number	2012-001062-15
Trial protocol	DE BG PL
Global end of trial date	25 December 2014

Results information

Result version number	v3 (current)
This version publication date	17 February 2019
First version publication date	15 July 2016
Version creation reason	• Correction of full data set Control of data

Trial information

Trial identification

Sponsor protocol code	BAY59-7939/16320

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01839357
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, 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	25 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to explore the effect of rivaroxaban on the complete resolution of left atrial (LA)/left atrial appendage (LAA) thrombi at the end-of-treatment visit (after 6 weeks of treatment) in subjects with nonvalvular atrial fibrillation (AF) or atrial flutter who had LA/LAA thrombus confirmed by transesophageal echocardiogram (TEE).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent explained to all subjects. Participating subjects 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	12 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Ukraine: 15
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	60
EEA total number of subjects	37

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)	23
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted in 17 study centers in 7 countries worldwide, from 12 August 2013 (first subject first visit) to 25 December 2014 (last subject last visit).

Pre-assignment

Screening details:

Overall, 61 subjects were screened and 60 of these subjects were enrolled. The 1 subject enrolled at the site in Russia was the screen failure. Of the 60 subjects enrolled in the study, 57 were from Eastern Europe and 3 were from Western Europe.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rivaroxaban (Xarelto, BAY59-7939)

Arm description:

Subjects received rivaroxaban 20 milligram (mg) orally once daily (od) for 6 weeks. Subjects with moderate to severe renal impairment (ie, Creatinine Clearence [CrCl] of 15 to 49 millilitre/minute [mL/min], inclusive) at screening received an adjusted dose of 15 mg orally od. Subjects were instructed to take rivaroxaban with food. The duration of study drug treatment was 6 (+2) weeks. A time window (maximum 2 weeks) were kept for the investigators to schedule the end-of-treatment TEE.

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:

Subjects received 20 mg of rivaroxaban tablet orally od for 6 weeks.

Number of subjects in period 1	Rivaroxaban (Xarelto, BAY59-7939)
Started	60
Completed	55
Not completed	5
Logistical Difficulties	1
Death	1
Adverse event	3

Baseline characteristics

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

Reporting group description:

Subjects received rivaroxaban 20 milligram (mg) orally once daily (od) for 6 weeks. Subjects with moderate to severe renal impairment (ie, Creatinine Clearence [CrCl] of 15 to 49 millilitre/minute [mL/min], inclusive) at screening received an adjusted dose of 15 mg orally od. Subjects were instructed to take rivaroxaban with food. The duration of study drug treatment was 6 (+2) weeks. A time window (maximum 2 weeks) were kept for the investigators to schedule the end-of-treatment TEE.

Reporting group values	Rivaroxaban (Xarelto, BAY59-7939)	Total	
Number of subjects	60	60	
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	69.6		
standard deviation	± 11	-	
Gender Categorical Units: Subjects			
Female	30	30	
Male	30	30	
Weight category Units: Subjects			
less than equal to (<=) 70 kilogram (kg)	13	13	
greater than (>) 70 and <= 90 kg	28	28	
> 90 kg	19	19	
CHADS2 score category			
CHADS2- predicts clinical risk of stroke and thromboembolism in atrial fibrillation incorporating these risk factors: Congestive heart failure, Hypertension, Age (greater than equal to [>=] 75 years), Diabetes mellitus, Stroke/transient ischemic attack; CHADS2 scores (low: 0, moderate: 1, high: >= 2).			
Units: Subjects			
Low (0)	3	3	
Moderate (1)	17	17	
High >=	40	40	
CHA2DS2VASc score category			
CHA2DS2VASc-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 to 74 years, Sex category (i.e., female); CHA2DS2VASc scores classification (low: 0 [or 1 if female only], moderate: 1 [except for female gender alone], high: >= 2).			
Units: Subjects			
Low (0, or 1 if female)	2	2	
Moderate (1, except for female)	8	8	
High >=	50	50	
Atrial fibrillation types and Atrial flutter Units: Subjects			

Atrial fibrillation: First-diagnosed	4	4	
Atrial fibrillation: Paroxysmal	2	2	
Atrial fibrillation: Persistent	27	27	
Atrial fibrillation: Long-standing persistent	5	5	
Atrial fibrillation: Permanent	14	14	
Atrial fibrillation: Missing	5	5	
Atrial flutter	3	3	
Prior anticoagulant medications			
Prior anticoagulant medications included the treatments with Heparin group, Other antithrombotic agent and Vitamin K antagonist drugs.			
Units: Subjects			
Subjects with prior anti-coagulant therapy	49	49	
Subjects with no prior anti-coagulant therapy	11	11	
Weight			
Units: Kilogram (kg)			
arithmetic mean	85.09		
standard deviation	± 17.64	-	
Body Mass Index (BMI)			
Units: Kilogram per meter square (Kg/m^2)			
arithmetic mean	30.68		
standard deviation	± 5.96	-	
CHADS2 score			
Units: units on a scale			
arithmetic mean	2.3		
standard deviation	± 1.4	-	

End points

End points reporting groups

Reporting group title	Rivaroxaban (Xarelto, BAY59-7939)

Reporting group description:

Subjects received rivaroxaban 20 milligram (mg) orally once daily (od) for 6 weeks. Subjects with moderate to severe renal impairment (ie, Creatinine Clearence [CrCl] of 15 to 49 millilitre/minute [mL/min], inclusive) at screening received an adjusted dose of 15 mg orally od. Subjects were instructed to take rivaroxaban with food. The duration of study drug treatment was 6 (+2) weeks. A time window (maximum 2 weeks) were kept for the investigators to schedule the end-of-treatment TEE.

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

Subject analysis set description:

All subjects who successfully completed the screening phase and entered the treatment phase (whether or not they were actually treated).

Subject analysis set title	Modified ITT (mITT) population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects with LA/ LAA thrombus at baseline who had an evaluable end-of-treatment TEE according to the adjudication committee.

Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the mITT population without major protocol deviations.

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

Subject analysis set description:

All subjects in the ITT analysis population who received at least 1 dose of study medication during the treatment period.

Primary: Percentage of Subjects With Complete Resolution of Left Atrial or Left Atrial Appendage (LA/LAA) Thrombus at the end of Treatment

End point title	Percentage of Subjects With Complete Resolution of Left Atrial or Left Atrial Appendage (LA/LAA) Thrombus at the end of Treatment[1]

End point description:

Complete resolution of LA/LAA thrombus is adjudicated and confirmed by Study Outcome Committee. Complete resolution is characterized as the subject is completely thrombus-free in his/her left atrium confirmed on transesophageal echocardiography.

End point type	Primary

End point timeframe:

Up to 8 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: EudraCT database does auto-addition of number of subjects analysed while reporting an explorative analysis of two or more treatment groups. Due to this format constraint, charts have been uploaded with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Rivaroxaban (Xarelto, BAY59-7939)			
Subject group type	Reporting group			
Number of subjects analysed	53[2]			
Units: percentage of subjects				
number (not applicable)				
Complete resolution – yes	41.51			
Complete resolution – no	58.49			

Notes:

[2] - mITT population

Attachments (see zip file)	16320_ Statistical Analyses_Primary_ Thrombus Reso/16320_

Statistical analyses

No statistical analyses for this end point

Secondary: Categories of Thrombus Outcome in Subjects: Resolved, Reduced, Unchanged, Enlarged or New

End point title	Categories of Thrombus Outcome in Subjects: Resolved, Reduced, Unchanged, Enlarged or New

End point description:

Individual thrombi were evaluated (in increasing order of severity) as resolved, reduced, unchanged, or enlarged since baseline, or new as compared to baseline, and subjects were categorized accordingly. 1) Resolved: absence of thrombus. 2) Reduced: decrease more than 1 millimetre (mm) by diameter (D) compared to baseline (average diameter [AD] is less than (<)10) or decrease more than 2 mm by D compared to baseline (AD is 10-20 mm) or decrease more than 3 mm by D compared to baseline (AD is > 20). 3) Unchanged: within 1 mm by D difference compared to baseline (AD is <10) or within 2 mm by D difference compared to baseline (AD is 10-20) or within 3 mm by D difference compared to baseline (AD is >20). 4) Larger: increase more than 1 mm by D compared to baseline (AD is <10) or increase more than 2 mm by D compared to baseline (AD is 10-20) or increase more than 3 mm by D compared to baseline (AD is >20). 5) New: new thrombus present. '99999' indicates that data were not calculated.

End point type	Secondary

End point timeframe:

Up to 8 weeks

End point values	Rivaroxaban (Xarelto, BAY59-7939)			
Subject group type	Reporting group			
Number of subjects analysed	53[3]			
Units: percentage of subjects				
number (not applicable)				
Resolved	41.5			
Reduced	18.9			
Unchanged	17			
Larger	22.6			
New	99999			
Missing	99999			

Notes:

[3] - mITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Combined Categories of Thrombus Outcome in Subjects

End point title	Combined Categories of Thrombus Outcome in Subjects

End point description:

Combined thrombi were evaluated as Resolved/reduced and Unchanged/enlarged/new.

End point type	Secondary

End point timeframe:

Up to 8 weeks

End point values	Modified ITT (mITT) population			
Subject group type	Subject analysis set			
Number of subjects analysed	53[4]			
Units: Percentage of subjects				
number (confidence interval 95%)				
Resolved/reduced	60.38 (46 to 73.55)			
Unchanged/enlarged/new	39.62 (26.45 to 54)			

Notes:

[4] - mITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Composite Number of Stroke and Non-central Nervous System (Non-CNS) Systemic Embolism Events

End point title	Composite Number of Stroke and Non-central Nervous System (Non-CNS) Systemic Embolism Events

End point description:

Stroke and Non-CNS Embolism were adjudicated and confirmed by Study Outcome Committee . 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 myocardial ischemia were excluded from the category).

End point type	Secondary

End point timeframe:

Approximately up to 10 weeks

End point values	Intent-to-treat (ITT) population	Modified ITT (mITT) population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	53		
Units: events	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of all Bleeding Events

End point title	Number of all Bleeding Events

End point description:

Bleeding was categorized as major and non-major bleeding. For major bleedings, the following characteristics were displayed according to the following hierarchy: fatal bleeding, non-fatal critical organ bleed, non-fatal noncritical organ bleeding (decrease in hemoglobin level of 2 grams per deciliter (g/dL) and/or transfusions >= 2 units). No major bleeding event was reported. The non-major bleeding events included two serious events (moderate ear hemorrhage and moderate epistaxis) and three nonserious bleeding events (mild gingival bleeding, mild gastrointestinal hemorrhage and mild petechiae).

End point type	Secondary

End point timeframe:

Approximately up to 10 weeks

End point values	Safety analysis (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	60[5]			
Units: events				
Major bleeding	0			
Non-major: serious	2			
Non-major: non-serious	3			
No-event	55			

Notes:

[5] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study treatment until the follow-up visit occurred 30 (+- 3) days after the end-of-treatment visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Rivaroxaban (Xarelto, BAY59-7939)

Reporting group description:

Subjects received rivaroxaban 20 milligram (mg) orally once daily (od) for 6 weeks. Subjects with moderate to severe renal impairment (ie, Creatinine Clearenve [CrCl] of 15 to 49 millilitre/minute [mL/min], inclusive) at screening received an adjusted dose of 15 mg orally od. Subjects were instructed to take rivaroxaban with food. The duration of study drug treatment is 6 (+2) weeks. A time window (maximum 2 weeks) were kept for the investigators to schedule the end-of-treatment transesophageal echocardiography (TEE)

Serious adverse events	Rivaroxaban (Xarelto, BAY59-7939)		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 60 (11.67%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to liver			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute left ventricular failure			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery disease			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure chronic			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Ear haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis chronic			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Rivaroxaban (Xarelto, BAY59-7939)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 60 (5.00%)		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2013	The title page of the noninterventional study protocol in Section 14.6 was removed and the synopsis was replaced with the new synopsis.
26 February 2014	This amendment also helped to enroll subjects from Western European Union (EU) countries as the availability of vitamin K antagonist(s) [VKA]/non-vitamin K antagonist or new oral anticoagulant(s) VKA/non-VKA or new oral anticoagulant(s) [NOAC]-naive subjects with atrial fibrillation is limited. Other revisions with Amendment 3 included: 1.Changed the Sponsor's medical expert, 2. Added information that specified inclusion criteria regarding prior VKA and NOAC treatment, 3. Added a Study Outcome Committee to apply protocol definitions and adjudicate and classify endpoints on TEE, 4. Deleted the time period of "1 year" from enrollment criteria, 5. Added "Active endocarditis" to cardiac-related exclusion criteria, 6. Clarified that all eligible subjects should receive the study drug within 24 hours after treatment assignment, 7. Clarified duration of treatment, 8. Modified the evaluation schedule to clarify timing of electrocardiogram (ECG), trans-esophageal echocardiography/echocardiogram (TEE), laboratory evaluations and baseline blood sample, 9. Changed the timing of Visit 1 (Screening) procedures from within "2" days to "3" days prior to the start of the study drug treatment, 10. Added baseline characteristics to determine subgroups, 11. Deleted text from Statistical and analytical plans to be consistent with the statistical analysis plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Occurrence of "±" in relation with geometric coefficient of variation is auto-generated and cannot be deleted. Decimal places were automatically truncated if last decimal equals zero.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25819852