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:	11528	NCT00395772
Study Phase:	II	
Study Title:	Once-daily oral direct factor Xa inhibitor BAY 59-7939 in patients with acute symptomatic deep-vein thrombosis. The Einstein-DVT dose-finding study. A phase II evaluation.	
Therapeutic Area:	Treatment of venous thromboembolism	
Name of Test Product:	BAY 59-7939 / Rivaroxaban	
Active Ingredient:	Rivaroxaban	
Dosage:	Rivaroxaban: 20 mg od, 30 mg od and 40 mg od	
Reference Therapy:	(LMW) heparin followed by vitamin K antagonist treatment	
Dosage:	(LMW) heparin: adjusted to bodyweight; 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, (LMW) heparin: subcutaneous or intravenous administration as applicable	
Treatment Duration:	12 weeks	
Study Period:	Date of first subjects' first visit:	24 Dec 2004
	Date of last subjects' last visit	07 Dec 2005
Methodology:	Randomized, parallel-group, double-blind for the BAY 59-7939 dosages, assessor blind for all groups, active-controlled, multicenter, and multinational study in subjects with confirmed acute symptomatic DVT.	
Study Site:	79 centers: Australia (7), Brazil (4), Canada (3), Czech Republic (7), Denmark (3), France (7), Italy (7), Israel (11), Netherlands (10), Poland (5), South Africa (5), Sweden (5), USA (5).	
Main Inclusion Criteria:	Confirmed acute symptomatic DVT, ie proximal or extensive calf-vein thrombosis involving at least the upper third part of the calf veins, without concomitant symptomatic PE.	
Study Objectives:	Overall: To assess the dose-effect relationship of once-daily BAY 59-7939 in the treatment of subjects with acute symptomatic deep-vein thrombosis (DVT) using the combination of low-molecular-weight (LMW) heparin and vitamin K antagonist (VKA) as comparator. To determine the optimum once-daily dose of BAY 59-7939 for use in phase III studies. Primary: Not applicable Secondary: Not applicable	

Evaluation Criteria:	Efficacy (Primary): The primary efficacy endpoint was the composite of symptomatic recurrent DVT or symptomatic fatal and non-fatal PE at 12 weeks and deterioration in thrombotic burden, as assessed by CUS and PLS, at baseline and at 12 weeks. Efficacy (Secondary): • All separate components of the primary efficacy outcome. • The proportion of subjects in each study arm with improvement, no change, and deterioration on the CUS and PLS assessment. Safety The principal safety outcome was clinically relevant bleeding (ie major and clinically relevant non-major bleeding) within 12 weeks from randomization. Secondary safety outcomes were: major bleedings, clinically relevant non-major bleedings, and adverse events. All safety analyses were performed on the valid-for-safety population. Pharmacokinetics: Not applicable.
Statistical Methods:	Efficacy (Primary): All efficacy analyses were performed in the valid-for-PP population (primary analysis). Trends among the BAY 59-7939 dose groups with respect to the primary efficacy outcome were assessed using logistic regression analysis. Pair-wise comparisons between each BAY 59-7939 dose group and (LMW) heparin/VKA comparator were done using the Fisher's exact test. The impact of baseline covariates on the primary efficacy outcome was described by calculating adjusted odds ratios and 95% confidence intervals of the treatment effect. Efficacy (Secondary): Efficacy analyses in the valid-for-ITT population. Safety The safety analysis was performed in the valid-for-safety population. The principal safety outcome was compared between the treatment groups using a similar approach to that used for the primary efficacy analysis. Pharmacokinetics: Not applicable.
Number of Subjects:	543 subjects randomized; 542 subjects treated with study drug (safety population).

Results Summary — Subject Disposition and Baseline

542 subjects were analyzed as safety population. 487 and 528 subjects were valid-for-ITT analysis and PP analysis, respectively.

Results Summary — Efficacy

A 12-week treatment with BAY 59-7939 using a 2-fold dose range in adult subjects with acute DVT was as effective as standard therapy with (LMW) heparin/VKA in preventing recurrent VTE, thus supporting the efficacy of BAY 59-7939 in this indication. VTE incidence rates observed with once-daily administration of all BAY 59-7939 doses were lower than those observed with (LMW) heparin/VKA (Table 1).

The results showed efficacy with each BAY 59-7939 dose; however, the study did not demonstrate any dose trend for BAY 59-7939 regarding the primary efficacy endpoint of confirmed symptomatic VTE events, which suggests that the no-effective dose of BAY 59-7939 has not yet been established.

The study failed to detect a trend for BAY 59-7939 in the dose-response relationship regarding the primary efficacy endpoint, ie, DVT, PE, VTE-related death, deterioration in CUS or PLS. All dose groups of BAY 59-7939 were at least as efficacious as (LMW) heparin/VKA treatment. The lack of a dose response suggests a broad therapeutic range for BAY 59-7939.

All doses of BAY 59-7939 had lower incidence rates of recurrent VTE events (1.7 to 3.6%) compared with (LMW) heparin/VKA (6.9%) in the PP population. The overall response to treatment (CUS, PLS, and confirmed symptomatic VTE) showed numerically less deterioration in the BAY 59-7939 doses (5 – 7%) compared with 10% in the (LMW) heparin/VKA group and was at least comparable to standard of care (Table 2).

22 deaths were reported in this study. In 5 cases, death was due to bleeding events or pulmonary embolism (PE).

Table 1: Incidence of confirmed symptomatic VTE events and deaths up to Day 98 following randomization or during follow-up (PP population) [a,b,c,d]

Endpoint	BAY 59-7939 20 mg od (N=115)	BAY 59-7939 30 mg od (N=112)	BAY 59-7939 40 mg od (N=121)	(LMW) heparin/VKA (N=101)
Any event	4 (3.5%)	6 (5.4%)	2 (1.7%)	7 (6.9%)
Recurrent DVT or PE or death of any cause	3 (2.6%)	4 (3.6%)	2 (1.7%)	7 (6.9%)
Death (any cause)	1 (0.9%)	2 (1.8%)	1 (0.8%)	1 (1.0%)
PE, non fatal	1 (0.9%)	1 (0.9%)	0 (0.0%)	1 (1.0%)
DVT	2 (1.7%)	1 (0.9%)	1 (0.8%)	7 (6.9%)
Recurrent DVT or PE or VTE-related death e	3 (2.6%)	4 (3.6%)	2 (1.7%)	7 (6.9%)
Death (VTE related)	0 (0.0%)	2 (1.8%)	1 (0.8%)	0 (0.0%)
PE, non fatal	1 (0.9%)	1 (0.9%)	0 (0.0%)	1 (1.0%)
DVT	2 (1.7%)	1 (0.9%)	1 (0.8%)	7 (6.9%)
Recurrent VTE (DVT or PE)	3 (2.6%)	2 (1.8%)	1 (0.8%)	7 (6.9%)
PE	1 (0.9%)	1 (0.9%)	0 (0.0%)	1 (1.0%)
DVT	2 (1.7%)	1 (0.9%)	1 (0.8%)	7 (6.9%)
Recurrent DVT	2 (1.7%)	1 (0.9%)	1 (0.8%)	7 (6.9%)
DVT, proximal	2 (1.7%)	1 (0.9%)	1 (0.8%)	6 (5.9%)
DVT, distal	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (4.0%)
Recurrent PE	1 (0.9%)	1 (0.9%)	0 (0.0%)	1 (1.0%)
PE, non fatal	1 (0.9%)	1 (0.9%)	0 (0.0%)	1 (1.0%)
Recurrent DVT or PE or VTE-related death during 30-day follow-up	1 (0.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)
Death (VTE related)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)
PE, non fatal	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)
Recurrent DVT or PE during 30-day follow-up	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)
PE	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)

a Incidence rate = # of subjects reporting the event after start of treatment / # of subjects in reference population.
b For the PP population, only events occurring not later than 10 days after the end of treatment were included.
c Except for the follow-up analysis, only events starting up to 98 days after start of treatment were included.
d Events during follow-up: Events starting between 1 day and 30 days after the end of treatment were included.
e Used for primary efficacy analysis.

Table 2: Overall response based on CUS, PLS, and confirmed symptomatic VTE events on Day 84 (PP population) [a,b]

Overall response	BAY 59-7939 20 mg od (N=115)	BAY 59-7939 30 mg od (N=112)	BAY 59-7939 40 mg od (N=121)	(LMW) heparin/ VKA (N=101)
Improved	89 (77%)	93 (83%)	89 (74%)	69 (68%)
Unchanged	19 (17%)	13 (12%)	24 (20%)	22 (22%)
Deteriorated	7 (6%)	6 (5%)	8 (7%)	10 (10%)

a Time window was Day 70 to Day 98 for CUS and PLS, up to Day 98 for VTE events, and not later than 10 days after the end of treatment.
b Response was defined as follows:
(1) Improvement – improvement in thrombus burden score (CUS) or in PLS without deterioration in either CUS and PLS and without any VTE event. If either CUS or PLS measurements were missing or outside the time window, the response was set to "missing".
(2) Unchanged – no change in thrombus burden score (CUS) or in PLS without deterioration in either CUS and PLS and without any VTE event. If either CUS or PLS measurements were missing or outside the time window, the response was set to "missing".
(3) Deterioration – deterioration in thrombus burden score (CUS) or in PLS or any VTE event.

Results Summary — Pharmacokinetics: The analysis of the pharmacokinetic results will be reported separately.

Results Summary — Safety

The percentages of major and non-major bleeding events did not differ to a relevant degree between the 3 BAY 59-7939 treatment groups and were nominally the same or lower than in the (LMW) heparin/VKA group (Table 3). The BAY 59-7939 40 mg od group had a numerically significant (*P* = 0.030) lower number of major and clinically relevant non-major bleeding events compared with (LMW) heparin/VKA.

Major bleeding events with BAY 59-7939 treatment were infrequent and comparable to standard of care. Of the major bleeding events, only the 2 events observed in the control group fulfilled the criteria of a fatal bleeding events (n=1) or of a critical bleeding event (n=2). No treatment arm was stopped because of bleeding events or other safety concerns. The results indicate that the optimal net benefit with regard to incidence rates of confirmed symptomatic VTE events, CUS deterioration, PLS deterioration, and clinically relevant bleeding events was obtained with BAY 59-7939 40 mg od compared, whereas the lowest net benefit was observed in the (LMW) heparin/VKA group. Results of optimal net benefit with regard to incidence rates of confirmed symptomatic VTE events and major bleeding events were similar. The effects were not dose dependent with regard to BAY 59-7939.

22 deaths were reported in this study. In 10 cases, cause of death was cancer related and 5 were due to bleeding events or PE.

For this medium-term duration of exposure, BAY 59-7939 did not reveal any substance-specific effects on laboratory parameters, including liver enzymes, and was not different from (LMW) heparin/VKA.

The net clinical benefit of the individual treatments was assessed based on a composite endpoint given by VTE events (recurrent DVT, PE, VTE-related death) and bleeding events. According to the relevance of clinically relevant bleedings in this trial, the net clinical benefit is given for major bleeding events as well as for clinically relevant non-major bleeding events. It is also done for VTE events as well as for VTE events combined with CUS or PLS deterioration, as the latter reflects the primary efficacy outcome. Low incidences of the composite endpoint may indicate a high net clinical benefit. The lowest incidence rate and thus the highest net clinical benefit was observed in the BAY 59-7939 40 mg od dose group (8.7%). The highest incidence rate and thus the lowest net clinical benefit was observed with (LMW) heparin/VKA treatment (16.4%).

BAY 59-7939 did not reveal any substance-specific effects on laboratory parameters, including liver enzymes, and was not different from (LMW) heparin/VKA. No signal for late (up to 12 weeks) liver-enzyme increases was detected.

Table 3: Incidence rates of clinically relevant bleeding events (major or clinically relevant non-major bleedings) (safety population) [a]

Bleeding event	BAY 59-7939 20 mg od (N=135)	BAY 59-7939 30 mg od (N=134)	BAY 59-7939 40 mg od (N=136)	(LMW) heparin/ VKA (N=137)
Any event	31 (23.0%)	29 (21.6%)	29 (21.3%)	38 (27.7%)
Major bleeding	1 (0.7%)	2 (1.5%)	0 (0.0%)	2 (1.5%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)
Intracranial	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Rectal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Clinically overt bleeding associated with a fall in hemoglobin ≥2 mg/dL	1 (0.7%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
Clinically overt bleeding leading to blood transfusion ≥2 units of blood	1 (0.7%)	2 (1.5%)	0 (0.0%)	1 (0.7%)
Non-major bleeding	30 (22.2%)	27 (20.1%)	29 (21.3%)	36 (26.3%)
Any clinically relevant non-major bleeding	7 (5.2%)	6 (4.5%)	3 (2.2%)	10 (7.3%)

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

Conclusion(s)

No dose-trend for the primary efficacy endpoint was shown. This study supports evidence for the efficacy of BAY 59-7939 in the treatment of acute symptomatic deep-vein thrombosis. The optimal net benefit with regard to incidence rates of confirmed symptomatic venous-thromboembolism events, compression-ultrasound deterioration, perfusion-lung-scan deterioration, and clinically relevant bleeding events was obtained with BAY 59-7939 40 mg od.

The overall risk-benefit assessment compared favorably with the with the (low-molecular-weight) heparin/vitamin-K-antagonist group.

Publication(s): BULLER, H. R., LENSING, A. W., PRINS, M. H., AGNELLI, G., COHEN, A., GALLUS, A. S., MISSELWITZ, F., RASKOB, G., SCHELLONG, S. & SEGERS, A. (2008) A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. Blood, 112, 2242-7.

Updated: 28 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	

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