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:	Bayer HealthCare Pharmaceuticals Inc.	
Study Number:	11355	NCT00362232
Study Phase:	3	
Study Title:	**RECORD 4 Study**: **RE**gulation of **C**oagulation in **OR**thopedic Surgery to Prevent **D**VT and PE; a controlled, double-blind, randomized study of BAY 59-7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement	
Therapeutic Area:	cardiovascular	
Name of Test Product:	rivaroxaban	
Active Ingredient:	rivaroxaban	
Dosage:	10 mg od	
Reference Therapy:	Lovenox® (enoxaparin sodium)	
Dosage:	30 mg bid	
Placebo:	matching placebo tablets and injection	
Route of Administration:	oral (rivaroxaban or placebo); SC injection (enoxaparin or placebo)	
Treatment Duration:	12 ± 2 days	
Study Period:	Date of first subjects' first visit:	16 Jun 2006
	Date of last subjects' last visit	31 Jan 2008
Methodology:	Prospective, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multicenter, and multinational trial in patients undergoing elective total knee replacement.	
Study Site:	131 centers in the following countries screened subjects for inclusion in this study (number of centers in parentheses): United States (48), Canada (18), Bulgaria (3), Denmark (6), India (15), Israel (7), Lithuania (5), Mexico (7), Pakistan (3), Poland (10), Sri Lanka (3), and Sweden (6).	
Main Inclusion Criteria:	Men and women ≥ 18 years of age undergoing elective TKR.	
Study Objectives:	The objective of this trial was to assess the efficacy and safety of rivaroxaban 10 mg once daily dosing in prevention of venous thromboembolic events (VTE) in men and women aged 18 years or above undergoing elective total knee replacement (TKR).	

Evaluation Criteria:	**Efficacy (Primary):** The primary efficacy endpoint was a composite endpoint of: • Any DVT (proximal and/or distal), • Non-fatal pulmonary embolism (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 efficacy endpoint was the incidence of the composite endpoint comprising proximal DVT, non-fatal PE, and VTE-related death (ie, "major VTE"). Additional secondary endpoints were: • Incidence of DVT (total, proximal, distal) • Incidence of symptomatic VTE (DVT, PE) • Incidence of symptomatic VTE during follow-up (ie, after the end of the time window for primary efficacy assessment) • 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 [proximal and/or distal] and non-fatal 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 non-fatal PE and death from all causes) An additional study endpoint was healthcare utilization, assessed by duration of hospitalization, any re-hospitalization during the entire study period, and rehabilitation center stay following hospital discharge. **Safety** The main safety endpoint was the incidence of treatment-emergent major bleeding observed no later than 2 days after the last intake of study drug. Major bleeding observed after this period was assessed separately. The analysis of the primary safety endpoint was based solely on the assessment and classification made by the Bleeding Event Committee. Adverse events that started > 2 days after the last intake of study drug were not considered to be "treatment-emergent." Other safety variables included: • Incidence of any treatment-emergent bleeding observed no later than 2 days after last intake of study drug • Incidence of non-major treatment-emergent bleeding observed no later than 2 days after last intake of study drug • Incidence of postoperative bleeding (ie, any, non-major, major) • Incidence of surgical site bleedings associated with ≥ 2 g/dL fall in hemoglobin or leading to infusion of ≥ 2 units of whole blood or packed cells • Treatment-emergent adverse events • Treatment-emergent serious adverse events • Deaths • Adverse events starting > 2 days after stop of treatment • Adjudicated cardiovascular events (on treatment/off treatment) • Incidence of (prolonged) hospitalization • Transfusion requirements • Discontinuations due to adverse events • Amount of intra-operative blood loss • Postoperative volume in drainage • Laboratory parameters **Pharmacokinetics** Not applicable.

Statistical Methods:	**Populations:** The safety population comprised those subjects who received at least 1 dose of study drug. A subject was considered valid for the MITT analysis if the subject was (1) valid for safety analysis, (2) had undergone the appropriate surgery, and (3) had an adequate assessment of thromboembolism. The PP population was to include subjects who were (1) valid for the MITT analysis; (2) had an adequate assessment of thromboembolism that, in case of a positive finding, was done no later than 36 hours after stop of study drug or, in case of a negative finding, was done no later than 72 hours after stop of study drug; and (3) had no major protocol deviations. **Efficacy (Primary):** For the primary efficacy variable, the PP population was the primary population used for the test for non-inferiority of rivaroxaban as compared to enoxaparin and the MITT population was the primary population used for the test for superiority of rivaroxaban as compared to enoxaparin. For the primary efficacy endpoint, the difference between treatments with respect to the incidence rate was estimated and the corresponding asymptotic 2-sided 95% confidence interval (CI) was calculated. For non-inferiority testing, the hypothesis of relevant inferiority was rejected in favor of non-inferiority if the upper limit of the 95% CI for the treatment difference was below the pre-specified non-inferiority limit of 4% (absolute). If non-inferiority had been met in the PP population, a superiority test was performed based on the MITT population; the hypothesis of equality was rejected in favor of superiority if the upper limit of the 95% CI determined for the treatment difference (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 CIs. For major VTE, the major secondary endpoint, a superiority test was preceded by a non-inferiority test based on a non-inferiority limit of 1.5%. **Safety** The safety analysis was performed in the population of subjects valid for safety analysis. 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:	A total of 3148 subjects were randomized; 3034 subjects were treated with study drug (safety population). Of these, 1924 subjects were valid for the modified intent to treat (MITT) analysis and 1742 subjects were valid for the per protocol (PP) analysis.

Results Summary — Subject Disposition and Baseline

In total, 3418 subjects were screened for study eligibility; 270 subjects were screening failures and were not randomized. One center in the United States screened, but did not randomize any subjects. Therefore, 3148 subjects were randomized at 130 study centers in 12 countries to treatment with either rivaroxaban 10 mg od (1584 subjects) or enoxaparin 30 mg bid (1564 subjects). The United States had the largest number of randomized subjects (1543 [49.0%]). The countries of India, Canada, and Poland followed with 495 (15.7%), 310 (9.8%), and 245 (7.8%) randomized subjects, respectively. The countries of Sweden, Pakistan, and Bulgaria had the smallest number of randomized subjects (34 [1.1%], 37 [1.2%], and 45 [1.4%], respectively.)

A total of 310 randomized subjects discontinued study medication prematurely (159 rivaroxaban 10 mg od subjects; 151 enoxaparin 30 mg bid subjects); the difference in the rates (10.0% rivaroxaban 10 mg od versus 9.6% enoxaparin 30 mg bid) was not statistically significant (P=0.70). The most common reason for discontinuation of study medication in both treatment groups was adverse events (3.8%) followed by withdrawal of consent (3.0%). The rates were similar between treatments. It should be noted that 10 of 1584 (0.6%) rivaroxaban 10 mg od subjects versus 18 of 1564 (1.2%) enoxaparin 30 mg bid subjects discontinued treatment prematurely due to reaching the clinical endpoint, which was either reporting of a DVT or PE. In total, 2838 subjects completed the scheduled 10 to 14 day treatment period.

All randomized subjects were to have entered the follow-up period, whether or not completing the treatment phase of the study. Of 2926 subjects entering the follow-up period, 77 subjects prematurely terminated (38 of 1471 [2.6%] rivaroxaban 10 mg od subjects; 39 of 1455 [2.7%] enoxaparin 30 mg bid subjects). The most common reason for premature termination from the study during the follow-up period was lost to follow-up (27 of 1471 [1.8%]) rivaroxaban 10 mg od subjects; 28 of 1455 [1.9%] enoxaparin 30 mg bid subjects).

Demographic data, which were similar across the safety, MITT and PP populations, are described here for the safety population: approximately two-thirds of the subjects were female. The majority of subjects were White (67%). Subjects had a mean age of 64.5 years, a mean weight of 84.6 kg, and a mean BMI of 30.8 kg/m^2. There were no statistically significant differences between the treatment groups for key demographic data.

Results Summary — Efficacy

Rivaroxaban 10 mg od was both effective and statistically superior to SC enoxaparin 30 mg bid in the prevention of the composite of total VTE and death in subjects undergoing elective TKR.

- Efficacy data were obtained from 1742 (PP) of the 3148 randomized subjects. Based on the non-inferiority margin of 4%, results for the composite primary efficacy endpoint demonstrated that the objective of non-inferiority against enoxaparin was met and that rivaroxaban was at least as effective as enoxaparin in preventing VTE.
- In 1924 MITT subjects, the composite primary efficacy endpoint occurred in 67 (6.9%) and 97 (10.1%) of subjects randomized to rivaroxaban or enoxaparin, respectively; a statistically significant difference ($P = 0.012$). This finding demonstrated the superiority of rivaroxaban over enoxaparin in preventing VTE. (Point estimate of Mantel-Haenszel weighted difference to enoxaparin: -3.2% [95% CI: -5.67%, -0.71%]).
- All components of the primary composite efficacy endpoint were reduced in the presence of rivaroxaban compared with enoxaparin, including proximal DVT (0.8% versus 1.5%), distal DVT (5.9% versus 8.6%), non-fatal PE (0.5% versus 0.8%), and death (0.2% versus 0.3%), (MITT population)
- For the major secondary endpoint, major VTE, there was a lower incidence in subjects treated with rivaroxaban (1.1%) compared to enoxaparin (1.5%) (PP population valid for major VTE). The upper limit of the 95% CI for the Mantel-Haenszel weighted treatment difference (rivaroxaban minus enoxaparin) was below 1.5, but greater than 0, thereby establishing non-inferiority (based on the non-inferiority margin of 1.5%), but not superiority of rivaroxaban 10 mg od over enoxaparin 30 mg bid. (Point estimate of Mantel-Haenszel weighted difference to enoxaparin: -0.4% [95% confidence interval: -1.34%, - 0.60%]; PP population valid for major VTE)
- For symptomatic VTE, a lower incidence was observed in subjects treated with rivaroxaban (0.7%) when compared with enoxaparin (1.2%), (safety population)
- In the PP and MITT analyses, rivaroxaban had lower incidence rates of Composite Endpoint II (DVT, non-fatal PE, and VTE-related death), and Composite Endpoint IV (proximal DVT, non-fatal PE, and all-cause death) compared to enoxaparin
- The results of locally reported DVTs and PEs were consistent with the results of the respective adjudicated events
- Clotting parameters (eg, PT) 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 (PP and MITT Populations)

PER PROTOCOL POPULATION		
Endpoint/component n (%)	**Rivaroxaban 10 mg od (N=864)**	**Enoxaparin30 mg bid (N=878)**
Primary efficacy endpoint		
Any event	58 (6.7)	82 (9.3)
Death (any cause)	1 (0.1)	2 (0.2)
Non-fatal PE	3 (0.4)	4 (0.5)
Proximal and/or distal DVT	55 (6.4)	76 (8.7)
Components		
Death (VTE-related)	1 (0.1)	0
Death (not VTE-related)	0	0
Death (unexplained)	0	2 (0.2)
DVT, proximal	8 (0.9)	11 (1.2)
DVT, distal	51 (5.9)	72 (8.2)
MITT POPULATION		
	Rivaroxaban 10 mg od (N=965)	**Enoxaparin 30 mg bid (N=959)**
Primary efficacy endpoint		
Any event	67 (6.9)	97 (10.1)
Death (any cause)	2 (0.2)	3 (0.3)
Non-fatal PE	5 (0.5)	8 (0.8)
Proximal and/or distal DVT	61 (6.3)	86 (9.0)
Components		
Death (VTE-related)	1 (0.1)	0
Death (not VTE-related)	1 (0.1)	0
Death (unexplained)	0	3 (0.3)
DVT, proximal	8 (0.8)	14 (1.5)
DVT, distal	57 (5.9)	82 (8.6)

Abbreviations: bid=twice daily; DVT=deep vein thrombosis; MITT=modified intent to treat; od=once daily; PE=PE; PP=per protocol; and VTE=venous thromboembolism events.

Results Summary — Pharmacokinetics

Not applicable.

Results Summary — Safety

Of the 3148 randomized subjects, 3034 were exposed to study drug. Results indicated a comparable safety profile of rivaroxaban to enoxaparin(see Table 2 and Table 3). This conclusion is based on the following findings:

- The incidence of treatment-emergent major bleeding events was low in both treatment groups, with a few more observed with rivaroxaban (0.7% rivaroxaban versus 0.3% enoxaparin). The difference between the treatment groups was not statistically different. There was one fatal bleeding event reported (in the rivaroxaban treatment group). With regard to critical bleeding events, there was one retroperitoneal bleeding event (rivaroxaban), one intracranial bleeding (enoxaparin), and one intraspinal/haemorrhagic puncture event (enoxaparin).
- The incidence of treatment-emergent major and non-major clinically relevant bleeding events (46 [3.0%] subjects in the rivaroxaban treatment group versus 34 [2.2%] subjects in the enoxaparin treatment group) as well as all bleeding events (160 [10.5%] subjects in the rivaroxaban treatment group versus 142 [9.4%] subjects in the enoxaparin treatment group) was numerically higher in the rivaroxaban treatment group, but not statistically significantly different from enoxaparin.
- The rates of major bleeding leading to re-operation (0.3% rivaroxaban versus 0.1% enoxaparin), and extra-surgical site bleeding associated with a fall in hemoglobin ≥ 2 g/dL (0.3% versus 0%) or leading to an infusion ≥ 2 units whole blood/packed cells (0.3% versus 0%) were too small to draw conclusions
- Twelve subjects died during the study; 6 subjects were randomized to rivaroxaban 10 mg od and 6 subjects were randomized to enoxaparin 30 mg bid. Five deaths occurred during the treatment portion of the study (2 rivaroxaban 10 mg od subject and 3 enoxaparin 30 mg bid subjects).
- The incidence of treatment-emergent adverse events (80% rivaroxaban versus 81% enoxaparin), including those that were considered to be treatment related (20% rivaroxaban versus 20% enoxaparin), was similar between the 2 treatment groups
- The incidence of treatment-emergent serious adverse events was similar between the 2 treatment groups (5% rivaroxaban, 7% enoxaparin)
- The incidence of adverse events starting more than 2 days after stop of study drug was similar between the 2 treatment groups (16% rivaroxaban, 16% enoxaparin)
- During the treatment period, the number of subjects with ALT (SGPT) elevations > 3 x ULN was numerically less with rivaroxaban than with enoxaparin. During the treatment phase, 1 subject in the rivaroxaban group and 3 subjects in the enoxaparin group had ALT (SGPT) elevations > 3 x ULN and a total bilirubin > 2 x ULN. Although the number of subjects in this study with clinically relevant post-operative abnormalities in liver function tests was small, the results of this study do not suggest an adverse effect of rivaroxaban on hepatic function when compared to enoxaparin.

Table 2: Incidence of Treatment-Emergent Bleeding Events (Central Adjudication [Safety Population])

Endpoint/components n (%)	Rivaroxaban 10 mg od (N=1526)	Enoxaparin 30 mg bid (N=1508)
Any bleeding	160 (10.5)	142 (9.4)
Any major or non-major clinically relevant bleeding	46 (3.0)	34 (2.2)
Major bleeding		
Any event	10 (0.7)	4 (0.3)
Fatal bleeding	1 (0.1)	0
Critical bleeding	1 (0.1)	2 (0.1)
Clinically overt extra-surgical site bleeding associated with a fall in hemoglobin of 2 g/dL or more	4 (0.3)	0
Clinically overt extra-surgical site bleeding leading to transfusion of 2 or more units of whole blood or packed cells	4 (0.3)	0
Bleeding leading to re-operation	5 (0.3)	2 (0.1)
Non-major bleeding		
Any event	155 (10.2)	138 (9.2)
Any clinically relevant non-major bleeding event	39 (2.6)	30 (2.0)
Other non-major bleeding	124 (8.1)	112 (7.4)

Abbreviations: bid=twice daily; DVT=deep vein thrombosis; and od=once daily

Table 3: Adverse Event Summary (Safety Population)		
Adverse event type n (%)	**Rivaroxaban** 10 mg od (N=1526)	**Enoxaparin** 30 mg bid (N=1508)
Any adverse event or death	1319 (86.4)	1312 (87.0)
Any adverse event	1319 (86.4)	1312 (87.0)
Any serious adverse event	114 (7.5)	134 (8.9)
Any death	6 (0.4)	6 (0.4)
Any treatment-emergent event	1222 (80.1)	1216 (80.6)
Any treatment-emergent event, excluding bleeding, acute DVT and PE events	1206 (79.0)	1181 (78.3)
Any treatment-emergent bleeding event	172 (11.3)	151 (10.0)
Any treatment-emergent acute DVT or PE event	65 (4.3)	92 (6.1)
Any drug-related treatment emergent event	310 (20.3)	295 (19.6)
Any drug-related treatment-emergent event, excluding bleeding, acute DVT and PE events	256 (16.8)	244 (16.2)
Any drug-related treatment-emergent bleeding event	89 (5.8)	77 (5.1)
Any drug-related treatment-emergent acute DVT or PE event	0 (0.0)	0 (0.0)
Any adverse event starting more than 2 days after stop of study drug	244 (16.0)	239 (15.8)
Any serious treatment-emergent event	80 (5.2)	106 (7.0)
Any drug-related serious treatment emergent event	21 (1.4)	11 (0.7)
Any serious event starting more than 2 days after stop of study drug	36 (2.4)	35 (2.3)
Any adverse event resulting in permanent discontinuation of study drug	60 (3.9)	68 (4.5)
Any adverse event resulting in (prolonged) hospitalization	90 (5.9)	106 (7.0)
Abbreviations: bid=twice daily; DVT=deep vein thrombosis; and od=once daily		

Conclusion(s)

In this large double-blind study, oral administration of rivaroxaban 10 mg od was both effective and statistically superior to enoxaparin 30 mg SC bid in the prevention of VTE in subjects undergoing elective TKR. Rivaroxaban met the pre-specified primary and secondary efficacy objectives. 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 numerically higher with rivaroxaban, but not statistically significantly different from enoxaparin.

The efficacy and safety results of this study provide evidence for the net clinical benefit of rivaroxaban in the prevention of VTE for subjects undergoing elective TKR.

Publication(s)

Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD; RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009 May 16;373(9676):1673-80. doi: 10.1016/S0140-6736(09)60734-0. Epub 2009 May 4.

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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	

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