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.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare Pharmaceuticals Inc.	
Study Number:	11702	NCT00439777
Study Phase:	III	
Official Study Title:	Oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic pulmonary embolism - The EINSTEIN PE Study	
Therapeutic Area:	Cardiology/Coagulation	
Test Product		
Name of Test Product:	Rivaroxaban (Xarelto, BAY59-7939)	
Name of Active Ingredient:	Rivaroxaban	
Dose and Mode of Administration:	Oral tablets, 15 mg twice daily for 3 weeks, followed by 20 mg once daily	
Reference Therapy/Placebo		
Reference Therapy:	Enoxaparin (Enox) and pre-specified vitamin K antagonist (VKA, acenocoumarol or warfarin)	
Dose and Mode of Administration:	Enoxaparin 1 mg/kg was given twice daily, subcutaneously, until international normalized ratio (INR) of ≥2.0 for two consecutive measurements at least 24 hours apart was achieved. Individually titrated doses of VKA wer given orally to achieve a target INR of 2.5 (range: 2.0 - 3.0).	
Duration of Treatment:	For test product therapy, the duration of treatment was 3, 6 or 12 months (determined by the investigator individually before randomization). For reference therapy, enoxaparin was given for a minimum duration of 5 days, overlapping with start of VKA and then VKA was continued for a total treatment duration of 3, 6 or 12 months (determined by the investigator individually before randomization).	
Studied period:	Date of first subjects' first visit:	29 Mar 2007

	Date of last subjects' last visit:	01 Dec 2011
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 21 Mar 2007) was valid only for centers in Germany and it clarified the exclusion criterion regarding contraceptive measures. Amendment no. 2 (dated 05 Jul 2007) specified the following modifications: · Strong CYP 3A4 inhibitors were added to the list of prohibited concomitant medications and limited the use (up to two days) of strong CYP 3A4 inducers. In case treatment with CYP 3A4 inducers was needed for more than two days, the subject was withdrawn from study treatment. · The requirement to extend follow-up of pregnancies which occurred following the administration of the study drugs to the father prior to sexual intercourse was removed. Amendment no. 3 (dated 11 Oct 2007) described the Day 1 dosing of rivaroxaban for cases where the subject took the first rivaroxaban dose of 15 mg in the afternoon or in the evening then the second dose of 15 mg was to be taken in the evening of the same day. In such instances, two 15 mg doses could be taken at once if the subject couldn't take the first dose until the evening of the first day. Amendment no. 4 (dated 06 May 2009) prolonged the permitted pre-randomization treatment with anticoagulants from 36 hours to a maximum of 48 hours. Amendment no. 5 (dated 13 Jul 2010) clarified that the subjects participating in the dose confirmation analysis were included in the primary analysis, for which 2930 subjects in total were required (1465 subjects per treatment group).	
Study Center(s):	264 centers screened subjects (1 center in Brazil screened but did not recruit subjects) and 263 centers recruited subjects in Andorra (1), Australia (23), Austria (6), Belgium (12), Brazil (2), Canada (4), China (15), Czech Republic (7), Denmark (1), Estonia (1), Finland (2), France (34), Germany (25), Hong Kong (2), Hungary (10), India (1), Indonesia (1), Ireland (1), Israel (10), Italy (13), Lithuania (2), Latvia (1), Malaysia (1), Netherlands (6), New Zealand (5), Norway (3), Philippines (1), Poland (7), Singapore (1), South Africa (10), South Korea (4), Spain (8), Sweden (5), Switzerland (6), Taiwan (3), Thailand (3), United Kingdom (3), United States (23)	
Methodology:	This was a multi-center, randomized, open-label, parallel-group, active-controlled, event-driven non-inferiority study with a treatment duration of 3, 6, or 12 months. The decision to treat for 3, 6 or 12 months was based on the risk profile of the subject and on local treatment guidelines. All subjects were intended to have a 30-day observational period (starting the day after the last intake of study medication) after cessation of study treatment regardless of the duration of study drug administration. Events for primary efficacy (recurrent venous thromboembolism [VTE], i.e. the composite of recurrent deep vein thrombosis [DVT], or non-fatal or fatal PE) and safety outcomes (composite of major and clinically relevant non-major	

	bleeding events) were evaluated by a central, blinded, independent adjudication committee (CIAC).
Indication/ Main Inclusion Criteria:	Indication: Treatment of PE and secondary prevention of DVT and PE Included were subjects with confirmed acute symptomatic PE with or without symptomatic DVT
Study Objectives:	Primary: The primary efficacy objective for this Einstein-PE study was to evaluate whether rivaroxaban is at least as effective as enoxaparin/vitamin K antagonist (VKA; either warfarin or acenocoumarol) in the treatment of patients with acute symptomatic PE with or without symptomatic deep-vein thrombosis (DVT) for the prevention of recurrent thromboembolic events. Secondary: Principal safety outcome: composite of major and clinically relevant non-major bleeding events.
Evaluation Criteria:	Efficacy (Primary): Primary efficacy outcome was symptomatic recurrent VTE, i.e., the composite of recurrent DVT or non-fatal PE. Efficacy (Secondary): • Secondary outcome was a composite of recurrent DVT, non-fatal PE and all cause mortality • Net clinical benefit 1 was a composite of recurrent DVT or non-fatal or fatal PE (the primary efficacy outcome) and major bleeding events • Net clinical benefit 2 was a composite of recurrent DVT or non-fatal or fatal PE (the primary efficacy outcome), major bleeding events, cardiovascular (CV) deaths, myocardial infarctions (MIs), strokes, and non-central nervous system (CNS) systemic embolism (post-hoc analysis) • Individual components of the primary and secondary efficacy outcomes above Safety: Principal safety outcome: composite of major bleeding events and clinically relevant non-major bleeding events Secondary safety outcomes: all deaths, other cardiovascular events, laboratory variables
Statistical Methods:	Efficacy (Primary) - if applicable: For the primary efficacy analysis, the time to the first event of the composite primary efficacy outcome was analyzed using a Cox's proportional hazards model, with intended treatment duration as stratum and adjusted for the baseline presence of malignancy. The rivaroxaban-to-comparator hazard ratio was computed with two sided 95% confidence intervals (CIs). Based on this model, rivaroxaban was to be considered at least as effective as the comparator if the upper limit of the CI was less than 2.0. In the PE dose confirmation phase, the initial consecutive 400 subjects with symptomatic PE (with or without DVT) had repeat lung imaging [ventilation / perfusion lung scan (VPLS) or spiral computed

	tomography (sCT), depending on the test used for confirmation of the index event] at 3 weeks (Day 21). The paired sets of lung imaging tests were assessed by central adjudication for deterioration of thrombotic burden (i.e. extension of perfusion defect for VPLS or new intraluminal filling defect for sCT). The dose confirmation analysis was based on the composite of asymptomatic deterioration on VPLS or sCT and the primary efficacy outcome at 3 weeks. The 1 sided 95% CI of the absolute difference between observed incidence rates was calculated using the exact methods. If the 1 sided 95% CI of the difference of the observed incidence rates did not exceed 8.0%, the EINSTEIN PE Study was planned to be continued as planned. Efficacy (Secondary) - if applicable: The secondary efficacy outcomes were summarized similarly to the primary efficacy outcome, including calculation of hazard ratio (adjusted for baseline malignancy) and corresponding 95% CI of the treatment effect. The same approach was applied for the comparison of rivaroxaban to each of the VKAs (acenocoumarol vs. warfarin). Safety: To maintain a two-sided error of 0.05 for the primary efficacy analysis and the principal safety analysis, a closed testing procedure was applied, using a stepwise testing approach for the principal safety analysis. If the primary efficacy analysis showed that rivaroxaban was at least as effective as the comparator, the time (person time free from complication) to the principal safety outcome was to be compared between treatment groups, using a stratified Cox's proportional hazard model with stratum and covariate as in the primary efficacy analysis. If the difference was statistically significant in favor of rivaroxaban (at a two-sided significance level of 0.05), time to major bleeding only was also to be tested formally at the same significance level. The log (partial) likelihood ratio test was applied to the test of superiority. The incidences of all investigator-reported adverse events including bleeding events were tabulated using the Medical Dictionary for Regulatory Affairs (MedDRA) version 14.1.
	Other: Health economics and outcomes: Health care resource utilization (HCRU) data was described by country and was analyzed by treatment group with appropriate statistical methods: categorical variables by frequency tables and continuous variables by sample statistics and t-tests. The HCRU data associated with suspected DVT, PE and bleeding events was also analyzed for use in cost-effectiveness analysis.

Number of Subjects:	Planned: In this event-driven study, the goal was to reach 88 confirmed recurrent thromboembolic events; number of subjects randomized was based on the observed overall incidence of symptomatic recurrent VTE. The expected number was 2930 randomized subjects (1465 per treatment group). Analyzed: Intention to treat analysis: 4832 (2419 rivaroxaban and 2413 enoxaparin/VKA) Safety analysis: 4817 (2412 rivaroxaban and 2405 enoxaparin/VKA) Per protocol analysis: 4462 (2224 rivaroxaban and 2238 enoxaparin/VKA)

Study Results

Results Summary — Subject Disposition and Baseline

In this study, 4843 subjects were enrolled, of whom 4833 were randomized at 263 study centers in 38 countries: 2420 subjects were randomized to rivaroxaban and 2413 were randomized to enoxaparin/VKA. With respect to intended treatment duration, 249 subjects had been assigned to an intended treatment duration of 3 months by their investigators, 2775 subjects to 6 months, and 1809 subjects to 12 months. Overall, 4832 subjects were valid for intent-to-treat (ITT) analysis; 1 subject was randomized but not valid for ITT because of lack of signed informed consent. From the ITT population, 7 subjects in the rivaroxaban group and 8 subjects in the enoxaparin/VKA group did not receive any study medication and were excluded from the safety population. The safety population consisted of 2412 subjects treated with rivaroxaban and 2405 subjects treated with enoxaparin/VKA. Of these, 355 subjects (188 in the rivaroxaban and 167 in the enoxaparin/VKA group) were excluded from the PP population, which consisted of 4462 subjects (rivaroxaban: 2224, enoxaparin/VKA: 2238). Of the 4833 randomized subjects, 258 rivaroxaban subjects (11%) and 297 enoxaparin/VKA subjects (12%) were considered as having prematurely terminated study treatment before the end of intended treatment duration. The categories "death", "study terminated by sponsor", and "site closed by investigator" were counted separately from other reasons of premature termination of study treatment and are not included in the above figures. The most frequently reported reason for premature termination of treatment was the study design: the study was stopped once it could be expected that the planned number of 88 confirmed recurrent thromboembolic events would be reached with the subjects already in the study. After this, the last randomized subjects had to be treated until they reached a total treatment duration of at least 6 months, or of at least 3 months if they were in the cohort with 3 months intended treatment duration.

All subjects were intended to have a 30-day observational period after cessation of study treatment. The length of this period was 30 days starting on the day after the last intake of study treatment. Eligible subjects could alternatively rollover into the EINSTEIN Extension study; these subjects did not enter the 30-day observational period.

The termination of the study according to the study protocol affected 125 subjects (5%) in the rivaroxaban group and 132 subjects (6%) in the enoxaparin/VKA group. Other frequent reasons for premature termination of treatment included adverse events (111 subjects [5%] in the rivaroxaban and 92 subjects [4%] in the enoxaparin/VKA group), withdrawal of consent (66 subjects [3%] in the rivaroxaban and 118 subjects [5%] in the enoxaparin/VKA group) and reaching the clinical endpoint (26 subjects [1%] in the rivaroxaban and 13

subjects [1%] in the enoxaparin/VKA group). For 8 subjects in the rivaroxaban group (<1%) and 10 subjects in the enoxaparin/VKA group (<1%), the reason documented for premature discontinuation of treatment was 'loss to follow-up'.

Overall, demographic and baseline characteristics of subjects valid for ITT analysis were similar between treatment groups. 54% and 52% of subjects in the rivaroxaban and enoxaparin / VKA groups were men. Race was documented as "white" in about 66% of subjects in both treatment groups. For about 24% of subjects, race was not documented since in accordance with local laws, it was not permitted to collect data on subjects' race. Age ranged from 18 to 97 years in both treatment groups, with a mean age of approximately 58 years in both groups. With respect to age groups, about 17 - 18% of subjects were between 18 and 40 years of age, about 32 - 33% between 40 and <60 years, about 31% between 60 and <75 years and about 19 - 20% ≥75 years. Using the alternative age groups, about two thirds of subjects (rivaroxaban: 60%; enoxaparin / VKA: 61%) were <65 years of age. Mean body weight was about 83 kg, ranging from 35 to 220 kg. The mean body mass index (BMI) was about 28 kg/m^2 (SD around 6 kg/m^2), ranging from 13 to 71 kg/m^2. The proportion of obese subjects (defined as those with a BMI of ≥30 kg/m^2) was 31% for both treatment groups. Mean height was about 171 cm (SD around 10 cm), ranging from 140 to 205 cm.

In the ITT population, the most commonly reported risk factor was idiopathic DVT / PE, reported for approximately 49% of subjects in both treatment groups, followed by previous episode(s) of DVT / PE (about 20% of subjects), recent surgery or trauma (about 17% of subjects), and immobilization (about 16% of subjects). Active cancer was reported as risk factor in about 4.6% of subjects.

Severity of the index PE (extent of the perfusion defect) was documented using the perfusion score. A perfusion score = 0 means perfusion defect in all lung lobes, perfusion score = 0.75 means no perfusion defect in 75% of the large vessels, and perfusion score = 1 means no perfusion defect at all. Perfusion score results were similar in the 2 treatment groups (mean 0.81 in both groups). There were no notable differences in perfusion score results between cohorts with 3, 6, and 12 months intended treatment duration.

Results Summary — Efficacy

This study met its objective by showing non-inferiority in the primary efficacy analysis of the rivaroxaban treatment regimen (15 mg oral rivaroxaban b.i.d. for 3 weeks followed by 20 mg o.d.) vs. enoxaparin / VKA treatment, with a hazard ratio of 1.123 (95% CI: 0.749 - 1.684; ITT population). As the upper limit of the confidence interval was below the pre-defined non-inferiority margin of 2.0 and the 1-sided p-value for non-inferiority was 0.0026, it was shown that rivaroxaban was non-inferior to the enoxaparin / VKA treatment regimen. The hazard ratio of the primary efficacy between the rivaroxaban treatment group vs. enoxaparin / VKA treatment *among subjects who did not participate in the dose confirmation* part was 1.063 (95% CI: 0.694 - 1.626). There was no evidence that the hazard ratio was different in the 2 study parts (dose confirmation part and subjects enrolled after the dose confirmation part; p-value for interaction: 0.426).

The incidence rate of the primary efficacy outcome (ITT population) was lower than 3.0% in both treatment groups, i.e. lower than the assumed overall incidence rate as specified in the study protocol as basis of the calculation of the required number of primary efficacy outcome events. This was the reason why more subjects had to be recruited to reach the pre-specified number of subjects with primary efficacy outcome.

The study showed consistency throughout the individual components of the primary efficacy

outcome, and also throughout pre-defined subgroups comprising geographic region, intended treatment duration, demographics, baseline characteristics, and coagulation status.

The incidence rates of the primary and secondary efficacy outcomes were as follows (ITT population):

Outcome / components	Rivaroxaban n = 2419 (100%)	Enox / VKA n = 2413 (100%)
Primary efficacy outcome (pre-specified)	50 (2.1%)	44 (1.8%)
Death (PE)	3 (0.1%)	1 (<0.1%)
Death (PE cannot be excluded)	8 (0.3%)	6 (0.2%)
Symptomatic PE and DVT	0 (0.0%)	2 (<0.1%)
Symptomatic recurrent PE only	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT only	18 (0.7%)	17 (0.7%)
Secondary efficacy outcome (pre-specified)	97 (4.0%)	82 (3.4%)
Death (PE)	3 (0.1%)	1 (<0.1%)
Death (PE cannot be excluded)	8 (0.3%)	6 (0.2%)
Death (bleeding)	5 (0.2%)	4 (0.2%)
Death (cardiovascular)	10 (0.4%)	3 (0.1%)
Death (other)	32 (1.3%)	36 (1.5%)
Symptomatic PE and DVT	0 (0.0%)	2 (<0.1%)
Symptomatic recurrent PE only	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT only	18 (0.7%)	17 (0.7%)
Net clinical benefit 1 (pre-specified)	83 (3.4%)	96 (4.0%)
Death (PE)	3 (0.1%)	1 (<0.1%)
Death (PE cannot be excluded)	8 (0.3%)	6 (0.2%)
Symptomatic PE and DVT	0 (0.0%)	2 (<0.1%)
Symptomatic recurrent PE only	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT only	18 (0.7%)	17 (0.7%)
Major bleeding	33 (1.4%)	57 (2.4%)
Net clinical benefit 2 (post-hoc)	110 (4.5%)	115 (4.8%)
Death (PE)	3 (0.1%)	1 (<0.1%)
Death (PE cannot be excluded)	8 (0.3%)	6 (0.2%)
Death (cardiovascular)	10 (0.4%)	3 (0.1%)
Symptomatic PE and DVT	0 (0.0%)	2 (<0.1%)
Symptomatic recurrent PE only	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT only	18 (0.7%)	17 (0.7%)
Major bleeding	33 (1.4%)	57 (2.4%)
ST elevation myocardial infarction	5 (0.2%)	2 (<0.1%)
Non-ST elevation myocardial infarction	2 (<0.1%)	11 (0.5%)
Ischemic stroke	11 (0.5%)	7 (0.3%)
Non CNS systemic embolism	6 (0.2%)	3 (0.1%)

The results for the primary efficacy outcome were consistent across all analysis sets:

Population	ITT [a]	ITT on treatment [b]	PP (on treatment) [c]
Incidence rate of primary efficacy outcome			
Rivaroxaban group	50 / 2419 (2.1%)	44 / 2412 (1.8%)	38 / 2224 (1.7%)
Enox/VKA group	44 / 2413 (1.8%)	39 / 2405 (1.6%)	36 / 2238 (1.6%)
Cox's proportional hazard model for rivaroxaban vs. enox/VKA			
Hazard ratio	1.123	1.115	1.045
Confidence interval	0.749 - 1.684	0.725 - 1.717	0.662 - 1.648
p-value for non-inferiority	0.0026	0.0040	0.0026
p-value for superiority	0.5737	0.6194	0.8504

[a] events until end of intended treatment duration irrespective of study medication intake (for ITT population)
[b] events on treatment until last documented study medication intake + 2 days (for ITT on treatment population)
[c] events on treatment until last documented study medication intake + 2 days (for PP population)

The vast majority of subjects entered the planned 30-day observational period after the end of actual treatment (rivaroxaban: 2206 [91.2%]; enoxaparin/VKA: 2197 [91.0%]. Of the subjects entering the planned 30-day observational period, 82 (rivaroxaban: 41 [1.7%]; enoxaparin/VKA: 41 [1.7%]) did not complete the observational period.
Subjects who did not enter the planned 30-day observational period entered the EINSTEIN Extension Study instead (rivaroxaban: 121 [5.0%]; enoxaparin / VKA: 104 [4.3%]).

The actual duration of the observational period was defined as the time (in days) from the day of last study medication to the observational period visit. For the ITT population, the mean duration (± SD) of the observational period after the end of treatment was 25.7 ± 5.5 days in the rivaroxaban group (range: 0-30 days) and 26.2 ± 5.2 days in the enoxaparin/VKA group (range: 0-30 days).

During the 30-day observational period in the ITT population (Table 3), the incidence rates of the primary efficacy outcome were 0.9% (20 / 2211) in the rivaroxaban group and 0.7% (15 / 2201) in the enoxaparin / VKA group.

Table 3: Incidence rates of efficacy outcomes and their components in the observational period (ITT population who entered the observational period)

Outcome / components	Rivaroxaban	Enox / VKA
Primary efficacy outcome	20 / 2211 (0.9%)	15 / 2201 (0.7%)
Death (PE)	2 / 2211 (<0.1%)	0 / 2201 (0.0%)
Death (PE cannot be excluded)	0 / 2211 (0.0%)	1 / 2201 (<0.1%)
Symptomatic PE and DVT	2 / 2211 (<0.1%)	0 / 2201 (0.0%)
Symptomatic recurrent PE only	12 / 2211 (0.5%)	11 / 2201 (0.5%)
Symptomatic recurrent DVT only	5 / 2211 (0.2%)	3 / 2201 (0.1%)
Secondary efficacy outcome	46 / 2213 (2.1%)	33 / 2203 (1.5%)

Death (PE)	2 / 2213 (<0.1%)	0 / 2203 (0.0%)
Death (PE cannot be excluded)	0 / 2213 (0.0%)	1 / 2203 (<0.1%)
Death (bleeding)	2 / 2213 (<0.1%)	2 / 2203 (<0.1%)
Death (cardiovascular)	6 / 2213 (0.3%)	1 / 2203 (<0.1%)
Death (other)	18 / 2213 (0.8%)	16 / 2203 (0.7%)
Symptomatic PE and DVT	2 / 2213 (<0.1%)	0 / 2203 (0.0%)
Symptomatic recurrent PE only	12 / 2213 (0.5%)	11 / 2203 (0.5%)
Symptomatic recurrent DVT only	5 / 2213 (0.2%)	3 / 2203 (0.1%)
Recurrent DVT	7 / 2210 (0.3%)	3 / 2201 (0.1%)
Symptomatic recurrent PE and DVT, proximal	2 / 2210 (<0.1%)	0 / 2201 (0.0%)
DVT, proximal	4 / 2210 (0.2%)	2 / 2201 (<0.1%)
DVT, distal	1 / 2210 (<0.1%)	1 / 2201 (<0.1%)
Net clinical benefit 1	26 / 2212 (1.2%)	26 / 2201 (1.2%)
Death (PE)	2 / 2212 (<0.1%)	0 / 2201 (0.0%)
Death (PE cannot be excluded)	0 / 2212 (0.0%)	1 / 2201 (<0.1%)
Symptomatic PE and DVT	2 / 2212 (<0.1%)	0 / 2201 (0.0%)
Symptomatic recurrent PE only	12 / 2212 (0.5%)	11 / 2201 (0.5%)
Symptomatic recurrent DVT only	5 / 2212 (0.2%)	3 / 2201 (0.1%)
Major bleeding	7 / 2212 (0.3%)	11 / 2201 (0.5%)
Net clinical benefit 2 (post-hoc)	34 / 2213 (1.5%)	30 / 2201 (1.4%)
Death (PE)	2 / 2213 (<0.1%)	0 / 2201 (0.0%)
Death (PE cannot be excluded)	0 / 2213 (0.0%)	1 / 2201 (<0.1%)
Death (cardiovascular)	6 / 2213 (0.3%)	1 / 2201 (<0.1%)
Symptomatic PE and DVT	2 / 2213 (<0.1%)	0 / 2201 (0.0%)
Symptomatic recurrent PE only	12 / 2213 (0.5%)	11 / 2201 (0.5%)
Symptomatic recurrent DVT only	5 / 2213 (0.2%)	3 / 2201 (0.1%)
Major bleeding	7 / 2213 (0.3%)	11 / 2201 (0.5%)
ST elevation myocardial infarction	1 / 2213 (<0.1%)	0 / 2201 (0.0%)
Non-ST elevation myocardial infarction	0 / 2213 (0.0%)	2 / 2201 (<0.1%)
Ischemic stroke	2 / 2213 (<0.1%)	1 / 2201 (<0.1%)
Non CNS systemic embolism	1 / 2213 (<0.1%)	0 / 2201 (0.0%)

Note: Incidence rate = number of events / number at risk, where:
number of events = number of subjects with onset of the event >1 day after the last dose of study treatment up to 30 days after the last dose of study treatment
number at risk = number of subjects in reference population
Subjects who entered observational period are subjects for whom the investigator indicated in the eCRF that the subject entered the observational period or the subject had a confirmed event >1 day after the last dose of study treatment up to 30 days after the last dose of study treatment as a component of the respective composite variable.
If the same subject had several events, the subject may have been counted for several components so that numbers for the components may not add up to those for the composite outcome.
CNS = central nervous system; DVT = deep vein thrombosis; enox = enoxaparin;
ITT = intent to treat; PE = pulmonary embolism

Results Summary — Safety

The safety population comprised 4817 subjects, 2412 treated with rivaroxaban and 2405 treated with enoxaparin / VKA. Incidence rates of bleeding were similar in both treatment groups, but incidence rates of major bleeding events were significantly lower in the rivaroxaban treatment group. For the rivaroxaban treatment group, the safety analyses did not indicate a signal for an increase in liver abnormalities or an increased incidence rate of acute coronary syndromes. The incidence rates of adverse events and deaths were similar between the treatment groups.

This conclusion is based on the following findings:

Principal safety outcome

The incidence rate of the principal safety outcome (treatment-emergent major bleeding events or clinically relevant non-major bleeding events in the safety population) was similar in both the rivaroxaban treatment group (10.3% [249/2412]) and the enoxaparin / VKA treatment group (11.4% [274/2405]). The hazard ratio (rivaroxaban vs. enoxaparin / VKA) was 0.90 (p-value for superiority: 0.2305; HR 0.900 [95% CI: 0.758 to 1.069]).

In all pre-specified subgroups analyses for the principal safety outcome, incidence rates between both treatment groups were consistently similar.

There was no indication that creatinine clearance had an impact on the principal safety outcome in rivaroxaban-treated subjects.

Major bleeding events

The incidence rate of all confirmed treatment-emergent major bleeding events was significantly lower in the rivaroxaban group (1.1% [26/2412]) than in the enoxaparin / VKA group (2.2% [52/2405]) (HR 0.49; 95% CI: 0.31 to 0.79; unadjusted p-value for superiority 0.0032).

The major bleeding events (all bleeding events) comprised:

- Fatal bleeding events: <0.1% (2/2412) rivaroxaban vs. 0.1% (3/2405) enoxaparin / VKA.
- Non-fatal critical organ bleeding events: 0.3% (7/2412) rivaroxaban treatment vs. 2.2% (26/2405) enoxaparin / VKA treatment group. Intra-cranial bleeding events (<0.1% [1/2412] rivaroxaban vs. 0.4% [10/2405] enoxaparin / VKA) and retroperitoneal bleeding events (<0.1% [1/2412] rivaroxaban vs. 0.3% [7/2405] enoxaparin / VKA) had a lower incidence rate in the rivaroxaban group and were the main contributors to the difference between the treatment groups.
- Non-fatal non-critical organ bleeding events (i.e. fall in Hb ≥2 g/dL and/or transfusions ≥2 units): 0.7% [17/2412] rivaroxaban vs. 1.0% [25/2405] enoxaparin / VKA. Gastrointestinal bleeding events (0.4% [9/2412] rivaroxaban vs. 0.7% [16/2405] enoxaparin / VKA) had a lower incidence rate in the rivaroxaban group.

Non-fatal critical and non-critical organ bleeding events were the main contributors to the difference between the treatment groups.

Intracranial bleeding events – treatment-emergent

There were 15 treatment-emergent intracranial bleeds (0.1% [3/2412] rivaroxaban vs. 0.5% [12/2405] enoxaparin/VKA) all of them assessed as major bleeding events by the CIAC; 4 of them assessed as fatal major bleeding events (2 in each treatment group) and 11 of them assessed as non-fatal critical organ bleeding events (<0.1% [1/2412] rivaroxaban vs. 0.4% [10/2405] enoxaparin/VKA).

Abnormalities of liver function tests

The incidence rates of post-baseline ALT >3 x ULN (central laboratory) were 1.9% (45/2351) with rivaroxaban treatment and 3.0% (70/2324) with enoxaparin / VKA treatment. Most subjects either had a normalization of the observed laboratory abnormalities or a return to the level observed before or during the treatment. The incidence rate of combined concurrent elevations of post-baseline ALT >3 x ULN and total bilirubin > 2 x ULN (central and local laboratory) were 0.2% (5/2355) in the rivaroxaban treatment group vs. 0.2% (4/2327) in the enoxaparin / VKA treatment group. The data of this study do not provide evidence for liver injury caused by rivaroxaban.

Cardiovascular events

During the on-treatment period, 1.5% (35/2412) of subjects in the rivaroxaban group and 1.5% (37/2405) of subjects in the enoxaparin / VKA group had cardiovascular events. During the off-treatment period, the incidence rate of cardiovascular events was 0.4% (9/2206) in the rivaroxaban group and 0.1% (3/2197) in the enoxaparin / VKA group. The incidence rates of on-treatment acute coronary syndromes (i.e. STEMI, NSTEMI, UA), cerebrovascular events (i.e. ischemic stroke or TIA) and non-CNS systemic embolism were similar between the treatment groups as they were off-treatment.

The cardiovascular events also included death due to heart failure, death due to other vascular events or other cardiac death with a very low incidence rate of <0.1% in each treatment group when reported. Numerically, there were more events in the rivaroxaban treatment group than in the enoxaparin/VKA treatment group on-treatment as well as off-treatment.

Overall, the study did not indicate an increased incidence rate for rivaroxaban treated subjects for acute coronary syndromes (i.e. STEMI, NSTEMI, UA), cerebrovascular events (i.e. ischemic stroke or TIA) or non-CNS systemic embolism, neither on-treatment nor off-treatment.

Treatment-emergent adverse events

The incidence rate of treatment-emergent adverse events was similar in both treatment groups (80.3% in the rivaroxaban group vs. 79.0% in the enoxaparin / VKA group). The incidence rate of drug-related treatment-emergent adverse events was approximately 32% in both treatment groups. *Note that as stated in the study protocol, recurrent DVT and non-fatal PE were not regarded as AEs or SAEs.*

The incidence of treatment-emergent serious AEs was 19.5% (471/2412) in the rivaroxaban group versus 19.3% (463/2405) in the enoxaparin/VKA group and 17.2% (416/2412) in the rivaroxaban group versus 16.9% (406/2405) in the enoxaparin/VKA group when bleeding events were excluded.

A total of 5.1% of the subjects in the rivaroxaban treatment group and 4.1% in the enoxaparin / VKA treatment group prematurely discontinued the study medication due to treatment-emergent AEs.

Death (any death after randomization)

- There were 114 deaths (2.6% [63/2412] rivaroxaban vs. 2.1% [51/2405] enoxaparin / VKA) in the safety population. The 3 most frequently reported primary causes of death in both treatment groups were cancer (0.9% [22/2412] rivaroxaban vs. 1.0% [23/2405] enoxaparin / VKA), unexplained death for which PE could not be ruled out 0.3% [8/2412] enoxaparin / VKA vs. 0.2% [6/2405] enoxaparin / VKA), and infectious disease (0.4%) [9/2412] rivaroxaban vs. 0.2% [6/2405] enoxaparin / VKA).

Conclusion(s)

This EINSTEIN PE study demonstrated that the oral, single drug, fixed dose approach with rivaroxaban 15 mg twice daily for the initial 3 weeks of treatment followed by 20 mg once daily provided similar efficacy and safety as compared to the dual drug approach with body weight-adjusted twice daily subcutaneous administration of enoxaparin and INR-adjusted oral VKA therapy.

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Investigational Site List

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Name	Bayer Pharma AG
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Sponsor in Germany	
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125	Prof. Dr. Frank VERMASSEN	UZ Gent	De Pintelaan 185	9000	GENT,	BELGIUM
126	Dr. Rudi VOSSAERT	AZ St-Elisabeth	Godveerdegemstraat 96	9620	ZOTTEGEM,	BELGIUM
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128	Dr. Peter VERSTRAETEN	OL Vrouwziekenhuis	Dienst Interne Geneeskunde Moorselbaan 164	9300	AALST,	BELGIUM
129	Dr. Michel GUSTIN	CHR de la Citadelle	Service de Pneumologie Boulevard du 12e de Ligne 1	4000	LIEGE,	BELGIUM
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137	Dr Tomas Jonson	Södra Älvsborgs Sjukhus	Medicinkliniken	501 82	Borås,	SWEDEN
138	Doc Leif Lapidus	Sahlgrenska Universitetssjukh	Medicinkliniken	413 45	Göteborg,	SWEDEN
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144	Dr Per Morten Sandset	Ullevål Sykehus	Hematologisk avdeling Kirkeveien 166	0407	Oslo,	NORWAY
145	Dr David Adler	Sandton Medi Clinic	Cnr Hendrik Verwoerd & Peter Place Bryanson	2191	Johannesburg, Gauteng	SOUTH AFRICA
146	Prof Jan Becker	Pretoria Academic Hospital New	Corner Malan & Voortrekkers Street Gezina	0084	Pretoria, Gauteng	SOUTH AFRICA

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149	Prof Barry Jacobson	University of Witwatersrand	University of the Witwatersrand Charlotte Maxeke Johannesburg Academic Hospital Medical School 7 York Road Parktown	2132	Johannesburg, Gauteng	SOUTH AFRICA
150	Dr Louis van Zyl	Clinical Projects Research SA	42 Russell Street	6850	Worcester, Western Cape	SOUTH AFRICA
151	Dr Hannes Janse van Rensburg	Unitas Hospital	Unitas Hospital Clifton Ave Lyttleton Centurion	0157	Pretoria, Gauteng	SOUTH AFRICA
152	Dr S Schmidt	N1 City Hospital	Cnr Frans Conradie Drive & Manus Gerber Street Goodwood	7460	Cape Town, Western Cape	SOUTH AFRICA
153	Dr. Richard Siebert	Little Company of Mary	50 Totius St Groenkloof	0181	Pretoria, Gauteng	SOUTH AFRICA
154	Prof Barry Jacobson	University of Witwatersrand	University of the Witwatersrand Charlotte Maxeke Johannesburg Academic Hospital Medical School 7 York Road Parktown	2132	Johannesburg, Gauteng	SOUTH AFRICA
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159	Mr. Dr. Simon Jirat	Vseobecna fakultni nemocnice	II Interni Klinika VFN a 1.LF UK U nemocnice 499/2	12800	Praha 2,	CZECH REPUBLIC
160	Mr. Dr. Ivo Podpera	Hospital Kladno	Interni oddeleni Vancurova 1548	27259	Kladno,	CZECH REPUBLIC
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163	Dr. Dov Gavish	Edith Wolfson Medical Center	62 Halochamim Street P.O.B. 5	58100	Holon,	ISRAEL
164	Dr. Ron Hoffman	Rambam Medical Center	8, Haaliya Hashniya St. Bat Galim	31096	Haifa,	ISRAEL
165	Dr. Osamah Husein	Ziv Medical Center	P.O.B. 1008	13100	Safed,	ISRAEL
166	Prof. Michael Lishner	Meir Medical Center	Clalit Health Services 59, Tchernichovsky Street	44281	Kfar Saba,	ISRAEL
167	Prof. Gilles Lugassy	Barzilai Medical Center	3, Hahistadrut Street	78278	Ashkelon,	ISRAEL
168	Dr. Aida Inbal	Rabin Med Ct-Beilinson Campus	39 Jabotinski Street	49100	Petach Tikva,	ISRAEL
169	Prof. David Varon	Hadassah Ein Karem	P.O.B. 12000	91120	Jerusalem,	ISRAEL
170	Dr. David Zeltser	Sourasky Medical Center	Tel Aviv Sourasky Medical Center 6, Weizmann Street	64239	Tel Aviv,	ISRAEL
171	Dr. Devy Zisman	Lady Davis Carmel	7, Michal Street	34362	Haifa, Israel	ISRAEL
172	Dr Tim Brighton	Prince of Wales Hospital	Department of Haematology, Level 4 Campus Centre POWH, Barker St Randwick	2031	Sydney, New South Wales	AUSTRALIA
173	Dr Chris Ward	Royal North Shore Hospital	Level 4, Dept. of Haematology Pacific Highway	2065	St Leonards, New South Wales	AUSTRALIA
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176	Dr Andrew McCann	Princess Alexandra Hospital	Department of Vascular Medicine 1st Floor, Building 1, Room 1BS 19.1 Ipswich Road	4102	Woolloongabba, Queensland	AUSTRALIA
177	Professor Beng Chong	St George Hospital	Department of Clinical Haematology Ground Floor, W.R. Pitney Clinical Sciences Building Gray Street	2217	Kogarah, New South Wales	AUSTRALIA
178	Dr Michael Leahy	Fremantle Hospital	Alma Street	6160	Fremantle, Western Australia	AUSTRALIA
179	A/Prof. Eng Gan	Monash Medical Centre	Haematology Research, Level 4 246 Clayton Road	3168	Clayton, Victoria	AUSTRALIA
180	Dr Simon McRae	Queen Elizabeth Hospital	Department of Haematology-Oncology Level 8C, Clinical Trials Office 28 Woodville Road	5011	Woodville South, South Australia	AUSTRALIA
181	Dr Michael Leyden	Maroondah Hospital	Davey Drive Ringwood East	3135	Melbourne, Victoria	AUSTRALIA
182	Dr Peter Blombery	The Avenue Cardiovascular	42 The Avenue Windsor	3181	Melbourne, Victoria	AUSTRALIA
183	Dr Brent Richards	Gold Coast Hospital	Nerang Street	4215	Southport, Queensland	AUSTRALIA
184	Dr Alessandra Bianchi	Concord Hospital	Hospital Road Concord	2139	Sydney, New South Wales	AUSTRALIA
185	A/Prof Ross Baker	Royal Perth Hospital	197 Wellington Street	6000	Perth, Western Australia	AUSTRALIA
186	Dr Philip Crispin	The Canberra Hospital	The Canberra Hospital Haematology - 14A Yamba Drive	2605	Garran, Australian Capital Territory	AUSTRALIA

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190	A/Prof Paul Coughlin	ECRU - Box Hill	Eastern Clinical Research Unit Level 1 5 Arnold Street	3128	Box Hill, Victoria	AUSTRALIA
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193	A/Prof Alhossain Khalafallah	Launceston General Hospital	Holman Clinic 2 Charles Street	7250	Launceston, Tasmania	AUSTRALIA
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197	Univ. Prof. Dr. Peter Marschang	Universitätsklinik Innsbruck	Univ. Klinik für Innere Medizin I Anichstraße 35	6020	Innsbruck,	AUSTRIA
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245	Dr Wei-Ten Chang	National Taiwan Uni Hosp	Department of Internal Medicine, No.7, Chung-Shan South Rd.,	10016	Taipei,	TAIWAN
246	Dr. Tang-Jenn Yu	Taipei Veterans General Hos.	Taipei Veterans General Hospital 201 Sec. 2 Shih-Pai Road	11217	Taipei,	TAIWAN
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251	Dr Yuk Kong Lau	Ruttonjee Hospital	266 Queen's Road East Wanchai	0	Wanchai,	HONG KONG
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262	Dr. Chaicharn Pothirat	Maharaj Nakorn Chiang Mai Hosp	Division of Pulmonary, Critical Care and Allergy, Department of Internal Medicine, Faculty of Medici ne, Chiang Mai University	50200	Chiang Mai ,	THAILAND
263	Jorge Roig	Hospital Nostra Senyora de Meritxell	1-13 Fiter Rosell,	AD700	Escaldes-Engordany	Andora
264	Dr Iveta Sime	Liepajas regionala slimnica	Slimnicas iela 25	LV 3414	Liepaja,	LATVIA
265	Dr John Barton	Portiuncula Hospital	County Galway	0	Ballinasloe	IRELAND

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	

Date of last Update/Change: 04 Mar 2013