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 AG	
Study Number:	13238	NCT00786422
Study Phase:	IIa	
Official Study Title:	The EINSTEIN CYP cohort study - Oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep-vein thrombosis or pulmonary embolism using a strong CYP3A4 inducer	
Therapeutic Area:	Cardiology/Coagulation	
Test Product		
Name of Test Product:	Rivaroxaban (Xarelto, BAY59-7939)	
Name of Active Ingredient:	Rivaroxaban	
Dose and Mode of Administration:	Dose: 30 mg 2 times daily (bid) for the initial 3 weeks followed by 20 mg bid for the remaining duration of treatment along with a strong CYP3A4 inducer Mode of administration: Oral	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Three (3) months	
Studied period:	**Date of first subjects' first visit:**	22 MAY 2009
	Date of last subjects' last visit:	26 JUN 2011
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	None	
Study Centre(s):	Three (3) recruiting centers; all in South Africa.	
Methodology:	This was a multicenter, open-label, cohort study evaluating an adapted rivaroxaban dosing regimen in subjects with acute deep vein thrombosis (DVT) or acute pulmonary embolism (PE) who were using a strong CYP3A4 inducer (i.e., carbamazepine, phenytoin, rifampicin/rifampin, or rifabutin) for the entire 3-month duration. After cessation of treatment with rivaroxaban, all subjects had a 30-day follow-up period. The primary objective, characterization of the population pharmacokinetic (PK)/pharmacodynamic (PD) parameters of the adapted rivaroxaban dosing regimen, was planned to allow a comparison with the PD data obtained in the EINSTEIN VTE studies	

	and the PK data obtained in the ODIXa-DVT and EINSTEIN DVT dose-ranging studies. The efficacy outcome was symptomatic recurrent venous thromboembolic event (VTE), i.e., a composite of recurrent DVT or fatal or non-fatal PE. The principal safety outcome was the combination of major and clinically relevant non-major bleeding. Secondary safety outcomes were all deaths, other vascular events, and laboratory variables. All suspected recurrent VTEs, deaths, as well as all episodes of bleeding, and other vascular events were evaluated by the central independent adjudication committee (CIAC). Adjudication results were the basis for the final analyses. The independent Data Safety Monitoring Board (DSMB) monitored the subjects' safety during the study.
Indication/ Main Inclusion Criteria:	Indication: Treatment of acute, proximal DVT and/or acute PE Main inclusion criteria: Concomitant use of a strong CYP3A4 inducer, i.e., carbamazepine, phenytoin, rifampicin/rifampin, or rifabutin.
Study Objectives:	**Primary:** The primary objective of this EINSTEIN CYP cohort study was to characterize the population PK/PD of an adapted rivaroxaban dosing regimen in subjects with acute, proximal DVT or acute PE and concomitant use of a strong CYP3A4 inducer. **Secondary:** The secondary objectives of this study were to document the occurrence of: • Symptomatic VTE and • Major and clinically relevant non-major bleeding.
Evaluation Criteria:	**Primary study outcome measure**: Characterization of the population PK/PD of an adapted rivaroxaban dosing regimen in subjects with acute, proximal DVT or acute PE and concomitant use of a strong CYP3A4 inducer. **Efficacy (Primary):** **Secondary outcome measure 1:** Symptomatic recurrent DVT **Efficacy (Secondary):** Not applicable

	Safety: **Secondary outcome measure 2** (Principal safety outcome): Clinically relevant bleeding (composite of major bleeding events and clinically relevant non-major bleeding events). **Secondary outcome measure 3** (Secondary safety outcomes): All deaths, other vascular events, and laboratory variables.
	Pharmacokinetics: Area under the plasma concentration-time curve [$AUC(0\text{-}24)_{ss}$] and maximum ($C_{max,ss}$) and minimum ($C_{min,ss}$) plasma concentrations of rivaroxaban during the dosing interval at steady state. **Pharmacodynamics:** Prothrombin time (PT) and prothrombinase-induced clotting time (PICT)
Statistical Methods:	**Efficacy (Primary):** Descriptive statistical methods were used. No formal statistical testing was done. **Efficacy (Secondary):** Not applicable **Safety:** Descriptive statistical methods were used.
	Pharmacokinetics: Descriptive statistical methods were used. No formal statistical testing was done. **Pharmacodynamics:** Descriptive statistical methods were used. No formal statistical testing was done.
Number of Subjects:	Planned: 50 subjects Analyzed: 25 subjects were valid for safety analysis, 19 subjects were valid for PK.

Study Results

Results Summary — Subject Disposition and Baseline

A total of 25 subjects were enrolled at the 3 study centers in South Africa. All 25 subjects (12 men, 13 women; mean age 40.8 years, range 22.0 - 79.0 years) received at least 1 dose of rivaroxaban and were valid for safety analysis. They had a mean body mass index (BMI) of 22.4 kg/m^2 and none of them had a creatinine clearance <50 mL/min. Nineteen (19) subjects (8 men, 11 women; mean age 41.1 years, range 22.0 - 79.0 years) were valid for PK. They had a mean BMI of 22.0 kg/m^2. Thus, the 2 subject populations were very similar.

Overall, 23 subjects experienced spontaneous DVT/PE as index events and the other 2 secondary DVT/PE. A total of 14 subjects (56%) completed the study and 11 subjects (44%) did not complete the study: 2 subjects (8%) died during study treatment (and another subject died 32 days after the last dose of study drug), and 9 subjects (36%) terminated study drug treatment prematurely. The predominant reasons for premature termination of

study drug treatment were subject convenience (n=3), i.e., the end-of-study visit was performed up to 4 days earlier than planned per protocol due to conflicting appointments of the subject, and adverse events (n=2).

Concomitant medication with protocol-defined strong CYP3A4 inducers was used by 24 subjects, i.e., antimycobacterials (n=20) and antiepileptics (n=4). One subject did not take any protocol-defined strong CYP3A4 inducer. The CYP3A4 inducer she took was nevirapine. Thus, she was excluded from the population valid for PK analysis.

Results Summary — Efficacy

The efficacy outcome was symptomatic recurrent VTE, i.e., the composite of recurrent DVT or non-fatal or fatal PE. Fatal PE was defined as either PE based on objective diagnostic testing or autopsy, or death that could not be attributed to a documented cause and for which DVT/PE could not be ruled out (unexplained death).

There were 2 out of 25 subjects with an efficacy event on study treatment, which was later adjudicated and confirmed by the CIAC: 1 subject died and PE could not be excluded and the other subject experienced a symptomatic recurrent proximal DVT. The total number of subjects participating in this study was too small to allow for a meaningful assessment of the incidence of symptomatic recurrent VTE.

Results Summary — Safety

All 25 subjects enrolled in this study were included in the safety population. Eighteen (18) subjects (72%) had at least 1 treatment-emergent adverse event. Six (6) subjects (24%) had at least 1 mild, 7 subjects (28%) at least 1 moderate, and 5 subjects (20%) at least 1 severe treatment-emergent adverse event. Severe events were death, sudden death, hepatitis, cryptococcal meningitis, and human immunodeficiency virus (HIV) test positive. None of the treatment-emergent adverse events was assessed as drug-related by the investigators.

Two (2) subjects (8%) (Subjects 370150012 and 370150013) died during the study treatment. Causes of death as adjudicated by the CIAC were unexplained death and PE cannot be ruled out (Subject 370150012) and infectious disease (Subject 370150013). Another subject (Subject 370060010), a 59-year-old Black man, died 32 days after the last dose of study drug. The subject died at home and no autopsy was available. The investigator assessed the cause of death as due to natural causes but the CIAC adjudicated the primary cause of death as ischemic stroke. This was the only vascular event adjudicated by the CIAC as a safety outcome.

Another 3 subjects (12%) experienced treatment-emergent serious adverse events other than death: hepatitis (Subject 370150010), cryptococcal meningitis (Subject 370150003), and vascular dementia (Subject 370060010). None of the treatment-emergent serious adverse events were assessed as drug-related by the investigators. The investigator assessed the serious hepatitis event as being related to rifampicin treatment.

Rivaroxaban exposure measured in Subject 370060010 during rivaroxaban treatment was within the expected exposure range. In contrast, rivaroxaban exposures in Subject 370150012 and the subject with recurrent DVT (corresponding to the adverse events edema, peripheral edema, pain in extremity, and vein pain; Subject 370150006) were at the lower end of the expected exposure range.

Three (3) subjects had at least 1 treatment-emergent adverse event resulting in permanent discontinuation of study drug. Those events were neutropenia, edema, peripheral edema, hepatitis, pain in extremity, and vein pain.

No major bleeding event occurred during this study. Three (3) subjects experienced any confirmed treatment-emergent bleeding event: Subject 370150004 experienced a clinically relevant non-major bleeding event, i.e., moderate skin bleeding (other than injection site) and a trivial bleeding, i.e., mild pharyngeal bleeding. Subject 370150002 experienced a clinically relevant non-major bleeding event, i.e., mild urogenital bleeding, and Subject 370060001 experienced a trivial bleeding event, i.e., mild nasal bleeding. The rivaroxaban exposure of Subject 370150004 was at the upper end of the expected exposure range, whereas the rivaroxaban exposure of Subject 370150002 was in the center of the expected exposure range.

Subject 370150010, a 34-year-old Black man, had a hepatic disorder adverse event (severe rifampicin-induced hepatitis), which was a serious adverse event leading to permanent discontinuation of study drug. The maximum ALT test result documented in the Hepatic Event Assessment Committee (HEAC) package was >8 times the upper limit of normal (ULN) (381 U/L = 9.5 x ULN).

All pregnancy tests performed in the 10 women of child-bearing potential who participated in this study were negative.

Virtually all post-baseline local laboratory abnormalities were minor changes, transient, and without clinical relevance. There was no signal for study drug-induced laboratory parameter changes.

Results Summary — Pharmacokinetics/Pharmacodynamics

During initial treatment, the median rivaroxaban AUC(0-24)$_{ss}$ in this study was approximately 36% lower than that of the pooled study results from subjects of the Phase II studies treated with the usual 15 mg bid/20 mg od dosing regimen. During extended treatment, the median rivaroxaban AUC(0-24)$_{ss}$ in this study was approximately 15% lower than that of the pooled results from the Phase II studies. Lower rivaroxaban exposure was also determined for median $C_{max,ss}$: approximately 27% and 35% during initial and extended treatments, whereas median $C_{min,ss}$ was approximately 53% lower during initial treatment and approximately 35% higher during extended treatment. Overall, a comparable exposure was observed in subjects with CYP induction receiving an adapted dosing regimen and subjects without CYP induction receiving the usual 15 mg bid/20 mg od dosing regimen. Table 1 gives a comparison of the PK parameters from this study with Study 12143.

Table 1: Comparison of derived pharmacokinetic parameters from this study (Study 13812)[a] versus simulations based on the venous thromboembolism treatment evaluation (Study 12143)[b] [median (5%/95% percentiles)]

	With strong CYP3A4 / P-gp inducer: actual		With strong CYP3A4 / P-gp inducer: simulated		Phase II data: all subjects	
	Initial treatment	Extended treatment	Initial treatment	Extended treatment	Initial treatment	Extended treatment
	Study 13812[a]		Study 12143[b] with strong CYP3A4 / P-gp inducer		Study 12143[b] normal	
Parameter	30 mg bid	20 mg bid	30 mg bid	20 mg bid	15 mg bid	20 mg od
AUC(0-24)$_{ss}$ [(µg*h)/L]	2836 (1259 / 6877)	2319 (1059 / 5782)	3228 (1721 / 5921)	2714 (1447 / 4978)	4464 (2383 / 8187)	2719 (1452 / 4986)
$C_{max,ss}$ [µg/L]	200 (150 / 386)	167 (126 / 324)	268 (183 / 419)	225 (154 / 352)	274 (176 / 459)	255 (179 / 397)
$C_{min,ss}$ [µg/L]	42 (1 / 170)	35 (1 / 143)	34 (6 / 124)	29 (5 / 104)	99 (32 / 237)	26 (4 / 99)

AUC(0-24)$_{ss}$ AUC from time 0 to 24 hours after first dosing on a day at steady state
$C_{max,ss}$ maximum observed drug concentration in measured matrix at steady state during a dosage interval
$C_{min,ss}$ minimum observed drug concentration in measured matrix at steady state during a dosage interval
CYP3A4 cytochrome P450 isoenzyme 3A4
P-gp P-glycoprotein
bid *bis in die*, 2 times daily
od once daily
[a] Study 13812, report under finalization
[b] PH-36357

The interpretation of the analyses of PT and PICT was limited by the small numbers of subjects in each bleeding category (2 subjects in each category: clinically relevant non-major bleeding event and trivial bleeding).

Conclusion(s)

This EINSTEIN CYP cohort study showed that the oral, single-drug, fixed-dose approach with rivaroxaban 30 mg 2 times daily for 3 weeks followed by 20 mg 2 times daily for the remainder of the 3-month treatment may be an appropriate approach to treating subjects who present with acute, proximal deep vein thrombosis or acute pulmonary embolism and who require a concomitant strong CYP3A4 inducer since the exposure is similar to the standard regimen without CYP inducers.

Publication(s):	None		
Date Created or Date Last Updated:	15 MAY 2012	**Date of Clinical Study Report:**	22 DEC 2011

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	Investigator Name	Facility Name	Street	ZIP Code	City	Country
1	Prof Barry Jacobson	Folateng Charlotte Maxeke Johannesburg Academic Hospital	Johannesburg Hosptial Folateng Private Section 7 York Road Parktown	2193	Johannesburg	SOUTH AFRICA
2	Prof Jan Becker	Pretoria Academic Hospital New	Corner Malan & Voortrekkers Street Gezina	0084	Pretoria	SOUTH AFRICA
3	Prof Barry Jacobson	University of Witwatersrand	Jhb General Hospital Clinical Haematology Dept, Room 21, Area 454 York Road PARKTOWN	2132	Johannesburg	SOUTH AFRICA

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Xarelto
Brand/Trade Name(s) ex-US	Xarelto
Generic Name	rivaroxaban
Main Product Company Code	BAY59-7939
Other Company Code(s)	
Chemical Description	IUPAC Name: 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide
Other Product Aliases	

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