Clinical Study Synopsis

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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.

Webposting Clinical Trial Results Synopsis

Study Sponsor:	BSP AG Germany/Bayer Healthcare Pharmaceuticals	
Study Number:	11357	NCT00332020
Study Phase:	III	
Study Title:	**RECORD 2 Study**: **RE**gulation of **C**oagulation in **OR**thopedic Surgery to Prevent **D**VT and PE, Controlled, Double-Blind, Randomized Study of BAY59-7939 in the Extended Prevention of VTE in Patients Undergoing Elective Total Hip Replacement.	
Therapeutic Area:	Prevention of venous thromboembolism (Elective total hip replacement)	
Name of Test Product:	BAY 59-7939 / Rivaroxaban	
Active Ingredient:	Rivaroxaban	
Dosage:	Rivaroxaban: 10 mg od	
Reference Therapy:	Enoxaparin	
Dosage:	Enoxaparin: 40 mg od	
Placebo:	In accordance with the double-blind design of the study rivaroxaban and enoxaparin placebo were administered to the respective treatment groups to maintain blindness	
Route of Administration:	Rivaroxaban: oral administration, Enoxaparin: subcutaneous administration	
Treatment Duration:	10-14 days for enoxaparin/placebo and 35 days for rivaroxaban/placebo	
Study Period:	Date of first subjects' first visit:	19 Feb 2006
	Date of last subjects' last visit	26 Jun 2007
Methodology:	Prospective, randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national study.	
Study Site:	123 active centers in 21 countries: Australia (6), Brazil (10), Canada (11), China (11), Colombia (5), Denmark (9), Estonia (2), India (6), Indonesia (2), Latvia (3), Lithuania (4), Mexico (2), New Zealand (2), Norway (5), Peru (7), Portugal (4), South Africa (8), South Korea (4), Sweden (9), United Kingdom (8), United States (5).	
Main Inclusion Criteria:	Men and women ≥ 18 years of age undergoing elective total hip replacement were to be enrolled.	

Study Objectives:	<u>Overall:</u> Comparison of the efficacy and safety of VTE prophylaxis with rivaroxaban 10 mg once daily administered for 5 weeks to enoxaparin 40 mg once daily administered for 10-14 days followed by placebo up to Day 35 in men and women aged 18 years or above undergoing elective THR. The efficacy and safety parameters of primary interest were centrally adjudicated by Adjudication Committees. <u>Primary:</u> Not applicable <u>Secondary:</u> Not applicable

Evaluation Criteria:	Efficacy (Primary): The primary efficacy endpoint was defined as a composite endpoint of any DVT (proximal and/or distal) and non-fatal PE and death from all causes. The analysis of the primary efficacy endpoint (and all secondary efficacy endpoints related to VTE) was based solely on the assessments made by the Independent Central Adjudication Committee (ICAC) and VTE Adjudication Committees (AC/VTE). Efficacy (Secondary): The major secondary endpoint was the incidence of the composite endpoint comprising proximal DVT, non-fatal PE and VTE-related death (referred to as 'major VTE'). Further secondary endpoints were: Incidence of symptomatic VTE (DVT, PE); incidence of DVT (total, proximal, distal); incidence of symptomatic VTE during follow-up; incidence of PE; 'net clinical benefit' assessed by the composite endpoint comprising major VTE and treatment-emergent major bleeding; incidence of the composite endpoint that results from the primary endpoint by substituting VTE related death for all death (composite of any DVT and nonfatal PE and VTE-related death); incidence of the composite endpoint that results from major VTE by substituting all cause mortality for VTE related death (composite of proximal DVT and nonfatal PE and death from all causes) Safety The main safety endpoint was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding observed after this period was to be considered separately. Pharmacokinetics: Not applicable.
Statistical Methods:	Efficacy (Primary): For the primary efficacy variable, the MITT population was the primary population used for the test for superiority of rivaroxaban as compared to enoxaparin and the PP population was used for supportive analysis. The hypothesis of equality was rejected in favor of superiority if the upper limit of the 95% CI determined for the treatment difference of rivaroxaban minus enoxaparin (with respect to the incidence) was below 0. Efficacy (Secondary): The incidence of the secondary efficacy endpoints was evaluated by estimating the difference in the incidence between treatment groups and calculating corresponding confidence intervals. Safety The safety analysis was performed in the population of subjects valid for safety analysis. Adverse events were descriptively analyzed. For the incidence of major bleeding, between-treatment differences were estimated and the corresponding 2-sided 95% CI was calculated. The incidences of any bleeding, non-major bleeding, and treatment-emergent adverse events were tabulated and stratified by treatment group. Pharmacokinetics: Not applicable.
Number of Subjects:	2509 subjects randomized; 2457 subjects treated with study drug (safety population).

Results Summary — Subject Disposition and Baseline

2457 subjects were analyzed as safety population. 1733 and 1615 subjects were valid-for-MITT analysis and PP analysis, respectively.

Results Summary — Efficacy

A 5 week rivaroxaban 10 mg od treatment regimen was both clinically effective and statistically superior to a 2 week SC enoxaparin 40 mg od treatment regimen in the prevention of VTE in subjects undergoing elective total hip replacement. Rivaroxaban met the pre-specified primary and secondary efficacy objectives.

- The primary efficacy endpoint was obtained from the MITT population which comprised 1733 subjects of the 2509 randomized subjects. The composite primary efficacy endpoint occurred in 17 (2.0%) and 81 (9.3%) of subjects randomized to rivaroxaban or enoxaparin, respectively; a statistically significant difference (P<0.001). This finding demonstrated the superiority (95% CI: -9.41%, -5.15%) of rivaroxaban regimen over enoxaparin regimen in preventing VTE.
- The relative risk reduction (unweighted relative risks) was 78.9% **[**95% CI: 64.7%; 87.4%**]** for the primary efficacy endpoint in the MITT population.

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- All components of the primary composite efficacy endpoint were reduced in the rivaroxaban regimen compared with the enoxaparin regimen, including proximal DVT (5 subjects vs 44 subjects [0.6% vs 5.1%]), distal DVT (11 vs 49 [1.3% versus 5.6%]), non-fatal PE (1 vs 4 [0.1% versus 0.5%]), and death (2 vs 6 [0.2% versus 0.7%]), (MITT population).
- For the major secondary endpoint, major VTE, the rivaroxaban regimen (6 subjects [0.6%]) was statistically superior to the enoxaparin regimen (49 subjects [5.1%]); (*P*<0.001; MITT population for major VTE).
- For symptomatic VTE, the rivaroxaban regimen (3 subjects [0.4%]) was statistically superior to the enoxaparin regimen (15 subjects [1.7%]) (MITT population).
- In the PP and MITT analyses, the rivaroxaban regimen was also statistically superior to the enoxaparin regimen in the incidences of Composite Endpoint II (DVT, non-fatal PE, and VTE-related death), DVT (proximal DVT and distal DVT) and symptomatic venous thromboembolism (non-fatal PE, fatal PE, proximal DVT, and distal DVT).
- In the PP and MITT for major VTE analysis the rivaroxaban regimen was also statistically superior to the enoxaparin regimen in the incidence of Composite Endpoint IV (proximal DVT, non-fatal PE, and all cause death).
- The rivaroxaban regimen was statistically superior to the enoxaparin regimen in the analysis of net clinical benefit which was the composite of major VTE and treatment-emergent major bleeding (7 subjects [0.7%] vs 50 subjects [5.2%] of the population valid for net clinical benefit).
- The results of locally reported DVTs and PEs were consistent with the results of the respective adjudicated events.
- Clotting parameters (eg, PT, PiCT) were affected as expected by the mode of action.

Table 1: Incidence of primary efficacy endpoint and its individual components as assessed by the central adjudication committee (MITT populations)

	MITT population	
Endpoint/component	**Rivaroxaban 10 mg od (N=864) n (%)**	**Enoxaparin 40 mg od (N=869) n (%)**
Primary efficacy endpoint		
Any event	17 (2.0)	81 (9.3)
Death (any cause)	2 (0.2)	6 (0.7)
Nonfatal PE	1 (0.1)	4 (0.5)
Proximal and/or distal DVT	14 (1.6)	71 (8.2)
Components		
Death (VTE related)	0 (0.0)	1 (0.1)
Death (not VTE related)	0 (0.0)	4 (0.5)
Death (unexplained)	2 (0.2)	1 (0.1)
DVT, proximal	5 (0.6)	44 (5.1)
DVT, distal	11 (1.3)	49 (5.6)

Abbreviations: MITT=modified intent-to-treat; od=once daily; PP=per protocol; PE=pulmonary embolism; DVT=deep vein thrombosis; VTE=venous thromboembolism

Note the MITT population was the primary efficacy population

Results Summary — Pharmacokinetics: Not applicable.

Results Summary — Safety

Of the 2509 randomized subjects, 2457 were exposed to study drug (rivaroxaban: 1228, enoxaparin: 1229) and included in the safety population. Generally, the safety results indicated a comparable safety profile of rivaroxaban to enoxaparin despite different treatment durations between the two treatment groups resulting in a longer exposure to active study medication for the rivaroxaban 10 mg od treated subjects. This conclusion is based on the following findings:

- The incidence of treatment-emergent adverse events (62.5% rivaroxaban vs 65.7% enoxaparin), including those that were considered to be treatment-related (20.0% rivaroxaban vs 20.3% enoxaparin), and the incidence of discontinuations due to adverse events (3.8% rivaroxaban vs 5.2% enoxaparin) were numerically slightly higher in the enoxaparin 40 mg od group, but essentially similar between the 2 treatment groups.
- The incidence of adverse events starting >2 days after stop of study drug (*ie*, post-treatment adverse events) was similar between the 2 treatment groups (8.7% rivaroxaban, 9.0% enoxaparin). The incidence of serious treatment-emergent adverse events was numerically slightly higher on treatment with enoxaparin (7.3% rivaroxaban, 10.7% enoxaparin).

- There were 10 deaths in the safety population (2 rivaroxaban and 8 enoxaparin) and one additional death in a subject randomized to rivaroxaban who did not receive study medication and thus, was not included in the safety population.
- The incidence of treatment-emergent major bleeding events was very low in both treatment groups (one subject each; <0.1%). There were no fatal bleeding events reported in either treatment group.
- The incidence of treatment-emergent major and non-major clinically relevant bleeding events (3.3% rivaroxaban vs 2.8% enoxaparin) as well as all treatment-emergent bleeding events (6.6% rivaroxaban vs 5.5% enoxaparin) was relatively low and similar between the 2 treatment groups. Likewise, the respective statistical tests did not show significant differences (*P*>0.05) between the 2 treatment groups.
- The rates of major bleeding events including clinically overt bleeding associated with a fall in hemoglobin ≥ 2 g/dL and clinically overt bleeding leading to transfusions ≥2 units of whole blood or packed cells were comparable between treatment groups (1.9% rivaroxaban vs 1.6% enoxaparin).
- The incidence rates of pre-defined abnormal liver function tests were similar in both treatment groups.

The number of subjects in this study with significant post-operative abnormalities in liver function tests was too low to draw a conclusion regarding any potential effect of either study drug on hepatic function.

Table 2: Adverse event summary (safety population)

Adverse event type	Rivaroxaban 10 mg od (N=1228) n (%)	Enoxaparin 40 mg od (N=1229) n (%)
Any treatment-emergent event	768 (62.5)	807 (65.7)
Any treatment-emergent event, excluding bleeding, acute DVT and PE events	742 (60.4)	758 (61.7)
Any treatment-emergent bleeding event	91 (7.4)	75 (6.1)
Any treatment-emergent acute DVT or PE event	38 (3.1)	88 (7.2)
Any drug-related treatment-emergent event	245 (20.0)	249 (20.3)
Any drug-related treatment-emergent event, excluding bleeding, acute DVT, and PE events	213 (17.3)	221 (18.0)
Any drug-related treatment-emergent bleeding event	51 (4.2)	40 (3.3)
Any drug-related treatment-emergent acute DVT or PE event	0 (0.0)	0 (0.0)
Any adverse event starting >2 days after stop of study drug	107 (8.7)	110 (9.0)
Any serious treatment-emergent event	90 (7.3)	131 (10.7)
Any drug-related serious treatment-emergent event	13 (1.1)	17 (1.4)
Any serious event starting >2 days after stop of study drug	25 (2.0)	27 (2.2)
Any adverse event resulting in permanent discontinuation of study drug	46 (3.8)	64 (5.2)
Any adverse event resulting in (prolonged) hospitalization	84 (6.8)	114 (9.3)

Abbreviations: DVT = deep vein thrombosis; od = once daily; PE = pulmonary embolism

Conclusion(s)

In this large double-blind study, comparing oral administration of rivaroxaban 10 mg od in the extended prevention (5 weeks) of VTE in subjects undergoing elective total hip replacement vs 10 to 14 day treatment with subcutaneous enoxaparin 40 mg , rivaroxaban was both clinically effective and statistically superior to enoxaparin. Rivaroxaban met the prespecified primary and secondary efficacy objectives. The relative risk reduction (unweighted relative risks) was 78.9% for the primary efficacy endpoint. The clinical benefit of rivaroxaban was accompanied by a favorable safety profile, which was comparable to enoxaparin in terms of adverse event rates, treatment-emergent as well as during follow-up. The incidence of major and non-major clinically relevant bleeding events as well as all bleeding events was similar between the 2 treatment groups.

The efficacy and safety results of this study support the beneficial use of rivaroxaban in the extended prevention (5 weeks) of VTE for subjects undergoing elective total hip replacement.

Publication(s): Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008;372(9632):31-9.

Updated: 17 Oct 2008

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