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	NCT00440193
Study Phase:	III	
Official Study Title:	Oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis - The EINSTEIN DVT 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:	Rivaroxaban 15 mg was given orally, twice daily for 3 weeks, followed by 20 mg once daily.	
Reference Therapy/Placebo		
Reference Therapy:	Enoxaparin 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:**	22 MAR 2007
	Date of last subjects' last visit:	12 APR 2010
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 fom 36 hours to a maximum of 48 hours. Amendment no. 5 (dated 13 JUL 2010) only affected the pulmonary embolism (PE) study (not covered in this report).
Study Centre(s):	There were 252 recruiting centers: 19 in Australia, 5 in Austria, 11 in Belgium, 8 in Brazil, 5 in Canada, 14 in China, 7 in Czech Republic, 3 in Denmark, 28 in France, 23 in Germany, 1 in Hong Kong, 8 in Hungary, 3 in India, 5 in Indonesia, 12 in Israel, 13 in Italy, 2 in Republic of Korea, 1 in Malaysia, 7 in the Netherlands, 6 in New Zealand, 4 in Norway, 2 in the Philippines, 11 in Poland, 2 in Singapore, 11 in South Africa, 5 in Spain, 4 in Sweden, 5 in Switzerland, 3 in Taiwan, 2 in Thailand, 4 in the United Kingdom, and 18 in the United States.
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 DVT and secondary prevention of DVT and PE Main Inclusion criteria Confirmed acute symptomatic proximal DVT without symptomatic PE
Study Objectives:	**Primary:** To evaluate whether rivaroxaban is at least as effective as enoxaparin/VKA (VKA: either warfarin or acenocoumarol) in the treatment of subjects with acute symptomatic deep vein thrombosis without symptomatic pulmonary embolism for the prevention of recurrent venous thromboembolic events. **Secondary:** The principal safety objective was the evaluation 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 or 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 vascular events, laboratory variables
	Health economics and outcomes: Key parameters of health care resource utilization and satisfaction with treatment (anti-clot treatment scale, ACTS) (the latter in a subset of subjects only).
Statistical Methods:	**Efficacy (Primary):** 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. **Efficacy (Secondary):** 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. **Safety:** The principal safety outcome was clinically relevant bleeding events, i.e. the composite of major bleeding events and other clinically relevant non-major bleeding events. 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 at the same significance level. The log (partial) likelihood ratio test was applied to the test of superiority. Also, the incidence of bleeding events was tabulated by the treatment duration stratum and by baseline malignancy. Bleeding events occurring more than 2 days after stop of study medication were tabulated descriptively. The incidences of all investigator-reported adverse events including bleeding events were tabulated using the Medical Dictionary for Regulatory Affairs (MedDRA) version 13.0.
	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:	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 (88 confirmed recurrent thromboembolic events). The expected number was 2930 randomized subjects (1465 per treatment group). Subjects analyzed: Intention-to-treat analysis (ITT): 3449 (1731 rivaroxaban and 1718 enoxaparin/VKA) Safety analysis: 3429 (1718 rivaroxaban and 1711 enoxaparin/VKA) Per protocol (PP) analysis: 3096 (1525 rivaroxaban and 1571 enoxaparin/VKA)

Study Results

Results Summary — Subject Disposition and Baseline

In this study, 3459 subjects were enrolled, of whom 3449 were randomized at 253 study centers in 32 countries (1731 subjects were randomized to rivaroxaban and 1718 were randomized to enoxaparin/VKA). With respect to intended treatment duration, 411 subjects had been assigned to an intended treatment duration of 3 months by their investigators, 2166 subjects to 6 months, and 872 subjects to 12 months.

The ITT population used for the primary efficacy evaluation was identical to the population of all randomized subjects. From the ITT population, 7 subjects in the rivaroxaban group and 13 subjects in the enoxaparin/VKA group did not receive any study medication and were excluded from the safety population. In addition, 6 subjects who had been randomized to rivaroxaban actually received only enoxaparin/VKA treatment during the study. As a result,

they were assigned to the enoxaparin/VKA group for the safety population, but remained in the rivaroxaban group for the ITT population. Thus, the safety population consisted of 1718 subjects treated with rivaroxaban and 1711 subjects treated with enoxaparin/VKA.

Of the 3429 subjects who were randomized and took study medication (1724 subjects randomized to rivaroxaban, 1705 subjects randomized to enoxaparin/VKA), 333 subjects (199 in the rivaroxaban and 134 in the enoxaparin/VKA group) were excluded from the PP population, which consisted of 3096 subjects. From the ITT population, 298 rivaroxaban subjects (17%) and 338 enoxaparin/VKA subjects (20%) did not continue their study medication until the intended end of treatment. 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.

The decision to treat for 3, 6, or 9 months was based on the risk profile of the subject and on local treatment guidelines and was made by the investigator at the time of randomization. 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 the day after the last intake of study medication. Subjects entering the follow-up study did not enter such a 30-day observational period.

The termination of the study according to the study protocol affected 102 subjects (6%) in the rivaroxaban group and 94 subjects (6%) in the enoxaparin/VKA group. Other frequent reasons for premature termination of treatment included AEs (74 subjects [4%] in the rivaroxaban and 67 subjects [4%] in the enoxaparin/VKA group), withdrawal of consent (36 subjects [2%] in the rivaroxaban and 77 subjects [5%] in the enoxaparin/VKA group) and reaching the clinical endpoint (28 subjects [2%] in the rivaroxaban and 25 subjects [2%] in the enoxaparin/VKA group). For 12 subjects in the rivaroxaban group (1%) and 18 subjects in the enoxaparin/VKA group (1%), the reason documented for premature discontinuation of treatment was "lost to follow-up".

With regard to the ITT population, there were no relevant differences between treatment groups for the baseline and demographic parameters. About 57% of subjects were male. The race of about 77% of subjects was described as White, for about 13% as Asian, and for about 2% as Black. For just over 7% of subjects, no information was available as according to local laws it was not permitted to collect data on subjects' race.

Age ranged from 18 - 95 years in the rivaroxaban and from 18 - 97 years in the enoxaparin/VKA group, with a mean of approximately 56 years in both groups. With respect to age groups, about 17% of subjects were between 18 and 40 years of age, about 38% between 40 and 60 years, about 30% between 60 and 75 years and about 15% over 75 years. Using alternative age groups, about two-thirds of subjects (rivaroxaban: 66%; enoxaparin/VKA: 65%) were below 65 years, while about one-third was above.

Mean body weight was about 82 kg, ranging from 33 to 193 kg. The mean body mass index (BMI) was about 28 kg/m^2, with ranges from approximately 13 to 65 kg/m^2.

For 99% of subjects, symptomatic proximal DVT at baseline was confirmed by the CIAC. The index DVT at baseline was assessed as spontaneous DVT for about 62% of subjects and as secondary DVT for about 38% of subjects.

The most commonly reported risk factor for thromboembolism was idiopathic DVT/PE, reported for approximately 48% of subjects, followed by recent surgery or trauma (about

20% of subjects), previous episode(s) of DVT/PE (about 19% of subjects) and immobilization (about 15% of subjects).

Results Summary — Efficacy

The primary efficacy analysis for the ITT population resulted in a hazard ratio for rivaroxaban vs enoxaparin/VKA of 0.680 (95% confidence interval (CI): 0.443-1.042). As the upper limit of the confidence interval was below the pre-defined non-inferiority margin of 2.0 and the one-sided p-value for non-inferiority was less than 0.0001, it was proven that rivaroxaban was at least as effective as the enoxaparin/VKA treatment regimen.

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 and baseline characteristics. With respect to the secondary efficacy outcomes, rivaroxaban consistently showed numerically lower event rates as compared to the enoxaparin/VKA treatment regimen, further suggesting that rivaroxaban was at least as effective as enoxaparin/VKA. Lower event rates were also observed when combining major bleeding events with the primary efficacy outcome (net clinical benefit 1).

The incidence rates of both primary and secondary efficacy outcomes are summarized in ITT population in Table 1.

Table 1: Incidence rates of the primary and secondary efficacy outcomes in ITT population

Outcome/ components	Rivaroxaban N=1731 (100%)	Enox/VKA N=1718 (100%)
Primary efficacy outcome (pre-specified)	36 (2.1%)	51 (3.0%)
Death (PE)	1 (<0.1%)	0
Death (PE cannot be excluded)	3 (0.2%)	6 (0.3%)
Symptomatic PE and DVT	1 (<0.1%)	0
Symptomatic recurrent PE only	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT only	14 (0.8%)	28 (1.6%)
Secondary efficacy outcome (pre-specified)	69 (4.0%)	87 (5.1%)
Death (PE)	1 (<0.1%)	0
Death (PE cannot be excluded)	3 (0.2%)	6 (0.3%)
Death (bleeding)	1 (<0.1%)	5 (0.3%)
Death (cardiovascular)	2 (0.1%)	4 (0.2%)
Death (other)	31 (1.8%)	34 (2.0%)
Symptomatic PE and DVT	1 (<0.1%)	0
Symptomatic recurrent PE only	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT only	14 (0.8%)	28 (1.6%)
Net clinical benefit 1 (pre-specified)	51 (2.9%)	73 (4.2%)
Death (PE)	1 (<0.1%)	0
Death (PE cannot be excluded)	3 (0.2%)	6 (0.3%)
Symptomatic PE and DVT	1 (<0.1%)	0
Symptomatic recurrent PE only	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT only	14 (0.8%)	28 (1.6%)
Major bleeding	15 (0.9%)	23 (1.3%)
Net clinical benefit 2 (post-hoc)	62 (3.6%)	81 (4.7%)
Death (PE)	1 (<0.1%)	0
Death (PE cannot be excluded)	3 (0.2%)	6 (0.3%)
Death (cardiovascular)	2 (0.1%)	4 (0.2%)
Symptomatic PE and DVT	1 (<0.1%)	0
Symptomatic recurrent PE only	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT only	14 (0.8%)	28 (1.6%)
Major bleeding	15 (0.9%)	23 (1.3%)
STEMI	1 (<0.1%)	0
NSTEMI	5 (0.3%)	1 (<0.1%)
Ischemic Stroke	3 (0.2%)	5 (0.3%)
Non CNS systemic embolism	2 (0.1%)	2 (0.1%)

The results for the primary efficacy outcome were consistent across all analysis sets (Table 2).

Table 2: Statistical analysis of primary efficacy outcome in different analyses sets

Population	ITT [a]	ITT on treatment [b]	PP (on treatment) [c]
Incidence rate of primary efficacy outcome			
Rivaroxaban group	36/1731 (2.1%)	34/1718 (2.0%)	32/1525 (2.1%)
Enox/VKA group	51/1718 (3.0%)	49/1705 (2.9%)	46/1571 (2.9%)
Cox's proportional hazard model for rivaroxaban vs. enox/VKA			
Hazard ratio	0.680	0.671	0.698
Confidence interval	0.443-1.042	0.433-1.039	0.444-1.097
p-value for non-inferiority	<0.0001	<0.0001	<0.0001
p-value for superiority	0.0764	0.0737	0.1191

[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: 82.3%; enoxaparin/VKA: 81.9%). Of the subjects entering the planned 30-day observational period, 83 (2.4%; rivaroxaban: 45 [2.6%]; enoxaparin/VKA: 38 [2.2%]) did not complete the observational period.

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 25.4 ± 5.9 days in the rivaroxaban group (range: 0-30 days) and 25.9 ± 5.4 days in the enoxaparin/VKA group (range: 0-30 days).

During the 30-day observational period (Table 3), the incidence rates of the primary efficacy outcome were 0.8% (12/1425) in the rivaroxaban group and 0.5% (7/1408) in the enoxaparin/VKA group.

Table 3: Incidence rates of efficacy events during observational period

(ITT population)

Outcome/ components	Rivaroxaban	Enox/VKA
Primary efficacy outcome (pre-specified)	12/1425 (0.8%)	7/1408 (0.5%)
Death (PE)	0/1425	0/1408
Death (PE cannot be excluded)	1/1425 (<0.1%)	1/1408 (<0.1%)
Symptomatic PE and DVT	0/1425	0/1408
Symptomatic recurrent PE only	4/1425 (0.3%)	2/1408 (0.1%)
Symptomatic recurrent DVT only	8/1425 (0.6%)	4/1408 (0.3%)
Secondary efficacy outcome (pre-specified)	32/1430 (2.2%)	25/1413 (1.8%)
Death (PE)	0/1430	0/1413
Death (PE cannot be excluded)	1/1430 (<0.1%)	1/1413 (<0.1%)
Death (bleeding)	1/1430 (<0.1%)	2/1413 (0.1%)
Death (cardiovascular)	1/1430 (<0.1%)	4/1413 (0.3%)
Death (other)	18/1430 (1.3%)	12/1413 (0.8%)
Symptomatic PE and DVT	0/1430	0/1413
Symptomatic recurrent PE only	4/1430 (0.3%)	2/1413 (0.1%)
Symptomatic recurrent DVT only	8/1430 (0.6%)	4/1413 (0.3%)
Recurrent DVT	8/1425 (0.6%)	4/1408 (0.3%)
Deep Vein Thrombosis, Proximal	8/1425 (0.6%)	4/1408 (0.3%)
Deep Vein Thrombosis, Distal	0/1425	0/1408
Net clinical benefit 1 (pre-specified)	15/1425 (1.1%)	15/1410 (1.1%)
Death (PE)	0/1425	0/1410
Death (PE cannot be excluded)	1/1425 (<0.1%)	1/1410 (<0.1%)
Symptomatic PE and DVT	0/1425	0/1410
Symptomatic recurrent PE only	4/1425 (0.3%)	2/1410 (0.1%)
Symptomatic recurrent DVT only	8/1425 (0.6%)	4/1410 (0.3%)
Major bleeding	3/1425 (0.2%)	8/1410 (0.6%)
Net clinical benefit 2 (post-hoc)	17/1426 (1.2%)	19/1410 (1.3%)
Death (PE)	0/1426	0/1410
Death (PE cannot be excluded)	1/1426 (<0.1%)	1/1410 (<0.1%)
Death (cardiovascular)	1/1426 (<0.1%)	4/1410 (0.3%)
Symptomatic PE and DVT	0/1426	0/1410
Symptomatic recurrent PE only	4/1426 (0.3%)	2/1410 (0.1%)
Symptomatic recurrent DVT only	8/1426 (0.6%)	4/1410 (0.3%)
Major bleeding	3/1426 (0.2%)	8/1410 (0.6%)
STEMI	0/1426	0/1410
NSTEMI	1/1426 (<0.1%)	0/1410
Ischemic Stroke	0/1426	1/1410 (<0.1%)
Non CNS systemic embolism	0/1426	1/1410 (<0.1%)

Notes: Incidence = # of events / # at risk, where # of events = # of subjects with onset of the event more than one day after last dose and up to 30 days after the last dose, and # at risk = # of subjects in reference population. Subjects entering observational period were subjects for whom the investigator indicated on the eCRF that the subject entered the observational period or had a confirmed event more than one day and up to 30 days after the last dose as a component of the respective composite outcome.

DVT = deep vein thrombosis, Enox = enoxaparin, ITT = intention to treat, PE = pulmonary embolism

Results Summary — Safety

Of the 3449 randomized subjects, 3429 were included in the safety population; a total of 1718 subjects were treated with rivaroxaban and 1711 subjects were treated with enoxaparin/VKA. The results of the safety analysis indicated an acceptable safety profile of rivaroxaban which was comparable to the profile of the enoxaparin/VKA treatment regimen. This conclusion is based on the following findings:

- The incidence rates of the principal safety outcome (based on first treatment-emergent major or clinically relevant non-major bleeding event occurring in a subject) were similar in

the two treatment groups (8.1% in both groups: 139/1718 in the rivaroxaban treatment group and 138/1711 in the enoxaparin/VKA treatment group). Accordingly the hazard ratio (rivaroxaban versus enoxaparin/VKA) was close to 1 (p-value for superiority: 0.77; hazard ratio 0.966 [0.763 to 1.222]).

- There were 93 deaths (rivaroxaban: 41 [2.4%]; enoxaparin/VKA: 52 [3.0%]) in the safety population. The most frequently reported primary causes for death in both treatment groups by CIAC assessment were cancer (rivaroxaban: 1.6% [27/1718]; enoxaparin/VKA: 1.2% [20/1711]), unexplained death for which PE could not be ruled out (rivaroxaban: 0.2% [3/1718]; enoxaparin/VKA: 0.4% [6/1711]), infectious disease (rivaroxaban: 0.2% [3/1718]; enoxaparin/VKA: 0.5% [9/1711]), and bleeding (rivaroxaban: 0.1% [2/1718]; enoxaparin/VKA: 0.3% [5/1711])

- The incidence rate of all confirmed treatment-emergent major bleeding events was lower in the rivaroxaban treatment group (0.8% [14/1718]) and the enoxaparin/VKA treatment group (1.2% [20/1711]). The major bleeding events comprised fatal bleeding events (<0.1% [1/1718] rivaroxaban vs 0.3% [5/1711] enoxaparin/VKA), non-fatal critical organ bleeding events (0.2% [3/1718] rivaroxaban treatment vs 0.2% [3/1711] enoxaparin/VKA treatment group) and non-fatal non-critical organ bleeding events (0.6% [10/1718] rivaroxaban vs 0.7% [12/1711] enoxaparin/VKA).

- There were 6 subjects with treatment-emergent fatal bleeding events: 1 subject on rivaroxaban with a fatal bleeding event due to gastrointestinal bleeding; 5 subjects on enoxaparin/VKA with fatal bleeding events (2 subjects due to gastrointestinal bleeding, 1 due to thoracic bleeding, and 2 due to intracranial bleeding).

- There were 4 treatment-emergent major bleeding events related to intracranial bleeding (2 in the rivaroxaban treatment group and 2 in the enoxaparin/VKA treatment group), out of which 2 were fatal (both of them in the enoxaparin/VKA treatment group). Both subjects of the enoxaparin/VKA treatment group had their INR measured on the day of the event which was above the therapeutic range.

- The incidence of treatment-emergent AEs was comparable between the treatment groups (63% in both treatment groups), as were those assessed as drug-related (23% 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 12.0% (207/1718) in the rivaroxaban group versus 13.6% (233/1711) in the enoxaparin/VKA group, and 10.2% (176/1718) in the rivaroxaban group and 12.1% (207/1711) in the enoxaparin/VKA group when bleeding events were excluded.

- A total of 5% of the subjects in both treatment groups prematurely discontinued the study medication due to treatment-emergent AEs.

- There was neither a fatal outcome related to hepatic disorder AEs, nor was there a report of liver transplantation. The incidence of ALT >3 x upper limit of normal (ULN) was 1.5% (25/1680) of subjects in the rivaroxaban treatment group compared to 3.8% (62/1649) in the enoxaparin/VKA group. Most subjects either had a normalization of the observed laboratory abnormalities or a return to the level observed before or during the treatment. For about 50% of the subjects in the enoxaparin/VKA treatment group, the abnormalities occurred during the first 2 weeks of treatment, when initial enoxaparin treatment still had an impact. Thereafter, no difference was seen between the treatment groups. The incidence of combined concurrent elevations of ALT >3 x ULN and total bilirubin >2 x ULN (central or local laboratory) were 0.1% (2/1682) in the rivaroxaban treatment group vs 0.2% (4/1648) in the enoxaparin/VKA treatment group. The data of this study do not indicate differences between the 2 treatment groups with respect to the occurrence of liver

related laboratory abnormalities, apart from the observation of an increased incidence of ALT elevations at start of therapy in the enoxaparin/VKA treatment group compared to the rivaroxaban treatment group, which is explained by the enoxaparin treatment. The differences between the treatment groups of reported AEs categorized as hepatic disorders (based on the hepatic disorder standardized MedDRA query [SMQ]) were small. Most of the differences were related to laboratory abnormalities.

- During the treatment period, 12/1718 (0.7%) subjects in the rivaroxaban group and 14/1711 (0.8%) subjects in the enoxaparin/VKA group had vascular events (acute coronary syndromes, ischemic stroke, transient ischemic attack, non-CNS systemic embolism and vascular death). During the off-treatment period, the number of subjects with vascular events was 2/1423 (0.1%) in the rivaroxaban group and 6/1410 (0.4%) in the enoxaparin/VKA group. During the treatment phase, 1 death in the rivaroxaban group occurred (subject had a history of chronic ischemic heart disease, aortic valve stenosis and other cardiac risk factors). During the off-treatment phase, 6 deaths were reported (rivaroxaban: 1; enoxaparin/VKA: 5). This comparator-controlled study did not present any differences in incidence rates of vascular events occurring either on- or off-treatment, taking into account the low number of reported vascular events.

Conclusion(s)

In this study, oral, single-drug, fixed-dose approach with rivaroxaban 15 mg twice daily followed by 20 mg once daily showed 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. This study also focused on a second indication (Pulmonary Embolism). The results for this indication will be presented in a separate report.

Publication(s):	EINSTEIN Investigators; Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010 Dec 23;363(26):2499-510. Epub 2010 Dec 3. Cohen AT, Dobromirski M. The use of rivaroxaban for short- and long-term treatment of venous thromboembolism. Thromb Haemost. 2012 Jun;107(6):1035-43. doi: 10.1160/TH11-12-0859. Epub 2012 Feb 28.		
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Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Pharma AG
Postal Address	D-13342 Berlin Deutschland
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Prince of Wales Hospital	Department of Haematology, Level 4 Campus Centre POWH, Barker St Randwick	2031	Sydney	AUSTRALIA
2	Royal North Shore Hospital	Level 4, Dept. of Haematology Pacific Highway	2065	St Leonards	AUSTRALIA
3	Redcliffe Hospital	Research Department Redcliffe Hospital Anzac Avenue	4020	Redcliffe	AUSTRALIA
4	Flinders Medical Centre	SouthPath Level 6 Flinders Medical Centre Flinders Drive Bedford Park	5042	Adelaide	AUSTRALIA
5	Princess Alexandra Hospital	Department of Vascular Medicine 1st Floor, Building 1, Room 1BS 19.1 Ipswich Road	4102	Woolloongabba	AUSTRALIA
6	St George Hospital	Department of Clinical Haematology Ground Floor, W.R. Pitney Clinical Sciences Building Gray Street	2217	Kogarah	AUSTRALIA
7	Fremantle Hospital	Alma Street	6160	Fremantle	AUSTRALIA

8	Monash Medical Centre	Haematology Research, Level 4 246 Clayton Road	3168	Clayton	AUSTRALIA
9	Maroondah Hospital	Davey Drive Ringwood East	3135	Melbourne	AUSTRALIA
10	The Avenue Cardiovascular Centre	42 The Avenue Windsor	3181	Melbourne	AUSTRALIA
11	Concord Repatriation General Hospital	Hospital Road Concord	2139	Sydney	AUSTRALIA
12	Royal Perth Hospital	197 Wellington Street	6000	Perth	AUSTRALIA
13	The Canberra Hospital	The Canberra Hospital Haematology - 14A Yamba Drive	2605	Garran	AUSTRALIA
14	Geelong Hospital	The Andrew Love Cancer Centre Haematology 70 Swanston St	3220	Geelong	AUSTRALIA
15	Gosford Hospital	Holden Street	2250	Gosford	AUSTRALIA
16	Sutherland Hospital & Community Health Service	430 The Kingsway Caringbah	2229	Sydney	AUSTRALIA
17	Eastern Clinical Research Unit - Box Hill	Eastern Clinical Research Unit Level 1 5 Arnold Street	3128	Box Hill	AUSTRALIA
18	Lismore Base Hospital	Uralba Street	2480	LISMORE	AUSTRALIA
19	Royal Brisbane & Women's Hospital	Dept Internal Medicine Level 4, James Mayne Building Butterfield St Herston	4029	Brisbane	AUSTRALIA

20	Allgemeines Krankenhaus der Stadt Wien Universitätskliniken	Univ. Klinik f. innere Med. II Klin. Abteilung f. Angiologie Währinger Gürtel 18-20	1090	Wien	AUSTRIA
21	Hanusch-Krankenhaus Wien	Heinrich-Collin-Straße 30	1140	Wien	AUSTRIA
22	Universitätsklinikum Innsbruck	Univ. Klinik für Innere Medizin I Anichstraße 35	6020	Innsbruck	AUSTRIA
23	Landeskrankenhaus Feldkirch	Innere Medizin Carinagasse 47	6807	Feldkirch	AUSTRIA
24	Medizinische Universität Graz	Med. Universitätsklinik klin. Abteilung f. Angiologie Auenbruggerplatz 15	8036	Graz	AUSTRIA
25	UZ Leuven Gasthuisberg	Dienst Inwendige Geneeskunde Bloedings - en Vaatziekten Herestraat 49	3000	LEUVEN	BELGIUM
26	CU de Mont-Godinne	CU de Mont-Godinne Dienst Cardiologie Avenue Docteur G. Therasse 1	5530	YVOIR	BELGIUM
27	AZ Sint-Maarten	Campus Duffel Rooienberg 25	2570	DUFFEL	BELGIUM
28	H. Hartziekenhuis Lier	Kolveniersvest 20	2500	LIER	BELGIUM
29	Centre Hospitalier Régional de Namur	Avenue Albert Ier 185	5000	NAMUR	BELGIUM
30	CU Saint-Luc/UZ St-Luc	Avenue Hippocrate 10 Hippocrateslaan	1200	BRUXELLES - BRUSSEL	BELGIUM
31	Hôpital Erasme/Erasmus Ziekenhuis	Route de Lennik 808 Lenniksebaan	1070	BRUXELLES - BRUSSEL	BELGIUM

32	CHU de Liège	Hôpital du Sart Tilman Service Cardiologie Domaine Universitaire du Sart Tilman Bâtiment B35	4000	LIEGE	BELGIUM
33	Virga Jesse Ziekenhuis	Virga Jesse Ziekenhuis Stadsomvaart 11	3500	HASSELT	BELGIUM
34	UZ Gent	De Pintelaan 185	9000	GENT	BELGIUM
35	AZ St-Elisabeth	Godveerdegemstraat 96	9620	ZOTTEGEM	BELGIUM
36	Hospital Universitário Cajuru da PUC PR	Avenida São José, 300	80050-350	Curitiba	BRAZIL
37	Conjunto Hospitalar de Sorocaba	Av. Comendador Pereira Inacio, 564	18031-000	Sorocaba	BRAZIL
38	Hospital da Beneficiência Portuguesa	Rua Maestro Cardim , 769 - Paraiso	01323-001	São Paulo	BRAZIL
39	Hospital Universitario Pedro Ernesto	Av. 28 de Setembro, 77 - 20551-030		Rio de Janeiro	BRAZIL
40	Inst. de Assistência Médica ao Sérvidor Público Estadual	Rua Pedro de Toledo, 1800	04039-004	São Paulo	BRAZIL
41	Hospital Universitário Regional do Norte do Paraná	Av. Robert Koch, 60 - Vl Operário	86038440	Londrina	BRAZIL
42	Hospital do Cancer de Sao Paulo - A. C. Camargo	Departamento de Oncologia Clínica R. Prof° Antonio Prudente, 211-2° andar	01509-900	Sao Paulo	BRAZIL

43	Hospital das Clínicas de Botucatu - UNESP Botucatu	Distrito de Rubião Junior s/n Bairro Rubião Junior	18618 000	Botucatu	BRAZIL
44	St. Joseph's Health Centre - Toronto	Department of Medicine Rm. 318/3rd floor SSWE 30 The Queensway	M6R 1B5	Toronto	CANADA
45	London Health Sciences Centre	Hematology Division Room A2-401 800 Commissioners Road East	N6A 4G5	London	CANADA
46	Sunnybrook Health Sciences Centre	Room D-674 2075 Bayview Avenue	M4N 3M5	Toronto	CANADA
47	St. Boniface General Hospital	Room C-5116 409 Tache Avenue	R2H 2A6	Winnipeg	CANADA
48	Ottawa Hospital - Civic Campus	Division of Hematology Suite F6-49 1053 Carling Avenue	K1Y 4E9	Ottawa	CANADA
49	Vascular Surgical Institute, Shanghai Zhongshan Hospital	180 Fenglin Road, Xuhui District,	200032	Shanghai	CHINA
50	Shanghai Renji Hospital	145 Middle Shangdong Road,	200001	shanghai	CHINA
51	The First Affiliated Hospital of Sun Yat-Sen University	No.58 Zhongshan Er Road, Yuexiu District,	510080	guangzhou	CHINA
52	Chinese PLA General Hosp.	28th Courtyard, Fuxing Road,	100853	Beijing	CHINA
53	Beijing Anzhen Hospital of the Capital University of Medical	Anzhenli, Andingmenwai, Chaoyang Disctrict,	100029	Beijing	CHINA

54	Peking Union Medical College Hospital	No.1 Shuai Fuyuan, Dongcheng District, No.41 Damucang Hutong, Xicheng District,	100730	Beijing	CHINA
55	Peking Univ. People's Hosp.	No.11 South Avenue, Xizhimen, Xicheng District,	100044	Beijing	CHINA
56	the People's Hospital of Liaoning Province	33 Wenyi Road Shenhe District,	110016	shenyang	CHINA
57	Cardiovascular Institute and Fuwai Hospital, CAMS & PUMC	NO.167, North Li-Shi road, Xi Cheng District,	100037	Beijing	CHINA
58	Changhai Hospital of Second Military Medical University	No.174 Changhai Road , Yangpu District,	200433	Shanghai	CHINA
59	Tongji Hosp. of Huazhong Univ. of Science & Technology	Department of Vascular Surgery, Wuhan Union Hospital Affiliated to Tongji Medical College , Huazhong University of Science & Technology, No.1277, Jiefang Ave.,	430022	Wuhan	CHINA
60	The 2nd Affiliated Hospital of Soochow University	Department of Vascular Surgery, No.1055, Sanxiang Road,	215004	Suzhou	CHINA
61	Shanghai Pulmonary Hospital, Tongji University	No.507, Zhengmin Road,	200433	Shanghai	CHINA
62	Sir Run Run Shaw Hosp Med College of Zhejiang University	Department of Respiratory Disease, No.3, East Qingchun Road,	310016	Hangzhou	CHINA
63	Fakultni nemocnice Motol	Clinic of Internal Medicine V uvalu 84	150 00	Prague 5	CZECH REPUBLIC

64	Mestska nemocnice Ostrava	Oddeleni interna II Nemocnicni 20	728 80	Ostrava	CZECH REPUBLIC
65	Fakultni nemocnice s poliklinikou Ostrava	Interni klinika 17 Listopadu 1790	708 52	Ostrava-Poruba	CZECH REPUBLIC
66	Masaryk Hospital Usti n/L	II Dpt. of Internal Medicine Socialni pece 12/A	401 13	Usti nad Lebem	CZECH REPUBLIC
67	Nemocnice Na Fratisku	Interni Oddeleni Na frantisku 847/8	110 00	Praha 1	CZECH REPUBLIC
68	Vseobecna fakultni nemocnice	II Interni Klinika VFN a 1.LF UK U nemocnice 499/2	12800	Praha 2	CZECH REPUBLIC
69	Hospital Kladno	Interni oddeleni Vancurova 1548	27259	Kladno	CZECH REPUBLIC
70	H:S Frederiksberg Hospital	Dept. of Cardiology and Endocrinology Nedre Fasanvej 57	2000F	Frederiksberg	DENMARK
71	Aarhus Amstsygehus	Medical-Cardiological dept. A Tage Hansens Gade 2	8000	Aarhus C	DENMARK
72	Bredstrup sygehus	Thrombosis Center Medical dept.	8740	Braedstrup	DENMARK
73	Hôpital Nord-SAINT ETIENNE	Hôpital Bellevue Unité de Pharmacologie Clinique boulevard Pasteur	42055	SAINT ETIENNE	FRANCE
74	Centre hospitalier Intercommunal - Vernon	Centre Hospitalier Intercommunal Eure Seine Service de Pneumologie 5 rue du Docteur Burnet	27200	VERNON	FRANCE

75	Centre Hospitalier - Valenciennes Cedex	Centre Hospitalier Service de Cardiologie et Soins Intensifs Avenue Desandrouins	59322	VALENCIENNES CEDEX	FRANCE
76	Hôpital Saint André - Bordeaux	C.H.U Bordeaux - Groupe Hospitalier Saint André-Jean Abadie Hôpital Saint André Service de Médecine Interne 1, rue Jean Burgel	33000	BORDEAUX	FRANCE
77	Hopital Européen Georges Pompidou - Paris	Hopital Européen Georges Pompidou Département Médecine Vasculaire et Hypertension 20-40 rue Leblanc	75908	PARIS CEDEX 15	FRANCE
78	Hôpital Pasteur - Nice	Hôpital Pasteur Service de Cardiologie 30, avenue de la Voie Romaine	06002	NICE	FRANCE
79	Hôpital Dupuytren - Limoges Cedex	C.H.R.U. Hôpital Dupuytren Service de Chirurgie Thoracique et cardiovasculaire 2, avenue Martin Luther King	87042	LIMOGES	FRANCE
80	Hôtel Dieu - Paris	Hôtel Dieu Service de Médecine Interne 1, place du Parvis de Notre Dame	75004	PARIS	FRANCE
81	Hôpital du Bocage - Dijon	C.H.R.U. Dijon Service d'Hématologie Hôpital du Bocage 2 boulevard de Lattre de Tassigny	21000	DIJON	FRANCE
82	Hôpital Louis Mourier - Colombes Cedex	Hôpital Louis Mourier Service de Médecine Interne V 178, rue des Renouillers	92701	COLOMBES CEDEX	FRANCE
83	Hopital J. Minjoz - Besançon	Centre Hospitalier Universitaire Hopital J. Minjoz Service de Cardiologie Boulevard Flemming	25000	BESANCON	FRANCE

84	Hopital Européen Georges Pompidou - Paris	Hopital Européen Georges Pompidou Service de Pneumologie 20-40 rue Leblanc	75015	PARIS	FRANCE
85	Hôpital La Cavale Blanche - Brest Cedex	Hôpital La Cavale Blanche Service de Médecine I et Pneumologie Boulevard Tanguy Prigent	29609	BREST CEDEX	FRANCE
86	Hôpital Antoine Béclère - Clamart	Hôpital Antoine Béclère Service de Pneumologie 157, rue de la Porte Trivaux	92141	CLAMART	FRANCE
87	Centre Hospitalier Universitaire - Grenoble	Centre Hospitalier Universitaire Hôpital Michalon Centre d'Investigation Clinique BP 217	38043	GRENOBLE	FRANCE
88	Hôpital Hôtel Dieu - Nantes Cedex	C.H.U. Nantes Hôpital Hôtel Dieu Service d'Accueil des Urgences 2, place Alexis Ricordeau	44000	NANTES	FRANCE
89	Hôpital Saint-Eloi - Montpellier Cedex	Hôpital Saint Eloi Service de Médecine Interne et Maladies Vasculaires 80 avenue Augustin Fliche	34295	MONTPELLIER CEDEX	FRANCE
90	Centre Hospitalier Universitaire - Angers	Centre Hospitalier Universitaire Service d'Accueil des Urgences 4, rue Larrey	49033	ANGERS CEDEX 01	FRANCE
91	Hôpital Gabriel Montpied - Clermont Ferrand	Hôpital Gabriel Montpied Service d'Accueil des Urgences 58 rue Montalembert	63000	CLERMONT FERRAND	FRANCE
92	Hôpital Lariboisière - Paris	Groupe Hospitalier Lariboisière - F. Widal - St Lazare Hôpital Lariboisière Service de Médecine Interne A 2, rue Ambroise Paré	75475	PARIS	FRANCE
93	Hôpital Civil - Strasbourg	Hôpitaux Universitaires Hôpital Civil Service d'Hypertension et Maladies Vasculaires 1, place de l'Hôpital	67091	STRASBOURG CEDEX	FRANCE

94	Hopital Général - Agen	Hopital Général Département des Urgences - SAMU/SMUR Route de Villeneuve	47923	AGEN CEDEX 9	FRANCE
95	Centre Hospitalier Lyon Sud - Pierre Bénite	Hospices civils de Lyon Centre Hospitalier Lyon Sud Service de Médecine Interne et Angiologie 165, chemin du Grand Revoyet	69495	PIERRE BENITE	FRANCE
96	Centre Hospitalier - Arras	Centre Hospitalier Service de Cardiologie Boulevard Georges Besnier	62000	ARRAS	FRANCE
97	Hôpital de Rangueil - Toulouse	C.H.U. Hôpital de Rangueil Service de medecine vasculaire 1, avenue Poulhes	31403	TOULOUSE	FRANCE
98	Hôpital Font Pré - Toulon	Hopital Font Pré médecine Vasculaire et Médecine Interne Bat M - 5eme etage - Aile C 1208 avenue Colonel Picot	83000	TOULON	FRANCE
99	Clinique du Parc	Clinique du Parc service d'angiologie	34170	CASTELNAU LE LEZ	FRANCE
100	Groupe Hospitalier Sud - Amiens	C.H.U. Groupe Hospitalier Sud Chirurgie Vasculaire Avenue René Laennec	80000	AMIENS	FRANCE
101	Klinikum der Eberhard-Karls-Universität Tübingen	Medizinische Universitätsklinik und Poliklinik Innere Medizin IV Otfried-Müller-Str. 10	72076	Tübingen	GERMANY
102	SRH Klinikum-Karlsbad-Langensteinbach gGmbH	Innere Medizin Guttmannstr. 1	76307	Karlsbad	GERMANY
103	St. Josefskrankenhaus	Innere Medizin Landhausstr. 25	69115	Heidelberg	GERMANY

104	Klinikum Innenstadt der Ludwigs-Maximilians-Universität	Medizinische Poliklinik Pettenkoferstr 8a	81377	München	GERMANY
105	Forschungszentrum Ruhr - KliFoCenter GmbH	Pferdebachstrasse 30	58455	Witten	GERMANY
106	Wenckebach-Krankenhaus	Innere Medizin II Wenckebachstr. 23	12099	Berlin	GERMANY
107	Brüderkrankenhaus St. Josef	Innere Medizin Husener Str. 46	33098	Paderborn	GERMANY
108	Universitätsklinikum Hamburg Eppendorf (UKE)	Klinik und Poliklinik für Innere Medizin Abteilung für Klinische Chemie Martinistr. 52	20251	Hamburg	GERMANY
109	Praxis für Innere Medizin u. Gefäßkrankheiten HBE	Halberstädter Strasse 49	39112	Magdeburg	GERMANY
110	Klinikum der Johann Wolfgang Goethe Universität Frankfurt	Gefäßzentrum-Frankfurt, Schwerpunkt Angiologie Theodor-Stern-Kai 7	60590	Frankfurt	GERMANY
111	Praxis Hr. Dr. W. Mondorf	Praxis und Labor zur Diagnostik und Therapie von Blutgerinnungstörungen Gartenstraße 134	60596	Frankfurt	GERMANY
112	Medizinische Fakultät Carl Gustav Carus	-Universitätsklinikum- Medizinische Klinik III / Bereich Angiologie Fetscherstraße 74	01307	Dresden	GERMANY

113	Praxis Hr. Dr. P. Baron von Bilderling	Gefäßpraxis Tal 13	80331	München	GERMANY
114	Med. Fakultät der Martin-Luther-Universität Halle-Wittenberg	Klinik und Poliklinik für Innere Medizin III Ernst-Grube-Straße 40	06120	Halle	GERMANY
115	Klinikum der Universität Würzburg	Medizinische Klinik und Poliklinik II Josef-Schneider-Str. 2	97080	Würzburg	GERMANY
116	Diakoniekranken-haus	I. Medizinische Klinik Elise-Averdieck-Str. 17	27342	Rotenburg	GERMANY
117	Praxis Hr. Dr. F. Heckmann	Bahnhofstr. 62	69151	Neckargemünd	GERMANY
118	Fürst Stirum Klinik	Radiologie Gutleutstraße 1 - 14	76646	Bruchsal	GERMANY
119	Klinikum der Ernst-Moritz-Arndt-Universität	Klinik und Poliklinik für Innere Medizin B Pneumologie und Infektiologie Friedrich-Löffler-Straße 23a	17475	Greifswald	GERMANY
120	Klinikum der Eberhard-Karls-Universität Tübingen	Universitäts Hautklinik Sektion Dermatologische Onkologie Liebermeisterstraße 25	72076	Tübingen	GERMANY
121	Medizinische Fakultät Carl Gustav Carus	Innere Medizin Fetscherstraße 74	01307	Dresden	GERMANY

122	Johannes-Gutenberg-Universität Mainz	II. Medizinische Klinik und Poliklinik Kardiologie Geb. 209 / 2.OG Langenbeckstr. 1	55131	Mainz	GERMANY
123	Dr. Bauersachs		64283	Darmstadt	GERMANY
124	Queen Mary Hospital	Block K, 20/F, Division of Haematology / Medical Oncology and Bone Marrow Transplantation Unit, Depa rtment of Medicine, The University of Hong Kong, Pokfulam Road,		Hong Kong	HONG KONG
125	Szent Istvan Hospital	IV Belgyogyaszat Nagyvarad te. 1	1096	Budapest	HUNGARY
126	Bacs-Kiskun Country Hospital	II Belgyogyaszat Nyiri u. 38	6000	Kecskemet	HUNGARY
127	Borsod County Hospital	III Sz. Belgyogyszat-Angiologia Szntpeteri kapu 72-76	3526	Miskolc	HUNGARY
128	Szent Imre Hospital	Angiologiai Profil Tetenyi ut. 12-16	1115	Budapest	HUNGARY
129	University of Debrecen Medical&Health Science Center	II Internal Medicine Department Nagyerdei krt. 98.	4032	Debrecen	HUNGARY
130	Flor Ferenc Hospital	II Dept. of Internal Medicine Semmelweis ter. 1	2143	Kistarcsa	HUNGARY
131	Dr Bugyi Istvan Hospital	I Internal Medicine Department Sima Ferenc u. 44-58	6600	Szentes	HUNGARY

132	Vas Megyei Markusovszky Korhaz	I Belgyogyaszat Markusovszky ut. 3	9700	Szombathely	HUNGARY
133	Ruby Hall Clinic	Department of Vascular Surgery	411001	Pune	INDIA
134	Nizam's Institute of Medical Sciences	Department of Vascular Surgery NIMS	500082	Hyderabad	INDIA
135	Amrita Institute of Medical Sciences	Dept. of Vascular Surgery	682026	Kochi	INDIA
136	Cipto Mangunkusumo Hospital	Division of Hematology-Medical Oncology Department of Internal Medicine, University of Indonesia, Jl Salemba Raya No. 6,	10430	Jakarta	INDONESIA
137	Hasan Sadikin Hospital	Division of Hematology-Medical Oncology, Department of Internal Medicine, Padjajaran University, Jl Pasteur No 38,	40161	Bandung	INDONESIA
138	University of Diponegoro, Dr Kariadi Teaching Hospital	Division of Hematology-Medical Oncology Department of Internal Medicine, Jl DrSoetomo No 16,	50241	Semarang	INDONESIA
139	St Elisabeth Hospital	Antithrombotic Clinic St Elisabeth Hospital Jl. H. Misbah No. 7	20152	Medan	INDONESIA
140	PGI Cikini Hospital	Jl. Raden Saleh No. 40	10330	Jakarta	INDONESIA
141	Haemek Medical Center	Rabin Road	18101	Afula	ISRAEL
142	Edith Wolfson Medical Center	62 Halochamim Street P.O.B. 5	58100	Holon	ISRAEL

143	Rambam Medical Center	8, Haaliya Hashniya St. Bat Galim	31096	Haifa	ISRAEL
144	Ziv Medical Center	P.O.B. 1008	13100	Safed	ISRAEL
145	Meir Medical Center	Clalit Health Services 59, Tchernichovsky Street	44281	Kfar Saba	ISRAEL
146	Barzilai Medical Center	3, Hahistadrut Street	78278	Ashkelon	ISRAEL
147	Bnai Zion Medical Center	47, Golomb Street P.O.B. 4940	31048	Haifa	ISRAEL
148	Rabin Medical Center - Beilinson Campus	39 Jabotinski Street	49100	Petach Tikva	ISRAEL
149	Hadassah University Hospital Ein Kerem	P.O.B. 12000	91120	Jerusalem	ISRAEL
150	Tel Aviv Sourasky Medical Center	Tel Aviv Sourasky Medical Center 6, Weizmann Street	64239	Tel Aviv	ISRAEL
151	Lady Davis Carmel Medical Center	7, Michal Street	34362	Haifa	ISRAEL
152	Kaplan Medical Center	P.O.B. 1	76100	Rehovot	ISRAEL
153	IRCCS Policlinico San Matteo	Angiologia - Malattie Tromboemboliche Piazzale Golgi, 19	27100	Pavia	ITALY
154	A.O. Osp Circolo e Fond.Macchi	Medicina Interna I Viale L.Borri, 57	21100	Varese	ITALY
155	AULSS 12 Veneziana - Veneto	Medicina I P.O. SS Giovanni e Paolo Castello 6776	30122	Venezia	ITALY

156	A.O. San Paolo Polo Universitario	Ematologia e Trombosi Via A. Di Rudinì, 8	20142	Milano	ITALY
157	IRCCS Fondazione San Raffaele	Laboratorio Coagulazione ed Unità Ricerca Trombosi Istituto Scientifico Universitario San Raffaele Via Olgettina, 60	20132	Milano	ITALY
158	A.O. di Reggio Emilia	Angiologia - Dipartimento di Medicina I Arcispedale Santa Maria Nuova Viale Risorgimento, 80	42100	Reggio Emilia	ITALY
159	AUSL Piacenza - Emilia Romagna	Centro Emostasi e Trombosi Medicina Interna Area Critica Ospedale Guglielmo da Saliceto Via Taverna, 49	29100	Piacenza	ITALY
160	IRCCS Fond. Ca' Granda Ospedale Maggiore Policlinico	Centro Emofilia e Trombosi A.Bianchi Bonomi Medicina Interna 2 Via Pace, 9	20122	Milano	ITALY
161	A.O.U. di Bologna	Angiologia e Malattie della Coagulazione Policlinico S.Orsola-Malpighi Via Albertoni, 15	40138	Bologna	ITALY
162	AUSL 2 Lanciano-Vasto-Chieti - Abruzzo	Medicina Interna Ospedale Clinicizzato SS. Annunziata Via dei Vestini, 31	66013	Chieti	ITALY
163	A.O. di Padova	Dip. Scienze Mediche e Chirurgiche Clinica Medica II Viale Ospedale Civile, 105	35128	Padova	ITALY
164	A.O.U. di Parma	Medicina Interna ad indir. Angiologico e Coagulativo Via Gramsci, 14	43100	Parma	ITALY
165	A.O.U. Policlinico Giaccone	Malattie Cardiovascolari e Nefrourologiche Dip. Medicina Interna Via del Vespro, 129	90127	Palermo	ITALY
166	Daegu Catholic University Medical Center	3056-6 Daemyung 4-Dong Namgu	705-718	Daegu	KOREA, REPUBLIC OF

167	Keimyung University Dongsan Medical Center	194 Dong San Dong	700-712	Taegu	KOREA, REPUBLIC OF
168	Hospital Ampang	Department of Hematology, Jalan Mewah Utara, Pandan Mewah, Ampang 68000	68000	Selangor	MALAYSIA
169	Spaarne Ziekenhuis	Afdeling Interne Geneeskunde, Spaarnepoort 1	2134 TM	HOOFDDORP	NETHER-LANDS
170	Medisch Spectrum Twente, Locatie Ariensplein	Afd. Interne Geneeskunde - Ariënsplein 1	7511 JX	ENSCHEDE	NETHER-LANDS
171	Academisch Medisch Centrum Universiteit van Amsterdam	Afd. Interne geneeskunde, Meibergdreef 9	1105 AZ	AMSTERDAM	NETHER-LANDS
172	Ziekenhuis Rijnstate	Afd. Inwendige Geneeskunde - Wagnerlaan 55	6815 AD	ARNHEM	NETHER-LANDS
173	Academisch Ziekenhuis Maastricht	Afd. Hematologie - P. Debyelaan 25	6229 HX	MAASTRICHT	NETHER-LANDS
174	Universitair Medisch Centrum Groningen	Afdeling Interne Geneeskunde, Hanzeplein 1	9713 GZ	GRONINGEN	NETHER-LANDS
175	Isala Klinieken, Locatie Sophia	Afdeling Haematologie, Dr. van Heesweg 2	8025 AB	ZWOLLE	NETHER-LANDS
176	Haematology Service, Canterbury Health Laboratories	corner Hagley Avenue and Tuam Street Christchurch Central	8011	Christchurch	NEW ZEALAND
177	North Shore Hospital	Shakespeare Road Takapuna North Shore City	0622	Auckland	NEW ZEALAND
178	Thrombosis Unit	Regional Cancer and Blood Services Level 6, Building 8, Auckland City Hospital Park Road Grafton	1023	Auckland	NEW ZEALAND

179	Middlemore Hospital	Hospital Road Mangere East	2024	Auckland	NEW ZEALAND
180	Palmerston North Hospital	50 Ruahine Street Roslyn	4414	Palmerston North	NEW ZEALAND
181	Wellington Hospital	Riddiford Street Newtown	6021	Wellington South	NEW ZEALAND
182	Östfold Hospital Trust Fredrikstad	Dept of Medicine PO Box 16	1603	Fredrikstad	NORWAY
183	Sykehuset Asker og Bærum	Dept of Medicine Munthe Kaasvei 100	1309	Rud	NORWAY
184	Oslo Universitetssykehus HF, Ullevål	Hematologisk avdeling Kirkeveien 166	0407	Oslo	NORWAY
185	St Olav Hospital HF	Dept of hematology	7006	Trondheim	NORWAY
186	Philippine Heart Centre	Room 409, Medical Arts Building	0850	Quezon City	PHILIPPINES
187	St. Luke's Medical Centre Cathedral Heights	Heart Institute E. Rodriguez Sr. Blvd. Philippines	1102	Quezon City	PHILIPPINES
188	Szpital Kliniczny	Katedra i Klinika Angiologii, Nadcisnienia Tetniczego i Diabetologii ul. Poniatowskiego 2	50-326	Wroclaw	POLAND
189	SP Szpital Kliniczny AM w Bialymstoku	Klinika Hematologii z pododdzialem Chorób Naczyn UM w Bialymstoku Uniwersytecki Szpital Kliniczny w Bialymstoku ul. Marii Sklodowskiej-Curie 24a	15-276	Bialystok	POLAND
190	Szpital Uniwersytecki w Krakowie	Oddzial Autoimmunologii i Zaburzen Hemostazy ul. Skawinska 8	31-066	Krakow	POLAND

191	Szpital Kliniczny	Katedra i Klinika Chirurgii Naczyniowej, Ogolnej i Transplantacyjnej ul. Poniatowskiego 2	50-326	Wroclaw	POLAND
192	Instytut Gruzlicy i Chorob Pluc	Oddzial Intensywnej Terapii Pneumonologiczno-Kardiologicznej ul. Plocka 26	01-138	Warszawa	POLAND
193	Wojewodzki Szpital Specjalistyczny	Oddzial Chirurgii Ogolnej i Naczyniowej ul. Kamienskiego 73A	51-124	Wroclaw	POLAND
194	SPSK nr 1	Katedra i Klinika Chirurgii Naczyn i Angiologii ul. Staszica 11	20-081	Lublin	POLAND
195	Szpital im. N. Barlickiego	Klinika Chirurgii Ogólnej i Transplantacyjnej ul. Kopcinskiego 22	90-153	Lodz	POLAND
196	ZOZ MSWiA	Klinika Chirurgii Ogólnej i Naczyniowej oraz Angiologii ul. Dojazd 34	60-631	Poznan	POLAND
197	Szpiatal Kliniczny nr 1 Przemienienia Panskiego	Oddzial Chirurgii Ogolnej i Naczyn ul. Dluga 1/2	61-848	Poznan	POLAND
198	Wojew. Szpital Zespolony	Katedra i Klinika Chirurgii Ogolnej i Onkologicznej ul. Sw. Jozefa 53/59	87-100	Torun	POLAND
199	Tan Tock Seng Hospital	Department of General Medicine CSO 5B, 11 Jalan Tan Tock Seng,	308433	Singapore	SINGAPORE

200	Singapore General Hospital	Department of Haematology Block 6 Level 5,	169608	Singapore	SINGAPORE
201	Sandton Medi Clinic	Cnr Hendrik Verwoerd & Peter Place Bryanson	2191	Johannesburg	SOUTH AFRICA
202	Pretoria Academic Hospital New	Corner Malan & Voortrekkers Street Gezina	0084	Pretoria	SOUTH AFRICA
203	Helderberg Medical Clinical Trials	7G Arun Place Sir Lowry's Pass Road	7130	Somerset West	SOUTH AFRICA
204	Mayo Clinic	William Nicol Drive Floracliffe	1724	Roodepoort	SOUTH AFRICA
205	University of Witwatersrand	University of the Witwatersrand Charlotte Maxeke Johannesburg Academic Hospital Medical School 7 York Road Parktown	2132	Johannesburg	SOUTH AFRICA
206	Clinical Projects Research SA	42 Russell Street	6850	Worcester	SOUTH AFRICA
207	Unitas Hospital	Unitas Hospital Clifton Ave Lyttleton Centurion	0157	Pretoria	SOUTH AFRICA
208	N1 City Hospital	Cnr Frans Conradie Drive & Manus Gerber Street Goodwood	7460	Cape Town	SOUTH AFRICA
209	Little Company of Mary Hospital	50 Totius St Groenkloof	0181	Pretoria	SOUTH AFRICA
210	Sunninghill Hospital	c/o Nanuke & Witkoppen Drive Sunninghill	2157	Johannesburg	SOUTH AFRICA

211	University of Witwatersrand	University of the Witwatersrand Charlotte Maxeke Johannesburg Academic Hospital Medical School 7 York Road Parktown	2132	Johannesburg	SOUTH AFRICA
212	Hospital Clínic i Provincial de Barcelona	Servicio de Medicina Interna C/ Villarroel, 170	08036	Barcelona	SPAIN
213	Hospital de la Santa Creu i de Sant Pau	Servei de Hematología Pabelló Nostra Senyora de Montserrat Avda. Sant Antoni María Claret, 167	08025	Barcelona	SPAIN
214	Hospital Josep Trueta	Servicio de Medicina Interna 8ª Planta B Avda. de França, s/n	17007	Girona	SPAIN
215	Hospital Virgen del Camino	Servicio de Medicina Interna. Planta 6ª C/ Irunlarrea, 4	31008	Pamplona	SPAIN
216	Hospital de la Mútua de Terrassa	Servei d'Hematologia Plaza del Dr. Robert 5	08221	Terrassa	SPAIN
217	SU/Östra	Medicinkliniken	416 85	Göteborg	SWEDEN
218	Länssjukhuset Ryhov	Kardiosektionen/Medicinkliniken	551 85	Jönköping	SWEDEN
219	Södra Älvsborgs Sjukhus	Medicinkliniken	501 82	Borås	SWEDEN
220	Länssjukhuset Sundsvall-Härnösand	Medicinkliniken	851 86	Sundsvall	SWEDEN
221	Luzerner Kantonsspital	Angiologie Spitalstrasse	6000	Luzern	SWITZER-LAND

222	Hôpital Cantonal Universitaire de Genève	Division d'angiologie et d'hémostase Unité d'angiologie Rue Gabrielle-Perret-Gentil 4	1211	Genéve 14	SWITZER-LAND
223	Universitätsspital Zürich	Department Innere Medizin Abt. Infektionskrankheiten und Spitalhygiene Haldenbachstr. 14	8091	Zürich	SWITZER-LAND
224	Centre Hospitalier Universitaire Vaudois (CHUV)	Commission d'ethique de la recherche clinique Décanat de la Faculté de Médicine Champ de l'Air Rue du Bugnon 21	1005	Lausanne	SWITZER-LAND
225	Kantonsspital Graubünden	Innere Medizin Loëstrasse 170	7000	Chur	SWITZER-LAND
226	National Taiwan University Hospital	Department of Internal Medicine, No.7, Chung-Shan South Rd.,	10016	Taipei	TAIWAN
227	Veterans General Hospital	Taipei Veterans General Hospital 201 Sec. 2 Shih-Pai Road	11217	Taipei	TAIWAN
228	Far Eastern Memorial Hospital	13F, No. 21, Sec. 2, Nan-Ya South Road Pan Chiao	220	Taipei	TAIWAN
229	Chulalongkorn University Hospital	Division of Hematology Department of Internal Medicine Chulaongkorn University	10330	Pathumwan, Bangkok	THAILAND
230	Ramathibodhi Hospital	Division of Hematology Department of Medicine Ramathibodi Hospital Rama VI Road	10400	Bangkok	THAILAND
231	Kings College Hospital	Department of Vascular Sugery 2nd Floor, West Entresol (off Hambledon Wing) Bessemer Road Denmark Hill	SE5 9RS	London	UNITED KINGDOM
232	St Thomas' Hospital	Lambeth Palace Road	SE1 7EH	London	UNITED KINGDOM

233	Derriford Hospital	Derriford Road Crownhill	PL6 8DH	Plymouth	UNITED KINGDOM
234	West Middlesex University Hospital	Twickenham Road	TW7 6AF	Isleworth	UNITED KINGDOM
235	Spokane Respiratory Consultants	104 West Fifth Avenue	99204	Spokane	UNITED STATES
236	Cancer Care Centers of South Texas	4411 Medical Drive Suite 100	78229	San Antonio	UNITED STATES
237	University of North Carolina	UNC School of Medicine CB-7035 903 Mary Ellen Jones Bldg.	27599-7035	Chapel Hill	UNITED STATES
238	Oklahoma University Health Science Center	OU Medical Center 1200 N. Everett Drive	73104	Oklahoma City	UNITED STATES
239	Pulmonary Associates of Fredericksburg, Inc.	521 Park Hill Drive	22401	Fredericksburg	UNITED STATES
240	University of Utah Medical Center	Health Sciences Center Division of Hematology 30 North 1900 East	84132	Salt Lake City	UNITED STATES
241	Eastern Idaho Medical Consultants	3200 Channing Way Suite 205	83404	Idaho Falls	UNITED STATES
242	Heritage Cardiology Associates	425 North 21st Street	17011	Camp Hill	UNITED STATES

243	San Juan VA Medical Center	Pulmonary & Critical Care 10 Casia Street (111)	00927	San Juan	UNITED STATES
244	Moses H. Cone Memorial Hospital	Dep't. of Critical Care Medicine 1200 North Elm Street	27401	Greensboro	UNITED STATES
245	Dr. Banish		70433	Covington	UNITED STATES
246	JRMD, Inc.	964 Creek View Lane	92373	Redlands	UNITED STATES
247	Sinai Hospital of Baltimore	Dep't.of General Internal Medicine 2401 West Belvedere Avenue	21215	Baltimore	UNITED STATES
248	Wesley Long Community Hospital	501 North Elam Avenue	27403	Greensboro	UNITED STATES
249	The Western Pennsylvania Hospital	4800 Friendship Avenue Suite MZ-52	15224	Pittsburgh	UNITED STATES
250	Tacoma General Hospital	MultiCare Health System Department of Inpatient Services 315 Martin Luther King Jr. Way	98405	Tacoma	UNITED STATES
251	Intermountain Medical Center	Dep't. of Pulmonary Critical Care Dept. 795 5121 South Cottonwood Street	84107	Murray	UNITED STATES
252	University of Miami	Department of Medicine 1120 NW 14th Street	33136	Miami	UNITED STATES

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