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:	11527	NCT00396786
Study Phase:	IIb	
Study Title:	Controlled, Double-Blind, Randomized, Dose-ranging Study of once-daily regimen of BAY59-7939 in the Prevention of VTE in Patients Undergoing Elective Total Hip Replacement -ODIXa-OD.HIP Study	
Therapeutic Area:	Prevention of venous thromboembolism	
Name of Test Product:	BAY 59-7939 / Rivaroxaban	
Active Ingredient:	Rivaroxaban	
Dosage:	Rivaroxaban: 5 mg od, 10 mg od, 20 mg od, 30 mg od and 40 mg od	
Reference Therapy:	Enoxaparin	
Dosage:	Enoxaparin: 40 mg od	
Placebo:	Rivaroxaban and enoxaparin placebo were administered to maintain blindness (double-blind study)	
Route of Administration:	Rivaroxaban: oral administration, Enoxaparin: subcutaneous administration	
Treatment Duration:	9 ± 2 days.	
Study Period:	Date of first subjects' first visit:	12 Nov 2004
	Date of last subjects' last visit	27 Jul 2005
Methodology:	Prospective, randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national trial, dose finding study in patients undergoing elective primary total hip replacement.	
Study Site:	48 centers: Germany (8), Poland (6), Israel (5), Italy (5), Austria (4), Denmark (4), Sweden (4), Belgium (3), the Netherlands (3), Norway (3), and Spain (3).	
Main Inclusion Criteria:	Men ≥18 years of age and postmenopausal women undergoing elective primary total hip replacement.x	
Study Objectives:	<u>Overall:</u> Assessment of the efficacy and safety of BAY 59-7939 5 mg – 40 mg administered once daily for the prevention of VTE in patients undergoing elective primary total hip replacement. Population pharmacokinetics and pharmacodynamics (Factor Xa activity, PT, PT INR, aPTT and HepTest). <u>Primary:</u> Not applicable <u>Secondary:</u> Not applicable	

Evaluation Criteria:	Efficacy (Primary): The primary efficacy endpoint was a composite endpoint of: • Any deep vein thrombosis (DVT) (proximal and/or distal). • Non-fatal pulmonary embolism (PE). • Death from all causes. The primary efficacy endpoints were assessed by the Venography and VTE Adjudication Committees. Efficacy (Secondary): Secondary efficacy endpoints were: Incidence of DVT (total, proximal, distal); incidence of symptomatic venous thromboembolism (VTE); incidence of major VTE (proximal DVT, PE, VTE-related death); the composite endpoint that results from the primary endpoint by substituting VTE-related deaths for all deaths; incidence of symptomatic VTE (total, PE, DVT) within 30 days after stop of treatment with the study drug. The secondary efficacy endpoints related to VTE were assessed by the Venography and VTE Adjudication Committees. Safety Main safety endpoint: the incidence of major bleeding observed after the first post-operative intake of study drug and not later than 2 days after last intake of study drug. The analysis of the primary safety endpoint was assessed by the Bleeding Adjudication Committee. Other safety variables included: Incidence of non-major bleeding (clinically significant and minor bleeding); treatment-emergent adverse and serious adverse events; deaths; adverse events starting >7 days after stop of treatment; incidence of (prolonged) hospitalization; laboratory parameters. Pharmacokinetics: The analysis of the pharmacokinetic results are reported separately.
Statistical Methods:	Efficacy (Primary): The primary efficacy analysis was performed in patients valid for per-protocol (PP) analysis. The dose-response relationship of BAY 59-7939 was investigated by a trend test. Subsequent to the trend test, each of the individual BAY 59-7939 treatment groups was compared with enoxaparin. Efficacy (Secondary): Not applicable. Safety The safety analysis was performed in the population of patients valid for safety analysis. Incidence rates of post-operative major bleeding were analyzed by a logistic regression model. Fisher's exact test was used for individual comparisons of each BAY 59-7939 treatment group with enoxaparin. Pharmacokinetics: Not applicable.
Number of Subjects:	877 subjects enrolled, 873 randomized; 852 treated, 845 valid for safety.

Results Summary — Subject Disposition and Baseline

845 subjects were analyzed as safety population. 650 and 618 subjects were valid-for-ITT analysis and PP analysis, respectively.

Results Summary — Efficacy

A short term treatment with BAY 59-7939 using an 8-fold dose range (5 to 40 mg od) was effective in preventing VTE in adult subjects undergoing elective hip replacement compared with enoxaparin, thus supporting evidence for the efficacy of BAY 59-7939 in this indication. All treatment groups receiving BAY 59-7939 had substantially lower VTE incidence rates (primary composite endpoint) than the enoxaparin group.

The study failed to detect a trend for BAY 59-7939 in the dose-response relationship regarding the primary efficacy endpoint (*P*=0.0852). This is primarily caused by the good efficacy observed in the lower dose groups, in which incidence rates were substantially lower than anticipated for sample size determination. In the PP population the VTE incidence rates (primary composite endpoint) in subjects receiving BAY 59-7939 declined from 14.9% (BAY 59-7939 5 mg od) to 6.4% (BAY 59-7939 40 mg od) compared with 25.2% in the enoxaparin group (Table 1). The incidence rate of 13.5% seen in the 30 mg od dose group is not in line with a monotonous dose response relationship, but is likely caused by random variation. During the assessment period of the primary endpoint there was no observation of non-fatal PE or death from all causes.

All doses of BAY 59-7939 except for the 5 mg od dose had lower incidence rates of *major* VTE than enoxaparin (0.9 – 2.7% vs 2.8%). Major VTE incidence rates were lowest at doses of 20 and 40 mg od (0.9 and 1.1%), the incidence rate with 5 mg was 8.5%.

Dose-dependent decreases in factor Xa activity and prolongation of PT and PT INR were observed with increasing doses of BAY 59-7939.

Table 1: Incidence rate of primary efficacy endpoint (PP population)

Endpoint n (%)	BAY 59-7939 5 mg od (N=94)	BAY 59-7939 10 mg od (N=113)	BAY 59-7939 20 mg od (N=106)
Primary efficacy endpoint	14 (14.9%)	12 (10.6%)	9 (8.5%)
Death (any cause)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis	14 (14.9%)	12 (10.6%)	9 (8.5%)
Endpoint n (%)	**BAY 59-7939 30 mg od (N=104)**	**BAY 59-7939 40 mg od (N=94)**	**Enoxaparin 40 mg od (N=107)**
Primary efficacy endpoint	14 (13.5%)	6 (6.4%)	27 (25.2%)
Death (any cause)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis	14 (13.5%)	6 (6.4%)	27 (25.2%)

Results Summary — Pharmacokinetics: Results will be reported separately.

Results Summary — Safety

The percentages of *major post-operative* bleeding events increased with increasing BAY 59-7939 doses indicating a clear dose-response. Percentages of *major* bleedings were similar for BAY 59-7939 at doses of 5 and 10 mg od and enoxaparin, which also was the case for any *post-operative* bleedin events. It is important to note that there were neither fatal bleedings or bleedings in critical organs, nor clinically significant bleedings that could not be treated. All bleedings adjudicated as major were related to the surgical site.

The number of postoperative bleeding events increased with increasing BAY 59-7939 doses indicating a clear dose-response (Table 2). Differences between enoxaparin and any of the BAY 59-7939 dose groups with regard to the number of post-operative major bleeding events were not statistically significant. About 65% of post-operative bleeding events occurred on the day of surgery or within 3 days after surgery and 7% of first post-operative bleeding events occurred 6 or 7 days after surgery.

Table 2: Incidence rates of post-operative bleeding events (safety population)[a]

Bleeding event n (%)	BAY 59-7939 5 mg od (N=128)	BAY 59-7939 10 mg od (N=142)	BAY 59-7939 20 mg od (N=139)
Any event	10 (8%)	9 (6%)	13 (9%)
Major bleeding	3 (2%)	1 (1%)	6 (4%)
Clinically overt bleeding associated with fall in Hb [b]	2 (2%)	0 (0%)	4 (3%)
Clinically overt bleeding leading to blood transfusion [c]	3 (2%)	1 (1%)	5 (4%)
Bleeding leading to re-operation	0 (0%)	0 (0%)	1 (1%)
Clinically overt bleeding warranting treatment cessation	0 (0%)	0 (0%)	1 (1%)
Bleeding event n (%)	**BAY 59-7939 30 mg od (N=142)**	**BAY 59-7939 40 mg od (N=137)**	**Enoxaparin 40 mg od (N=157)**
Any event	18 (13%)	25 (18%)	14 (9%)
Major bleeding	7 (5%)	7 (5%)	3 (2%)
Clinically overt bleeding associated with fall in Hb [b]	6 (4%)	5 (4%)	1 (1%)
Clinically overt bleeding leading to blood transfusion [c]	6 (4%)	6 (4%)	3 (2%)
Bleeding leading to re-operation	1 (1%)	0 (0%)	0 (0%)
Clinically overt bleeding warranting treatment cessation	0 (0%)	1 (1%)	0 (0%)

a Bleeding events starting more than 2 days after last study medication intake were not considered.

b Associated with a fall in Hb of ≥2 g/dL within 24 h from first post-operative day.

c Leading to transfusion of ≥2 units of blood.

The net clinical benefit of the individual treatments was assessed based on a composite endpoint of major VTE (proximal DVT, PE, VTE-related death) and post-operative major bleeding events. Low incidences of the composite endpoint indicate a high net clinical benefit. The lowest incidence rate with 3.5% and thus the highest net clinical benefit was seen in the BAY 59-7939 10 mg od dose group. The incidence rate for the 20 mg dose group of BAY 59-7939 was 6.1% and still comparable to 5.2% as observed in the enoxaparin group. Incidence rates ranged from 8.0% to 11.1% in the other BAY 59-7939 dose groups.

A summary overview of adverse events is presented in Table 3. The most frequent drug related treatment emergent events were of MedDRA system organ class investigations related to liver enzyme parameters and decrease of hemoglobin as well as vascular disorders related to hematoma. Decrease of hemoglobin was not considered serious. Of the hematoma 3 (2 in the 30 mg Bay 59-7939 group and 1 in the 40 mg Bay 59-7939 group) were considered drug-related and treatment emergent serious. Increases in liver enzymes were reported as serious treatment emergent adverse event most frequently in the 30 mg Bay 59-7939 group, whereas all other doses presented comparable to enoxaparin.

Table 3: Summary of adverse events (safety population)

Adverse event type n (%)	BAY 59-7939 5 mg od (N=128)	BAY 59-7939 10 mg od (N=142)	BAY 59-7939 20 mg od (N=139)
Treatment-emergent adverse events (AEs)	93 (72.7%)	100 (70.4%)	106 (76.3%)
Drug-related treatment emergent AEs	35 (27.3%)	30 (21.1%)	35 (25.2%)
Discontinuations of study drug due to AEs	4 (3.1%)	0 (0.0%)	3 (2.2%)
Treatment-emergent SAEs	8 (6.3%)	2 (1.4%)	14 (10.1%)
Drug-related treatment emergent SAEs	3 (2.3%)	1 (0.7%)	9 (6.5%)
AEs leading to (prolonged) hospitalization	7 (5.5%)	3 (2.1%)	11 (7.9%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adverse event type n (%)	**BAY 59-7939 30 mg od (N=142)**	**BAY 59-7939 40 mg od (N=137)**	**Enoxaparin 40 mg od (N=157)**
Treatment-emergent AEs	111 (78.2%)	109 (79.6%)	125 (79.6%)
Drug-related treatment emergent AEs	41 (28.9%)	48 (35.0%)	42 (26.8%)
Discontinuations of study drug due to AEs	4 (2.8%)	7 (5.1%)	6 (3.8%)
Treatment-emergent SAEs	17 (12.0%)	12 (8.8%)	9 (5.7%)
Drug-related treatment emergent SAEs	11 (7.7%)	3 (2.2%)	4 (2.5%)
AEs leading to (prolonged) hospitalization	8 (5.6%)	7 (5.1%)	4 (2.5%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)

BAY 59-7939 did not have untoward effects on ECG parameters including QTc.

BAY 59-7939 did not reveal any substance-specific effects on laboratory parameters, including liver enzymes, when compared with enoxaparin. No signal of liver toxicity was detected.

Conclusion(s)

Incidence rates of venous thromboembolic events (VTE) observed with BAY 59-7939 (5 to 40 mg administered once daily orally) were lower than that observed with enoxaparin (40 mg administered once daily subcutaneously). The study showed that a short term treatment with BAY 59-7939 prevented VTEs in adult subjects undergoing elective hip replacement, thus supporting the efficacy of BAY 59-7939 in this indication. The analysis of laboratory and ECG parameters did not indicate untoward effects of BAY 59-7939 when compared with enoxaparin. The net clinical benefit (as assessed by the composite endpoint of major bleeding events plus major VTE) of the 10 and 20 mg doses was comparable to that of enoxaparin. Overall, the study supports the use of 10 mg BAY 59-7939 once daily as recommended dose.

Publication(s)

Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. A Once-Daily, Oral, Direct Factor Xa Inhibitor, Rivaroxaban (BAY 59-7939), for Thromboprophylaxis After Total Hip Replacement. Circulation 2006;114(22):2374-81.

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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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