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:	11223	NCT00839163
Study Phase:	II	
Study Title:	Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients with Acute Symptomatic Proximal Deep Vein Thrombosis. - ODIXa-DVT Study. A prospective randomized, multinational, multicenter, partially blinded, parallel-group, open-label active comparator controlled phase II dose finding and proof of principle trial.	
Therapeutic Area:	Acute symptomatic proximal deep vein thrombosis.	
Name of Test Product:	BAY 59-7939 / Rivaroxaban	
Active Ingredient:	Rivaroxaban	
Dosage:	Rivaroxaban: 10 mg bid; 20 mg bid; 30 mg bid and 40 mg od	
Reference Therapy:	Enoxaparin for 5-7 days followed by vitamin K antagonist treatment	
Dosage:	Eonxaparin: 1 mg /kg bodyweight bid; vitamin K antagonist (VKA): dose adjusted to maintain the INR with the therapeutic range of 2-3.	
Placebo:	Rivaroxaban placebo tablets for maintaining blindness between the rivaroxaban treatment arms.	
Route of Administration:	Rivaroxaban and vitamin K antagonists: oral administration, Enoxaparin: subcutaneous administration	
Treatment Duration:	The planned treatment duration was 84 days with a follow-up period of 1 month.	
Study Period:	Date of first subjects' first visit:	24 Mar 2004
	Date of last subjects' last visit	05 Oct 2005
Methodology:	Prospective, randomized, multinational, multicenter, partially blinded, parallel-group, open-label active comparator controlled study. It was a proof-of-principle and dose finding study for acute symptomatic deep vein thrombosis treatment.	
Study Site:	107 active centers in 19 countries: Australia (7), Austria (3), Belgium (2), Brazil (2), Canada (9), Colombia (3), Czech Republic (7), Germany (10), Hungary (4), Israel (7), Italy (10), Netherlands (7), New Zealand (3), Peru (3), Poland (8), South Africa (5), Spain (8), Sweden (5), and Switzerland (4).	
Main Inclusion Criteria:	Men and women ≥18 years of age with acute symptomatic proximal deep vein thrombosis (objectively confirmed by complete compression ultrasound [CCUS]) were included.	
Study Objectives:	Overall: Assessment of the efficacy and safety of BAY 59-7939 for the treatment of acute symptomatic proximal deep vein thrombosis (objectively confirmed by complete compression ultrasound; CCUS) in adult subjects. Primary: Not applicable. Secondary: Assessment of pharmacokinetic and pharmacodynamic parameters (including activated partial thrombin time, prothrombin time, Factor Xa activity and Heptest).	

Evaluation Criteria:	Efficacy (Primary): The primary efficacy endpoint was the response to treatment as determined by CCUS after 3 weeks of treatment. A positive response was defined as an improvement in the CCUS score by 4 score points compared to baseline. However, any confirmed symptomatic recurrence or extension of DVT, any confirmed symptomatic pulmonary embolism (PE) or any venous thromboembolism (VTE)-related death up to Day 21 defined a negative response even in case of an improved CCUS at Day 21. Efficacy (Secondary): Secondary efficacy endpoints were: response to treatment on Day 21 as determined by CCUS and perfusion lung scan (PLS), where a positive response was defined as an improvement in the CCUS and/or PLS without any deterioration in either, response to treatment at Day 84 as assessed by CCUS, residual vein diameter as assessed by CCUS on Day 84 (actually, this endpoint was not evaluated as no data were provided by CCUS adjudication center), incidence of symptomatic and confirmed recurrence or extension of DVT during the 3-month treatment period, incidence of symptomatic and confirmed PE during the 3-month treatment period, composite endpoint of symptomatic and confirmed recurrence and extension of DVT and symptomatic PE (nonfatal DVT and/or nonfatal PE) and deaths during the 3 months treatment period, composite endpoint of symptomatic and confirmed recurrence and extension of DVT and symptomatic PE (nonfatal DVT and/or nonfatal PE) and deaths related to VTE during the 3 months treatment period, and incidence of symptomatic and confirmed recurrence and extension of DVT and symptomatic PE within 30 days after stop of treatment with study drug. The analysis of the efficacy endpoints was based on the assessments made by the adjudication committees. Safety The primary safety endpoint was the incidence of treatment-emergent major bleeding events (fatal bleeding, clinically overt bleeding associated with a fall in hemoglobin level of ≥2 g/dL, clinically overt bleeding leading to transfusion of ≥2 units of packed cells or whole blood, and bleeding into critical organ, *eg*, retroperitoneal, intracranial, intraocular, intra-articular bleeding, and clinically overt bleeding warranting treatment cessation) starting not later than 7 days after the last intake of study drug. Major bleeding observed after this period were to be considered separately. The analysis of the primary safety endpoint was solely based on the classification made by the adjudication 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 with regard to the response rate was investigated by a trend test (likelihood ratio test within a logistic regression model including the total daily dosage of BAY 59-7939 as a covariate and country as a fixed effect). Subsequent to the trend test, each of the individual BAY 59-7939 treatment groups was compared with enoxaparin using 2-sided Fisher's exact test Efficacy (Secondary): Not applicable. Safety The safety analysis was performed in the safety population. The incidence rates of major bleedings was tabulated stratified by treatment group and analyzed using a logistic regression model (including "dosage" as covariate) for the trend analysis and 2-sided Fisher's exact test for the pair-wise comparisons with the comparator VKA/enoxaparin. Pharmacokinetics: Not applicable.
Number of Subjects:	613 subjects randomized; 604 subjects treated with study drug (safety population).

Results Summary — Subject Disposition and Baseline

604 subjects were analyzed as safety population. 543 and 528 subjects were valid-for-ITT analysis and PP analysis, respectively.

Results Summary — Efficacy

Generally, VTE events and major bleedings were rare in each treatment group. The primary analysis at visit Day 21 showed that the response rate within the BAY 59-7939 groups ranged between 44% (BAY 59-7939 40 mg od group) and 59% (BAY 59-7939 20 mg bid group); the response rate in the comparator group was 46% (see Table 1).

Table 1: Response to treatment based on CCUS thrombus score and confirmed VTE events at visit Day 21 (PP population)[a]

Cut Off Score		BAY 59-7939 10 mg bid (N=100)	BAY 59-7939 20 mg bid (N=98)	BAY 59-7939 40 mg od (N=112)	BAY 59-7939 30 mg bid (N=109)	VKA / enoxaparin (N=109)
1 point	Unchanged	13 (13.0%)	9 (9.2%)	16 (14.3%)	13 (11.9%)	18 (16.5%)
	Improved	84 (84.0%)	88 (89.8%)	92 (82.1%)	94 (86.2%)	89 (81.7%)
	Deteriorated	3 (3.0%)	1 (1.0%)	4 (3.6%)	2 (1.8%)	2 (1.8%)
2 points	Unchanged	21 (21.0%)	21 (21.4%)	26 (23.2%)	23 (21.1%)	30 (27.5%)
	Improved	77 (77.0%)	76 (77.6%)	83 (74.1%)	86 (78.9%)	79 (72.5%)
	Deteriorated	2 (2.0%)	1 (1.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)
3 points	Unchanged	35 (35.0%)	30 (30.6%)	51 (45.5%)	37 (33.9%)	53 (48.6%)
	Improved	64 (64.0%)	67 (68.4%)	60 (53.6%)	72 (66.1%)	56 (51.4%)
	Deteriorated	1 (1.0%)	1 (1.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
4 points	Unchanged	46 (46.0%)	39 (39.8%)	63 (56.3%)	47 (43.1%)	59 (54.1%)
	Improved	53 (53.0%)	58 (59.2%)	49 (43.8%)	62 (56.9%)	50 (45.9%)
	Deteriorated	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
30% change	Unchanged	44 (44.0%)	50 (51.0%)	68 (60.7%)	52 (47.7%)	64 (58.7%)
	Improved	54 (54.0%)	47 (48.0%)	42 (37.5%)	57 (52.3%)	45 (41.3%)
	Deteriorated	2 (2.0%)	1 (1.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)

a For the PP population only those measurements and events were taken into account that occurred not later than 3 days after end of treatment.
bid – twice a day, od – once daily, VKA - vitamin K antagonist, PP – per protocol,
CCUS - complete compression ultrasound

The confirmatory trend analysis did not show a significant effect of the BAY 59-7939 dosage on the response rate (P = 0.67 for the PP population). Thus, a dose-response relationship could not be established with this study. No statistically significant differences were observed with regard to the pair-wise comparison of the response rates between each BAY 59-7939 dosage group and the comparator vitamin K antagonist plus enoxaparin.

Table 2 summarizes the incidence rates of DVT, confirmed symptomatic VTE events and deaths of any cause up to Day 26 (PP population).

The primary analyses in the ITT population showed results, which were similar to the analysis of the PP analysis Likewise, the analysis of the other secondary endpoints and the visit Day 84 assessments yielded consistent findings.

Table 2: Incidence rates of DVT, confirmed symptomatic VTE events and deaths of any cause up to Day 26 (PP population)[a, b]

Event	BAY 59-7939 10 mg bid (N=100)	BAY 59-7939 20 mg bid (N=98)	BAY 59-7939 40 mg od (N=112)	BAY 59-7939 30 mg bid (N=109)	VKA / enoxaparin (N=109)
Any event	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recurrent or extended DVT or PE or death of any cause	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recurrent or extended DVT or PE or VTE-related death	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recurrent or extended DVT or PE	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recurrent or extended DVT	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT, proximal	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT, distal	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

a Incidence rate = # of events / # at risk, where: # of events = # of subjects reporting the event after start of treatment.
at risk = # of subjects in reference population.
b For the PP population only those event were included that occurred not later than 3 days after end of treatment.
Abbreviations: bid – twice a day, od – once daily, VKA - vitamin K antagonist, PP – per protocol, DVT – deep vein thrombosis, VTE - venous thromboembolism, PE – pulmonary embolism

Results Summary — Pharmacokinetics

Due to the low number of patients with full profile data no separate PK/PD and subsequent statistical evaluations have been performed for this cohort. Instead of the data were completely added to the data set for the PK/PD modeling evaluations.

Results Summary — Safety

14 subjects died during the course of the study. Most of them had suffered from malignancies; the death of 4 subjects was associated with either a PE (3 subjects) or a bleeding (1 subject). No drug-related serious adverse events with fatal outcome were reported.

The percentages of major and non-major bleeding events did not differ to a clinically relevant degree between the 4 BAY 59-7939 treatment groups, and the trend analysis did not indicate a statistically significant influence of the dosage on major bleedings. Thus, no relevant dose-dependent effect with regard to the occurrence of major bleedings was seen in this study.

Compared with the BAY 59-7939 groups, the incidence rate of major bleeding events was numerically in favor of VKA/enoxaparin (due to the fact that no major bleeding occurred in this group), but the number of observed cases in general was low and the explorative statistical analysis of both major bleedings and all bleeding events did not show statistically significant differences between the incidence rates in each of the BAY 59-7939 groups compared with VKA/enoxaparin. No treatment arm was stopped because of bleeding events or other safety concerns. There was 1 subject with a 'late' (start ≥2 days after last intake of study drug) major and fatal bleeding (BAY 59-7939 20 mg bid group). The subject received BAY 59-7939 (20 mg bid) for one day and 16 days later she experienced severe peritoneal hemorrhage and died within 2 days. A causal relationship between the event and the study drug was not assumed.

Table summarizes the incidence rates of all bleeding events in the safety population.

Numerically, there appeared to be more TEAEs related to gastrointestinal disorders on treatment with BAY 59-7939 than on VKA/enoxaparin, whereas the incidence of TEAEs related to increases in liver enzymes was numerically higher in the VKA/enoxaparin group than in any of the BAY 59-7939 groups. Generally, BAY 59-7939 did not reveal any obvious substance-specific effects on laboratory parameters and was not relevantly different from VKA/enoxaparin.

Table 3: Incidence rates of all bleeding events (safety population)[a]

Bleeding event	BAY 59-7939 10 mg bid (N=119) n (%)	BAY 59-7939 20 mg bid (N=117) n (%)	BAY 59-7939 40 mg od (N=121) n (%)	BAY 59-7939 30 mg bid (N=121) n (%)	VKA / enoxaparin (N=126) n (%)
Any event	6 (5.0%)	11 (9.4%)	14 (11.6%)	13 (10.7%)	8 (6.3%)
Major bleeding	2 (1.7%)	2 (1.7%)	2 (1.7%)	4 (3.3%)	0 (0.0%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clin. overt bleeding[b]	2 (1.7%)	2 (1.7%)	2 (1.7%)	2 (1.7%)	0 (0.0%)
Clin. overt bleeding[c]	2 (1.7%)	0 (0.0%)	1 (0.8%)	2 (1.7%)	0 (0.0%)
Clin. overt bleeding[d]	1 (0.8%)	2 (1.7%)	1 (0.8%)	3 (2.5%)	0 (0.0%)
Non-major bleeding	4 (3.4%)	9 (7.7%)	12 (9.9%)	11 (9.1%)	8 (6.3%)

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. c Leading to transfusion of ≥2 units blood.
d Warranting treatment cessation. Abbreviations: bid – twice a day, od – once daily, VKA - vitamin K antagonist

Conclusion(s)

In conclusion, this study aimed at the treatment of deep vein thrombosis indicates that BAY 59-7939 at oral daily doses of 20 to 60 mg is as safe and efficacious as the current standard treatment consisting of subcutaneous enoxaparin plus an oral vitamin K antagonist. No trends towards a dose-response relationship for BAY 59-7939 with regard to the treatment response and the occurrence of major bleedings, thereby indicating the broad therapeutic range of BAY 59-7939. Although the number of critical events (ie, venous thromboembolism events and major bleedings) was low in each of the treatment groups and sample sizes would be required to provide more information, the results of this study suggested that BAY 59-7939 at oral daily doses of 20 to 60 mg is as safe and efficacious as the reference treatment with subcutaneous enoxaparin plus an oral vitamin K antagonist for the prophylactic treatment of subjects with deep vein thrombosis. Furthermore, BAY 59-7939 provides additional benefit in terms of an exclusively oral and thereby more convenient mode of administration at fixed doses and without need for continuous coagulation monitoring for necessary dose modifications as required for oral vitamin K antagonists.

Publication(s)

AGNELLI, G., GALLUS, A., GOLDHABER, S. Z., HAAS, S., HUISMAN, M. V., HULL, R. D., KAKKAR, A. K., MISSELWITZ, F. & SCHELLONG, S. (2007) Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. Circulation, 116, 180-7.

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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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