Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	15572	NCT No: NCT01442792 EudraCT No: 2011-001094-58
Study Phase:	II	
Official Study Title:	Prospective, multi-center, randomized, heparin-controlled dose-finding trial to evaluate the efficacy and safety of rivaroxaban, a direct factor Xa inhibitor, on the background of standard dual antiplatelet therapy to support elective percutaneous coronary intervention (X-Plorer)	
Therapeutic Area:	Cardiology/Coagulation	
Test Product		
Name of Test Product:	Rivaroxaban (Xarelto, BAY59-7939)	
Name of Active Ingredient:	Rivaroxaban	
Dose and Mode of Administration:	10 mg or 20 mg single dose (oral tablet), or 10 mg single dose followed by unfractionated heparin 50 IU/kg bolus	
Reference Therapy/Placebo		
Reference Therapy:	unfractionated heparin (UFH)	
Dose and Mode of Administration:	70-100 IU/kg bolus intravenous	
Duration of Treatment:	1 day	
Studied period:	Date of first subjects' first visit:	12 OCT 2011
	Date of last subjects' last visit:	04 MAR 2013
Premature Study Suspension / Termination:	Not applicable	
Substantial Study Protocol Amendments:	The study was conducted according to the original study protocol Version 1 dated 12 APR 2011 and included no amendments.	

Study Centre(s):	7 investigational sites treated patients in 2 countries: 3 centers in Belgium and 4 centers in the Netherlands.
Methodology:	This study was designed to assess the potential of rivaroxaban, on the background of standard dual antiplatelet therapy, to provide an adequate level of anticoagulation to support a standard percutaneous coronary intervention (PCI). One hundred and five (n=105) intervened subjects were to be randomized (2:2:2:1) to either of the two doses of rivaroxaban (study treatment) or one dose rivaroxaban combined with UFH (combined arm) or UFH alone (control arm). All subjects were to be followed for a period up to 30 + 7 days post index PCI procedure.
Indication/ Main Inclusion Criteria:	Indication: Treatment of obstructive coronary artery disease (CAD) in subjects on rivaroxaban for long term systemic anticoagulation. Main inclusion criteria: Symptomatic CAD subjects due to undergo an elective (non-emergency) PCI procedure on one or two lesions in the native coronary vessel(s). Cardiac standard troponin at baseline must have been within the normal limits.
Study Objectives:	Primary: To assess whether rivaroxaban, as compared to UFH, on the background of standard dual antiplatelet therapy (DAPT), could effectively suppress thrombosis, and related adverse ischemic events, upon balloon inflation and stent expansion, during elective PCI, without increasing bleeding. Secondary: To investigate the safety of rivaroxaban plus DAPT in the setting of elective PCI. Secondary objectives were safety criteria with respect to bleeding (thrombolysis in myocardial infarction [TIMI] major, TIMI minor and Bleeding Academic Research Consortium [BARC] type 2, 3 and 5) and the composite of clinical ischemic events (all death, non-fatal myocardial infarction [MI], non-fatal stroke and Target Lesion Revascularization [TLR]) were to be determined up to 30 days after index PCI.
Evaluation Criteria:	Efficacy (Primary): The primary efficacy variable was the anticoagulant effect of rivaroxaban defined during the PCI procedure as the percentage of subjects who: •Required bail-out anticoagulant therapy in the context of an ischemic coronary event and/or •Experienced an angiographic flow limiting thrombotic event (i.e., abrupt vessel closure, visible thrombus, no-reflow) and/or •Experienced thrombus formation on the PCI equipment (i.e., guiding catheter and guide wire thrombus) and/or •Experienced a MI due to the PCI procedure (i.e., procedural MI). Efficacy (Secondary): Secondary efficacy variables included all the end points previously described in the primary efficacy plus: •Clinical ischemic events up to 30 days post index PCI procedure

	assessed by the composite endpoint of all death, non-fatal myocardial infarction, stroke, and clinically indicated TLR. •The incidence of clinically indicated TLR up to 30 days post index PCI procedure. •Definite and probable stent thrombosis up to 30 days post index PCI procedure according to the Academic Research Safety: The safety variables for this study were: •Bleeding events up to 30 days post index PCI procedure: (1) Incidence of clinically significant bleeding according to: TIMI major, TIMI minor, requiring medical attention. (2) Incidence of bleeding according to BARC type 2, 3 and 5. •Any other serious adverse events (SAEs) up to 30 days post index PCI procedure.
	Pharmacokinetics: The following pharmacokinetic (PK) parameters were evaluated: •Primary PK parameters: AUC, AUC(0-tn), Cmax •Secondary PK parameters: AUC/D, AUCnorm, Cmax/D, Cmax,norm, CL/F, tmax, t1/2 •Other PK parameters: AUC(tn-infinity), points terminal.
Statistical Methods:	Efficacy: The primary efficacy analysis was based on the modified intent-to-treat (mITT) population. Treatment group comparisons were based on absolute differences and/or odds ratios and corresponding exact two-sided 95% confidence intervals. No imputation of data was performed. Safety: The 10 mg and 20 mg rivaroxaban groups, and the 10 mg rivaroxaban plus UFH group were compared to the control group. Only descriptive statistics were planned for plasma concentration analysis including geometric means and geometric standard deviations. Differences between treatments were expressed in point estimates of the means and their matching 95% confidence intervals for the different planned sampling time points. No imputation of data was performed. Pharmacokinetics - if applicable: For all coagulation parameters median vs. time curves were plotted by treatment on the linear scale according to: • Individual plots per treatment with the median vs. time curve including boxplots at the different time points • One figure including the median vs. time curves of all treatments No imputation of data was performed. No imputation of data was performed
Number of Subjects:	One hundred and five subjects were planned to participate in this study. Overall, 111 subjects were enrolled and 108 (50 in Belgium

	and 58 in the Netherlands) of these subjects were randomized to treatment.

Study Results

Results Summary — Subject Disposition and Baseline

Overall, 111 subjects were enrolled and 108 (50 in Belgium and 58 in the Netherlands) of these subjects were randomized to treatment including 30 randomized to rivaroxaban 10 mg, 32 randomized to rivaroxaban 20 mg, 30 randomized to rivaroxaban 10 mg + UFH, and 16 randomized to UFH.

There were no relevant differences in the baseline demographic characteristics between treatment groups. The majority of subjects in the intent-to-treat (ITT) population were men (75.9%) and White (96.3%). Subjects ranged in age from 39 to 88 years (mean age 64.4 years) and 50% of subjects were <65 years of age. Medical and surgical history was similar between treatment groups. This study consisted of subjects with symptomatic coronary artery disease who were due to undergo an elective PCI on 1 or 2 lesions in the native coronary vessel. 107 of the 108 subjects underwent PCI and were included in the modified ITT. Most subjects were treated for 1 lesion (62.6%) in the right coronary artery target vessel (43.0%) and had 1 stent implanted (57.9%). The total mean duration of the procedure was 24.9 ± 19.5 minutes and the total median was 22 (3, 118) minutes.

Results Summary — Efficacy

Efficacy is based on mITT (N=107)- all randomized subjects that underwent PCI. Overall, 12 subjects (11.2%) experienced one or more primary endpoint events. One subject (0.9%) required a bail out and 12 subjects (11.2%) experienced a procedural MI event during the PCI procedure.

A total of 5 (31.3%) subjects in the UFH group experienced a primary endpoint event of procedural MI. Among the 5 subjects with procedural MI in the UFH group, one Subject also required bail-out anti-coagulant therapy.

No subject in any of the rivaroxaban 10 mg, rivaroxaban 20 mg, or rivaroxaban 10 mg + UFH group required bail-out anti-coagulant therapy.

No subject from any of the rivaroxaban groups or the UFH group experienced angiographic flow limiting thrombotic event or thrombus formation on the PCI equipment.

None of the subjects (total 30) in the rivaroxaban 10 mg group had any primary endpoint event.

In comparison to the UFH group with 5 (31.3%) subjects experiencing procedural MI, the number of subjects experiencing procedural MI in other treatment groups were:

3 (9.4%) in rivaroxaban 20 mg group with an odd ratio of 0.23 (95% CI: 0.03, 1.44);

4 (13.8%) in rivaroxaban 10 mg + UFH group an odd ratio of 0.35 (95% CI: 0.06, 2.04).

With regards to second efficacy endpoints, 12 (11.2%) subjects experienced ischemic events up to 30 days post index PCI procedure. All events were non-fatal myocardial infarctions. There were no deaths, strokes, or clinically indicated TLR reported in this study.

A total of 5 (31.3%) subjects in the UFH group experienced a secondary endpoint event of any clinical ischemic event.

None of the subjects (total 30) in the rivaroxaban 10 mg group had any secondary endpoint event.

Additionally, there were no definite or probable stent thrombosis up to 30 days post index PCI procedure reported in this study.

The rivaroxaban 10 mg group showed the best efficacy results since no subjects experienced a primary or secondary endpoint event.

Results Summary — Safety

The safety population included 107/108 of randomized subjects. One Subject randomized to the rivaroxaban 10 mg + UFH treatment group, was excluded from the safety analysis set (SAF), as this subject did not receive any treatment. All subjects in the safety population received their assigned dose of rivaroxaban 10 mg PO single dose, rivaroxaban 20 mg PO single dose, rivaroxaban 10 mg PO single dose followed by UHF IV, or UFH IV alone.

Adverse events occurred in nearly half (49.5%) of all subjects in the safety analysis population: 17/30 (56.7%) subjects in the rivaroxaban 10 mg group, 10/32 (31.3%) subjects in the rivaroxaban 20 mg group, 17/29 (58.6%) subjects in the rivaroxaban 10 mg + UFH group, and 9/16 (56.3%) subjects in the UFH alone group. The incidence of adverse events (AEs) in the rivaroxaban 20 mg group was notably lower (≥ 25 percentage points) compared to all other treatment groups. Comparing type and incidence of adverse events in the rivaroxaban 10 mg versus 20 mg, there is no specific adverse event which drives the difference between these 2 treatment groups. Numerically higher total incidence of adverse events spread among the different System Oragn Classes (SOC) by random coupled to the low sample size may be an alternative explanation for the difference.

At least 1 treatment emergent adverse event (TEAE) was reported in 30 (28%) subjects in the SAF population. The incidence rate of TEAEs in the rivaroxaban 20 mg group was notably lower (≥ 14 percentage points) compared to the other treatment groups.

Bleeding events were measured up to 30 days post PCI procedure. There were 4 (13.3%) TIMI clinical significant bleeding events in the rivaroxaban 10 mg group, 1 (3.1%) in the rivaroxaban 20 mg group, 5 (17.2%) in the rivaroxaban 10 mg + UFH group, and 4 (25%) in the UFH alone group. The BARC type 2 bleedings reported were 3 (10%) in the rivaroxaban 10 mg group, 1 (3.1%) in the rivaroxaban 20 mg group, 4 (13.8%) in the rivaroxaban 10 mg + UFH group, and 3 (18.8%) in the UFH alone group. No other bleeding events were reported.

The overall incidence of non-treatment emergent AEs was lowest in the rivaroxaban 10 mg + UFH group (17.2%), followed by the UFH and rivaroxaban 20 mg groups (18.8% each). The rivaroxaban 10 mg group (30%) had the highest incidence rate of AEs when compared with the other groups.

Serious adverse events were reported in 8/107 (7.5%) subjects. The UFH alone group (2/16 [12.5%]) had the highest percentage incidence of SAEs compared to all other treatment groups. No difference was apparent between the rivaroxaban treatment groups (10 mg: 6.7%, 20 mg: 6.3%, 10 mg + UFH: 6.9%).

Treatment-emergent serious adverse events (TESAEs) were reported in 4/107 (3.7%) subjects. Both the rivaroxaban + 10 mg group and the UFH alone group had 2 subjects with TESAEs. However, the incidence rate of the rivaroxaban + 10 mg group, was almost half when compared to the UFH alone group (6.9 % vs. 12.5%). There were no TESAEs in either the rivaroxaban 10 mg group nor in the rivaroxaban 20 mg group.

There were no deaths or pregnancies reported in this study.

The rivaroxaban 20 mg group showed the best safety results since it had the least number of AEs and TEAEs when compared to the other treatment groups (≥ 25 and ≥ 14 percentage points respectively). It had 1 (3.1%) TIMI clinical significant bleeding event and 1 (3.1%) BARC type 2 bleeding event. Serious adverse events were reported in 2 (6.3%) subjects, and there were no TESAEs present.

Coagulation parameters were rivaroxaban dose dependent as expected. For the prothrombin

time (PT), activated partial thromboplastin time (aPTT), and endogenous thrombin potential (ETP) parameters, the most pronounce effects were seen in the UFH alone group followed by rivaroxaban 10 mg + UFH group and rivaroxaban 20 mg group. The least effect was seen in the rivaroxaban 10 mg group. Anti-Xa activity was also dose dependent. The 10 mg + UFH group showed the most pronounced activity compared to pre-PCI values. Additionally, TT results were not impacted by factor Xa inhibition. The UFH group and the rivaroxaban + 10 mg group showed a thrombin time (TT) increase compared to pre-PCI. Prothrombin fragment 1+2 (F1+2) showed median values within normal range. Regarding the activated coagulation time (ACT), as rivaroxaban achieved an anticoagulant effect without dependence on anti-thrombin III, less effects were observed in the rivaroxaban only groups. Platelet count changes were not clinically meaningful in any treatment group.

Results Summary — Pharmacokinetics

The PK of rivaroxaban behaved dose linear from the 10 mg dose strength to the 20 mg dose strength. The PK parameters of the 10 mg dose strength were comparable across both treatment groups. AUC(0-tlast) and Cmax were slightly higher in the group receiving rivaroxaban in addition to UFH (increase by 17% and 21%, respectively). These slightly higher PK parameters in the group receiving rivaroxaban in addition to UFH can be considered a chance finding and clinically not relevant.

AUC(0-tlast) was 830 µg*h/L, 1510 µg*h/L and 992 µg*h/L in patients receiving 10 mg, 20 mg rivaroxaban or 10 mg rivaroxaban in addition to UFH. Cmax was 176 µg/L, 278 µg/L and 213 µg/L in patients receiving 10 mg, 20 mg rivaroxaban or 10 mg rivaroxaban in addition to UFH.

In total, 90 profiles were evaluated. The following table summarizes the primary PK parameters as well as dose normalized AUC/D and Cmax/D per treatment group.

Parameter (unit)	n	Rivaroxaban 10 mg n=30	n	Rivaroxaban 20 mg n=32	n	UFH + Rivaroxaban 10 mg n=29
AUC (µg*h/mL)	29	1237.6 / 59.7 (670.1 - 12074.9)	32	2327.2 / 46.5 (815.0 - 7812.3)	27	1447.0 / 41.1 (809.4 - 4831.7)
AUC/D*1000 (h/L)	29	123.8 / 59.7 (67.01 – 120.7)	32	116.4 / 46.5 (40.75 – 390.6)	27	144.7 / 41.1 (80.94 – 483.2)
AUC(0-t_{last}) (µg*h/L)	30	830.2 / 37.5 (254.8 - 1949.4)	32	1510.1 / 40.4 (618.8 - 3055.7)	28	992.4 / 26.5 (547.9, 1563.8)
C_{max} (µg/L)	30	175.7 / 31.6 (110.6 - 384.8)	32	278.4 / 41.5 (113.0 - 639.3)	28	212.7 / 24.9 (123.0 - 347.9)
C_{max}/D*1000 (1/L)	30	17.57 / 31.6 (11.06 – 38.48)	32	13.92 / 41.5 (5.65 – 31.97)	28	21.27 / 24.9 (12.30 – 34.79)

Abbreviations: UFH= unfractionated heparin; AUC = area under the curve; cmax = maximum drug concentration in plasma.

Conclusion(s)

The present study was not powered to detect a significant difference in clinical outcome measures between UFH and rivaroxaban. However, the number of primary and secondary endpoint events were numerically lower in the rivaroxaban groups. Of note, the UFH group had lower sample size, longer time of procedure (mean and median) higher number of vessels intervened and number of stents compared to the rivaroxaban groups, but this is also true for the UFH group in the D-fine study in terms of sample size (dabigatran 110 or 150 mg: n=43 versus UFH: n=10), number of stents implanted (dabigatran 110 or 150 mg: 1

stent used: 55% versus UFH: 1 stents used: 40%; 2 stents used: 50%) and number of vessels intervened (2-vessel PCI: dabigatran 110 or 150 mg: 17.5% versus UFH: 20%).

The D-fine investigators discussed whether the reported laboratory data, coupled with the cases of flow-limiting thrombus in the dabigatran groups, indicate that the differences between UFH and dabigatran with regard to the attenuation of coagulation activation may be clinically relevant. Based on this assumption, results in the laboratory data together with the numerical lower incidence of primary efficacy endpoint events as well as the secondary efficacy/safety endpoint events in the rivaroxaban groups may indicate a sufficient anticoagulation during elective PCI.

Overall, due to the small sample size of this trial, results should be considered preliminary and require confirmation in a larger clinical study.

Publication(s):	none		
Date Created or Date Last Updated:	3 February 2014	Date of Clinical Study Report:	TBD

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Xarelto
Brand/Trade Name(s) ex-US	Xarelto
Generic Name	rivaroxaban
Main Product Company Code	BAY59-7939
Other Company Code(s)	
Chemical Description	IUPAC Name: 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide
Other Product Aliases	

Date of last Update/Change: 04 Mar 2013