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Clinical Study Synopsis

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Webposting Clinical Trial Results Synopsis

Study Sponsor:	BSP AG Germany/Bayer Healthcare Pharmaceuticals	
Study Number:	10942	NCT00839826
Study Phase:	IIa	
Study Title:	**O**ral **Di**rect Factor **Xa** Inhibitor BAY 59-7939 in the Prevention of VTE in Patients Undergoing Total **Hip** Replacement. **ODiXahip** - a phase IIa dose escalating proof-of-principle trial	
Therapeutic Area:	Prevention of venous thromboembolism	
Name of Test Product:	BAY 59-7939 / Rivaroxaban	
Active Ingredient:	Rivaroxaban	
Dosage:	Rivaroxaban: 2.5 mg bid, 5 mg bid, 10 mg bid, 20 mg bid, 30 mg bid and 30 mg od	
Reference Therapy:	Enoxaparin	
Dosage:	Enoxaparin: 40 mg od	
Placebo:	Not applicable	
Route of Administration:	Rivaroxaban: oral administration, Enoxaparin: subcutaneous administration	
Treatment Duration:	8 days for rivaroxaban and enoxaparin	
Study Period:	Date of first subjects' first visit:	15 Dec 2002
	Date of last subjects' last visit	19 Dec 2003
Methodology:	Prospective, randomized, open-label, active comparator controlled, multi-center and multi-national trial designed as a proof-of-principle dose finding study in patients undergoing elective primary total hip replacement.	
Study Site:	41 centers: Germany (7), Poland (7), Belgium (4), Denmark (4), Israel (4), Austria (3), France (3), Norway (3), Sweden (3), the Netherlands (2), and the UK (1).	
Main Inclusion Criteria:	Men ≥18 years of age and postmenopausal women undergoing elective primary total hip replacement.	

Study Objectives:	<u>Overall:</u> Assessment of safety, tolerability, and efficacy of BAY 59-7939 at oral doses of 2.5, 5, 10, 20, and 30 mg bid and 30 mg od compared with subcutaneously administered enoxaparin 40 mg in the prevention of venous thromboembolism in men and postmenopausal women undergoing elective primary total hip replacement. <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 endpoint was evaluated 5 - 9 days after surgery. The analysis of the primary efficacy endpoint was solely based on the assessments made by the adjudication committee. Efficacy (Secondary): Secondary efficacy endpoints were: Incidence of DVT (total, proximal, distal); incidence of symptomatic venous thromboembolism (VTE); the composite endpoint that results from the primary endpoint by using VTE-related death; incidence of symptomatic VTE (total, PE, DVT) within 30 days after stop of treatment with the study drug. The secondary efficacy endpoints were assessed by the adjudication committee. Safety The main safety endpoint was the incidence of major bleeding events observed after the first intake of study drug and not later than 2 days after last intake of study drug. Major bleeding observed after this period was assessed separately. The primary safety endpoint was assessed by the Safety Committee and Bleeding Committee. Pharmacokinetics: Not applicable
Statistical Methods:	Efficacy (Primary): The primary efficacy analysis was performed in patients valid for per-protocol (PP) analysis. The intent-to-treat (ITT) analysis was performed as a supportive 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): The incidence rates of secondary efficacy parameters were tabulated stratified by treatment group. Safety The safety analysis was performed in the population of patients valid for safety analysis. Safety variables were tabulated stratified by treatment group. No formal statistical tests were performed for safety variables. Interim analysis: Major bleeding events were continuously monitored by the Steering Committee in an unblinded manner for each of the dose stages. Stopping rules were specified in the study protocol. It had been recommended to terminate a dose stage prematurely either in case that the lower limit of the 2-sided 95% confidence interval for the event rate of major bleeding exceeded 5% or if 6 or more major bleedings had been observed in the corresponding dose stage. Pharmacokinetics: Not applicable
Number of Subjects:	642 patients enrolled and 641 randomized at 41 centers.

Results Summary — Subject Disposition and Baseline

625 subjects were analyzed as safety population. 491 and 466 subjects were valid-for-ITT analysis and PP analysis, respectively.

Results Summary — Efficacy

An 8-day treatment with BAY 59-7939 using a wide, 12-fold dose range (2.5 to 30 mg bid) prevented VTE in adult subjects undergoing elective hip replacement compared with enoxaparin, thus confirming the proof-of-principle of BAY 59-7939 in this indication. All tested BAY 59-7939 doses including the lowest dose of 2.5 mg bid showed results that were within the confidence limits of enoxaparin and thus indicate a broad therapeutic range. However, caution must be exercised not to over interpret the data in any specific direction because of widely overlapping confidence intervals and the open-label design of the study.

The reduction of the VTE incidence rates (primary composite endpoint comprising DVT, PE, and death) by BAY 59-7939 was dose-dependent in the range from 2.5 to 20 mg bid with incidence rates declining from 22.2% to 10.2% compared with 16.8% in the enoxaparin group. The incidence rate in the 30 mg bid dose group was 17.4% (Table 1).

Total daily doses of 20, 30, and 40mg of BAY 59-7939 had lower incidence rates of major VTE than enoxaparin. Major VTE incidence rates occurring with 60 mg BAY 59-7939 and enoxaparin were similar.

The increase in total VTE with the 30 mg bid dose after a decrease in the incidence rates from 2.5 to 20 mg bid cannot be explained at this time. Whether the 30 mg bid or possibly the 20 mg bid results are chance findings is currently unclear. A 16.8% VTE incidence rate for enoxaparin is in line with published data.

Testing for a dose trend regarding the primary efficacy endpoint of total VTE resulted in a *P* value of *P*=0.0504, which slightly exceeded the pre-specified limit of 0.05. The hypothesis of no trend could not be rejected, which means that statistically no trend could be shown. On the other hand, a non-confirmatory analysis of major VTE incidence rates showed a statistically significant dose trend (*P*=0.0108) for BAY 59-7939 to lower the incidence rates of major VTE. Thus, there is evidence for a clear dose-response relationship with regard to the treatment effects of BAY 59-7939.

As expected, dose-dependent decreases in factor Xa activity and increases in PTINR were observed with increasing doses of BAY 59-7939.

Table 1: Incidence rate of primary efficacy endpoint and its individual components (PP population)

Endpoint	BAY 59-7939 2.5 mg bid (N = 63) n (%)	BAY 59-7939 5 mg bid (N = 63) n (%)	BAY 59-7939 10 mg bid (N = 55) n (%)	BAY 59-7939 30 mg od (N = 73) n (%)
Primary efficacy endpoint	14 (22.2%)	15 (23.8%)	11 (20.0%)	11 (15.1%)
Death (any cause)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Pulmonary embolism	2 (3.2%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
DVT, all	13 (20.6%)	15 (23.8%)	11 (20.0%)	9 (12.3%)

Endpoint	BAY 59-7939 20 mg bid (N = 59) n (%)	BAY 59-7939 30 mg bid (N = 46) n (%)	Enoxaparin 40 mg od (N = 107) n (%)
Primary efficacy endpoint	6 (10.2%)	8 (17.4%)	18 (16.8%)
Death (any cause)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT, all	6 (10.2%)	8 (17.4%)	18 (16.8%)

Results Summary — Pharmacokinetics: Not applicable

Results Summary — Safety

There were 2 deaths: 1 patient in the BAY 59-7939 2.5 mg dose group due to pulmonary embolism and 1 patient receiving BAY 59-7939 30 mg od for an unknown cause. None of the deaths was considered related to study drug.

The number of post-operative major bleeding events increased with increasing BAY 59-7939 doses indicating a monotonous dose-response (Table 2Table 2). However, it is important to note that there were neither fatal bleeds or bleeds in critical organs, nor clinically significant bleeds that could not be treated. Most bleeds adjudicated as major were related to the surgical site and no wound healing complications were reported in these subjects. Since this trial had an open-label design, the limitations of making meaningful interpretations of bleeding events must be recognized.

Discontinuations of study drug due to adverse events were reported in 13 subjects (17.6%) receiving BAY 59-7939 30 mg bid. In retrospect, such discontinuations were not justified in at least 3 subjects, who were discontinued because of increased INR values (2.76, 3.1, and 3.69) without any concomitant bleeding events. In these cases, the investigators were obviously wrongly led by falsely elevated INR values, although they had been advised not to include the INR parameter into any safety considerations.

More than 90% of first post-operative major bleeding events occurred on the day of surgery or within 3 days after surgery and less than 10% of post-operative major bleeding events started 4 or 5 days after surgery.

Adverse events leading to (prolonged) hospitalization were considered of special clinical relevance and a hard safety criterion in an open-label trial. When pooling the overall numbers of subjects receiving BAY 59-7939 and comparing them with the number of subjects receiving enoxaparin, the overall percentage of subjects with (prolonged) hospitalizations was slightly lower with BAY 59-7939 (5.8%) than with enoxaparin (6.8%).

BAY 59-7939 did not have untoward effects on ECG parameters. In particular, there was no indication for any treatment-emergent QT-prolonging effects of the drug in a total of 418 subjects with normal QT at baseline receiving BAY 59-7939.

BAY 59-7939 did not reveal any substance-specific effects on laboratory parameters, including liver enzymes, for the treatment duration used in this study when compared with enoxaparin. In considering any laboratory changes, interventions related to surgery and anesthesiology must be taken into account.

The steering committee of the trial evaluated the 30 mg bid dose as the maximum tolerated dose and decided to stop further BAY 59-7939 dose escalation because of the increased number of post-operative major bleeding events observed in this dose group. For this reason the BAY 59-7939 dose of 40 mg bid, which was foreseen in the study protocol, was not tested.

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

Bleeding classification	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Any bleeding event	7 (9.2%)	7 (8.8%)	7 (10.3%)	19 (21.6%)
Any major bleeding event	0 (0.0%)	2 (2.5%)	2 (2.9%)	4 (4.5%)
Clinically overt bleeding associated with fall in Hb	0 (0.0%)	2 (2.5%)	1 (1.5%)	4 (4.5%)
Clinically overt bleeding leading to blood transfusion	0 (0.0%)	2 (2.5%)	2 (2.9%)	3 (3.4%)
Bleeding leading to re-operation	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
Bleeding warranting treatment cessation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Bleeding classification	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Any bleeding event	14 (18.2%)	18 (24.3%)	11 (6.8%)
Any major bleeding event	5 (6.5%)	8 (10.8%)	0 (0.0%)
Clinically overt bleeding associated with fall in Hb	3 (3.9%)	7 (9.5%)	0 (0.0%)
Clinically overt bleeding leading to blood transfusion	0 (0.0%)	6 (8.1%)	0 (0.0%)
Bleeding leading to re-operation	0 (0.0%)	1 (1.4%)	0 (0.0%)
Bleeding warranting treatment cessation	2 (2.6%)	3 (4.1%)	0 (0.0%)

Note: Bleeding events starting more than 2 days after last study medication intake not considered.

Conclusion(s)

This study demonstrated the proof-of-principle of BAY 59-7939 in preventing DVT, PE, and death (primary composite endpoint) in subjects undergoing elective hip replacement. BAY 59-7939 may also work when administered once daily. Higher BAY 59-7939 doses than 30 mg bid are not recommended because the net clinical benefit (sum of the incidence rates of major VTE and post-operative major bleeding) would disappear. The results of this study will serve as the basis for further phase II development of the compound.

Publication(s)

Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. Dose-escalation study of rivaroxaban (BAY 59-7939)--an oral, direct Factor Xa inhibitor--for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thromb Res 2007;120(5):685-93.

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