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PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

12 FEB 2009

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NDA 22-406
XARELTO™ (rivaroxaban)

New Drug Application
FDA Advisory Committee Meeting
March 19, 2009
Briefing Document

Dear Ms. Ferguson:

Reference is made to the original New Drug Application (NDA) for XARELTO™ (rivaroxaban) immediate release tablets for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery, filed July 28th, 2008 by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) on behalf of Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI). This submission was provided electronically in Common Technical Document (eCTD) format to the Division of Medical Imaging and Hematology Drug Products.

In accordance with the Federal Advisory Committee Act (FACA) and the Draft Guidance "Guidance for Industry Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members" (Feb 2007), Johnson & Johnson Pharmaceutical Research and Development is submitting 30 CD copies (in PDF format) and 10 paper copies of the Sponsor's Briefing Document for rivaroxaban. The briefing materials have been marked as "AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION" for distribution to the Advisory Committee and FDA Staff as background materials for the Cardiovascular and Renal Drugs Advisory Committee Meeting scheduled for March 19, 2009.

J&JPRD hereby certifies that we have taken precautions to ensure that the briefing materials submitted on CD is free of computer viruses and authorizes CDER to use anti-virus software as appropriate. The following software was run to check for viruses: McAfee VirusScan Enterprise + Spyware Module 8.0.0, virus definitions 5514, Scan Engine 5300, copyright 1995-2004, Network Associates Technology, Inc.

Should you have any questions regarding this submission or require additional information, please contact me directly at (908) 927-6522 or my colleague, Sanjay Jalota at (908) 927 2637.

Sincerely,

Andrea Kollath, DVM,
Director, Regulatory Affairs
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Enclosure:
cc. Marcus Cato, FDA Project Manager, Division of Medical Imaging and Hematology Drug Products.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Advisory Committee Briefing Book

Rivaroxaban for the Prophylaxis of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) in Patients Undergoing Hip or Knee Replacement Surgery

JNJ-39039039 (BAY 59-7939, rivaroxaban)

Issue Date: 12 FEBRUARY 2009
Prepared by: Johnson & Johnson Pharmaceutical Research & Development, L.L.C
Department: Drug Development
Document No.: EDMS-PSDB-9099123:2.0

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EXECUTIVE SUMMARY

Rivaroxaban is an oral anticoagulant that is a direct inhibitor of factor Xa (FXa). Inhibition of FXa produces antithrombotic effects by decreasing the amplified generation of thrombin by the prothrombinase complex, thus diminishing thrombin-mediated activation of both coagulation and platelets, without affecting the activity of thrombin itself. Rivaroxaban is chemically and mechanistically distinct from unfractionated and low molecular weight heparins, fondaparinux, vitamin K antagonists and direct thrombin inhibitors.

Rivaroxaban is approved in the European Union (30 September 2008), Canada (15 September 2008), and a number of other countries worldwide for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

The proposed indication for rivaroxaban is:

> prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement or knee replacement surgery.

The recommended dose of rivaroxaban is 10 mg taken orally once daily without any laboratory monitoring or dose adjustment. The recommended duration of dosing is 35 days after hip replacement surgery and 14 days after knee replacement surgery.

The clinical program supporting this indication is extensive, consisting of over 50 Phase 1 studies (1129 rivaroxaban subjects evaluated for safety), 4 Phase 2 studies in joint replacement surgery (2232 rivaroxaban subjects evaluated for safety and efficacy), and 4 Phase 3 studies in joint replacement surgery (6183 rivaroxaban subjects evaluated for safety and efficacy). The results of this program support the efficacy and safety of the fixed 10 mg once daily dosing regimen of rivaroxaban in the proposed indication. Safety data from other clinical studies in other indications, some of which are still ongoing and/or include longer term dosing, are also supportive.

Thromboprophylaxis after Joint Replacement Surgery

Total hip replacement (THR) and total knee replacement (TKR) surgeries are known to be associated with a high risk for the development of postoperative DVT and PE and the benefits of anticoagulant prophylaxis have been established as reflected in current treatment guidelines. Enoxaparin and other low molecular weight heparins (LMWHs), fondaparinux, and adjusted-dose vitamin K antagonists like warfarin are all considered appropriate therapeutic options to achieve prophylaxis by The Eighth

American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy (Grade 1A recommendations).

Despite the availability and widespread use of these effective agents, clinically symptomatic VTE is still the most common serious complication observed following elective THR and TKR surgeries, occurring in about 2-3% of patients in clinical practice. With over 700,000 THR and TKR procedures performed in the US in 2005 (CDC 2005) and the annual number of procedures projected to increase with the aging of the population, this represents a substantial burden of potentially preventable morbidity and mortality.

Even though most patients receive some form of anticoagulant prophylaxis, full adherence to both the dose and duration (for at least 10 days) recommendations of the American College of Chest Physicians was observed in only 47% of THR and 61% of TKR patients. Adherence rates for warfarin (THR 33%, TKR 48%) were substantially lower than with LMWH (THR 63%, TKR 72%) (Friedman 2008). These data highlight the need for an anticoagulant that is efficacious, has a simple dosing regimen and route of administration, and that does not require laboratory monitoring or dose adjustment.

Rivaroxaban addresses this need. Rivaroxaban is highly efficacious in the prevention of DVT and PE in patients undergoing THR or TKR and is administered orally once daily. In addition, rivaroxaban has a predictable pharmacokinetic profile, and has a low potential for drug-drug or drug-food interactions, and thus does not require laboratory monitoring or dose adjustment.

Nonclinical summary

In vitro, rivaroxaban competitively inhibits human FXa (Ki 0.4 nM) with more than 10,000-fold selectivity when compared to other serine proteases.

Rivaroxaban inhibits FXa within the prothrombinase complex (IC_{50} 2.1 nM) as well as endogenous FXa in the plasma (IC_{50} 21 nM). In vivo, rivaroxaban showed efficacy in various nonclinical thrombosis models.

In vitro investigations with rivaroxaban uncovered no inhibitory or inductive potential towards major human CYP isoforms and no clinically relevant inhibitory potential towards P glycoprotein (Pgp) and breast cancer resistance protein (BCRP). However rivaroxaban was found to be a substrate of both Pgp and BCRP. In vivo metabolism in rats and dogs showed no major differences to human metabolism. The nonclinical safety profile of rivaroxaban was mainly characterized by findings related to

exaggerated pharmacological activity. Nonclinical safety testing did not reveal any target organ toxicity.

Clinical Pharmacology

Rivaroxaban has a predictable pharmacokinetic (PK) and pharmacodynamic (PD) profile with a close relationship between PK and PD. Rivaroxaban has a rapid onset and offset of action. Following oral administration, rivaroxaban is rapidly absorbed with the peak plasma concentration attained around 2-4 hours post dosing. Rivaroxaban at a dose of 10 mg has a high oral bioavailability (>80%) and can be given irrespectively of food.

Rivaroxaban has multiple elimination pathways. Approximately 1/3 of the drug is excreted unchanged by the kidneys (mainly by active renal secretion, but also by glomerular filtration). The remaining approximately 2/3 of the drug is metabolized by the liver (approximately 18% of the dose is metabolized via CYP3A4/3A5, 14% via CYP2J2, and 14% via CYP-independent hydrolysis), and the rest is unchanged in feces (7%) or are non-identified or non-recovered structures (11%). Half of the metabolized fraction is excreted in urine and the other half excreted in feces. There are no active circulating metabolites. Because of the multiple elimination pathways, rivaroxaban has a low potential for clinically relevant drug-drug interactions. Only concomitant use of drugs that are strong inhibitors of both hepatic metabolism and active renal secretion result in a clinically relevant increased systemic exposure of rivaroxaban.

Inter-subject variability in rivaroxaban exposure following oral administration is low-to-moderate (30-40%). There were no relevant PK or PD differences for age, gender, ethnicity or weight (i.e., differences between subgroups were within the overall magnitude of inter-subject variability). With increasing renal impairment, exposure increased to about 1.4-, 1.5-, and 1.6-fold in subjects with mild, moderate or severe renal impairment, respectively. Mild hepatic impairment did not affect PK or PD of rivaroxaban. Subjects with moderate hepatic impairment had pronounced increases (> 2 fold) both for pharmacokinetics and pharmacodynamics due to underlying disease. Rivaroxaban administration did not result in QT prolongation.

The pharmacokinetic and pharmacopynamic profile enable dosing of 10 mg rivaroxaban once daily in a wide range of patients, without dose adjustment or need for laboratory monitoring.

Clinical Program Overview

The efficacy and safety of rivaroxaban have been demonstrated in the RECORD program (REgulation of Coagulation in ORthopedic Surgery to prevent DVT and

PE), which includes 4 randomized, double-blind, Phase 3 comparative trials with enoxaparin (RECORD 1 [Study 11354], RECORD 2 [Study 11357], RECORD 3 [Study 11356], and RECORD 4 [Study 11355]).

Phase 2 studies in THR or TKR included 1 randomized, open-label trial (Study 10942), and 3 randomized, double-blind trials (Studies 10944, 10945, and 11527).

The 4 Phase 3 RECORD studies included 12,729 randomized subjects (10 mg rivaroxaban 6356, enoxaparin 6373) undergoing elective THR or TKR with 12,383 included in the safety analyses (rivaroxaban 6183, enoxaparin 6200). RECORD 1 and 2 were THR studies. RECORD 3 and 4 were TKR studies. The rivaroxaban dose (10 mg once daily) and start time (6-8 hours postoperatively) were the same in all studies. The duration of dosing was for 35±4 days after THR (RECORD 1,2) and for 12±2 days after TKR (RECORD 3,4). Enoxaparin was chosen as the comparator agent since it is the most widely used agent for THR and TKR VTE prophylaxis worldwide (including the US). The dose of subcutaneous enoxaparin was 30 mg twice daily started postoperatively for 12±2 days (RECORD 4), or 40 mg once daily started preoperatively for either 36±4 days (RECORD 1), 13±2 days (RECORD 3), or 13±2 days followed by placebo until Day 35 (RECORD 2). Bilateral venography for the assessment of DVT was scheduled for the day after the planned completion of blinded study drug in each study. Overall, a total of 17,864 subjects were included in the safety analyses in 65 completed Phase 1, 2 and 3 studies.

Efficacy Results

Endpoints including Venographic Assessments

Each of the 4 RECORD studies individually met or exceeded its primary efficacy objective by showing a greater reduction in the primary efficacy endpoint of total VTE (any DVT, nonfatal PE or death) in the rivaroxaban group than in the enoxaparin group that was statistically significant and clinically important. The efficacy of rivaroxaban was assessed in RECORD 1, RECORD 3, and RECORD 4 first with a non-inferiority test, and then secondly with a superiority test. Rivaroxaban met non-inferiority and then showed superiority to enoxaparin in RECORD 1, 3, and 4, and showed superiority in RECORD 2, which had only superiority testing. The results for the THR and TKR studies were consistent with each other.

Incidence of Total VTE (Primary Endpoint) in RECORD 1, 2, 3, and 4- MITT Population

	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	ARD (95% CI)	p-value
RECORD 1 [a]	18/1595	58/1558	-2.62%	p<0.001
	1.13 %	3.72 %	(-3.69, –1.54)	
RECORD 2[a]	17/864	81/869	-7.28%	p<0.001
	1.97%	9.32%	(-9.41, –5.15)	
RECORD 3 [a]	79/824	166/878	-9.15%	p<0.001
	9.59 %	18.91%	(-12.40, –5.89)	
RECORD 4[b]	67/965	97/959	-3.19	p=0.012
	6.94%	10.11%	(-5.67, –0.71)	

Note: ARD means absolute risk difference

[a] The enoxaparin dosing regimen was 40 mg once daily started preoperatively . In RECORD 2, enoxaparin was administered until day 12 followed by placebo until day 35

[b] The enoxaparin dosing regimen was 30 mg twice daily started post-operatively

The efficacy results from the integrated analysis of the RECORD studies were consistent across all important subgroups in the subject categories of sex, age, race, weight, BMI, and creatinine clearance, with each subgroup that contained a sufficient number of subjects demonstrating statistical superiority of rivaroxaban over enoxaparin. There were also no clinically meaningful differences in results across geographic regions, with the results from the US being well within the range of the overall findings.

For the prespecified main secondary endpoint of major VTE (proximal DVT, nonfatal PE and VTE related death), clinically important and statistically significant risk reductions were observed for the rivaroxaban group relative to the enoxaparin group in RECORD 1, 2 and 3, while in RECORD 4 a substantial risk reduction (41% relative risk reduction) was observed that did not reach statistical significance. As seen for the primary endpoint analyses, the results for major VTE were robust for both the THR and TKR studies and for all important subgroups.

Incidence of Major VTE (Secondary Endpoint) in RECORD 1, 2, 3, and 4- MITT Population

	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	ARD (95% CI)	p-value
RECORD 1 [a]	4/1686	33/1678	-1.74%	p<0.001
	0.24 %	1.97 %	(-2.45, –1.03)	
RECORD 2[a]	6/961	49/962	-4.49%	p<0.001
	0.62%	5.09%	(-5.97, –3.01)	
RECORD 3 [a]	9/908	24/925	-1.59%	p=0.010
	0.99 %	2.59 %	(-2.80, –0.38)	
RECORD 4[b]	13/1122	22/1112	-0.80%	p=0.124
	1.16%	1.98%	(-1.82, 0.22)	

Note: ARD means absolute risk difference

[a] The enoxaparin dosing regimen was 40 mg once daily started preoperatively . In RECORD 2, enoxaparin was administered until day 12 followed by placebo until day 35

[b]The enoxaparin dosing regimen was 30 mg twice daily started post-operatively

Enoxaparin performed well in all 4 RECORD studies with efficacy endpoint incidence rates similar to or lower than those reported in the literature. The further reductions observed with rivaroxaban are therefore clinically relevant and indicate that rivaroxaban offers additional protection for both total VTE and major VTE events beyond that provided by enoxaparin.

In summary, rivaroxaban has demonstrated consistent, clinically important, and statistically significant superior efficacy compared with enoxaparin for the prophylaxis of total VTE and major VTE after both THR and TKR surgery.

Symptomatic Event Endpoints

As screening for asymptomatic DVT is not done in clinical practice, the most relevant benefit for the practicing physician regarding VTE prophylaxis after THR and TKR surgery is the prevention of symptomatic events.

For the prespecified RECORD 1-4 integrated analysis of symptomatic events, the incidence of the primary composite efficacy endpoint, symptomatic VTE or death from all causes, during the treatment phase was statistically significantly lower in the rivaroxaban group (35 [0.57%]) than in the enoxaparin group (82 [1.32%]) (hazard ratio 0.42, $p<0.001$). This difference was due to an approximately 2 to 3 fold lower incidence in the rivaroxaban group of all components of the primary endpoint and was consistent for both the THR and TKR studies separately. The cumulative incidence rate curves for rivaroxaban and enoxaparin began to separate shortly after surgery and continued to diverge throughout the entire treatment period with no evidence for any loss of efficacy during the follow-up period.

It is generally accepted that the occurrence of asymptomatic distal (calf) DVT is usually an intermediate step in a progression to proximal DVT, symptomatic DVT, and/or PE. Therefore, the symptomatic event results observed in the RECORD program are entirely consistent with the venographic endpoint results of total VTE and major VTE. The results for all 3 efficacy endpoints using relative scale assessments are summarized below. These results show that rivaroxaban demonstrates statistically significant superior efficacy for both asymptomatic and symptomatic events compared with enoxaparin after both THR and TKR surgery.

Efficacy Endpoint Relative Risks/Hazard Ratios (95% CI) for Rivaroxaban Compared With Enoxaparin During the Treatment Phase

Study or Pool	Total VTE MITT population	Major VTE MITT population	Symptomatic VTE or Death Safety population
RECORD 1	0.30 (0.18, 0.51)	0.12 (0.04,0.34)	0.67 (0.30,1.48)
RECORD 2	0.21 (0.13 0.35)	0.12 (0.05,0.28)	0.25 (0.09,0.66)
RECORD 3	0.51 (0.39, 0.65)	0.38 (0.18,0.82)	0.31 (0.14,0.68)
RECORD 4	0.69 (0.51, 0.92)	0.59 (0.30,1.16)	0.56 (0.28,1.15)
RECORD 1-2	0.25 (0.17,0.36)	0.12 (0.06, 0.23)	0.43 (0.23,0.78)
RECORD 3-4	0.57 (0.47,0.70)	0.48 (0.29,0.80)	0.42 (0.25,0.72)
RECORD 1-4	0.46 (0.39,0.54)	0.25 (0.17,0.37)	0.42 (0.29,0.63)

Note: Relative Risk was provided for Total VTE and Major VTE; Hazard Ratio was provided for Symptomatic VTE or Death

Safety Results

Rivaroxaban is well tolerated relative to enoxaparin when administered 10mg once daily without routine laboratory monitoring. The vast majority of the safety exposures in support of rivaroxaban use for DVT and PE prophylaxis after elective THR or TKR comes from the four Phase 3 RECORD studies. As shown in the summary table of adverse events below, the incidence of adverse events was similar or lower on rivaroxaban compared to enoxaparin.

Adverse Event Incidence
(Subjects Valid for Safety Analysis in pooled RECORD 1-4 Studies)

	Rivaroxaban N=6183	Enoxaparin N=6200
Incidence of:	n (%)	n (%)
Any death	13 (0.21%)	25 (0.40%)
Any serious treatment emergent adverse event	406 (6.57%)	528 (8.52%)
Any treatment emergent adverse event	4179 (67.59%)	4306 (69.45%)
Any adverse event starting >2 days after stop of study drug	627 (10.14%)	621 (10.02%)
Any adverse event resulting in permanent discontinuation of study drug	230 (3.72%)	288 (4.65%)

The most commonly reported adverse event terms by investigators included nausea, pyrexia, vomiting, constipation, and deep vein thrombosis, all of which are expected in a perioperative population.

As with any anticoagulant, bleeding was identified as an adverse event of special interest. All bleeding events from each of the RECORD studies were adjudicated centrally in a blinded manner. The primary prespecified safety endpoint in each of the RECORD studies was the incidence of treatment-emergent major bleeding events observed no later than 2 days after the last intake of study drug. The table below

summarizes the incidence of treatment-emergent major bleeding events from each of the RECORD studies. The absolute risk increase ranged from 0% to 0.39%.

Major Bleeding Events in RECORD 1, 2, 3, and 4 Safety Population

	Rivaroxaban N=6183 n (%)	Enoxaparin N=6200 n (%)	ARD (95% CI)	p-value
RECORD 1[a]	6 (0.27%)	2 (0.09%)	0.18% (-0.07, 0.44)	0.155
RECORD 2[a]	1 (0.08%)	1 (0.08%)	0% (-0.23, 0.22)	0.980
RECORD 3[a]	7 (0.57%)	6 (0.48%)	0.08% (-0.49, 0.66)	0.774
RECORD 4[b]	10 (0.66%)	4 (0.27%)	0.39% (-0.09, 0.88)	0.110
RECORD 1-4	24 (0.39%)	13 (0.21%)	0.18% (-0.01, 0.37)	0.069

Note: ARD means absolute risk difference HR means hazard ratio

[a] The enoxaparin dosing regimen was 40 mg once daily started preoperatively . In RECORD 2, enoxaparin was administered until day 12 followed by placebo until day 35.

[b] The enoxaparin dosing regimen was 30 mg twice daily started post-operatively.

Pooling all 4 RECORD studies together, the absolute risk increase in major bleeding events was 0.18% (95% CI: -0.01%, 0.37%) for rivaroxaban compared with enoxaparin. For other bleeding endpoints including major bleeding with surgical site bleeding events included, major or non-major clinically relevant bleeding events, or any bleeding event the absolute risk increases ranged from 0.42% to 0.64%.

Since there were few major bleeding events, subgroup analyses were performed instead on the composite endpoint of major or non-major clinically relevant bleeding as well as the composite endpoint of any bleeding. The effect in most subgroups was directionally consistent with the effect observed in the overall population. In addition, the relative risk of bleeding for rivaroxaban compared with enoxaparin was not substantially influenced by concomitant medication use (including nonsteroidal anti-inflammatory agents).

The development of events after treatment with rivaroxaban or enoxaparin that could be considered cardiovascular rebound was rare. In the pooled RECORD studies, after stopping active study medication, there were a total of 16 (0.26%) and 14 (0.23%) subjects in the rivaroxaban and enoxaparin groups respectively that experienced an event of myocardial infarction, ischemic stroke, cardiovascular death or unexplained death.

Liver safety has been carefully evaluated in the rivaroxaban development program. In Phase 2 VTE prophylaxis studies involving a 12-fold dose range from 2.5 mg twice daily to 30 mg twice daily, the incidence of ALT > 3x ULN did not increase with dose and was lower on rivaroxaban compared to enoxaparin. In the pooled RECORD studies, the incidence of ALT abnormalities at thresholds of >3x ULN and >5x ULN were lower on rivaroxaban compared to enoxaparin. At higher thresholds

(ie. >8x, >10x, and >20x ULN), the incidence was similar in the two groups. It is important to note that enoxaparin, the active control agent used in the RECORD studies, is known to be associated with benign ALT elevations. Therefore, a comparison of combined ALT >3x ULN and TB >2x ULN elevations may be more reliable as a measure to detect a signal of drug-induced liver injury. In the RECORD program, the number of subjects experiencing an ALT>3x ULN with TB >2x ULN was similar in the two groups. The lower incidence of ALT >3x ULN on rivaroxaban compared to enoxaparin combined with a similar incidence of ALT >3x ULN combined with TB >2x ULN suggests that the potential for drug-induced liver injury with rivaroxaban is low.

Additional data from ongoing studies in indications other than VTE prophylaxis after THR or TKR surgery provide further evidence with respect to the liver safety of rivaroxaban. The duration of exposure duration from several of these ongoing studies is greater compared to the 35 day or less exposure duration in the RECORD studies. In addition, in several of these ongoing studies, the doses of rivaroxaban used were comparable or higher to the 10 mg dose used in the RECORD studies. As of 5-December-2008, a total of 5865, and 1557 subjects have been exposed to rivaroxaban for >180 days, and >360 days respectively. While many of these exposures come from blinded studies, one of these studies has recently been completed and unblinded. The ATLAS ACS TIMI 46 study is a Phase 2 study in subjects with acute coronary syndromes in which subjects received study drug for 6 months. In this study, the incidence of ALT >3x ULN was similar on rivaroxaban (3.7%) versus placebo (4.5%). These data, in combination with the totality of liver safety data from the RECORD studies and from the other ongoing studies suggest that the potential for drug-induced liver injury with rivaroxaban is low.

In conclusion, the safety of rivaroxaban has been well characterized when used as an anticoagulant for the prophylaxis of DVT and PE in patients undergoing THR or TKR surgery. Rivaroxaban has a favorable safety profile relative to enoxaparin when administered as a fixed, oral dosing regimen of 10 mg once daily in the absence of routine laboratory monitoring. Bleeding events were the only identified risk with rivaroxaban. The potential for cardiovascular rebound effects and drug-induced liver injury with rivaroxaban appears to be low.

Safety Surveillance Plan

A comprehensive pre-marketing risk assessment of the clinical trial safety database has determined the following: 1) an Identified Risk – Bleeding and 2) a Potential Risk - Transient elevation of liver laboratory tests. Additionally, it was determined that rivaroxaban would have the potential for chronic off-label use for non-approved

indications, due to its once daily oral dosing regimen that does not require laboratory monitoring.

The Sponsor is proposing, in addition to routine risk minimization measures, the utilization of a variety of additional tools to further assess and mitigate the identified and potential risks, when rivaroxaban is used for the prophylaxis of DVT and PE in patients undergoing THR or TKR. Also included in this plan are measures to address the potential for off-label use. The following routine measures and additional risk minimization tools are proposed: 1) U.S. Package Labeling, 2) Patient Package Insert, 3) Routine Pharmacovigilance Practices, 4) Enhanced Pharmacovigilance Activities for specific adverse events of interest (AEOI), 5) Drug Packaging Strategies, 6) Commercialization Strategies, 7) Education and Outreach Programs, 8) Post-Marketing Utilization Study, and 9) Post-Marketing Observational Study (Ex US). The following table outlines the pharmacovigilance activities and interventions to identify, characterize, prevent/minimize risks related to the use of rivaroxaban in the post-marketing setting.

	Identified Risk: Bleeding	**Potential Risk: Perioperative Transient elevation of liver laboratory tests**	**Potential for Off-label Use:**
Risk Minimization			
U.S. Product Labeling	√	NA	√
Patient Package Insert	√	NA	√
Pharmacovigilance Practices:			
Routine	√	√	√
Enhanced	√	√	√
Commercialization Strategies	√	NA	√
Education and Outreach Programs	√	NA	√
Drug Packaging Strategies	NA	NA	√
Risk Assessment			
Post-Marketing Drug Utilization Study	√	√	√
Post-Marketing Observational Cohort Study	√	√	NA

NA – Not Applicable

Benefit Risk

The favorable benefit-risk profile of rivaroxaban in DVT and PE prophylaxis after THR and TKR has been demonstrated throughout the RECORD program. Each of the four RECORD studies successfully demonstrated superiority in reducing the incidence of total VTE vs. the comparator, either enoxaparin, or, in the case of RECORD 2, an enoxaparin placebo combination. In three of the studies (RECORD 1, RECORD 3, and RECORD 4), the first objective was to demonstrate comparable efficacy (non-inferiority) in total VTE, but in each case, statistically significant and clinically meaningful reductions in events were achieved with rivaroxaban treatment.

Consistent reductions were also seen in Major and Symptomatic VTE. These occurred at the expense of a modest increase in bleeding events, most of which had relatively lesser clinical impact than the VTE events.

Comparisons of key efficacy and safety composites across the pooled data set consistently demonstrate a benefit-risk profile favoring rivaroxaban. In each comparison, rivaroxaban demonstrated an excess of benefit over risk compared with enoxaparin. This conclusion applies to a variety of endpoints examined (total VTE, major VTE, symptomatic VTE, major bleeding, major plus non-major clinically relevant bleeding, SAEs). Furthermore, analyses of the clinical importance of the symptomatic VTE events versus bleeding events indicate that the events prevented by rivaroxaban are, in general, of greater clinical impact than the bleeding events that occur as a result of treatment, further solidifying the favorable benefit-risk profile of rivaroxaban. Keeping in mind that enoxaparin is an accepted part of standard therapy in the proposed setting of THR/TKR, the results present a compelling argument that the benefit-risk balance of rivaroxaban is favorable. Considering the number of THR and TKR surgeries, the potential public health benefit is substantial.

In conclusion, data from the RECORD program, consisting of four pivotal Phase 3 studies, consistently demonstrate that rivaroxaban is highly efficacious versus an active comparator in the prevention of DVT and PE in patients undergoing THR or TKR, is well tolerated with only a modest increase in bleeding, and has a highly favorable benefit-risk ratio. As such, rivaroxaban represents an important advance in the treatment of patients undergoing THR and TKR, with the potential to significantly reduce the burden of thrombotic complications in this large patient population.

1. INTRODUCTION

Rivaroxaban (BAY 59-7939) is a selective direct factor Xa (FXa) inhibitor anticoagulant that is orally administered. It is being codeveloped through a joint collaboration between Bayer HealthCare Pharmaceuticals (Bayer) and Johnson & Johnson Pharmaceutical Research and Development, L.L.C (J&JPRD). Johnson & Johnson Pharmaceutical Research and Development (J&J PRD) submitted a New Drug Application (NDA) for rivaroxaban to the FDA Division of Medical Imaging and Hematology Products in July 2008 (NDA 22-406) for the proposed indication:

> prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement or knee replacement surgery.

The recommended dose of rivaroxaban is 10 mg taken orally once daily. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.

The duration of treatment depends on the individual risk of the patient for DVT and PE which is determined by the type of orthopedic surgery.

- For patients undergoing hip replacement surgery, a treatment duration of 35 days is recommended.
- For patients undergoing knee replacement surgery, a treatment duration of 14 days is recommended.

The clinical program supporting this NDA is extensive, consisting of over 50 Phase 1 studies (1129 rivaroxaban subjects evaluated for safety), 4 Phase 2 studies in joint replacement surgery (2232 rivaroxaban subjects evaluated for safety and efficacy), and 4 Phase 3 studies in joint replacement surgery (6183 rivaroxaban subjects subjects evaluated for safety and efficacy). The results of this program support the efficacy and safety of the fixed 10 mg once daily dosing regimen of rivaroxaban without the need for routine laboratory monitoring or dose adjustment. Clinical studies in other indications, some of which are still ongoing and/or include longer term dosing, are also reviewed briefly from a safety perspective.

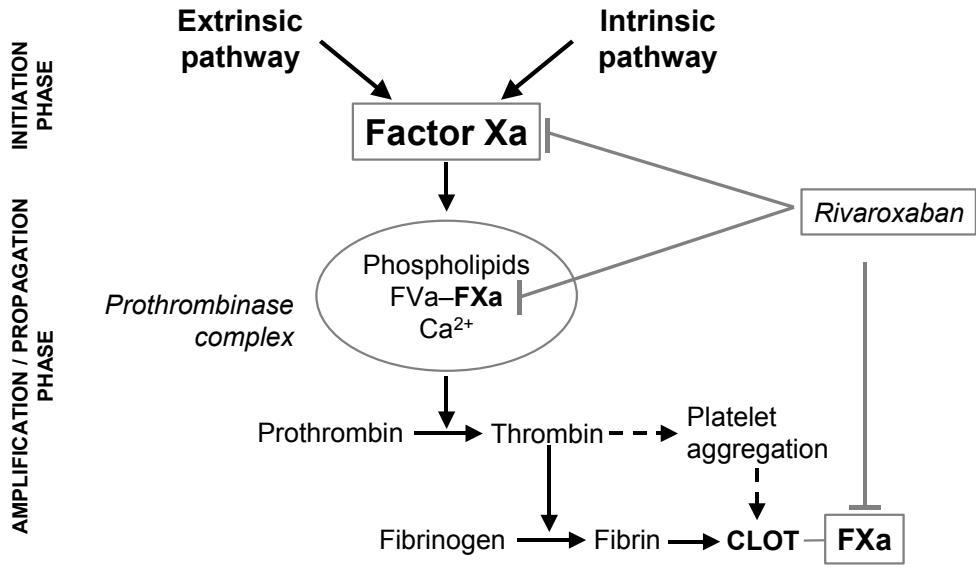
Rivaroxaban is approved in the European Union (30 September 2008), Canada (15 September 2008), and a number of other countries worldwide for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

1.1. Mechanism of Action and Chemical Class

Rivaroxaban is a selective orally administered direct FXa inhibitor anticoagulant. Activation of factor X to FXa via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation by mediating thrombin formation. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. The reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin generation. Thrombin has several functions in blood coagulation, including the conversion of fibrinogen to fibrin, the activation of platelets, and the feedback activation of other coagulation factors, resulting in the amplification of its own formation. Rivaroxaban produces antithrombotic effects by decreasing this amplified generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets, without affecting the activity of thrombin itself. The remaining low levels of thrombin should be sufficient to ensure primary hemostasis, resulting in a favorable efficacy to safety (bleeding) margin for

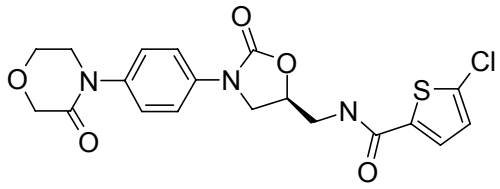
rivaroxaban (Roehrig 2005). The site of action of rivaroxaban in the coagulation cascade is shown in Figure 1-1.

Figure 1-1: Factor Xa - a Pivotal Point in the Coagulation Pathway.



The chemical name, structural formula and chemical characteristics of rivaroxaban are provided in Figure 1-2. Rivaroxaban is chemically and mechanistically distinct from unfractionated and low molecular weight heparins, fondaparinux, vitamin K antagonists and direct thrombin inhibitors.

Figure 1-2: Chemical Characteristics of Rivaroxaban

Structural formula	
Chemical name	5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide
Molecular formula	$C_{19}H_{18}ClN_3O_5S$
Molecular weight	435.89 g/mol
JNJ No. CAS No.	JNJ-39039039 366789-02-8
Chirality/Stereochemistry	Rivaroxaban has one chiral center
Other names	Rivaroxaban, BAY 59-7939

1.2. Epidemiology of Thromboembolic Disease and Current Therapies

Venous thromboembolism (VTE), which includes DVT and PE, is a serious condition that is a common cause of mortality and morbidity. Patients undergoing major

orthopedic surgery, including total hip replacement (THR) and total knee replacement (TKR) surgeries, represent a group that is at a particularly high risk for VTE (Geerts 2008). Without prophylaxis, the incidence of all DVT (asymptomatic detected by screening tests like venography and symptomatic) is approximately 40% to 60% following THR or TKR surgery with a 10-30 % incidence of proximal DVT (Geerts 2008). Even with modern surgical techniques, placebo data from studies conducted in Japan between 2001 and 2003 show that the incidence of DVT was still in this range (THR: any DVT 34%, any proximal DVT 12%; TKR: any DVT 65%, any proximal DVT 14%) (GlaxoSmithKline Clin Trials Reg; Studies DRI4090 and DRI4757). A more recent TKR study from Japan showed a placebo group VTE incidence of 48% again confirming that DVT and PE frequently occur in this setting if no prophylaxis is given (Lassen 2008, Fuji 2008).

A meta-analysis of studies comparing the addition of about a week of subcutaneous unfractionated heparin to standard therapy after general, orthopedic, and urologic surgery showed that anticoagulant prophylaxis reduces asymptomatic DVT, fatal PE, and all cause mortality with no increase in the risk of fatal bleeding events (Collins 1988). This effect was consistent across all 3 types of surgery with an overall reduction in PE from 3.0% in the control group (191/6426 with 55 fatal events) to 1.7% in the heparin group (109/6366 with 19 fatal events) The fatal PE odds reduction was 64% ($p<0.001$) and the nonfatal PE odds reduction was 40% ($p<0.0005$). Even though the use of unfractionated heparin has largely been replaced by low molecular weight heparins (LMWHs), this study is still the landmark one demonstating the benefits of anticoagulant prophylaxis for reducing fatal PE. Since the routine screening of patients for asymptomatic DVT is logistically difficult and not considered effective in preventing clinically important VTE (Leclerc 1998, Robinson 1997) the most appropriate strategy to reduce the incidence of VTE is anticoagulant prophylaxis for all patients undergoing THR or TKR. This strategy has been recommended by expert groups for over 2 decades based on the Collins meta-analysis and other data and has been widely adopted in orthopedic surgery practice with about 90-95% of THR and TKR patients receiving some form of postoperative prophylaxis (Friedman 2008, Cohen 2008) .

The Eighth American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy makes anticoagulant prophylaxis after joint arthroplasty surgery a Grade 1A recommendation, indicating that the clinical evidence and methodology that generated this recommendation are very strong, the results are consistent and the benefit-risk ratio is clear. Enoxaparin and other LMWHs, fondaparinux, and warfarin are all considered appropriate therapeutic options to achieve prophylaxis and are approved in the United States (US) for this indication

(Geerts 2008). The duration of prophylaxis should be at least 10 days for both THR and TKR. For patients undergoing THR, extended prophylaxis for up to 35 days after surgery is recommended (Grade 1A). Since the current duration of the inpatient period after these surgeries is only a few days prophylaxis needs to be administered primarily on an outpatient basis. Low dose unfractionated heparin and aspirin are not recommended since they are less effective for the prevention of total VTE (Grade 1A not to use). Mechanical methods of prophylaxis are recommended primarily for patients with a high risk of bleeding precluding the use of anticoagulants (Grade 1A) and possibly as an adjunct to anticoagulant therapy (Grade 2A). There are guidelines from the American Academy of Orthopedic Surgery that indicate that aspirin may be an acceptable option for some patients. However, these guidelines focus only on the prevention of PE and are based primarily on expert opinion (Eikelboom 2008).

Enoxaparin and other LMWHs provide effective and safe prophylaxis of VTE. However, they need to be administered subcutaneously, which is often associated with pain and subcutaneous bruising, and presents administration challenges in the outpatient setting. LMWHs may also trigger heparin-induced thrombocytopenia, although this occurs rarely. Enoxaparin is the most widely used LMWH after THR or TKR surgery, with placebo-controlled studies showing about an 80% relative risk reduction in the incidence of VTE after both surgeries (THR: all DVT placebo 46%, enoxaparin 10%, p=0.0002; TKR all DVT placebo 62%, enoxaparin 11%, p=0.0001; enoxaparin USPI 2007).

Fondaparinux, a pentasaccharide with specific, indirect inhibition of FXa, showed superiority in one study (Lassen 2002) and non-inferiority in another (Turpie 2002) when compared with enoxaparin in subjects undergoing elective THR and, in both cases, appeared to have a safety profile similar to enoxaparin. In subjects undergoing elective major TKR, prophylaxis with fondaparinux was significantly more effective in preventing VTE than enoxaparin, but was also associated with a higher incidence of major bleeding (Bauer 2001). Like enoxaparin, fondaparinux also needs to be administered subcutaneously. The incidence of liver transaminase elevations with fondaparinux was lower than with enoxaparin.

The only currently available oral anticoagulant for prophylaxis of VTE after TKR or THR surgery in the US is warfarin. Warfarin is challenging to use in clinical practice for the following reasons: (1) it has a narrow therapeutic window; (2) it exhibits considerable variability in dose response among patients; (3) it is subject to frequent interactions with other drugs and diet; (4) it requires dose adjustment to obtain and stay within the therapeutic range (target International Normalized Ratio [INR]) and this must be guided by frequent monitoring in the outpatient setting; and (5) it has a

slow onset and offset of action that is likely suboptimal for preventing VTE in the immediate postoperative period (Ansell 2004). In fact, direct comparisons of warfarin with LMWH for prophylaxis of VTE after major orthopedic surgery have shown that warfarin is not as effective as LMWH, although it may have an advantage of a lower bleeding risk in the immediate postoperative period perhaps due to its more delayed onset of action (Geerts 2008).

Despite the availability and widespread use of these effective agents, clinically symptomatic VTE is still the most common serious complication observed following elective THR and TKR surgeries. In a large California cohort study, the incidence of symptomatic VTE during the first 3 months following surgery was 2.8% (n/N=556/19,586 patients) for primary THR (median time to diagnosis of 17 days) and 2.1 % (n/N=508/24,059 patients) for primary TKR (median time to diagnosis of 7 days), with most events occurring after hospital discharge (White 1998). A more recent study from Scotland showed similar results, with 3-month incidence rates of symptomatic VTE of 2.3% after THR and 1.8% after TKR that were constant over the period from 1992 to 2001 (Howie 2005). Compared with a cataract surgery control group selected to have a minimal risk of VTE, the odds ratio for VTE was 14.8 (95% Confidence Interval [CI]: 12.9, 16.9) for THR and 11.6 (95% CI: 10.0, 13.5) for TKR with all the excess risk occurring in the first 3-month period. Mortality was 1.4% after THR and 0.8% after TKR, with thrombotic events (PE, myocardial infarction and stroke) representing the most common causes of death. Similarly, a recent registry study with 100 centers from 13 countries that included over 15000 THR or TKR patients showed a three month cumulative VTE incidence of 1.7% after THR (mean time of onset 21.5 days) and 2.3 % after TKR (mean onset 9.7 days) (Warwick 2007)

Definitively establishing that PE is the cause of death after surgery is problematic since the clinical presentation of PE is nonspecific and autopsies are rarely performed at most institutions. A review of 30,714 consecutive elective hip procedures at the Mayo Clinic over the period from 1969 to 1997 showed that the 30-day death rates declined from 0.94% in the 1970's to a stable rate of 0.15% in the 1990's. For almost half of the 90 deaths observed (41 cases) autopsies were performed and cited PE as the most frequent single cause of death (14 cases); the second most frequent cause of death cited was myocardial infarction (10 cases) (Parvizi 2001). A recent literature review of large cohort studies that did not rountinely include autopsy evaluations reports an overall mortality rate of 0.57 % for THR or TKR patients receiving prophylaxis with about 33% (0.18%) of these deaths being attributed to pulmonary embolism (Dahl 2005) .

These data show the continuing important consequences of VTE after THR and TKR surgery. With over 700,000 THR and TKR procedures performed in the US in 2005 (CDC 2005) and the annual number of procedures projected to increase with the aging of the population, this represents a substantial burden of potentially preventable disease.

Recent registry data indicate that there is still poor adherence to evidence-based VTE prophylaxis recommendations in the US. Even though most patients receive some form of prophylaxis full adherence to the type of prophylaxis as well as both the dose and duration (for at least 10 days) recommendations of the American College of Chest Physicians was observed in only 47% of THR and 61% of TKR patients. Adherence rates for warfarin (THR 33%, TKR 48%) were substantially lower than with LMWH (THR 63%, TKR 72%) (Friedman 2008). These data highlight the need for an anticoagulant that is efficacious, that has a simple dosing regimen and route of administration, and that does not require monitoring or dose adjustment.

1.3. Rationale for Venography and the Importance of Asymptomatic DVT

Venography is the most sensitive method available for the detection of DVT. Although compression ultrasonography is accepted as a diagnostic method for symptomatic DVT, it is not sensitive or specific for the diagnosis of asymptomatic DVT, particularly in the setting of elective orthopedic surgery (Schellong 2007). Therefore, in order to provide a rigorous assessment of the occurrence of all DVT in the rivaroxaban THR and TKR studies, bilateral venography was scheduled to be performed at the end of the study drug treatment period. Symptomatic DVT events, confirmed by compression ultrasound or venography, were also included in the efficacy analyses. In previous clinical studies evaluating anticoagulant agents for VTE prophylaxis after THR or TKR surgery venography has been the most commonly used method of DVT assessment and therefore a strong precedent exists for its use both in the scientific literature and for regulatory approval. An expected outcome with the use of venography is that not all subjects will be assessable for the primary efficacy endpoint because either the venography is not performed (subject refusal or technically not possible) or the quality of the venogram is not adequate for assessment. The impact of missing data on the efficacy assessments in this situation has been evaluated in a number of ways and has not been seen as sufficiently problematic to limit use (e.g. Quan 2007, Norrie 2007).

Since venography is not done after THR or TKR surgery in routine clinical practice the clinical importance of asymptomatic DVT detected with this test has been questioned. In fact, the majority of the DVT diagnosed by venography after THR and

TKR are confined to the calf and are clinically silent (Agnelli 1993, Lotke 1984, Philbrick 1988). However, approximately 10 to 20% of calf thrombi do extend to the proximal veins (Kearon 2003, Maynard 1991, Oishi 1994, Philbrick 1988). Also, there is a strong association between asymptomatic DVT, especially proximal DVT, and the subsequent development of symptomatic DVT, non-fatal PE and fatal PE (Collins 1988, Eikelboom 2001, Haas 1992, Moser 1981, Oishi 1994). There is also evidence that even asymptomatic DVT can lead to damage of the venous valves with a subsequent risk for the development of the postthrombotic syndrome. Finally, both fatal PE and severe postthrombotic syndrome are very unlikely to occur in the absence of venographic DVT, as evidenced from the event-free follow-up of patients undergoing THR who had no venographically detected DVT at discharge (Ricotta 1996).

Therefore, reductions in any DVT (proximal and distal) and especially in proximal DVT (which has a higher propensity for pulmonary embolization) detected by venography, even if asymptomatic, are considered to be clinically important. It should be noted that although the prevention of fatal PE is a major objective of thromboprophylaxis following THR and TKR surgery, the prevention of all symptomatic events (DVT and nonfatal PE) is important as well since these events are associated with acute morbidity, substantial use of health care resources (e.g anticoagulation therapy), and long-term clinical sequelae (e.g. postthrombotic syndrome) (Sullivan 2003).

2. NONCLINICAL DATA

2.1. Nonclinical Pharmacology

Rivaroxaban is a direct, specific, FXa inhibitor, which does not require a cofactor to inhibit FXa. It is a reversible (k_{off} = $5\times10^{-3}s^{-1}$) FXa inhibitor, with a rapid onset of action (k_{on} = 1.7×10^{7} M^{-1} s^{-1}). Inhibition of FXa by rivaroxaban was competitive (K_i = 0.4 nM), with >10,000 fold selectivity than for other serine proteases. Rivaroxaban also inhibited FXa within the prothrombinase complex responsible for the thrombin burst (IC_{50} 2.1 nM), reduced endogenous FXa activity in plasma (IC_{50} 21 nM), and inhibited clot-associated FXa activity (IC_{50} 92 nM). In human plasma, it demonstrated anticoagulant effects; prothrombin time (PT) was more sensitive than activated partial thromboplastin time (aPTT).

In vivo, rivaroxaban given prophylactically showed potent, dose-dependent antithrombotic activity in both venous (platelet-poor, fibrin-rich) thrombosis models in the rat (ED_{50} 0.1 mg/kg iv) and arterial (platelet-rich, fibrin-poor) thrombosis models in rats (ED_{50} 2 -10 mg/kg po; 1 mg/kg iv), in mice (ED_{50} 1 mg/kg iv), and in rabbits (ED_{50} 0.6 mg/kg po). In the arterial and venous thrombosis models,

rivaroxaban showed comparable efficacy as the comparator enoxaparin. In a rabbit model of venous thrombus growth (treatment model), oral rivaroxaban, when given non-prophylactically at a dose of 3.0 mg/kg, reduced thrombus growth.

The antihemostatic effect of rivaroxaban was evaluated in bleeding time models in rats and rabbits. Bleeding times are not significantly affected at doses required for antithrombotic efficacy in the rat and rabbit AV-shunt models. At higher dosages, bleeding times are dose-dependently prolonged. In these nonclinical models rivaroxaban shows an antithrombotic activity/bleeding risk ratio comparable to enoxaparin. Studies on co-administration of rivaroxaban with drugs showing anticoagulant or antiplatelet activity revealed an additive effect on rat bleeding times.

The anti-FXa activity of the metabolites was 10^2 to 10^4 times lower (M1, M4 and M7) than rivaroxaban, or metabolites were inactive (M13, M15, M16, M17 and M18). Metabolite M2 was 3-fold less potent than rivaroxaban. For a discussion of the rivaroxaban biotransformation pathways see Section 2.2. Considering that metabolite M1 covers < 10 % of total drug-related compound exposure in the circulation in man and other metabolites are not found in plasma, metabolites of rivaroxaban do not contribute to a relevant extent to the pharmacological activity of rivaroxaban.

In primate and rat, recombinant FVIIa, FEIBA and prothrombin complex concentrate partially reversed the increase in bleeding time induced by a high dose of rivaroxaban. In the rat, administration of activated charcoal 15 min after an oral rivaroxaban dose reduced rivaroxaban exposure (AUC) by approximately 65 %.

2.2. Nonclinical Pharmacokinetics and Drug Metabolism

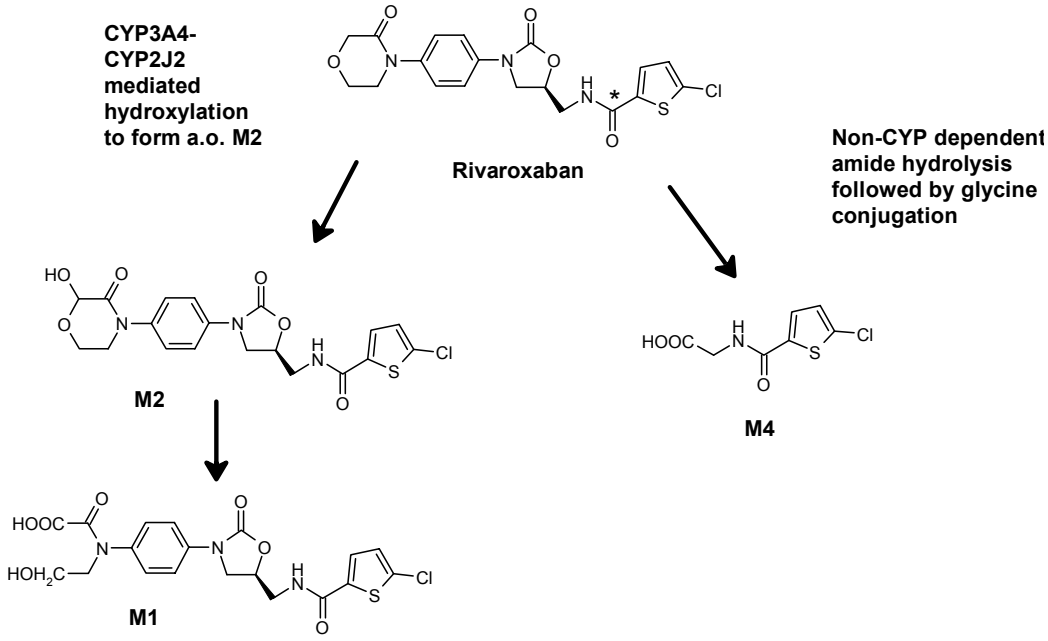
The oral bioavailability of rivaroxaban was 60 % in rats and 60 to 86 % in dogs. The plasma concentrations of rivaroxaban were almost dose-proportional within the dose-ranges of the pharmacokinetic studies in rats and dogs. The fraction unbound (f_u) ranged between 1 and 23 % in animals; in man it was 5 – 8 %. In human plasma protein binding was predominantly to albumin. The elimination of rivaroxaban occurred rapidly from rat and dog plasma with half-lives of about 1 h after i.v. and between 1 to 2.3 h after oral administration.

The overall organ and tissue distribution of [14C]rivaroxaban radioactivity (unchanged rivaroxaban and radio-labeled metabolites) can be judged as moderate after oral administration to rats. There was no irreversible binding or relevant retention of radioactivity in any organs and tissues of rats after single as well as after repeated oral administration of [14C]rivaroxaban. Highest levels of total radioactivity were observed in excretory organs liver and kidney and related organs (GI tract including content, bladder), with steady state tissue-to-plasma AUC ratios of 7 and 3

for liver and kidney, respectively. Other tissues showed lower total radioactivity levels. Lowest total radioactivity levels were observed in brain and spinal cord. The placental barrier was penetrated to a moderate extent, with fetal total radioactivity levels lower than maternal blood levels. [14C]Rivaroxaban-related radioactivity was secreted into the milk of lactating rats only to a low extent. The estimated amount of radioactivity excreted with milk was 2.1 % of dose within 32 h after administration. After repeated oral administration of [14C]rivaroxaban to rats (14 consecutive daily administrations), there was no unexpected accumulation of radioactivity based on the single dose distribution data.

The in vitro and in vivo biotransformation pathways of rivaroxaban are similar for man and the various animal species. A main metabolic pathway is formation of the monohydroxylated metabolite M2 at the morpholinone moiety, which was followed by ring opening to form M1. In addition hydrolysis of the amide bond (forming M13) followed by glycine conjugation to form M4 was observed to be an important metabolic pathway. Main rivaroxaban metabolic pathways are presented in Figure 2-1. In all investigated species, the degradation of the morpholinone moiety was the major site of biotransformation of rivaroxaban. Oxidative degradation of the morpholinone moiety was catalyzed in man by CYP3A4/3A5 and CYP2J2 and formed M1, M2, M3, M5, M6, M8, M10, and M11. Metabolites with ring-opening at the morpholinone moiety are M1, M5, M6, and M7. Hydroxylations in other part of the rivaroxaban molecule led to metabolites M9, M10, M11, and M12. Metabolites formed via non-CYP dependent amide bond hydrolysis are M7 and M13, the latter metabolite glycine-conjugated to form M4, and the M13 counterparts M15, M17 and M18. The in vitro and in vivo biotransformation pathways of rivaroxaban are similar for man and the various animal species. No major circulating metabolites were detected in plasma of rat, dog, and man. The main circulating metabolite observed was M1, which accounted for about 6 %, 5 % and 3 % of total plasma radioactivity AUC in rat, dog and man, respectively. FXa IC_{50} of M1 is about 10^3 times higher than that of rivaroxaban and thus M1 is considered not to contribute to the rivaroxaban pharmacological effect. No evidence for reactive metabolite structures was found in the in vitro and in vivo metabolism studies.

Figure 2-1: Main Rivaroxaban Metabolic Pathways, * Identifying Location of 14C Label



Excretion occurred via both renal and fecal/biliary routes in animal species and in man. In rat and dog, excretion of unchanged rivaroxaban was low, about 10 %, largely into urine. In man, unchanged rivaroxaban in urine accounted for about 36 % of the dose. Besides unchanged rivaroxaban, oxidative metabolite M1 was identified as main metabolite in the excreta of animals and man. In man, rivaroxaban was eliminated via three pathways: renally as unchanged drug by both glomerular filtration and an active, most likely transporter-mediated pathway; metabolically by an oxidative CYP2J2 and CYP3A4/3A5-mediated metabolic pathway; and metabolically by hydrolysis of the amide bond.

In in vitro investigations, rivaroxaban exhibited no inhibitory and no inductive potential on major human CYP isoforms as well as no clinically relevant inhibitory potential towards P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP). Rivaroxaban exhibited characteristics of a moderate Pgp substrate and a strong BCRP substrate.

2.3. Nonclinical Safety

A comprehensive GLP compliant program was conducted to characterize the nonclinical safety profile of rivaroxaban according to the regulatory requirements for the intended indications and current testing guidelines.

Nonclinical safety testing was mainly performed in rats and dogs using oral administration. Both species were responsive to the pharmacological mode of action of rivaroxaban and had human-like metabolic and kinetic profiles.

Repeat-dose toxicity to support long-term administration in patients was covered by studies with daily treatment up to 6 months in rats and up to 12 months in dogs.

Two-year carcinogenicity studies in rats and mice are ongoing to support the use of rivaroxaban in indications requiring long-term use.

In safety pharmacology studies, rivaroxaban caused no adverse effects on CNS, cardiovascular and respiratory system, renal function and metabolism, and gastrointestinal tract. There was no indication for a pro-arrhythmogenic potential. In all species, the nonclinical safety profile of rivaroxaban was mainly characterized by exaggerated pharmacological activity of rivaroxaban. As expected, blood coagulation was inhibited resulting in prolongation of coagulation time in all species tested (for multiples of exposure, refer to Table 2-1). In dogs, rivaroxaban treatment resulted in exaggerated pharmacological activity (antihemostatic effects) that led to severe, in individual cases to life threatening bleeding, with secondary anemia. In rats, no clinically overt bleeding was observed up to the highest doses tested. There was no evidence of organ-specific toxicity up to the highest attainable doses and exposures tested. A standard battery of in vitro and in vivo genotoxicity tests revealed no evidence for a genotoxic risk to patients. Rivaroxaban had no impact on fertility, and developmental toxicity studies revealed no evidence for a primary teratogenic potential of rivaroxaban. Maternal tolerability as well as embryo-fetal and pre- and early postnatal development was mainly influenced by the anti-coagulative properties of rivaroxaban and bleedings resulting from study drug administration.

Table 2-1: Multiples of Human Exposure at 10 mg/day as Observed in Repeat Dose Toxicity Studies

	Mouse[a] (M/F)	Rat[b] (M/F)	Dog
Cmax, unbound	112/116	51/84	110[c]
AUC unbound	34/47	29/60	66[d]/39[e]

[a] 13-week toxicity study
[b] 26-week toxicity study
[c] 4-week toxicity study
[d] 13-week toxicity study
[e] 52-week toxicity study

Rivaroxaban has a chemical structure similar to linezolid, a compound known to cause mitochondrial toxicity. This had raised concern about possible effect of rivaroxaban on the mitochondria. When tested in isolated mitochondria up to the limit of thermodynamic solubility in aqueous solutions (5 mg/mL), rivaroxaban did not produce inhibition of mitochondrial protein synthesis as was observed for linezolid at pharmacologically relevant concentrations. Furthermore, in vivo rivaroxaban did not reveal any effects on oxazolidinone-specific target organs (e.g. bone marrow). The

lack of any cumulative toxicity after prolonged treatment confirms that rivaroxaban does not induce linezolid-like mitochondrial toxicity. In addition, rivaroxaban did not show biologically relevant antibacterial activity against representative linezolid-sensitive reference strains.

2.3.1. Critical Review for Signals of Hepatotoxicity

The nonclinical liver data for rivaroxaban were critically reviewed regarding the potential to induce hepatotoxic effects. As further detailed below, the overall assessment of the complete nonclinical package to support rivaroxaban does not reveal a potential for hepatotoxicity. This also takes into account minor effects on liver parameters, which as such are not considered to constitute a marker for hepatotoxicity.

In 13 week and 26 week repeat dose studies in rats, at interim analyses a slight (≤ 2-fold) and isolated increase of ALT was seen. However, these changes were transient and normalized under continuous treatment. Furthermore, they were not exposure-related, restricted to males despite 2-fold higher exposure in females and not consistent across studies. None of the individual data showed an increase above 2-fold ULN (upper limit of normal; i.e. mean + 2 standard deviations). It is noted that an increase above 3xULN is generally considered as adverse according to the 'Concept Paper on Nonclinical Assessment of Potential Liver Toxicity in Man' (FDA Working Group, 2000). In addition, histopathological evaluation revealed no degenerative effects in any of the studies conducted.

In the repeat-dose studies in mice up to 13-week treatment duration, no effects on liver enzymes were seen. In one 13-week study, a slight increase of focal hepatocellular necroses was noted. Due the focal appearance of the lesions which is untypical of drug-induced lesions, and considering that the lesions are known background findings in mice, and that they were not reproduced in further 13-week studies with up to five times higher exposure, they are regarded as chance findings.

In the repeat-dose studies in dogs, individual animals showed a 2 fold to 3 fold isolated increase of ALT when compared to pretreatment values. However, the incidences were evenly distributed throughout all dose groups including controls and did not indicate treatment relationship. Histopathologically, in none of the animals degenerative liver lesions were seen. In the 52-week study, one high dose animal that died due to a severe bronchopneumonia following a gavage error showed a marked (> 20 fold) increase of ALT prior to death. This ALT increase was not associated with changes in AST, GGT, ALP and bilirubin, nor with changes in any functional (albumin) or metabolic (glucose, triglycerides, cholesterol) parameters, nor with histopathological liver changes.

In several studies in all three species investigated, slight increases of total bilirubin levels were seen. The changes were generally minor and far below the value of 17 mmol/L which is considered indicative for liver toxicity (FDA Working Group, 2000). The total bilirubin concentrations did not reach the threshold that would allow a meaningful differentiation into direct and indirect bilirubin. In rodents, the individual values were within the range of historical controls. In dogs, the bilirubin increases were transient and correlated well with bleeding episodes and reticulocyte increases indicating a direct relationship to blood resorption. In the absence of significant and concomitant effects on other liver parameters, especially ALP and GGT, these effects most likely reflect the occurrence of clinical and subclinical hemorrhages due to the exaggerated pharmacological mode of action.

In summary, the findings listed above were presented as being the only findings in the rivaroxaban nonclinical package in relation to any potential indication of a hepatotoxic effect. None of these findings are of a magnitude that indicates a significant and relevant adverse effect on the liver as defined in the FDA Working Group paper (FDA Working Group, 2000) and as such the findings are not considered to indicate a potential hepatotoxic risk to humans.

3. CLINICAL PHARMACOLOGY

3.1. Introduction

The pharmacokinetics and pharmacodynamics of rivaroxaban were studied in over 50 clinical pharmacology studies (a total of more than 1000 subjects received rivaroxaban). Covariates (including age, gender, body weight, renal function, co-medication) were further investigated via population pharmacokinetic, population pharmacodynamic, and population pharmacokinetic/pharmacodynamic analysis using Phase 2 and/or 3 data. In addition, the impact of certain covariates or special patient populations on the safety and efficacy of rivaroxaban were evaluated (Section 5.2.3.2 and Section 6.2.3.1.7).

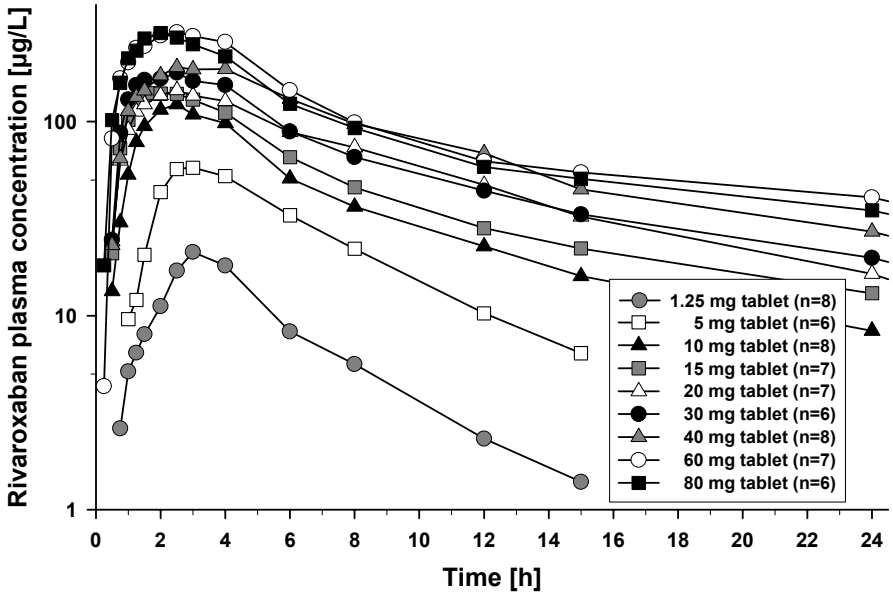
The exposure-response relationships for bleeding events were also explored in the studied patient population.

3.2. Human Pharmacokinetics

3.2.1. ADME Characteristics

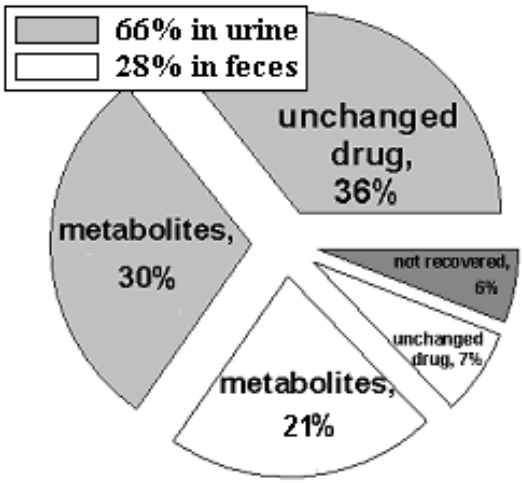
Rivaroxaban is rapidly absorbed after oral administration as immediate-release tablet with the peak plasma concentration attained around 2-4 hours post dosing. The terminal half-life is approximately 5–9 hours in healthy young male subjects (< 45 years of age) and 11–13 hours in healthy elderly subjects (> 60 years of age). The plasma concentration-time profile in healthy young volunteers is shown in Figure 3-1.

Figure 3-1: (Geometric) Mean Plasma Concentration-Time Profileof Rivaroxaban Following Single Dose of 1.25 – 80 mg Rivaroxaban Under Fasting Condition (Phase 1)



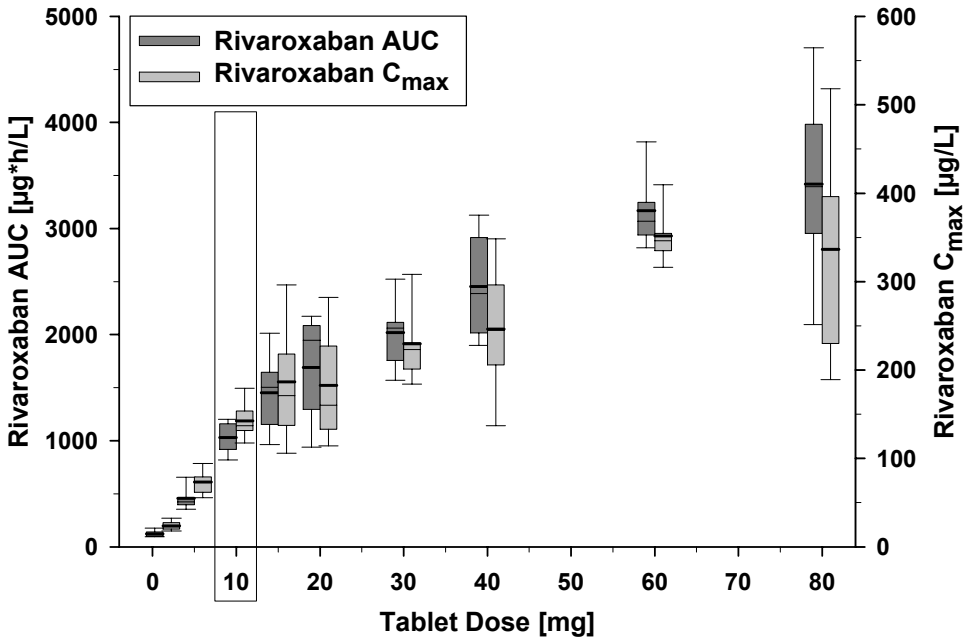
The oral bioavailability of rivaroxaban is high. The absolute bioavailability of the 5-mg tablet dose was complete while the absolute bioavailability of a 20-mg dose under fasting conditions was 66% compared with the intravenously administered dose. The absolute bioavailability of the 10-mg tablet is estimated to be 80-100%, irrespective of fasting/fed condition. The relative bioavailability (AUC) of a 10-mg tablet in comparison to the oral solution was close to 100%. The high oral bioavailability of the 10 mg tablet is supported by the human [^{14}C]rivaroxaban mass balance study where 87% of the administered 10-mg dose was recovered as unchanged drug and metabolites in urine (66%) or as metabolites in feces (21%). Unchanged drug in urine represented 36% of the dose (Figure 3-2), whereas 7% of the dose was recovered in feces as unchanged drug.

Figure 3-2: Renal and Fecal Excretion of Rivaroxaban



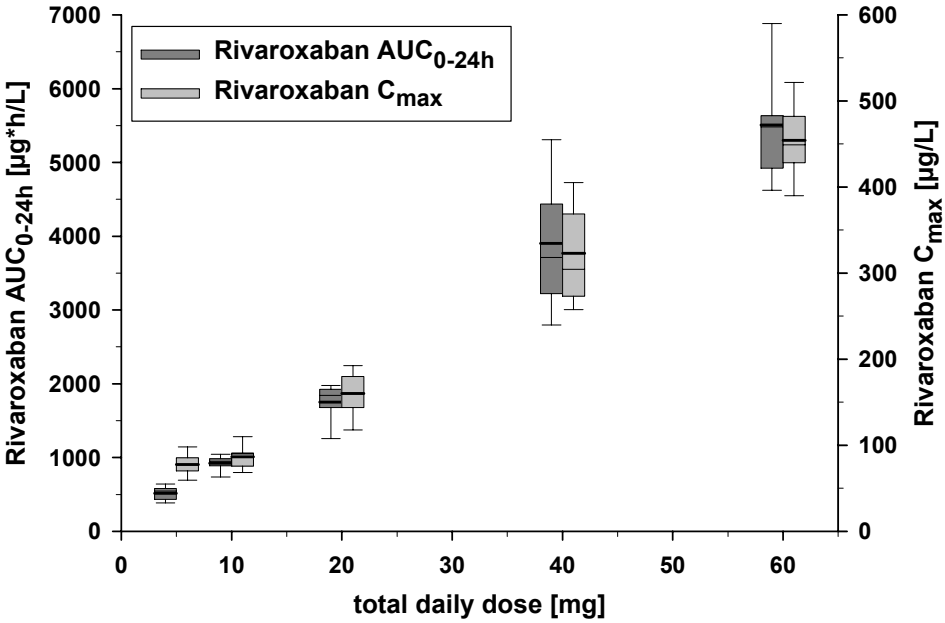
At doses up to and including 15 mg once daily, rivaroxaban exposure was dose proportional (Figure 3-3). Exposure increases less than dose-proportionally with doses above 15 mg under fasting conditions (with small increases beyond 40 mg) (Figure 3-3), indicating a decrease in absorption as a result of the limited aqueous solubility of rivaroxaban (5–7 mg/L, pH-independent).

Figure 3-3: Single-Dose Dose-Dependency in Rivaroxaban AUC and C_{max}: Single Dose of 1.25-80 mg Rivaroxaban Under Fasting Conditions (Phase 1) Box-Plot With 10-25-50-75-90 Percentiles Including Arithmetic Mean; n=6-8 per Group



Co-administration of rivaroxaban tablets with food improved the oral absorption at doses of 20 mg rivaroxaban and higher. When the 20-mg tablet was administered with food, the mean area under the plasma concentration-time curve (AUC) increased by approximately 39%, indicating complete oral absorption of the 20-mg dose under fed conditions. After multiple once- and twice-daily doses of rivaroxaban administered with food, AUC and C_{max} increased dose proportionally up to 30 mg twice daily, indicating complete absorption under fed conditions. There was no accumulation during multiple dosing beyond what is to be expected from the single-dose data (Figure 3-4).

Figure 3-4: Steady-State Dose-Proportionality in Steady State Rivaroxaban AUC and C_{max}: Multiple Doses of 5 mg Once Daily and 5-30 mg Twice Daily Rivaroxaban Under Fed Conditions (Phase 1) Box- Plot With 10-25-50-75-90 Percentiles Including Arithmetic Mean; n=7 per Group



Rivaroxaban has multiple elimination pathways. Approximately 1/3 of the drug is excreted unchanged by the kidney (mainly by active renal secretion, but also by glomerular filtration). The remaining approximately 2/3 of the drug is metabolized by the liver, with half of the metabolized fraction excreted in urine and the other half excreted in feces (Figure 3-2). Approximately 18% of the dose is metabolized via CYP3A4/3A5, approximately 14% via CYP2J2, and approximately 14% via CYP-independent hydrolysis. The rest of the dose is excreted unchanged in feces (7%), or are non-identified or non-recovered structures (11%). Unchanged drug was the main compound in plasma at all investigated time-points and accounted for 89% of the AUC of total radioactivity. No circulating active metabolites were detected in plasma (Section 2.2). Based on in vitro investigations (Section 2.2), rivaroxaban is a substrate of the transporter proteins Pgp and BCRP, both most likely responsible for active renal secretion of rivaroxaban.

Because of the multiple elimination pathways, rivaroxaban is not prone to major effects of single-organ dysfunction or drug-drug interactions.

Rivaroxaban is a low-clearance drug, with systemic clearance of approximately 10 L/h, indicating hardly any first pass metabolism. Renal clearance was approximately 4 L/h indicating active renal secretion.

The volume of distribution for rivaroxaban at steady-state is approximately 50 L (0.62 L/kg), indicating its low affinity to tissues. Within blood, rivaroxaban is mainly

distributed in plasma. Rivaroxaban is bound to plasma proteins at approximately 92% to 95%, with albumin being the main binding component. There was no concentration-dependency up to approximately 25-fold the (median) peak plasma concentration observed with 10 mg rivaroxaban. Due to its high plasma protein binding rivaroxaban is not expected to be dialyzable. The binding of rivaroxaban to plasma proteins is fully reversible. The human plasma-to-blood partition coefficient is 1.40.

The variability in pharmacokinetics (C_{max} and AUC) is moderate with inter-individual variability ranging from 30% to 40% (coefficient of variation). The intra-individual variability is on average 14-19% (median) for AUC and C_{max}, respectively.

3.2.2. Food and Pharmacokinetic Drug Interaction Potential

Administration of the 10 mg rivaroxaban tablet with a high-calorie/high-fat meal resulted in no significant food effects (Table 3-1). In the Phase 3 pivotal clinical studies, rivaroxaban 10 mg tablets were administered irrespective of food intake.

Table 3-1: Summary of Rivaroxaban in vivo Food and PK Interaction Studies, Presented as Mean Ratios of Rivaroxaban AUC and C_{max} and Associated 90% Confidence Intervals(Phase 1)

Influence of	AUC Ratio [90%CI]	C_{max} Ratio [90%CI]
High-fat, high-calorie meal 10-mg IR tablet (n=24)	0.99 [0.93-1.05]	1.03 [0.94-1.14]
Change in Gastric Ph		
Ranitidine 150 mg bid (n=12)	1.01 [0.85 – 1.20]	1.08 [0.77 – 1.50]
Absorption/Change in Gastric pH		
Antacid/Maalox® 10 mL (n=11)	0.95 [0.83 – 1.08]	0.87 [0.73 – 1.03]
CYP 3A4 Inhibitor (moderate)		
Erythromycin 500 mg tid (n=15)	1.34 [1.23 – 1.46]	1.34 [1.21 – 1.48]
CYP 3A4 Inhibitor (strong) and P-gp Inhibitor (weak to moderate)		
Clarithromycin 500 mg bid (n=15)	1.54 [1.44 – 1.64]	1.40 [1.30 – 1.52]
CYP 3A4 Inhibitor (strong) and P-gp Inhibitor (strong)		
Ketoconazole 200mg qd (n=12)	1.82 [1.59 – 2.08]	1.53 [1.27 – 1.85]
Ketoconazole 400mg qd (n=20)	2.58 [2.36 – 2.82]	1.72 [1.61 – 1.83]
Ritonavir 600 mg bid qd (n=12)	2.53 [2.34 – 2.74]	1.55 [1.41 – 1.69]
CYP 3A4/P-gp Inducer (strong)		
Rifampicin 600 mg (n=18)	0.51 [0.48 – 0.55]	0.78 [0.70 – 0.87]

bid: twice daily; qd: once daily; tid: three times a day

Rivaroxaban is not sensitive to interactions with respect to absorption processes. Coadministration with the H2-receptor antagonist ranitidine or the antacid aluminum hydroxide/magnesium hydroxide did not affect the bioavailability and pharmacokinetics of the 10 mg rivaroxaban dose (Table 3-1).

Rivaroxaban has a limited potential to be subject to drug-drug interactions because the elimination of rivaroxaban occurs by both the active renal secretion and multiple

metabolic pathways (with CYP3A4/3A5 mediated metabolism being the most important metabolic pathway, next to CYP2J2 mediated metabolism or non-CYP mediated hydrolysis). Hence, only concomitant administration with drugs that are strong inhibitors of both hepatic metabolism and active renal secretion are likely to result in a clinically relevant increase in systemic drug exposure to rivaroxaban (i.e., >2-fold). This is demonstrated by the results of drug interaction studies with high doses of ketoconazole and ritonavir, both strong inhibitors of both CYP3A4 and Pgp: (Table 3-1). Concomitant administration of 400 mg once daily ketoconazole or 600 mg twice daily ritonavir led to a 2.6-fold/2.5-fold increase in mean rivaroxaban steady-state AUC and a 1.7-fold/1.6-fold increase in mean rivaroxaban $C_{max,}$ respectively. Increases of > 2-fold were considered to be clinically relevant based on exposure-response (i.e. bleeding) data collected in Phase 2 (see Section 3.4.1). Hence, rivaroxaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and Pgp.

Inhibition of only one elimination route is not expected to have a clinically relevant effect on systemic exposure (i.e., the change in exposure will be within the variability range [i.e., 30-40%] of the overall population and less than 2-fold). The results of drug-drug interaction studies with clarithromycin, a strong inhibitor of CYP3A4 and a weak-to-moderate inhibitor of Pgp, and erythromycin, a moderate CYP3A4 inhibitor, support this position (Table 3-1). Coadministration with clarithromycin led to increases in mean rivaroxaban C_{max} and AUC by 1.4-fold/1.5-fold, respectively; co-administration with erythromycin resulted in a mean 1.3-fold increase. In Phase 3, an analysis of the bleeding risk in subjects who received concomitant CYP3A4 inhibitor (n=458) or P-gp inhibitor (n=128) with rivaroxaban compared to subjects not receiving these concomitant drugs did not indicate a clearly increased risk for bleeding in these patients (see also Section 6.2.3.1.8)

Concomitant use of rivaroxaban with strong CYP3A4 inducers lead to 50% lower rivaroxaban plasma concentrations, as shown following concomitant use of rifampicin (Table 3-1). These effects are considered as not clinically relevant based on efficacy data collected in Phase 2 and 3. In Phase 2, where rivaroxaban doses from 5 mg to 60 mg total daily dose were investigated, the incidence of total VTE with each of the doses of rivaroxaban was similar and did not indicate a clear dose-relationship (Figure 5-5; Section 5.2.1). In Phase 3, there seemed to be no clinically relevant loss in efficacy in subjects receiving concomitant inducers of CYP3A4 or Pgp inducers in a subgroup of subjects receiving these drugs (see also efficacy Section 5.2.3.2 for more details).

In vitro data (Section 2.2) demonstrated that rivaroxaban has no inhibiting nor inducing potential on major CYP isoforms or Pgp/BCRP transporters. In vivo drug interaction studies indicated that there were no mutual PK interactions between rivaroxaban and midazolam (substrate of CYP3A4), digoxin (substrate of Pgp) or atorvastatin (substrate of CYP3A4 and Pgp) (Table 3-2).

Table 3-2: Summary of in Vivo Mutual PK Interaction Studies With CYP3A4 and/or Pgp Substrates, Presented as Mean Test/Reference Ratios and Associated 90% Confidence Intervals (Phase 1)

Test	Reference	Analyte	Parameter	Ratio (90%CI)
Rivaroxaban - Midazolam Drug Interaction (n=12)				
Rivaroxaban + Midazolam	Rivaroxaban	Rivaroxaban	AUC	1.01 (0.92 – 1.12)
			C_{max}	0.88 (0.72 – 1.07)
	Midazolam	Midazolam	AUC	0.89 (0.75 – 1.05)
			C_{max}	1.01 (0.73 – 1.39)
		α-Hydroxy-midazolam	AUC	0.99 (0.85 – 1.14)
			C_{max}	1.11 (0.77 – 1.59)
Rivaroxaban - Digoxin Drug Interaction (n=17)				
Rivaroxaban + Digoxin	Rivaroxaban	Rivaroxaban	AUC	0.90 (0.83 – 0.97)
			C_{max}	1.00 (0.85 – 1.14)
	Digoxin	Digoxin	$AUC_{\tau,ss}$	1.08 (0.97 - 1.20)
			$C_{trough,ss}$ Day 7	0.95 (0.85 - 1.06)
			$C_{trough,ss}$ Day 8	1.03 (0.90 - 1.17)
			$C_{trough,ss}$ Day 9	0.95 (0.85 - 1.06)
Rivaroxaban - Atorvastatin Drug Interaction (n=19)				
Rivaroxaban + Atorvastatin	Rivaroxaban	Rivaroxaban	AUC	0.99 (0.91 – 1.08)
			C_{max}	0.98 (0.89 – 1.07)
	Atorvastatin	Atorvastatin acid	AUC	1.01 (0.93 - 1.09)
			C_{max}	1.03 (0.88 - 1.21)
		2-Hydroxy-atorvastatin	AUC	1.01 (0.94 - 1.09)
			C_{max}	1.00 (0.91 - 1.11)
		Atorvastatin-lactone	AUC	1.01 (0.92 - 1.11)
			C_{max}	1.06 (0.94 - 1.12)

Midazolam (7.5 mg): CYP3A4 substrate; Atorvastatin (20 mg once daily): CYP3A4 & Pgp substrate; Digoxin(0.375 mg once daily): Pgp substrate

In the food and pharmacokinetic interaction study, all pharmacodynamic effects closely followed the changes in pharmacokinetic concentration-time profiles of rivaroxaban in plasma.

3.3. Human Pharmacodynamics

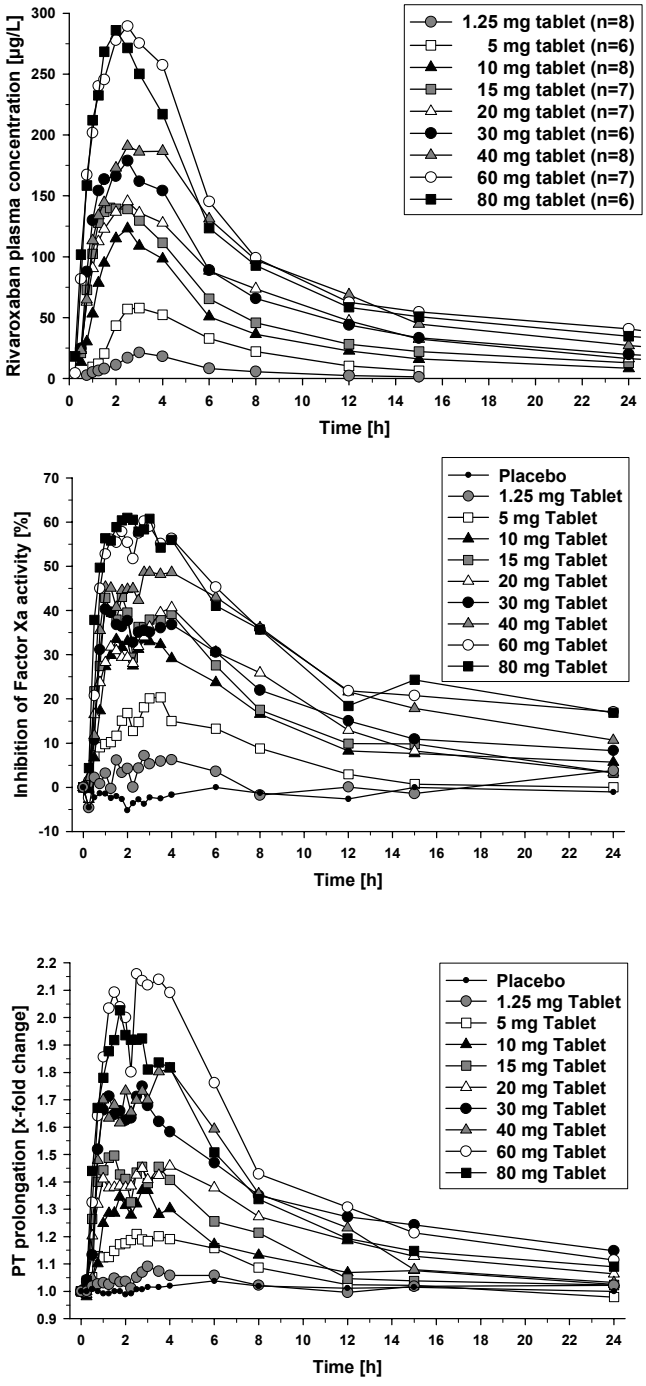
3.3.1. Effects on Blood Coagulation

Rivaroxaban is an oral direct Factor Xa inhibitor. Consequently, several specific (inhibition of Factor Xa activity) and global clotting tests (PT, aPTT, Heptest®) are affected by rivaroxaban.

Factor Xa was inhibited in a dose-dependent way by rivaroxaban. In addition, rivaroxaban prolongs prothrombin tine (PT), activated partial thromboplastin

time(aPTT) and HepTest® in a dose dependent way, closely following the changes in pharmacokinetic concentration-time profiles of rivaroxaban in plasma (Figure 3-5).

Figure 3-5: Single-Dose (Geometric) Mean Plasma Concentration-Time Profile of Rivaroxaban, Inhibition of Factor Xa Activity and Prolongation of Prothrombin Time: Single Dose of 1.25 mg – 80 mg Rivaroxaban Under Fasting Conditions (Phase 1)
PD: Median of Percentage Changes (Inhibition Factor XA activity) or Relative Change (PT Prolongation) From Baseline; n=6-8 per Dose Group



In accordance with the plasma concentration time profile, prolongation of PT reached half of the peak effect within 0.5-1 hours after drug intake and peak effect within 2-4

hours after administration of a tablet. The PT value should be reported in seconds, because the INR (International Normalized Ratio) is only calibrated and validated for coumarins and should not be used for rivaroxaban. In patients undergoing THR or TKR surgery (pooled Phase 3), the 5/95 percentiles for peak PT (i.e., 2-4 hours after tablet intake) at steady-state following 10 mg rivaroxaban once daily ranged from 13 to 26 seconds (median 18 seconds) (baseline values before surgery were between 12 to 16 seconds [median 13 seconds]). These values were obtained using PT Neoplastin®; other reagents may give different results. The offset of pharmacodynamic effect also parallels the pharmacokinetic elimination.

3.3.2. Pharmacodynamic Drug Interaction Potential

As an anticoagulant, rivaroxaban has the potential to interact with other drugs that influence hemostasis. Co-administration of rivaroxaban with acetylsalicylic acid, naproxen, diclofenac, warfarin, or clopidogrel showed additive but not potentiating effects on bleeding time prolongation in the rat bleeding model.

In a Phase 1 interaction study, co-administration of enoxaparin (40 mg single subcutaneous dose) with rivaroxaban (10 mg single oral dose) resulted in additive pharmacodynamic effects as measured by anti-Factor Xa assay (Figure 3-6), but not on the global clotting tests PT or aPTT compared to rivaroxaban alone (Table 3-3). No pharmacokinetic interaction was observed.

Figure 3-6: Rivaroxaban – Enoxaparin Drug Interaction (n=10): Anti-Factor Xa activity - Mean Change from Baseline (Phase 1)

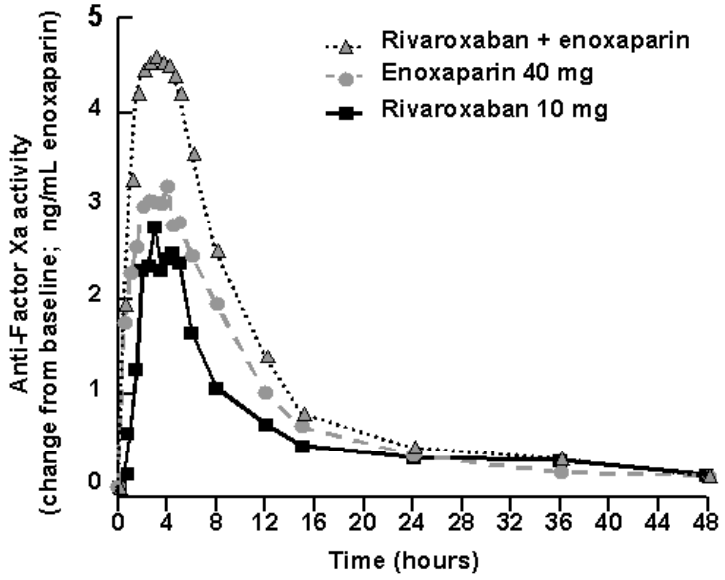


Table 3-3: Rivaroxaban – Enoxaparin Drug Interaction (n=10): Maximum Median Changes From Baseline of Inhibition of FXa Activity and Prolongation of Global Clotting Tests (Phase 1)

Test System	Treatment		
	Enoxaparin	Rivaroxaban	Rivaroxaban + Enoxaparin
Inhibition of FXa activity (%)	13.3	34.9	34.8
Prolongation PT (times baseline)	1.06	1.38	1.39
Prolongation aPPT (times baseline)	1.19	1.29	1.36
Prolongation HepTest® (times baseline)	4.68	1.63	1.88
Anti-Factor Xa activity (absolute change baseline)	3.22	2.80	4.59

Combined administration of rivaroxaban (single dose of 15 mg) and acetylsalicylic acid (500 mg on the first day and 100 mg on the next day), an inhibitor of thromboxane-mediated platelet aggregation, revealed a prolongation of bleeding time, which exceeded the response of acetylsalicylic acid alone (Figure 3-7). Although the difference was statistically significant, the degree of the change was small (difference in mean change 2 minutes, with a normal range of bleeding time of 2 to 8 minutes). No other pharmacodynamic or pharmacokinetic parameter indicated an interaction between the two drugs (Table 3-4).

Figure 3-7: Rivaroxaban – Acetylsalicylic Acid Drug Interaction (n=13): Mean ± SD Percentage Change from Baseline in Bleeding Time (Top) and Collagen-Stimulated Platelet Aggregation (Bottom) at 4 h Post-Dosing (Phase 1)

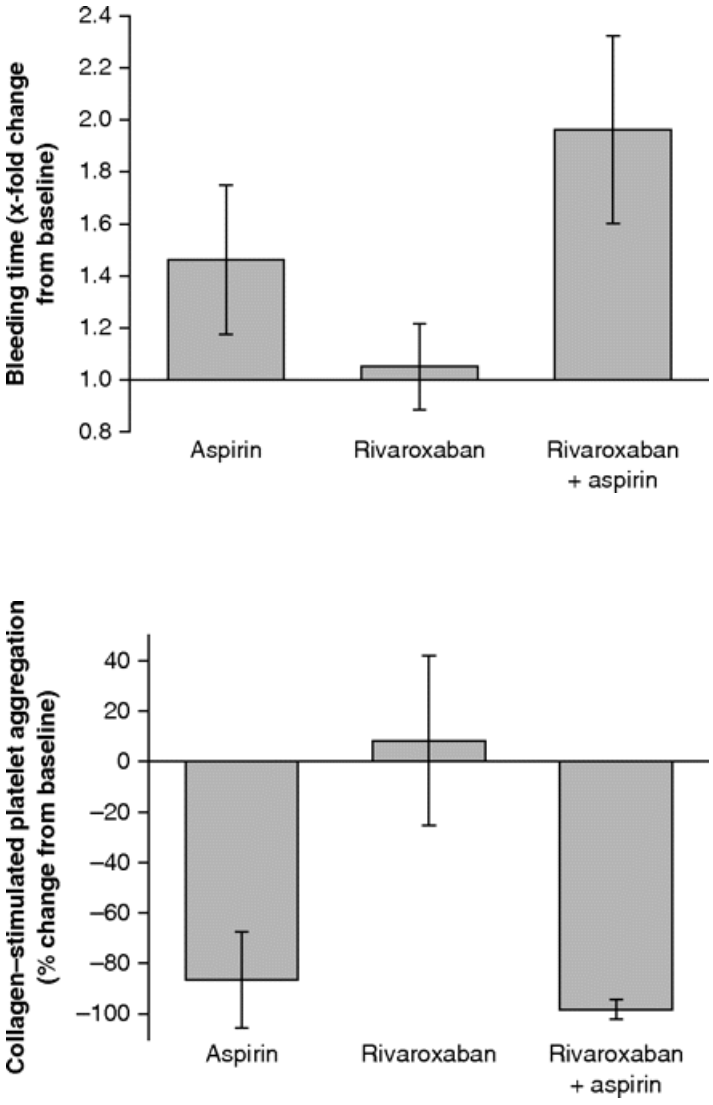


Table 3-4: Rivaroxaban – Acetylsalicylic Acid Drug Interaction (n=13): Maximum Median Changes From Baseline of Inhibition of FXa Activity and Prolongation of Global Clotting Tests (Phase 1)

Test System	Treatment		
	Aspirin	Rivaroxaban	Rivaroxaban + Aspirin
Inhibition of FXa activity (%)	-2.3	34.5	33.0
Prolongation PT (times baseline)	1.00	1.33	1.34
Prolongation aPTT (times baseline)	1.02	1.31	1.31
Prolongation HepTest® (times baseline)	1.07	1.79	1.87

The interaction study between rivaroxaban (single dose of 15 mg) and naproxen (500 mg on 2 consecutive days) as a representative for non-steroidal anti-inflammatory drugs [NSAIDs] showed an additive effect on bleeding time of (on average) 3.4 minutes (normal range of 2 to 8 minutes) as compared to the administration of naproxen alone without additionally affecting platelet aggregation (Figure 3-8). No effect on other pharmacodynamic parameters (Table 3-5) or on pharmacokinetics was observed.

Figure 3-8: Rivaroxaban – Naproxen Drug Interaction (n=11): Mean ± SD Percentage Change From Baseline in Bleeding Time (Top) and Collagen-Stimulated Platelet Aggregation (Bottom) at 4 h Post-Dosing (Phase 1)

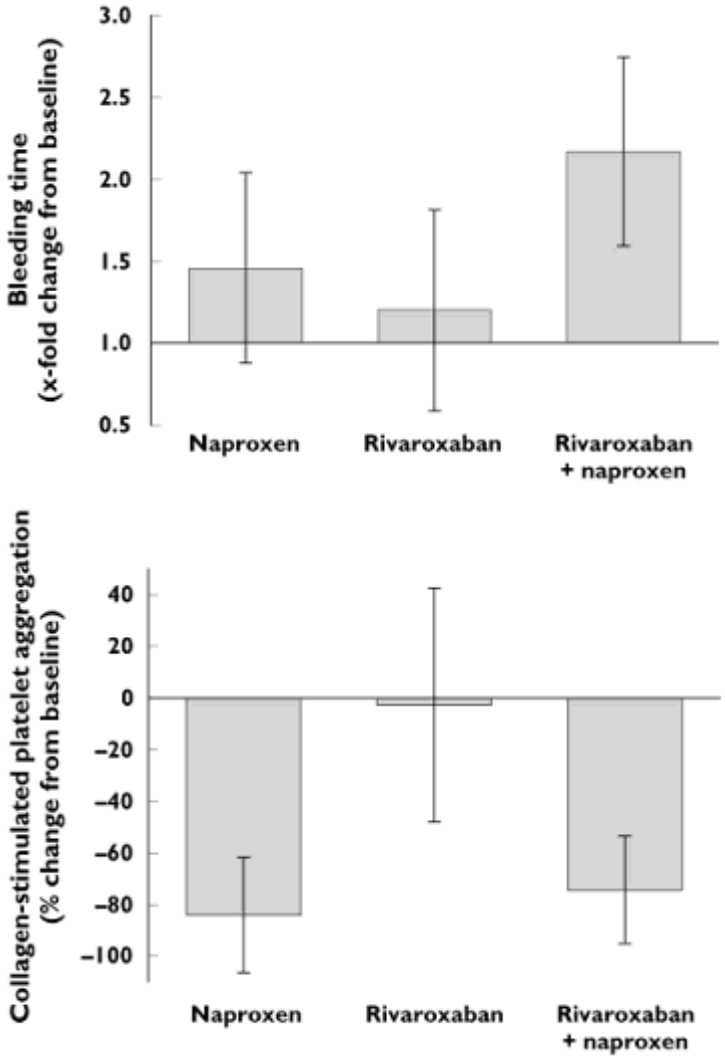


Table 3-5: Rivaroxaban – Naproxen Drug Interaction (n=11): Maximum Median Changes From Baseline of Inhibition FXa Activity and Prolongation of Global Clotting Test (Phase 1)

Test system	Treatment		
	Naproxen	Rivaroxaban	Rivaroxaban + Naproxen
Inhibition of FXa activity (%)	2.38	35.4	34.5
Prolongation PT (times baseline)	1.02	1.35	1.39
Prolongation aPTT (times baseline)	0.99	1.31	1.31
Prolongation HepTest® (times baseline)	1.02	1.92	1.88

Co-administration of clopidogrel (300 mg loading dose followed by 75 mg dose on the consecutive day), an inhibitor of ADP mediated platelet aggregation, and rivaroxaban (15 mg on Day 2) demonstrated a relevant increase in bleeding time in a subset of subjects (4 out of 13 subjects) which was not correlated to platelet aggregation, P-selectin or GPIIbIIIa levels. No relevant bleeding episodes were observed in these subjects. The observed changes of bleeding time (Figure 3-9) are comparable to those observed after the combined administration of acetylsalicylic acid and clopidogrel (Payne 2002). No other pharmacodynamic parameters were affected (Table 3-6). Likewise, no pharmacokinetic interaction was observed.

Figure 3-9: Rivaroxaban – Clopidogrel Drug Interaction (n=13): Mean ± SD Percentage Change from Baseline in Bleeding Time at 4 h Post-Dosing (Phase 1)

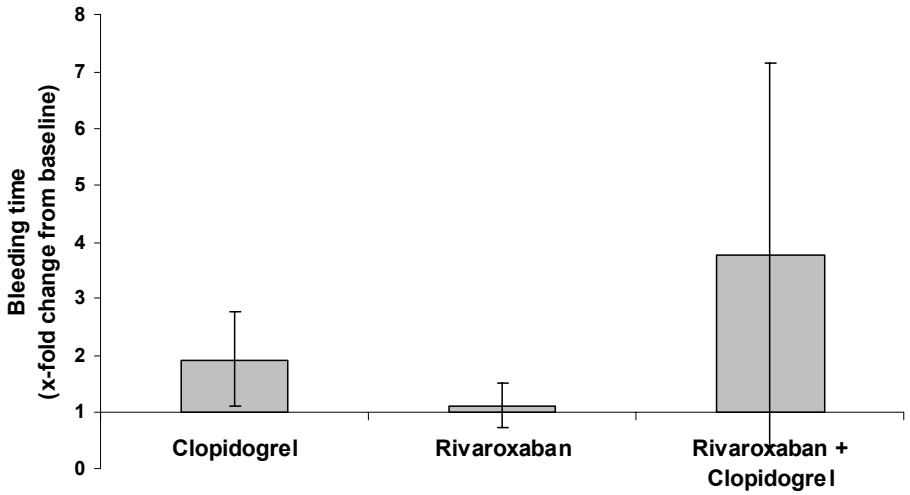


Table 3-6: Rivaroxaban – Clopigogrel Drug Interaction (n=13): Maximum Median Changes From Baseline of Inhibition of FXa Activity and Prolongation of Global Clotting Tests (Phase 1)

Test system	Treatment		
	Clopidogrel	Rivaroxaban	Rivaroxaban + Clopidogrel
Inhibition of FXa activity (%)	3.7	34.1	35.3
Prolongation of PT (times baseline)	1.02	1.42	1.39
Prolongation of aPTT (times baseline)	1.01	1.33	1.32
Prolongation of HepTest® (times baseline)	1.05	1.73	1.72

3.3.3. Human Pharmacokinetic/Pharmacodynamic Relationship

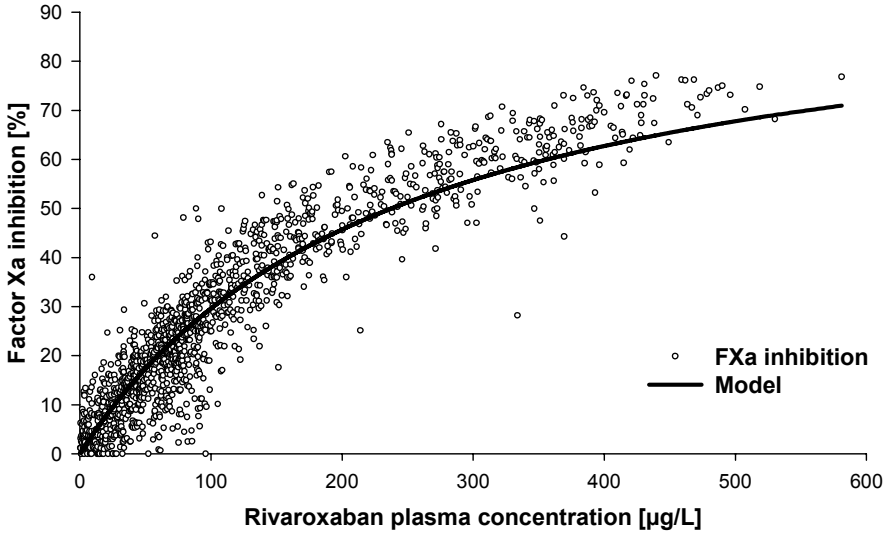
The relationship between plasma exposure and coagulation parameter (including Factor Xa activity, PT, aPTT and Heptest®) has been extensively studied in the clinical pharmacology Phase 1 program but also in the Phase 2 studies with population pharmacokinetic/pharmacodynamic analysis.

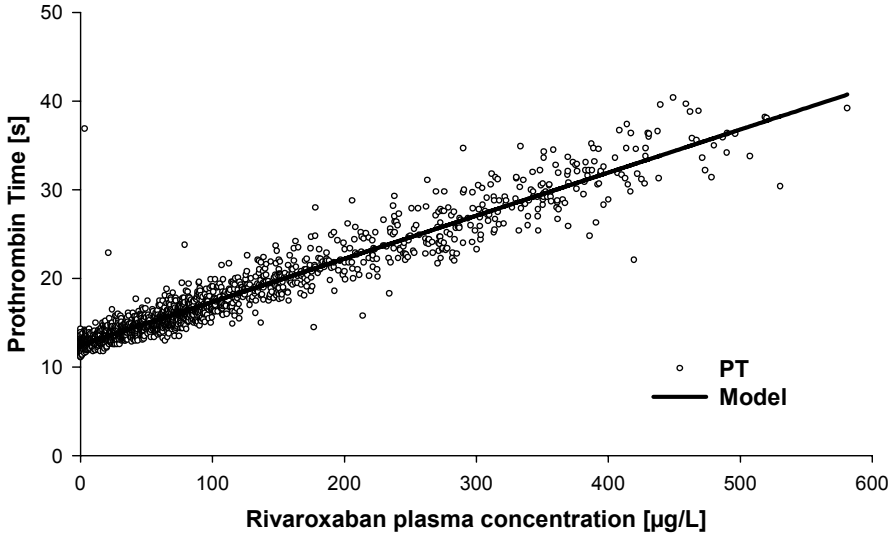
All pharmacodynamic parameters were influenced by rivaroxaban in a dose dependent way and correlated closely with the pharmacokinetics with r values of 0.97 for inhibition of Factor Xa activity, and 0.99 for both prolongation of aPTT and Heptest®. The r value for PT prolongation was 0.98 when Neoplastin® was used for the assay (other reagents may provide different r values).

However, as the correlation between inhibition of Factor Xa activity (Figure 3-10 - top) activity or Heptest® to plasma concentrations followed a non-linear model, these were considered less suitable to assess the pharmacodynamic effect of rivaroxaban. The rather flat and curve-linear response curve between plasma concentrations and aPTT, does not allow a sufficient discrimination at the relevant plasma concentrations.

As the correlation between PT and plasma concentrations is linear with a sufficient correlation and discrimination (Figure 3-10 – bottom) when Neoplastin® was used as the assay, PT appeared to be best for following the effect of rivaroxaban in clinical settings and was thus used as surrogate marker for plasma exposure in Phase 3. PT versus bleeding event analysis in Phase 3 indicated that PT was not indicative of bleeding as subjects with bleeding did not exhibit higher PT values than subjects without bleeding (see Section 3.4.2 and Figure 3-14).

Figure 3-10: Correlation Between Rivaroxaban Plasma Concentrations and Factor Xa Inhibition (top) or PT (bottom) in Healthy Subjects Following Multiple Dosing (Phase 1)





r values of 0.97 for inhibition of Factor Xa activity, 0.98 for PT, when the Neoplastin® assay was used. The median steady-state peak plasma concentration of rivaroxaban in patients is estimated to be 125 µg/L (with maximum C_{max} of 196 µg/L).

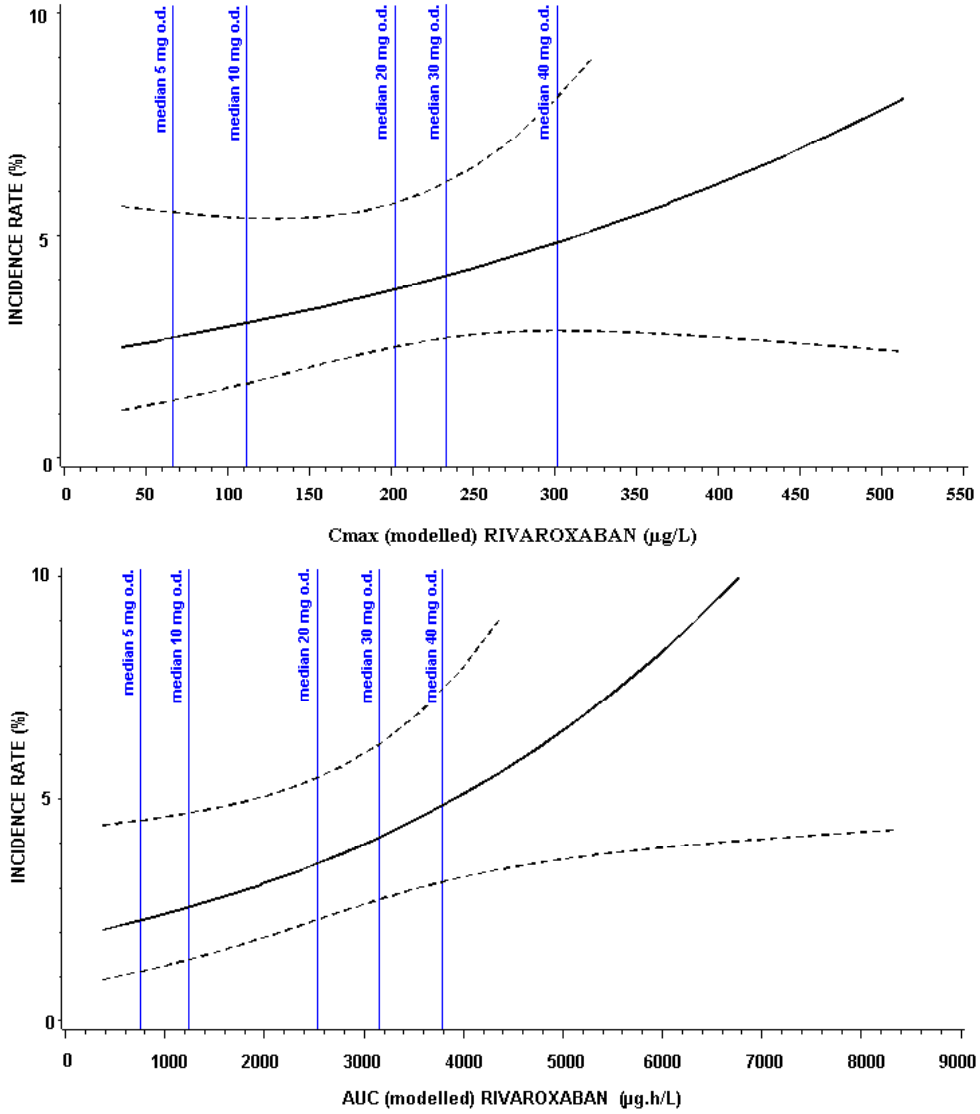
The pharmacokinetic/pharmacodynamic results at steady state in patients were consistent in all analyses and confirmed the results that were obtained in healthy subjects.

3.4. Exposure-Response relationship

3.4.1. Pharmacokinetics Versus Bleeding Incidence

In Phase 2, the dose-response analysis of the bleeding risk shows a trend towards a higher incidence of bleeding events with increasing dosage of rivaroxaban (see also Section 5.2.1 for additional efficacy and bleeding event dose response information). The relationship between the incidence of major bleeding with increasing C_{max} and AUC of rivaroxaban is shown in Figure 3-11. The risk of increases in the pharmacokinetic exposure range typical for rivaroxaban doses up to 20 mg once daily were small and PK parameters did not predict bleeding events better than dose alone.

Figure 3-11: Exposure-Safety Analysis: Logistic Regression of Rivaroxaban (Modelled) C_{max} and AUC vs Incidence Rate of Major Bleeding (Phase 2 Once Daily Study 11527; Subjects Valid For Safety Analysis Having Modeled PK Data)

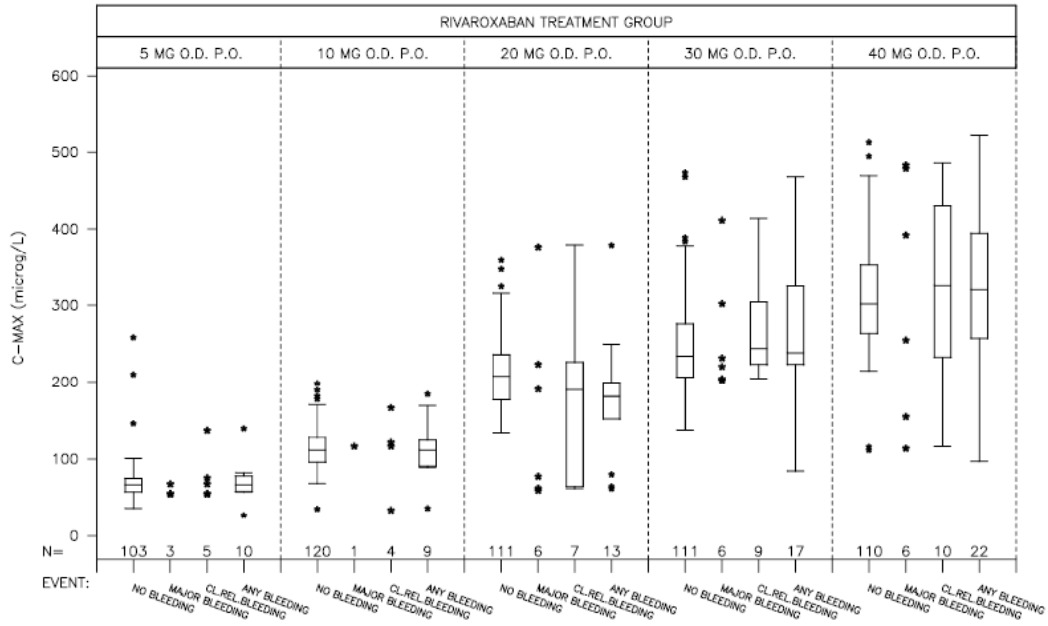


Number of events: 22; total number of subjects: 577. The solid line shows the (modeled) Rivaroxaban C_{max} and AUC – event rate curves estimated by logistic regression. The dotted lines represent the lower and upper 95% confidence limits. Day of the PK parameter for the logistic regression: day of the event or last day on study medication for patients without event. Hosmer and Lemeshow goodness-of-fit: p-value= 0.2042 (C_{max}) and 0.6839 (AUC).

Figure 3-12 shows the distribution of C_{max} at steady state derived from the population pharmacokinetic evaluations in subjects without and with a bleeding event (categorized into major bleeding, major or non-major clinically relevant bleeding and any bleeding). Within the individual rivaroxaban dose groups, there is no relevant

difference of C_{max} distribution with respect to the occurrence of bleeding events. Although C_{max} increases with rivaroxaban dose the data do not indicate that subjects with bleeding events exhibit higher C_{max} values compared to subjects without bleeding events (Figure 3-12). Similar conclusions are derived from analyses of AUC.

Figure 3-12: Distribution of Rivaroxaban (Modelled) C_{max} vs. Bleeding Event (Phase 2 Once Daily Study 11527)

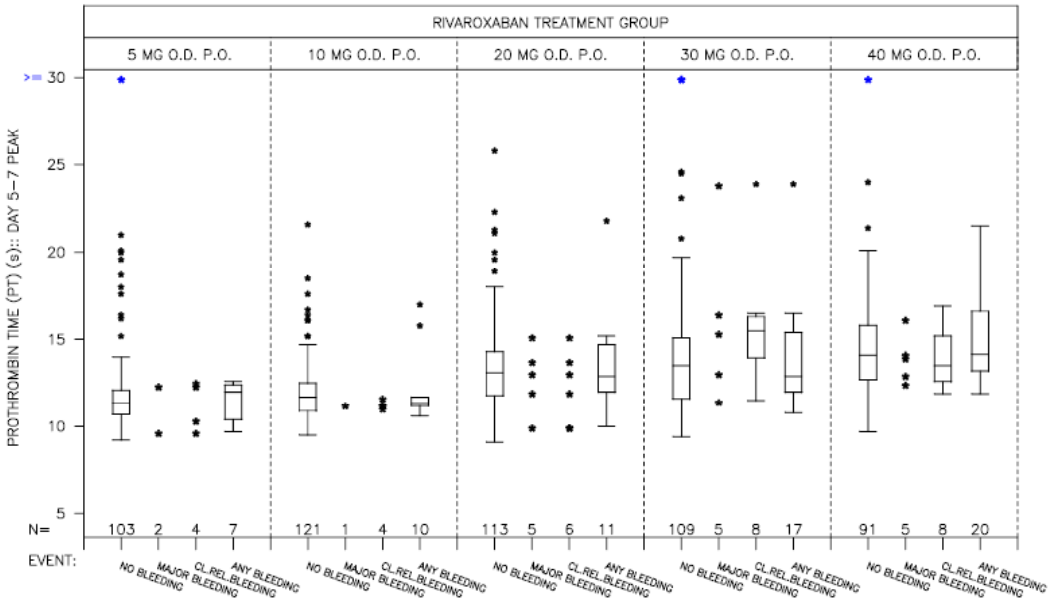


In Phase 2 where a 12-fold dose range of rivaroxaban from 2.5 to 30 mg rivaroxaban twice daily and an 8-fold dose range from 5 to 40 mg rivaroxaban once daily was investigated, the bleeding dose response for doses up to and including a 20-mg total daily dose (both once and twice daily) is considered to be similar with the responses of the comparator, enoxaparin, while doses over 20 mg had clearly increased rates of bleeding events compared to enoxaparin (see Section 5.2.1 for more details). Therefore, the clinically acceptable limit for increase in rivaroxaban exposure was proposed as a doubling of the 10 mg rivaroxaban exposure. An increase in exposure of less than 2-fold is considered unlikely to cause unacceptable bleeding rate increases.

3.4.2. Pharmacodynamics Versus Bleeding Incidence

An analysis of peak PT versus bleeding type in Phase 2 (Figure 3-13) - evaluating the distribution of PT at expected maximum concentrations (2-4 hours post tablet at study days 5-7) showed higher PT values with increasing dose levels, but largely similar distributions of peak PT values in subjects with or without bleeding events. Analyses of PT at trough as well as relative and absolute changes at study day 5-6 over baseline yield similar conclusions.

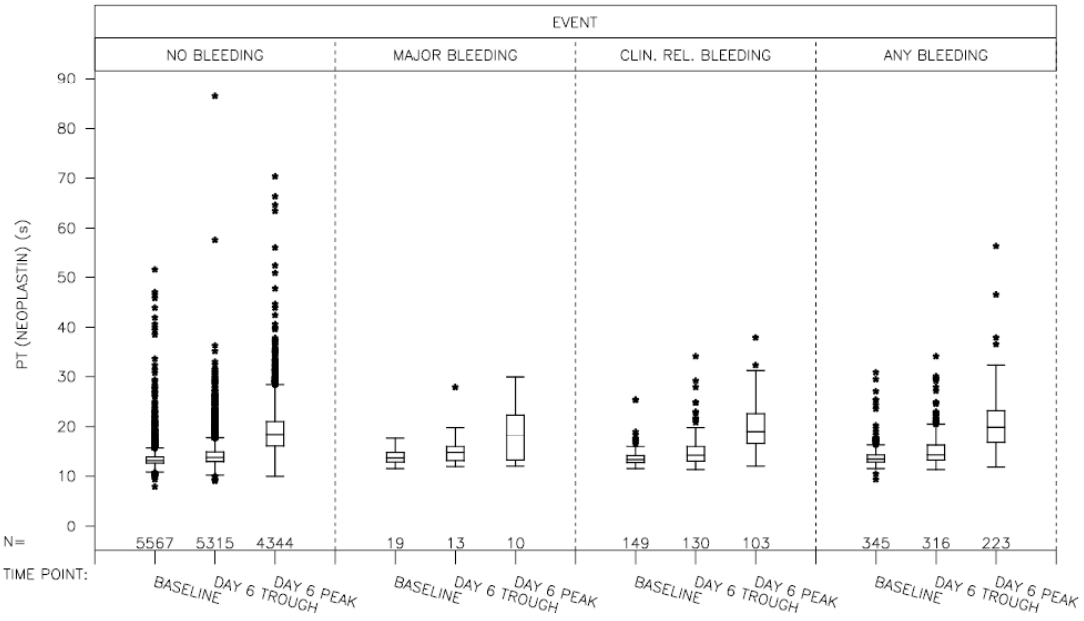
Figure 3-13: Distribution of PT vs. Bleeding Event (Phase 2 Once Daily Study 11527)



Peak measurements performed 2-4 hours post tablet at study days 5-7.

Similarly, PT vs. bleeding analysis in Phase 3 RECORD studies indicated that PT was not indicative of bleeding risk (Figure 3-14): subjects with bleeding did not exhibit higher PT values than subjects without bleeding.

Figure 3-14: Distrubution of PT vs. Bleeding Events (Pooled Phase 3 RECORD Studies)



3.5. Special Populations

All relevant subject covariates, such as age, gender, body weight, renal and hepatic function as well as ethnicity, have been investigated in detail in clinical pharmacology studies and via population pharmacokinetic, pharmacodynamic, and

pharmacokinetic/pharmacodynamic analyses in the Phase 2 dose-finding and/or Phase 3 studies and in the subgroup safety (Section 6.2.2.2.1) and efficacy (Section 5.2.3.2) analyses.

Age, Body weight, Sex, Ethnicity

A Phase 1 study in subjects older than 65 years, showed a mean 1.35 and 1.45-fold increase in C_{max} and AUC, respectively in elderly subjects when compared with young subjects (< 45 years). Results from another Phase 1 study in subjects older than 75 years showed an 1.41-fold increase in AUC compared to young subjects (< 45 years) (Table 3-7). No relevant age effects were observed for C_{max} or t_{max}. The terminal half-life in elderly was increased to 11 and 13 h. A reduced (apparent) total body clearance and renal clearance may explain these findings.

Compared to a body weight of 70 to 80 kg, extremes in body weight (<50 kg or >120 kg) had only a small influence (less than 25%) on rivaroxaban plasma exposure (Table 3-7).

There were no relevant differences in pharmacokinetics and pharmacodynamics between male and female subjects (Table 3-7).

Table 3-7: Effect of Intrinsic Factor on the Rivaroxaban Exposure, Presented as Mean Ratios of Rivaroxaban AUC and C_{max} and Associated 90% Confidence Intervals (Phase 1)

Influence of	AUC Ratio [90% CI]	C_{max} Ratio [90% CI]
Age (n=12/group)		
>75 years vs. <45 years	1.41 [1.20-1.66]	1.08 [0.94-1.25]
Body weight (n=12/group)		
≤50 kg vs 70-80 kg	1.14 [1.00 – 1.30]	1.24 [1.07 – 1.44]
>120 kg vs 70-80 kg	1.12 [0.98-1.28]	1.04 [0.90 – 1.20]
Gender (n=12/group)		
female vs male	0.93 [0.79 – 1.09]	0.99 [0.86 – 1.15]

Phase 1 studies designed to study effect of ethnicity indicated that differences in rivaroxaban exposure observed between the various investigated ethnic groups - Caucasians, African-Americans, Hispanics, Chinese and Japanese - were within the overall magnitude of inter-individual variability (30-40%; Table 3-8).

Table 3-8: Effect of Ethnicity on Rivaroxaban Exposure Following Single Dose of 10 mg Rivaroxaban, Presented as Geometric Mean (%CV) (Phase 1)

Ethnic Group	AUC (µg.h/L)	C_{max} (µg/L)
Caucasian		
young (< 45 years; mean BW: 68.6 kg; n=11)[a]	1175 (40%)	175 (33%)
African-American		
young (< 45 years; mean BW: 80.0 kg; n=11)[a]	1203 (20%)	179 (28%)
Hispanic		
young (< 45 years; mean BW: 72.3 kg; n=12)[a]	1288 (19%)	177 (12%)
Japanese		
young (< 34 years; mean BW: 62.6 kg; n=8)[a]	1564 (25%)	227 (19%)
elderly (> 60 years; mean BW: 58.1 kg)[a]	1261 (15%)	177 (29%)
Chinese		
young (< 39 years; mean BW: 62.1 kg; n=8)[a]	1022 (25%)	143 (27%)
elderly (> 59 years; mean BW: 61.6 kg; n=11)[a]	1060 (18%)	228 (20%)

[a] A specific inter-ethnic study compared (young) African-American, Hispanic and Caucasian subjects.
Japanese and Chinese subjects were studied in separate Phase 1 studies each; a specific inter-ethnic study compared young African-American, Hispanic and Caucasian subjects. BW=body weight

With respect to Factor Xa activity and PT, neither age, sex, body weight or ethnicity affected the PD parameter/rivaroxaban concentration relationship, i.e., all observed changes in PD were driven by the respective underlying plasma exposure in these specific subject populations.

Renal impairment

There was a shallow relationship between renal impairment and plasma exposure. In a Phase 1 study, rivaroxaban exposure increased in subjects with decreasing renal function. In subjects with mild (creatinine clearance 50 to <80 mL/min), moderate (creatinine clearance 30 to <50 mL/min) or severe renal impairment (creatinine clearance 15 to <30 mL/min), rivaroxaban plasma exposure (AUC) was increased by 1.4-, 1.5- and 1.6-fold, respectively. The overall inhibition of FXa activity was increased by 1.5-, 1.9- and 2.0-fold, respectively, compared with healthy subjects with normal renal function (creatinine clearance >80 mL/min). The observed increases in PT prolongation (AUC) were 1.3-, 2.2- and 2.4-fold in subjects with mild, moderate and severe renal impairment, respectively compared to subjects with normal renal function (Table 3-9).

Table 3-9: Effect of Renal Impairment: Mean (Stratum 2/Stratum 1) Ratios of Pharmacokinetic and Pharmacodynamic Parameters and Associated 90% Confidence Intervals (Phase 1)

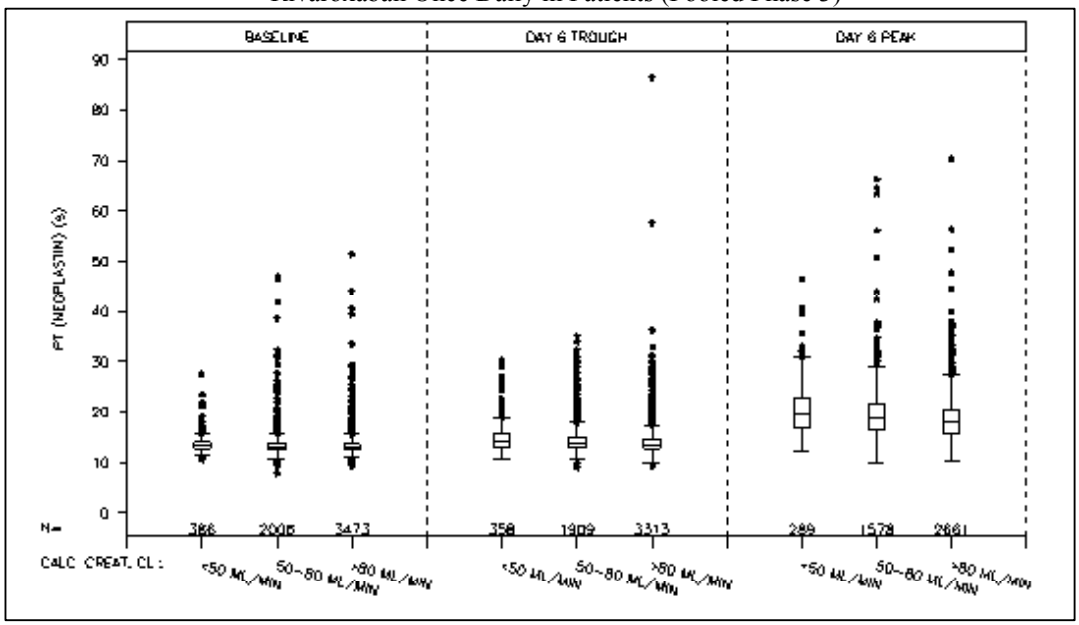
Stratum 1	Stratum 2	AUC	C_{max} or E_{max}
PK parameters AUC and C_{max}			
CL_{CR} ≥ 80 mL/min	CL_{CR} 50 – 79 mL/min	1.44 (1.08 - 1.92)	1.28 (1.07 - 1.55)
	CL_{CR} 30 – 49 mL/min	1.52 (1.15 - 2.01)	1.12 (0.93 - 1.34)
	CL_{CR} < 30 mL/min	1.64 (1.24 - 2.17)	1.26 (1.05 - 1.51)
Percent inhibition of FXa activity			
CL_{CR} ≥ 80 mL/min	CL_{CR} 50 – 79 mL/min	1.50 (1.07 - 2.10)	1.09 (0.96 - 1.25)
	CL_{CR} 30 – 49 mL/min	1.86 (1.34 - 2.59)	1.10 (0.97 - 1.26)
	CL_{CR} < 30 mL/min	2.00 (1.44 - 2.78)	1.12 (0.99 - 1.27)
Relative Polongation of PT			
CL_{CR} ≥ 80 mL/min	CL_{CR} 50 – 79 mL/min	1.33 (0.92 - 1.92)	1.04 (0.98 - 1.10)
	CL_{CR} 30 – 49 mL/min	2.16 (1.51 - 3.10)	1.17 (1.11 - 1.24)
	CL_{CR} < 30 mL/min	2.44 (1.70 - 3.49)	1.20 (1.13 - 1.27)

CL_{CR} = creatinine clearance
n=8/group

The Phase 1 pharmacodynamic data thus suggest a steeper correlation between drug activity (as determined by measuring Factor Xa inhibition and PT prolongation) and CL_{CR}. In interpreting these findings, it is important to consider that these data were obtained in a typical Phase 1 study that included only 8 subjects in each renal function category. The more pronounced effect of renal impairment on PD in the Phase 1 study was not observed in the Phase 2 or 3 data.

The pharmacokinetics/pharmacodynamics of rivaroxaban in patients with renal impairment were also evaluated in the Phase 2 dose-finding studies. Pharmacokinetic data were not collected in the Phase 3 studies; instead PT – being closely correlated to plasma exposure - was used as a surrogate marker for exposure in these studies. The pharmacodynamic findings in Phase 2 and Phase 3 were consistent with what would be expected from the pharmacokinetic characteristics. In addition, the pharmacodynamic data collected in Phase 2 and 3 did not indicate any undue accumulation in patients with renal impairment: trough and peak PT values were not increased to a substantial degree in patients with moderate or severe renal impairment (Figure 3-15). Furthermore, PT values were widely overlapping between the different renal function groups.

Figure 3-15: Effect of Renal Function on PT (Values at Baseline, Trough and Peak) Following 10 mg Rivaroxaban Once Daily in Patients (Pooled Phase 3)



Hepatic Impairment

Subjects with mild liver impairment (Child-Pugh Grade A) enrolled in a Phase 1 study exhibited only minor changes in rivaroxaban pharmacokinetics (1.2- fold increase for AUC on average) and pharmacodynamics (Table 3-11). Subjects with moderate hepatic impairment (Child-Pugh Grade B - all with baseline PT prolongations) showed a more pronounced effect in pharmacokinetics and pharmacodynamics, due to the underlying disease. Rivaroxaban plasma concentrations were significantly increased (2.3 fold for AUC on average) as were the pharmacodynamic effects compared to subjects with normal hepatic function (Table 3-10). Cirrhotic subjects with severe hepatic impairment (Child Pugh Grade C) were not investigated in this Phase 1 study.

Table 3-10: Effect of Hepatic Impairment - Mean Ratios (Stratum 2/Stratum 1) of Pharmacokinetic and Pharmacodynamic Parameters and Associated 90% Confidence Intervals (Phase 1)

Stratum 1	Stratum 2	AUC	Cmax or E_{max}
PK parameters AUC and Cmax			
Normal Hepatic Function	Child-Pugh A	1.15 (0.85 - 1.57)	0.97 (0.75 - 1.25)
	Child-Pugh B	2.27 (1.68 - 3.07)	1.27 (0.99 - 1.63)
Percent Inhibition of FXa activity			
Normal Hepatic Function	Child-Pugh A	1.08 (0.70 - 1.68)	0.98 (0.86 - 1.13)
	Child-Pugh B	2.59 (1.69 - 3.98)	1.24 (1.09 - 1.42)
Relative Prolongation of PT			
Normal Hepatic Function	Child-Pugh A	1.06 (0.79 - 1.42)	1.02 (0.93 - 1.12)
	Child-Pugh B	2.14 (1.61 - 2.84)	1.41 (1.28 - 1.54)

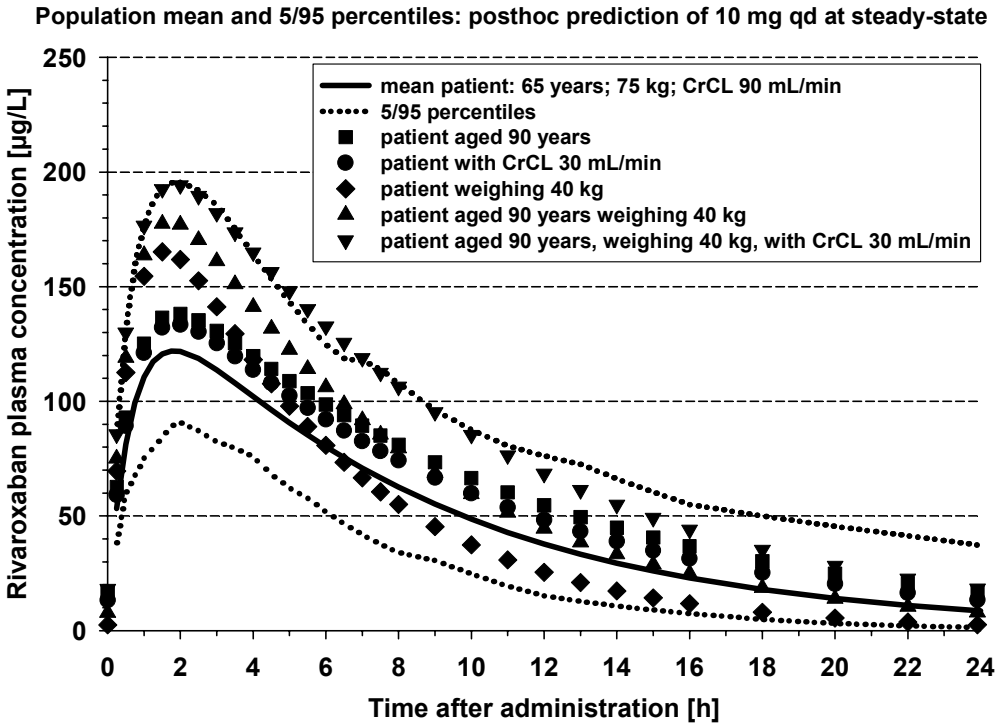
n=8/Child-Pugh class; n=16 for subjects with normal hepatic function

Patient population: subjects undergoing THR or THR surgery

There were no obvious alterations in rivaroxaban steady-state pharmacokinetics in VTE prevention subjects after THR or TKR surgery, when compared to healthy subjects, besides the anticipated changes in elderly subjects. Inter-subject variability in rivaroxaban plasma exposure at steady-state was low to moderate (CV % ranging from 30% to 40%) and comparable to healthy subject data.

The influence of relevant patient covariates on rivaroxaban exposure was investigated in population pharmacokinetic analysis on data collected in the Phase 2 studies. All patient characteristics significantly influencing rivaroxaban exposure - age, renal function and body weight - were predictable from the Phase 1 pharmacokinetic studies. The extent of variation in exposure due to these patient covariates seems to be moderate and within the observed variability of plasma-concentration time profiles in VTE patients, independent of the applied dosing regimen. Based on the established population PK model several different 'typical covariate extreme-case scenarios' were simulated and the predicted rivaroxaban plasma concentrations were compared with the inherent variability observed for the 10 mg once daily group in the Phase 2 once-daily study (Figure 3-16).

Figure 3-16: Rivaroxaban Exposure Predictions for Extremes in Age, Renal Function (Assessed via CrCL) and Body Weight (Phase 2 Once Daily Study 11527) Relationships Established in Population PK Model



3.6. Thorough QT Study

A thorough QT study performed in accordance with the ICH E14 guidance evaluating the effects of single supra-therapeutic doses of 15 and 45 mg rivaroxaban and of 400 mg moxifloxacin (positive control) or placebo did not show a QTc prolonging effect for rivaroxaban (n=50; male and female subjects of > 50 years of age). Mean baseline corrected and placebo subtracted changes in QTc (using Fridericia's or an individualized correction formula) obtained after both doses of rivaroxaban as well as the upper limits of the 95% confidence intervals thereof were below 5 ms at all timepoints after drug administration. Peak plasma concentrations of rivaroxaban (geometric mean: 222 µg/L and 480 µg/L for the 15 and 45 mg dose, respectively; with maximum C_{max} concentration of 543 µg/L and 1386 µg/L, respectively) exceeded the peak plasma concentration obtained during continuous once daily dosing with 10 mg rivaroxaban in patients (median: 125 µg/L, maximum C_{max}: 196 µg/L). In addition, C_{max} values observed with 15 mg and 45 mg rivaroxaban were higher than the peak plasma concentration observed with concomitant administration of 10 mg rivaroxaban with 400 mg ketoconazole (geometric mean C_{max} following co-adminstration: 237 µg/L; maximum C_{max}: 350 µg/L), a strong inhibitor of both PgP and CYP3A4, confirming that a supratherapeutic systemic exposure to rivaroxaban was achieved in the thorough QT study. Moxifloxacin established the assay

sensitivity by displaying a mean maximum QTc prolongations of approximately 10 ms. The ANCOVA treatment comparisons for QTcF are given in Table 3-11.

Table 3-11: Thorough QTc: ANCOVA Treatment Comparisons Based on LS-Mean Changes in QTcF From Baseline

Fridericia-corrected QT (QTcF)	Test Treatment	Reference Treatment	Difference (Lower – upper 95% CI)
QTcF after 3 h (primary analysis)	15 mg Rivaroxaban	Placebo	-1.83 (-4.19 – 0.54)
	45 mg Rivaroxaban	Placebo	-0.91(-3.33 – 1.52)
QTcF after 3 h (all treatments)	15 mg Rivaroxaban	45 mg Rivaroxaban	-0.47 (-2.93 – 2.00)
		Moxifloxacin	-11.3 (-13.6 – -8.88)
		Placebo	-1.49 (-3.88 – 0.90)
	45 mg Rivaroxaban	Moxifloxacin	-10.8 (-13.3 – -8.34)
		Placebo	-1.03 (-3.47 – 1.42)
	Moxifloxacin	Placebo	9.77 (7.39 – 12.15)
QTcF at time of t_{max}	15 mg Rivaroxaban	45 mg Rivaroxaban	-2.57 (-5.18 – 0.04)
		Moxifloxacin	-10.6 (-13.2 – -8.05)
		Placebo	-0.49 (-3.05 – 2.07)
	45 mg Rivaroxaban	Moxifloxacin	-8.04 (-10.7 – -5.43)
		Placebo	2.08 (-0.51 – 4.67)
	Moxifloxacin	Placebo	10.12 (7.56 – 12.68)
QTcF post-dose mean	15 mg Rivaroxaban	45 mg Rivaroxaban	-0.57 (-1.89 – 0.76)
		Moxifloxacin	-7.54 (-8.83 – -6.24)
		Placebo	-1.19 (-2.48 – 0.10)
	45 mg Rivaroxaban	Moxifloxacin	-6.97 (-8.29 – -5.65)
		Placebo	-0.62 (-1.93 – 0.68)
	Moxifloxacin	Placebo	6.35 (5.07 – 7.64)
QTcF post-dose maximum	15 mg Rivaroxaban	45 mg Rivaroxaban	-1.00 (-3.07 – 1.07)
		Moxifloxacin	-8.94 (-11.0 – -6.91)
		Placebo	-1.43 (-3.45 – 0.59)
	45 mg Rivaroxaban	Moxifloxacin	-7.94 (-10.0 – -5.87)
		Placebo	-0.43 (-2.47 – 1.61)
	Moxifloxacin	Placebo	7.51 (5.50 – 9.52)

The outlier categorical analysis of the QTc values or changes of QTc values from baseline showed comparable results for both rivaroxaban doses and placebo. No value exceeded 500 ms or displayed a change from baseline beyond 30 ms. The majority of QTc values was below 450 ms for all treatments. Frequencies of QTc values between 450 and 480 ms were similar for both doses of rivaroxaban and placebo. A substantial increase in frequencies of outliers was observed for moxifloxacin. After administration of moxifloxacin, frequencies of outliers in the category 450 to 480 was approximately triple the placebo frequency. About 1% of the moxifloxacin QTc changes from baseline were in the category of 30 to 60 ms. No change from baseline value exceeded 60 ms. A substantial increase in frequencies of outliers was observed for moxifloxacin. Similar results were observed for the QTc change (both QTcF and QTcI) from baseline: the vast majority of ECGs showed a change from baseline below 30 ms. In the category between 30 and 60 ms changes of QTc from baseline frequencies of ECGs were comparable between both doses of rivaroxaban and

placebo. Frequencies of ECGs for moxifloxacin in this category were distinctly higher than for the other three treatments. No value exceeded 60 ms.

3.7. Summary of Clinical Pharmacology

Rivaroxaban has a predictable PK and PD profile with a close relationship between PK and PD. Following oral administration, rivaroxaban is rapidly absorbed with the peak plasma concentration attained around 2-4 hours post dosing. Rivaroxaban at a dose of 10 mg has a high oral bioavailability (>80%) and can be given irrespectively of food.

Rivaroxaban has a limited potential for drug-drug interactions due to its multiple elimination pathways. Only for drugs that are strong inhibitors of both hepatic metabolism and active renal secretion, concomitant use resulted in a clinically relevant increased systemic exposure to rivaroxaban (> 2 fold). There are no active circulating metabolites. Rivaroxaban has no inhibiting nor inducing potential on major CYP isoforms or Pgp/BCRP transporters.

Intersubject variability in rivaroxaban exposure following oral administration is low-to-moderate (30-40%). There are no relevant PK or PD differences for age, gender, ethnicity or weight (i.e., differences between subgroups were within the overall magnitude of inter-subject variability). With increasing renal impairment, exposure increased to about 1.4-, 1.5-, 1.6-fold (mean ratio) in subjects with mild, moderate or severe renal impairment, respectively. Mild hepatic impairment did not effect PK or PD of rivaroxaban. Subjects with moderate hepatic impairment had pronounced increases (> 2 fold) both for PK and PD, due to the underlying disease. Rivaroxaban administration did not result in QT prolongation.

Rivaroxaban's profile with predictable PK and PD behavior and close PK/PD relationship following oral rivaroxaban administration enable fixed dosing of 10 mg rivaroxaban once daily without coagulation monitoring in the patient populations studied in the clinical studies.

4. OVERVIEW OF THE RIVAROXABAN CLINICAL PROGRAM

The focus of this NDA submission is the efficacy and safety of rivaroxaban in the prophylaxis of DVT and PE in patients undergoing THR or TKR surgery. The efficacy and safety of rivaroxaban have been demonstrated in the RECORD (REgulation of Coagulation in ORthopedic Surgery to prevent DVT and PE) program, which includes 4 randomized, double-blind, Phase 3 comparative trials with enoxaparin (THR: RECORD 1 [Study 11354], RECORD 2 [Study 11357]; TKR: RECORD 3 [Study 11356], and RECORD 4 [Study 11355]). Phase 2 studies in THR

and TKR surgery included 1 randomized, open-label trial (Study 10942), and 3 randomized, double-blind trials (Studies 10944, 10945, and 11527).

In addition, rivaroxaban is under development for the treatment of other thrombosis-mediated conditions. The 4 clinical development programs that are being conducted with rivaroxaban are:

- EINSTEIN program: Treatment and long-term secondary prevention of DVT/PE (ongoing);
- ROCKET program: Prevention of stroke and non-central nervous system systemic embolism in patients with nonvalvular atrial fibrillation (ongoing);
- ATLAS program: Secondary prevention of cardiovascular events (cardiovascular death, myocardial infarction and stroke) after Acute Coronary Syndrome (ACS) (ongoing); and
- MAGELLaN program: Prophylaxis of DVT and PE in Hospitalized Medically Ill Patients (ongoing).

An overview of the completed Phase 3 and Phase 2 clinical studies that evaluated the safety and efficacy of rivaroxaban in the prophylaxis of DVT and PE in patients undergoing THR or TKR surgery is summarized in Table 4-1. Completed supportive Phase 2 and Phase 1 studies are summarized in Table 4-2. Overall, a total of 17,864 subjects participated in 65 completed studies and contributed safety data (Table 4-1, Table 4-2). The ongoing studies are summarized and discussed in more detail from a safety perspective in Section 6.3.

Table 4-1: Overview of Studies Supporting Efficacy and Safety of Rivaroxaban in the Prophylaxis of DVT and PE in Patients Undergoing THR or TKR Surgery

Study Details Phase / Study Number	Rivaroxaban Dose	Control Group	Safety Pop/ RIVA Subjects in Safety Pop (any dose)[a] (N)	Scheduled duration of treatment
Phase 3: VTE Prevention				
THR RECORD 1 (11354)	10 mg qd	Enox 40 qd	4433/2209	35,36±4 days[b]
THR RECORD 2 (11357)	10 mg qd	Enox 40 qd	2457/1228	35±4,13±2 days[b]
TKR RECORD 3 (11356)	10 mg qd	Enox 40 qd	2459/1220	12,13±2 days[b]
TKR RECORD 4 (11355)	10 mg qd	Enox 30 bid	3034/1526	12±2 days
Total			**12,383/6,183**	
Phase 2: VTE Prevention				
THR 10942 (open-label)	2.5, 5, 10, 20, and 30 mg bid; 30 mg qd	Enox 40 qd	625/463	8, 9±2 days[b]
THR 10944 (double-blind)	2.5, 5, 10, 20, and 30 mg bid	Enox 40 qd	704/572[c]	8, 9±2 days[b]
TKR 10945 (double-blind)	2.5, 5, 10, 20, and 30 mg bid	Enox 30 bid	613/509	8±2 days
THR 11527 (double-blind)	5, 10, 20, 30, and 40 mg qd	Enox 40 qd	845/688[d]	8, 9±2 days[b]
Total			**2787/2232**	

[a] Summarizes the total number of subjects exposed to any dose of study drug (active or dummy).
[b] The first number refers to the duration on rivaroxaban, and the second number refers to the duration on enoxaparin.
[c] One additional subject received study drug but had no safety assessments; subject not included in the safety analyses
[d] Seven subjects received study drug but had no safety assessments; subjects not included in the safety analyses.
Key: RIVA = rivaroxaban; qd = once daily; bid = twice a day; Enox = Enoxaparin; VTE = venous thromboembolism

Table 4-2: Overview of Supportive Studies

Study Details Phase / Study Number	Rivaroxaban Dose	Control Group	Safety Pop/ RIVA Subjects in Safety Pop (any dose)[a] (N)	Scheduled duration of treatment
Phase 2: VTE Treatment				
11223	10, 20 and 30 mg bid; 40 mg qd	Enox/VKA	604/478	12 weeks
11528	20, 30, and 40 mg qd	Heparin/VKA	542/405	12 weeks
Total			**1146/883**	
Phase 2: Atrial Fibrillation (Japan)				
11390	10, 20 and 30 mg bid	NA	36/36	28 days
11866	10, 15 and 20 mg qd	Warfarin	102/75	28 days
12024	2.5, 5 and 10 mg bid	Warfarin	100/74	28 days
Total			**238/185**	
Phase 1: Clinical Pharmacology				
52 Studies	Variable[b]	Variable[b]	**1310/1129**	≤10 days[b]

[a] Summarizes the total number of subjects exposed to any dose of study drug (active or dummy).
[b] The majority of Phase 1 clinical pharmacology studies were uncontrolled or of a crossover design. Fifteen of 52 studies used a concurrent placebo group. More than 80% of subjects exposed to rivaroxaban received study drug for 1 day only. One of the 52 clinical pharmacology studies was recently completed and data from that study is included in the safety but not in the pharmacokinetic assessment presented in this document.
Key: RIVA = rivaroxaban; qd = once daily; bid = twice a day;
Enox/VKA = Enoxaparin followed by vitamin K antagonist; Heparin/VKA = heparin treatment followed by vitamin K antagonist; NA = not applicable; VTE = venous thromboembolism; Pop=population

All clinical studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices, and other applicable regulatory requirements.

5. EFFICACY OF RIVAROXABAN IN PHASE 2 AND 3 STUDIES

5.1. Statistical methods

5.1.1. Key Design Aspects

The 4 Phase 2 studies compared the efficacy and safety of rivaroxaban with enoxaparin in the prophylaxis of DVT and PE following either THR (Studies 10942, 10944, and 11527) or TKR (Study 10945). These studies were multicenter, randomized, open label (Study 10942 only) or double-blind, active comparator controlled, parallel group trials in men or women aged 18 years of age or older. The total daily doses of rivaroxaban administered in each of the 4 Phase 2 studies were similar; however, twice daily dosing was used in Studies 10942, 10944, and 10945 (total daily dose ranged from 5 to 60 mg) and once daily dosing (total daily dose ranged from 5 to 40 mg) was used in Study 11527. Bilateral venography was performed in these studies at the end of the treatment period. The duration of dosing was 8-9 days.

The 4 pivotal RECORD studies were designed to be similar in methodology and identical in the efficacy and safety parameters assessed. The rivaroxaban dose and start time were the same in all studies. Enoxaparin was chosen as the comparator agent since it is the most widely used agent for THR or TKR VTE prophylaxis on a worldwide (including the US) basis and has a well-documented efficacy and safety profile. The 4 RECORD protocols were submitted and agreed with FDA under the Special Protocol Assessment procedure. All 4 studies were double-blind using double-dummy methodology for masking treatment assignment (i.e. active and placebo tablets, active and placebo injections).

Treatment with rivaroxaban was 10 mg once daily for 35±4 days in the 2 THR studies (RECORD 1 and 2), and treatment with subcutaneous enoxaparin was 40 mg once daily for either 36±4 days (RECORD 1; Figure 5-1) or for 13±2 days followed by placebo until Day 35 (RECORD 2; Figure 5-2). The first dose of rivaroxaban was administered on Day 1, at least 6 to 8 hours after surgery (wound closure), and the first dose of enoxaparin was administered the evening before surgery.

Figure 5-1: RECORD 1 Study Design

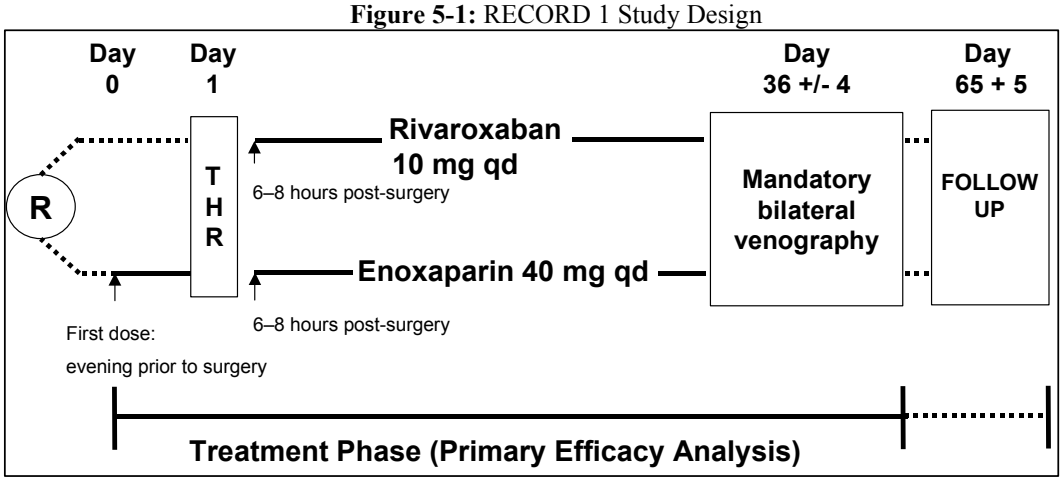
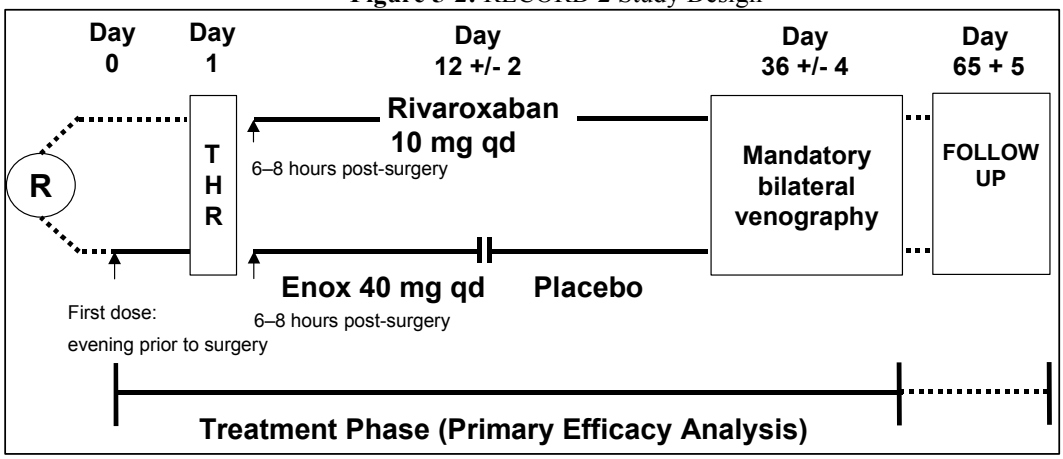


Figure 5-2: RECORD 2 Study Design



In the TKR studies, treatment with rivaroxaban was 10 mg once daily for 12±2 days, and treatment with subcutaneous enoxaparin was either 40 mg once daily for 13±2 days (RECORD 3; Figure 5-3) or 30 mg twice daily for 12±2 days (RECORD 4; Figure 5-4). In each of the studies, the first dose of rivaroxaban was administered on Day 1, at least 6 to 8 hours after surgery (wound closure), and the first dose of enoxaparin was to be administered the evening before surgery in RECORD 3 and 12 to 24 hours after surgery (wound closure) in RECORD 4

Figure 5-3: RECORD 3 Study Design

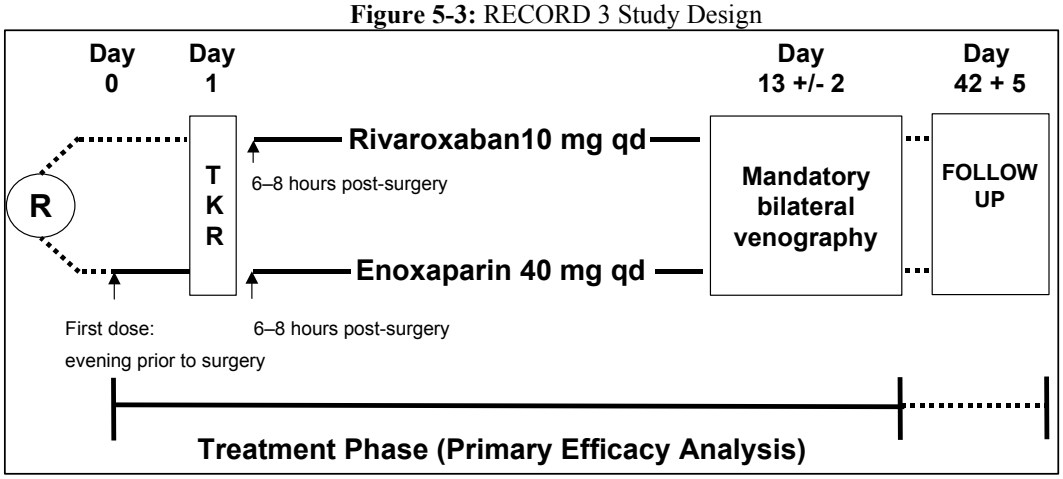
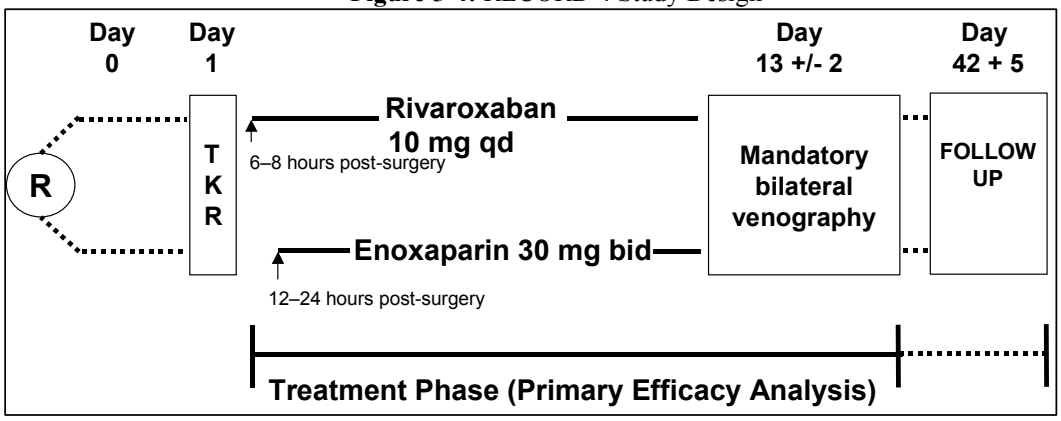


Figure 5-4: RECORD 4 Study Design



The RECORD 4 enoxaparin dosing regimen of 30 mg twice daily reflects the only approved enoxaparin regimen in the US for TKR. This regimen is also approved for THR in the US. The enoxaparin 40 mg once daily regimen is approved in the US for THR and in the majority of other countries for both TKR and THR. It is the only regimen approved for extended (i.e. up to 35 days) prophylaxis after THR surgery. In clinical practice enoxaparin 40 mg once-daily is commonly used once the subject leaves the hospital after TKR surgery even though this is not an approved dosing regimen.

The extended (35/36 days) and short-term (12/13 days) prophylaxis regimens evaluated were based on the treatment guidelines at the time of study design that recommended thromboprophylaxis of at least 10 days for subjects undergoing TKR surgery and extended prophylaxis for up to 35 days after THR surgery (Geerts 2004). RECORD 2 compared extended prophylaxis with rivaroxaban to short-term prophylaxis with enoxaparin since in some countries and in routine practice extended prophylaxis is not used even though it is guideline recommended. The other 3 studies

compared essentially equal durations of prophylaxis after THR for rivaroxaban and enoxaparin.

Bilateral venography is the most sensitive method available for the detection of DVT and was planned to be done on the day after the end of the scheduled study medication administration. Possible symptomatic DVT events occurring before or after the scheduled venography assessment time were evaluated by the investigator according to local routines by either compression ultrasound or venography and were also included in the efficacy analyses, if confirmed by the VTE Adjudication Committee.

The diagnosis of symptomatic PE in the rivaroxaban program allowed the use of pulmonary angiography, spiral CT scanning or perfusion /ventilation imaging according to local standards. All of these methods are generally accepted for establishing a diagnosis of PE and have been frequently used in previous studies.

In addition, blinded central adjudication of all efficacy endpoints was performed in all studies and centrally adjudicated results were used for the primary efficacy analyses. This standardizes the assessments across all the sites participating in the program. The committee that adjudicated the RECORD program venograms was based at McMaster University (Hamilton, Canada) and has extensive prior experience in these evaluations. The Phase 2 study venograms were adjudicated by a different radiologic group based at Sahlgrenska University Hospital/Ostra (Gothenburg, Sweden). Comparisons of the DVT rates after THR and TKR surgery between these two adjudication groups has shown that the Gothenberg group consistently reports higher rates of DVT than the Hamilton group probably due to differences in both the definitions used and the assessors involved (Quinlan 2007). The committee that adjudicated clinical events of DVT, PE and death also had extensive previous experience and was based at Sahlgrenska University Hospital (Gothenburg, Sweden) and this same clinical events committee adjudicated the events for both Phase 2 and 3.

5.1.2. Primary and Secondary Efficacy Measures

This section will refer primarily to the Phase 3 studies. The study populations and endpoint definitions were similar in Phase 2 studies. As part of the Special Protocol Assessment procedure, the predefined Statistical Analysis Plan of each RECORD study was agreed to by the Agency. In the individual RECORD studies, the primary efficacy endpoint (total VTE) was a composite of centrally adjudicated and confirmed incidences of any DVT (proximal and/or distal), nonfatal PE or death from all causes during the treatment phase, defined as the period from surgery (Day 1) to up to Day 17 (RECORD 3 and 4) or Day 42 (RECORD 1 and 2). The main prespecified

secondary endpoint (major VTE) was a composite of the incidences of proximal DVT, nonfatal PE, or VTE-related death, during the treatment phase, as defined for total VTE. Both total VTE and major VTE are a composite of asymptomatic events (ie DVTs detected through bilateral venography performed through the end of the treatment phase) and symptomatic events, reported at any time during the treatment phase up to Day 17 (RECORD 3 and 4) or Day 42 (RECORD 1 and 2). Events in the follow-up period were assessed separately.

In the integrated analysis of the 4 RECORD studies the prespecified primary efficacy endpoint was the composite of symptomatic VTE (DVT, PE) or death. The individual components of this endpoint were also prespecified endpoints while a new composite of symptomatic PE or death was not prespecified. The primary analysis included all symptomatic events occurring during the treatment phase, as defined for the primary analysis of total VTE. Additional analyses looking at different evaluation periods (e.g. including the follow-up period) are presented in Appendix 1.

The Independent Central Adjudication Committee assessed all scheduled venographies, and the Adjudication Committee/Venous Thromboembolic Events adjudicated all symptomatic DVTs, all PE events, and all deaths according to standardized criteria and always reached a consensus for the causality of an event. Table 5-1 summarizes all the main efficacy endpoints evaluated in the RECORD studies.

Table 5-1: Main Efficacy Endpoints in the RECORD Studies

	PrimaryEndpoint	Main Secondary Endpoint
Individual Phase 3 Studies	Total VTE ▪ All DVT (proximal and distal) ▪ Non-fatal PE ▪ All Deaths	Major VTE ▪ Proximal DVT ▪ Non-fatal PE ▪ VTE-related deaths
Pooled Phase 3 Studies	Symptomatic VTE (DVT and PE) or death	

5.1.2.1. Analysis Populations

Populations Defined

The valid for safety analysis population consisted of randomized subjects who received at least 1 dose of blinded study drug. This population was the primary one for the pooled analyses of symptomatic events. The modified intent-to-treat (MITT) analysis population consisted of subjects who received at least 1 dose of blinded study drug, had undergone the appropriate surgery, and had an adequate assessment of thromboembolism. This was the primary population for efficacy superiority analyses in the individual studies. The per protocol (PP) analysis population included

subjects from the MITT analysis dataset if they also had an adequate assessment of thromboembolism that had been performed not later than 36 hours, if positive, or 72 hours, if negative, after completing study drug treatment and had no major protocol violations. This was the primary population for efficacy non-inferiority analyses in the individual RECORD studies.

Invalid Venography Assessments for Asymptomatic DVT

One of the challenges with all studies based on venographic assessment of DVT is that it can be expected that a proportion of subjects will need to be excluded from the primary analysis populations since their assessment of thromboembolism is incomplete if either venography is not performed as scheduled or if the venogram performed is not adequate for interpretation (Norrie 2007; Quan 2007). Studies using bilateral venographic assessment typically have a rate of exclusion from the primary analysis that ranges from 15-30% (Bauer 2001; Colwell 2005). To ensure the required number of evaluable subjects in the MITT population for the RECORD studies, a predicted exclusion rate of 25% was used when calculating sample size.

Higher than expected rates of exclusion from the MITT population became apparent during the conduct of the RECORD program.

In order to compensate for the higher than expected rates of exclusion from the primary analysis due to missing venography data and still maintain 90% power, the sample sizes for RECORD 1, 3, and 4 were adjusted prior to database lock and unblinding the treatment codes (Table 5-2).

Table 5-2: Sample Size Adjustments – RECORD Studies

Study	Original Planned Sample Size	Final Sample Size	Reason for Increase
RECORD 1	4200	4541	Higher than expected rates of exclusion due to missing venography data
RECORD 2	2500	2509	Not applicable
RECORD 3	2300	2531	Higher than expected rates of exclusion due to missing venography data
RECORD 4	2300	3148	Higher than expected rates of exclusion due to missing venography data, lower than expected blinded aggregate primary endpoint event rate and availability of unblinded RECORD 3 study results

A variety of sensitivity analyses were done to assess the impact of the missing venography data on the findings from the primary analysis. These included assessments of the balance of missing data between treatment groups and the reasons for missing data across the treatment groups as well as various strategies for imputing missing data. It should also be noted that symptomatic events, which are already a

component of the primary efficacy endpoint, can be assessed in the broader safety population since negative confirmatory venographies are not required.

5.1.2.2. Analysis of the Primary Efficacy Endpoint in Individual Studies

In the Phase 3 RECORD studies, the primary efficacy endpoint was total VTE.

The efficacy of rivaroxaban was to be assessed in 2 steps in RECORD 1, 3, and 4. A non-inferiority test was performed based on the PP population. If non-inferiority was shown, a superiority test was to be performed subsequently based on the MITT population. Due to this hierarchical approach, no adjustment of the type I error rate was required. For RECORD 2, the primary efficacy analysis was performed for superiority only using the MITT analysis dataset due to the unbalanced active treatment durations for rivaroxaban and enoxaparin, and the PP analysis was performed as a supportive analysis.

For the primary efficacy analysis of each study, the absolute difference between treatment groups in the incidence of total VTE was estimated using a stratified estimator with Mantel Haenszel weights, with the weights based upon the sample sizes per geographic region, as defined in each study. The corresponding asymptotic 2-sided 95% confidence intervals (CIs) were determined based on an approximation to the normal distribution. The rivaroxaban treatment was considered non inferior to the enoxaparin treatment if the upper limit of the CI for the weighted treatment difference (rivaroxaban minus enoxaparin) was below the pre-specified non inferiority limit of δ=3.5% (absolute) in RECORD 1 or below δ=4% (absolute) in RECORD 3 and 4. These noninferiorty margins were prespecified in the statistical analysis plans of each study based on the expected event rates in the enoxaparin groups and maintaining a high proportion of the treatment effect of enoxaparin compared with placebo. In each of the Phase 3 studies, the rivaroxaban treatment was considered superior to the enoxaparin treatment if the upper limit of the CI for the treatment difference was below 0.

In order to compare results across studies that have differing event rates, relative risk reduction (RRR) estimates were also determined for total VTE, where the RRR was computed as 100% X (1 - the unstratified relative risk ratio of the crude rates of subjects with events: rivaroxaban vs. enoxaparin). The corresponding asymptotic 2 sided 95% CIs were also provided. This alternative presentation was not pre-specified in the original statistical analysis plans.

5.1.2.3. Analysis of Secondary Efficacy Endpoints in Individual Studies

The main predefined secondary endpoint in the Phase 2 studies and the Phase 3 RECORD studies was major VTE. Since this endpoint did not include distal DVT, which was included in the primary efficacy endpoint, the MITT and PP populations used for the analysis of major VTE were larger than those populations used for analysis of the primary efficacy endpoint due to the lower exclusion rate in this population for venograms that were inadequate. Subjects evaluated for major VTE required an adequate bilateral ascending venography for only the proximal segments. Other secondary endpoints included symptomatic VTE and other components of the primary endpoint.

As with the primary efficacy endpoint, the secondary efficacy endpoint of major VTE was evaluated by estimating the absolute difference between treatment groups using a stratified estimator with Mantel-Haenszel weights, and the corresponding asymptotic 2-sided 95% CIs were determined based on an approximation to the normal distribution. For the main secondary efficacy endpoint (major VTE) in RECORD 1, 3 and 4, the superiority test was preceded by a non-inferiority test, using a non-inferiority margin of 1.5% (absolute).

Similar to the analysis of the primary efficacy endpoint, relative risk reductions along with the corresponding 95% CIs were determined as a supplemental analysis of major VTE.

It should be noted that there was no adjustment for the multiplicity of tests. The 95% CIs and p values are given to quantify the observed treatment effects.

5.1.2.4. Integrated Analysis

A statistical analysis plan detailing the methods for the pooled analysis of the RECORD 1-3 studies was prepared prior to the unblinding of any RECORD study . In this plan the primary endpoint for the integrated analyses of the Phase 3 RECORD studies was prespecified as symptomatic VTE or death. An updated statistical analysis plan was finalized before the unblinding of the RECORD 4 study (RECORD 1, 2 and 3 results were available). These analyses were planned to obtain more precise estimates of treatment effects on low frequency events and larger sample sizes for subgroup analysis for both efficacy and safety endpoints. Pooling across the studies is appropriate because the:

- Designs of the RECORD studies were similar (e.g. same active comparator agent, same rivaroxaban dose, identical inclusion and exclusion criteria, bilateral venography assessments, schedule of adverse event and laboratory assessments, etc); and

- Definitions for all efficacy and safety endpoints were the same and all endpoints were assessed by the same central adjudication committees.

Phase 3 data were not pooled with Phase 2 data. The Phase 2 studies were dose-ranging studies with shorter treatment durations and often evaluated higher doses and differing dose regimens compared to the 10 mg once daily regimen used in the RECORD studies. In addition the venography adjudication groups were different for Phase 2 and Phase 3.

The primary efficacy endpoint for the integrated analysis that included pooled data from the 4 RECORD studies or the separately pooled THR and TKR studies was the composite of symptomatic VTE (DVT, PE) or death from all causes (i.e., time to first event of either symptomatic VTE or death) during the scheduled double-blind treatment phase up to Day 17 (RECORD 3 and 4) or Day 42 (RECORD 1 and 2) in subjects valid for safety analysis. This endpoint was the primary objective of the pooled analysis since these events are clinically important and also because the assessment of these events was possible in subjects regardless of the availability of an adequate venographic assessment. Pooling of subjects reporting these events was needed to increase statistical power because of their relatively lower rate of occurrence in each individual study. Other supportive endpoints examined included symptomatic VTE, symptomatic PE, death, and the composite of symptomatic PE or death.

Since symptomatic VTE events could occur at any time during the study, the time to first event analysis was performed for detecting the treatment effect. Studies with different treatment durations could be pooled for time to event analyses when subjects were censored at the end of the study. A Cox regression model was performed with study and treatment group as covariates to determine the hazard ratio and its 95% CI (rivaroxaban versus enoxaparin). The relative risk reduction was calculated as 100% X (1-hazard ratio). A Kaplan-Meier analysis was also done for accrued events over time for each treatment group. Similar analyses were conducted for individual studies and for components of the primary endpoint. The original planned integrated analysis for the RECORD 1-3 studies was for absolute differences similar to the individual study analyses. This was changed to the Cox model approach due to differential absolute event rates across studies. Study heterogeneity was assessed for the primary endpoints and components across individual studies based on the interaction test between treatment group and study.

In addition, subgroup analyses were performed to determine consistency of results across subgroups of subjects with various demographic, background, and baseline characteristics. Because of the low incidence of symptomatic events, efficacy

subgroup analyses were performed for total VTE that occurred during the treatment phase using the pooled Phase 3 MITT population, and the separately pooled THR and TKR studies. Similar efficacy subgroup analyses were performed for major VTE as were done for total VTE. Since asymptomatic DVT was assessed only at the end of the treatment phase (i.e., by venogram) and not during the entire study phase, as was symptomatic VTE, treatment groups were compared using odds ratios instead of time to event hazard ratios.

Integrated analyses for Phase 2 studies were performed on the pool of the 3 Phase 2 twice daily dosing studies for the total VTE endpoint in order to explore dose response relationships by using methods that correspond to those conducted for the individual studies. Logistic regression models included terms for study, age and gender in addition to rivaroxaban total daily dose.

In the pooled analyses throughout this briefing document, the label 'enoxaparin' is used for the active comparator group in the RECORD studies even though there was a placebo control period after Day 12 in the RECORD 2 study.

The definitions and analysis methods for safety (bleeding event) endpoints are described in Section 6.

5.2. Efficacy Results

5.2.1. Phase 2 Efficacy and Safety Results with Emphasis on Dose Selection

The selection of the rivaroxaban 10-mg once-daily dose for evaluation in the RECORD studies was based on the results of the Phase 2 THR or TKR surgery dose-ranging studies.

The 4 Phase 2 THR or TKR VTE prophylaxis studies used a 12-fold dose range of rivaroxaban when doses were administered twice daily (2.5 to 30 mg twice daily) (Studies 10942, 10944, and 10945) and a 8-fold dose range when doses were administered once daily (5 to 40 mg once daily) (Study 11527). The sample sizes for the studies are given in Table 4-1. The incidence of total VTE with each of the doses of rivaroxaban was similar to or lower than that seen in the enoxaparin groups of these studies. None of the individual studies demonstrated a statistically significant dose trend for rivaroxaban in preventing total VTE. Table 5-3 shows the incidence of total and major VTE by dose group in the per protocol population for the 2 twice-daily dosing blinded studies (10944, 10945) combined and with the addition of the open-label study (10942). The pool of the 2 blinded studies is the most rigorous methodologically while the pool of all 3 studies provides a summary including all of the Phase 2 twice daily dosing data. The logistic regression dose response analyses

for both endpoints in both study pools were not significant, except for the major VTE endpoint for the 3 combined studies (p=0.048).

Table 5-3: Incidence of Total VTE, Major VTE, Major Bleeding and Any Bleeding Events by Dose Group (Studies 10942, 10944, and 10945)

Outcome	RIVA 2.5 mg bid n/N (%)	RIVA 5 mg bid n/N (%)	RIVA 10 mg bid n/N(%)	RIVA 20 mg bid n/N (%)	RIVA 30 mg bid n/N (%)	ENOX 40 mg qd/30 mg bid n/N (%)
Total VTE (10944/10945) (PP population)	36/167 (21.6%)	38/166 (22.9%)	26/161 (16.1%)	38/156 (24.4%)	17/88 (19.3%)	49/176 (27.8%)
Total VTE (10942/10944/10945) (PP population)	50/230 (21.7%)	53/229 (23.1%)	37/216 (17.1%)	44/215 (20.5%)	25/134 (18.7%)	67/283 (23.7%)
Major VTE (10944/10945) (PP population)	5/167 (3.0%)	4/166 (2.4%)	5/161 (3.1%)	5/156 (3.2%)	1/88 (1.1%)	8/176 (4.5%)
Major VTE (10942/10944/10945) (PP population)	12/230 (5.2%)	9/229 (3.9%)	7/216 (3.2%)	5/215 (2.3%)	3/134 (2.2%)	13/283 (4.6%)
Postoperative Major bleeding event (10944/10945) (safety population)	2/232 (0.9%)	3/238 (1.3%)	5/236 (2.1%)	9/232 (3.9%)	10/143 (7.0%)	4/236 (1.7%)
Postoperative Major bleeding event (10942/10944/10945) (safety population)	2/308 (0.6%)	5/318 (1.6%)	7/304 (2.3%)	14/309 (4.5%)	18/217 (8.3%)	4/398 (1.0%)
Any postoperative bleeding event (10944/10945) (safety population)	15/232 (6.5%)	23/238 (9.7%)	23/236 (9.7%)	42/232 (18.1%)	27/143 (18.9%)	16/236 (6.8%)
Any postoperative bleeding event (10942/10944/10945) (safety population)	22/308 (7.1%)	30/318 (9.4%)	30/304 (9.9%)	56/309 (18.1%)	45/217 (20.7%)	27/398 (6.8%)

Key: bid= twice-daily; ENOX = enoxaparin; qd = once daily; RIVA = rivaroxaban

In the same studies there was an increased risk of bleeding events with increasing rivaroxaban dose (Table 5-3). The logistic regression dose response analyses for postoperative major and any bleeding events were significant for both combinations of studies (all $p<0.001$). Total daily doses from 5 to 20 mg rivaroxaban were considered to have similar major bleeding event rates to the comparator, enoxaparin, with increases of about 2 fold or less. All of the rivaroxaban doses over 20 mg had about a 2 fold or higher increase in the major bleeding event rates compared to both enoxaparin and the lower rivaroxaban doses, but these increased rates did not lead to the premature termination of any dosing level by the independent safety committee monitoring the studies. For the any bleeding event endpoint the pattern was similar with the largest increases in bleeding observed at rivaroxaban total daily doses higher than 20 mg. Other than bleeding related events, there were no adverse events that appeared to be increased or related to rivaroxaban dose compared with enoxaparin.

While the twice daily dosing studies were in progress additional clinical pharmacology information became available demonstrating that a single rivaroxaban 10 mg dose had a similar time course of anti-Factor Xa activity as enoxaparin 40 mg over a 24 hour period (Fig 3-6\Sec 3.3.2). There was also evidence that thrombin generation was inhibited for at least 24 hours after a 30 mg rivaroxaban dose and this once daily dose was included in Study 10942 with similar efficacy and safety results observed compared to the twice daily dosing regimens in this study. Therefore a once daily dose-ranging THR study (11527) was conducted. The total VTE, major VTE, post-operative major bleeding event and any post-operative bleeding event rates from this study are shown in Table 5-4. Similar to the twice-daily dosing studies, the dose response analysis for total VTE was not statistically significant ($p= 0.0852$) while post-operative major bleeding events showed a dose-related increase ($p = 0.0391$) (Figure 5-5). The incidence rates for postoperative any bleeding event were similar to enoxaparin for the doses of 20 mg and below while the two higher doses appeared to have higher rates of both major and any bleeding event compared to enoxaparin. The 5-mg once-daily dose group had a higher incidence of major VTE (due to the proximal DVT rate) compared with the enoxaparin and other rivaroxaban dose groups. The dose response relationship for major VTE was statistically significant ($p = 0.007$). A cross-study comparison of results did not identify any clear differences between rivaroxaban once daily and twice daily dosing regimens for either efficacy or safety (e.g. THR study 10944, 5 mg twice daily total VTE 15/109 [13.8%], major bleeding event 3/136 [2.2%]; THR study 11527, 10 mg once daily total VTE 12/113 [10.6%], major bleeding event 1/142 [0.7%] with other dose levels showing similar range of differences).

Figure 5-5: Post-Operative Major Bleeding and Total VTE: Observed and Predicted Incidence With Once Daily Dosing (Study 11527) -Safety Population

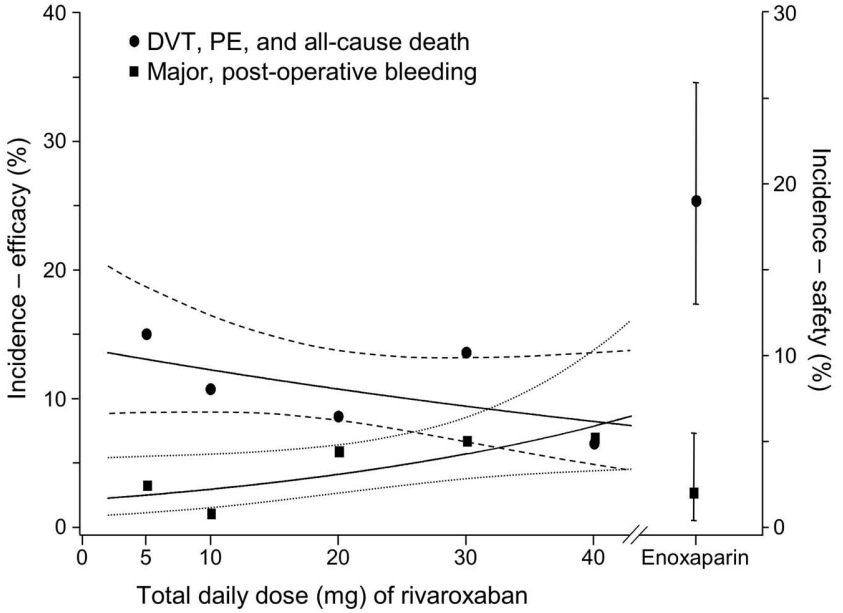


Table 5-4: Incidence of Total VTE, Major VTE, Major Bleeding and Any Bleeding Events by Dose Group (Study 11527)

Outcome	RIVA 5 mg qd n/N (%)	RIVA 10 mg qd n/N (%)	RIVA 20 mg qd n/N (%)	RIVA 30 mg qd n/N (%)	RIVA 40 mg qd n/N (%)	ENOX 40 mg qd n/N (%)
Total VTE (PP population)	14/94 (14.9%)	12/113 (10.6%)	9/106 (8.5%)	14/104 (13.5%)	6/94 (6.4%)	27/107 (25.2%)
Major VTE (PP population	8/94 (8.5%)	3/113 (2.7%)	1/106 (0.9%)	2/104 (1.9%)	1/94 (1.1%)	3/107 (2.8%)
Postoperative Major bleeding event (safety population)	3/128 (2.3%)	1/142 (0.7%)	6/139 (4.3%)	7/142 (4.9%)	7/137 (5.1%)	3/157 (1.9%)
Any postoperative bleeding event (safety population)	10/128 (7.8%)	9/142 (6.3%)	13/139 (9.4%)	18/142 (12.7%)	25/137 (18.2%)	14/157 (8.9%)

Key: ENOX = enoxaparin; qd = once daily; RIVA = rivaroxaban

In these Phase 2 studies the duration of treatment was short and the number of symptomatic events was limited. The occurrence of symptomatic VTE or death during the treatment period for all dose groups pooled across the 4 studies was 0.49% (11/2232) for rivaroxaban and 0.72% (4/555) for enoxaparin. The number of deaths during both treatment and follow-up was 0.31% (7/2232) for rivaroxaban and none for enoxaparin (0/555). Of the 7 deaths 3 occurred at the 5 mg dose level with 2 being reported as due to PE by the investigator.

Since total daily doses of rivaroxaban above 20 mg did not appear to offer significant improvements in efficacy and were associated with a higher incidence of bleeding events compared with lower doses and enoxaparin, the risk benefit profile of rivaroxaban indicated a target total daily dose range of 5 mg to 20 mg for consideration in the Phase 3 studies. For all rivaroxaban dose levels once daily dosing appeared comparably effective and safe to twice daily dosing except for the 5 mg total daily dose level where the major VTE rate appeared higher with the 5 mg once daily dose as discussed above. Therefore, the 10 mg once daily dose was selected to be investigated in the Phase 3 RECORD studies as the most promising dose regimen. These data were also the basis for defining clinically relevant increases in rivaroxaban exposures as being more than 2-fold since this would correspond to rivaroxaban total daily doses higher than 20 mg where the bleeding event rates were all clearly increased compared to the 10-mg dose level.

5.2.2. Phase 3 Results In The Prophylaxis of DVT and PE in Patients Undergoing Elective THR or TKR

5.2.2.1. Patient Populations

Inclusion/Exclusion and Demographics

In the RECORD studies, 12,729 subjects undergoing elective THR or TKR were randomized to treatment in 41 countries (10 mg rivaroxaban 6356, enoxaparin 6373).

Subjects were included that were men or women aged ≥18 years and scheduled for elective THR or TKR. Both primary and revision procedures were allowed as were bilateral procedures if done during the same surgery. There were also no restrictions relating to the methods of anesthesia or analgesia.

Subjects were excluded if they:

- had active bleeding or high risk of bleeding contraindicating treatment with LMWH;
- had contraindications listed in the labeling or conditions precluding subject treatment with enoxaparin requiring dose adjustment (e.g., severe renal impairment);
- had significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis);
- had conditions prohibiting bilateral venography (amputation of 1 leg, allergy to contrast media);
- used HIV-protease inhibitors concomitantly;
- had planned intermittent pneumatic compression; and
- had ongoing oral anticoagulant therapy that could not be stopped.

The demographic and baseline characteristics of the RECORD study safety populations are shown in Table 5-5. The data are shown for the combined treatment groups for the THR and TKR studies separately and for all 4 studies combined. The 2 treatment groups, rivaroxaban and enoxaparin, were well balanced with respect to demographic and baseline characteristics in the safety, intent to treat and per protocol populations and for the individual studies and pooled analyses. Tables summarizing the demographics of the RECORD THR and TKR study subjects by treatment group for the safety population are provided in Appendix 1.

Table 5-5: Demographics and Baseline Characteristics
(Subjects Valid for Safety Analysis in Pooled RECORD 1-4 Studies)

	Total for THR Studies (N=6890)	Total for TKR Studies (N=5493)	Total for All Studies (N=12383)
Sex N (%)			
Male	3110 (45%)	1841 (34%)	4951 (40%)
Female	3780 (55%)	3652 (66%)	7432 (60%)
Race N (%)			
White	5687 (83%)	4037 (73%)	9724 (79%)
Black	103 (1%)	181 (3%)	284 (2%)
Asian	498 (7%)	736 (13%)	1234 (10%)
American Indian	3 (<1%)	5 (<1%)	8 (<1%)
Hispanic	329 (5%)	353 (6%)	682 (6%)
Uncodable	40 (1%)	28 (1%)	68 (1%)
Missing	230 (3%)	153 (3%)	383 (3%)
Age (yrs.) Mean±SD	62.6 ±12.2	65.9 ±9.5	64.1 ±11.2
Age (categorized) N (%)			
<65 yrs	3532 (51%)	2288 (42%)	5820 (47%)
65-75 yrs	2460 (36%)	2275 (41%)	4735 (38%)
>75 yrs	898 (13%)	930 (17%)	1828 (15%)
Weight (kg) Mean±SD	77.0 ±16.2	82.8 ±18.2	79.6 ±17.4
Weight (categorized) N (%)			
<=50 kg	228 (3%)	81 (1%)	309 (2%)
>50-70 kg	2405 (35%)	1367 (25%)	3772 (30%)
>70-90 kg	2956 (43%)	2445 (45%)	5401 (44%)
>90-110 kg	1091 (16%)	1159 (21%)	2250 (18%)
>110 kg	198 (3%)	435 (8%)	633 (5%)
Missing	12 (<1%)	6 (<1%)	18 (<1%)
BMI (kg/m^2) Mean±SD	27.5±4.9	30.3 ±5.6	28.8 ±5.4
BMI (categorized) N (%)			
<18.5	92 (1%)	17 (<1%)	109 (1%)
18.5 - <25	2091 (30%)	808 (15%)	2899 (23%)
25 - <30	2800 (41%)	2116 (39%)	4916 (40%)
30 - <40	1764 (26%)	2222 (40%)	3986 (32%)
>=40	123 (2%)	322 (6%)	445 (4%)
Missing	20 (<1%)	8 (<1%)	28 (<1%)
Creatinine clearance (mL/min) Mean±SD	90.2±30.9	91.6 ±33.2	90.8 ±32.0
Creatinine clearance (categorized) N (%)			
>80 mL/min	4015 (58%)	3200 (58%)	7215 (58%)
50-80 mL/min	2333 (34%)	1874 (34%)	4207 (34%)
30-<50 mL/min	447 (6%)	342 (6%)	789 (6%)
<30 mL/min	35 (1%)	22 (<1%)	57 (<1%)
Missing	60 (1%)	55 (1%)	115 (1%)
Fragile subject[a] N (%)			
No	5633 (82%)	4360 (79%)	9993 (81%)
Yes	1257 (18%)	1133 (21%)	2390 (19%)

BMI=Body Mass Index
Note: Percentages are calculated including missing values.
[a] Fragile definition: Age >75 years and/or calculated creatinine clearance <50 ml/min and/or weight ≤50 kg

Overall, the study population was representative of TKR and THR patients (Warwick 2007). The study population consisted of different races (White 79%, Asian 10%, Hispanic 6%, Black 2%) with 60% being women. The mean age was 64 years with about 15% over 75 years of age. The mean body mass index (BMI) was 28.8 kg/m^2 with about one-third (36%) of the subjects having a BMI ≥30 kg/m^2. Six percent of the subjects had a creatinine clearance 30 to <50 mL/min (calculated according to the Cockcroft–Gault formula), i.e., at least moderate renal impairment with another 0.5% having a creatinine clearance <30 mL/min (i.e., severe renal impairment). Hepatic disease was reported in the medical history of 3% of subjects. There were no exclusions based on alanine aminotransferase (ALT) elevations. TKR subjects were more likely to be female, older and heavier compared to the THR subjects but both surgeries had representation across a wide range of demographic characteristics.

The characteristics of the population enrolled in the Phase 3 studies are representative of subjects with risk factors for VTE and bleeding (e.g the elderly) in clinical practice. There were limited numbers of subjects included that had revision or bilateral THR or TKR. There were also limited numbers of Black subjects, subjects with severe renal impairment (due to the exclusion related to enoxaparin) and subjects with hepatic impairment which is not uncommon in most Phase 3 clinical development programs.

Subject Disposition and Exposures

The inclusion of the randomized subjects in the various analysis populations for each study and for the pooled RECORD 1-2 (THR), RECORD 3-4 (TKR) and RECORD 1-4 studies is shown in Table 5-6. 97 % of subjects were included in the safety populations for RECORD 1-4 pooled (range 96% to 98% across studies). For the MITT analysis 67% of subjects were included in the analysis for total VTE (range 61% to70%) and about 73% were included in the analysis for major VTE (range 71% to 77%). The primary reason for exclusion from the total VTE and major VTE analyses was an inadequate assessment of thromboembolism although some subjects were also excluded because they did not undergo the planned surgery. Details for the reasons for exclusion from the MITT analysis for total VTE are provided in Table 5-7, 5-8\Sec 5.2.4.1. Analyses for the PP population were not done for the pooled studies. For the individual studies 2 to 6% fewer subjects were included in the PP compared with the MITT analyses.

Table 5-6: Subject Validity in RECORD Studies

Study Treatment Group	Randomized	Valid for Safety Analysis	Valid for MITT Analysis Of Total VTE	Valid for MITT Analysis of Major VTE	Valid for Per Protocol Analysis of Total VTE
	N	N	N	N	
RECORD 1					
Rivaroxaban	2266	2209 (97%)	1595 (70%)	1686 (74%)	1537 (68%)
Enoxaparin	2275	2224 (98%)	1558 (68%)	1678(74%)	1492 (66%)
Total	4541	4433 (98%)	3153(69%)	3364(74%)	3029 (67%)
RECORD 2					
Rivaroxaban	1252	1228(98%)	864(69%)	961(77)	812 (65%)
Enoxaparin	1257	1229(98%)	869(69%)	962(77%)	803 (64%)
Total	2509	2457(98%)	1733(69%)	1923(77%)	1615 (64%)
RECORD 3					
Rivaroxaban	1254	1220(97%)	824(66%)	908(72%)	793 (63%)
Enoxaparin	1277	1239(97%)	878(69%)	925(72%)	838 (66%)
Total	2531	2459(97%)	1702(67%)	1833(72%)	1631 (64%)
RECORD 4					
Rivaroxaban	1584	1526(96%)	965(61%)	1122(71%)	864 (55%)
Enoxaparin	1564	1508(96%)	959(61%)	1112(71%)	878 (56%)
Total	3148	3034(96%)	1924(61%)	2234(71%)	1742 (55%)
Pooled RECORD 1-2					
Rivaroxaban	3518	3437(98%)	2459(70%)	2647(75%)	NA
Enoxaparin	3532	3453(98%)	2427(69%)	2640(75%)	NA
Total	7050	6890(98%)	4886(69%)	5287(75%)	NA
Pooled RECORD 3-4					
Rivaroxaban	2838	2746(97%)	1789(63%)	2030(72%)	NA
Enoxaparin	2841	2747(97%)	1837(65%)	2037(72%)	NA
Total	5679	5493(97%)	3626(64%)	4067(72%)	NA
Pooled RECORD 1-4					
Rivaroxaban	6356	6183(97%)	4248(67%)	4677(74%)	NA
Enoxaparin	6373	6200(97%)	4264(67%)	4677(73%)	NA
Total	12,729	12383(97%)	8512(67%)	9354(73%)	NA

NA= not applicable.

There was a similar percentage of subjects who completed the scheduled study medication treatment in each of the individual studies (88% to 90%) and for each of the reasons of premature discontinuation, there was a similar percentage of subjects withdrawing in each of the RECORD studies (Table 5-7). The most common reasons for premature termination were adverse events and withdrawal of consent. Compliance with both study drug regimens measured as pill or syringe counts until the time of study medication discontinuation was high (mean > 95% for both treatment groups in each study). For the pooled studies, the number of subjects discontinuing study medication for the reason lost to follow-up was low for both rivaroxaban (8 [0.1%]) and enoxaparin (15 [0.2%]). Subject completion/withdrawal information by treatment is presented in Appendix 1.

Table 5-7: Subject Study Medication Completion/Withdrawal Information
(Randomized Population of the RECORD Studies)

	RECORD 1 n (%)	RECORD 2 n (%)	RECORD 3 n (%)	RECORD 4 n (%)	Pooled N (%)
Total no. Randomized Subjects	**4541**	**2509**	**2531**	**3148**	**12729**
Completed Treatment	**4021 (88.6)**	**2209 (88.0)**	**2249 (88.9)**	**2838 (90.2)**	**11317 (88.9)**
Premature Termination	**520 (11.5)**	**300 (12.0)**	**282 (11.1)**	**310 (9.9)**	**1412 (11.1)**
Adverse Event	174 (3.8)	98 (3.9)	78 (3.1)	118 (3.8)	468 (3.7)
Clinical Endpoint Reached	16 (0.4)	16 (0.6)	22 (0.9)	28 (0.9)	82 (0.6)
Consent Withdrawn	236 (5.2)	102 (4.1)	128 (5.1)	96 (3.1)	562 (4.4)
Investigator Decision, Not Protocol Driven	6 (0.1)	4 (0.2)	8 (0.3)	7 (0.2)	25 (0.2)
Lost to Follow-Up	10 (0.2)	7 (0.3)	2 (0.1)	4 (0.1)	23 (0.2)
Non-Compliant With Study Medication	34 (0.8)	16 (0.6)	9 (0.4)	9 (0.3)	68 (0.5)
Protocol Violation	40 (0.9)	53 (2.1)	33 (1.3)	43 (1.4)	169 (1.3)
Other	4 (0.1)	4 (0.2)	2 (0.1)	5 (0.2)	15 (0.1)

Note: RECORD 1 is Study 11354 (THR), RECORD 2 is Study 11357 (THR), RECORD 3 is Study 11356 (TKR), and RECORD 4 is Study 11355 (TKR).

5.2.2.2. Primary Endpoint: Total VTE

Each individual RECORD study demonstrated clinically important and statistically significant superior efficacy for rivaroxaban compared with enoxaparin for the primary endpoint of prevention of total VTE (any DVT, nonfatal PE or death).

In RECORD 1, analyses using the PP population showed a statistically significant ($p<0.001$) lower incidence in total VTE in the rivaroxaban group (13/1537 [0.9%]) than in the enoxaparin group (50/1492 [3.4%]). Analyses using the MITT population also showed a statistically significant ($p<0.001$) lower incidence in total VTE in the rivaroxaban group (18/1595 [1.1%]) than in the enoxaparin group (58/1558 [3.7%]), indicating the superiority of rivaroxaban. For both analysis populations, the upper limit of the two-sided 95% CI for the Mantel Haenszel-weighted absolute treatment difference (rivaroxaban minus enoxaparin) was well below 0, thereby establishing not only the non-inferiority (based on the non-inferiority margin of 3.5%), but also the superiority of rivaroxaban over enoxaparin.

In RECORD 2, analyses using the MITT population showed a statistically significant ($p<0.001$) lower incidence of total VTE in the rivaroxaban group (17/864 [2.0%]) than in the enoxaparin group (81/869 [9.3%]) indicating the superiority of rivaroxaban compared with enoxaparin in preventing VTE. Confirmation of the superiority of rivaroxaban was supported by the analyses of the PP population, which also showed a significantly ($p<0.001$) lower incidence of total VTE in the rivaroxaban group (11/812 [1.4%]) than in the enoxaparin group (66/803 [8.2%]).

The results for the primary endpoint and its components in the PP and MITT populations are shown for the RECORD 1 and 2 (THR) studies in Table 5-8. Supportive analyses of relative risk reduction are also provided and show total VTE reductions for rivaroxaban compared with enoxaparin in the MITT population of

70% (95% CI: 49%, 82%) for RECORD 1 and 79% (95% CI: 65%, 87%) for RECORD 2.

With the same rivaroxaban dosing regimen the rates of total VTE were consistent across the 2 studies while for enoxaparin the extended dosing regimen was associated with a lower incidence of total VTE. As would be expected the most frequently occurring component was asymptomatic DVT, which was reduced consistently in both studies. The number of symptomatic events was low making it difficult to assess treatment effects in these individual studies for this parameter.

Table 5-8: RECORD Program THR Primary Efficacy Endpoint – Total VTE and Components Through The Treatment Phase

Study	RECORD 1				RECORD 2			
	RIVA n/N (%)	ENOX n/N (%)	ARD (95% CI) p value	RRR (95% CI) p value	RIVA n/N (%)	ENOX/ PBO n/N (%)	ARD (95% CI) p value	RRR (95% CI) p value
Dose Regimen	10mg once daily	40mg once daily			10 mg once daily	40mg once daily		
Total VTE (PP)	13/1537 (0.85%)	50/1492 (3.35%)	-2.53% (-3.55, -1.51) p<0.001	75% (54, 86) p<0.001	11/812 (1.35%)	66/803 (8.22%)	-6.80% (-8.85, -4.75) p<0.001	84% (69, 91) p<0.001
Total VTE (MITT)	18/1595 (1.13 %)	58/1558 (3.72 %)	-2.62% (-3.69, –1.54) p<0.001	70% (49,82) p<0.001	17/864 (1.97%)	81/869 (9.32%)	-7.28% (-9.41, –5.15) p<0.001	79% (65, 87) p<0.001
Asymptomatic DVT	9	45			12	63		
Symptomatic DVT	3	9			2	10		
PE	4	2			1	5		
Death	4	4			2	6		

Note: Individual subjects can have more than 1 type of event. All p values are for superiority testing, the noninferiority margin in RECORD 1 was 3.5% . The Treatment Phase is up to Day 42. ENOX = enoxaparin; RIVA = rivaroxaban

For comparison, the results for the primary study endpoint in recently conducted Phase 3 THR studies are shown in Table 5-9. Enoxaparin performed well in RECORD 1 and 2 with rates either similar to (e.g. EPHESUS was comparable regimen to RECORD 2) or better (lowest observed rate for an extended dosing regimen like in RECORD 1 was 4.4%) than previous studies. The RECORD THR study rivaroxaban total VTE rates of 1-2 % demonstrate improved protection from any VTE with the 35-day duration regimen used.

Table 5-9: Primary Endpoint Results in Recent Phase 3 THR Studies With Thromboprophylactic Agents

Study	Treatment Regimen (Days)		Total VTE (%, n/N)[a,b]	
	Test	Control	Test	Control
Ephesus, (Lassen, 2002)	Fondaparinux 2.5 qd (5-9)	Enoxaparin 40 qd (5-9)	4.1[b] (37/908)	9.2[b] (85/919)
Pentathlon 2000, (Turpie, 2002)	Fondaparinux 2.5 qd (5-9)	Enoxaparin 30 bid (5-9)	6.1 [b] (48/787)	8.3 [b] (66/797)
Platinum –hip[c] (Colwell, 2003)	Ximelagatran 24 bid (7-12)	Enoxaparin 30 bid (7-12)	7.9[b,d] (62/782)	4.6[b] (36/775)
RE-NOVATE, (Eriksson, 2007a)	Dabigatran 220 qd (28-35)	Enoxaparin 40 qd (28-35)	6.0 [a] (53/880)	6.7 [a] (60/897)
Extended RxTHR meta-analysis of 6 studies, (Hull, 2001)	Enoxaparin/dalteparin-extended (19-29 additional days)	Enoxaparin /dalteparin-short (6-14 days)	Any DVT[e] 7.9 (72/911) lowest 4.4%	Any DVT[e] 22.5 (150/666) lowest 10.5%
RECORD 1	Rivaroxaban 10 qd (31-39)	Enoxaparin 40 qd (32-40)	1.1 [a] (18/1595)	3.7 [a] (58/1558)
RECORD 2	Rivaroxaban 10 qd (31-39)	Enoxaparin 40 qd (11-15)	2.0 [a] (17/864)	9.3 [a] (81/869)
RECORD 1-2	Rivaroxaban 10 qd (31-39)	Enoxaparin 40 qd (11-15 or 32-40)	1.4[a] (35/2459)	5.7[a] (139/2427)

[a] Total VTE endpoint includes death.
[b] Total VTE endpoint excludes death.
[c] unilateral venography
[d] statistically inferior to enoxaparin
[e] Any DVT endpoint does not include PE or death

In RECORD 3, analyses using the PP population showed a statistically significant ($p<0.001$) lower incidence in total VTE in the rivaroxaban group (74/793 [9.3%]) than in the enoxaparin group (152/838 [18.1%]). Analyses using the MITT population also showed a statistically significant ($p<0.001$) lower incidence in total VTE in the rivaroxaban group (79/824 [9.6%]) than in the enoxaparin group (166/878 [18.9%]). For both analysis populations, the upper limit of the two-sided 95% CI for the Mantel-Haenszel-weighted treatment difference (rivaroxaban minus enoxaparin) was well below 0, thereby establishing not only non-inferiority (based on the non-inferiority margin of 4%) but also superiority of rivaroxaban over enoxaparin.

In RECORD 4, analyses using the PP population showed a statistically significant (p=0.036) lower incidence in total VTE in the rivaroxaban group (58/864 [6.7%]) than in the enoxaparin group (82/878 [9.3%]). Analyses using the MITT population also showed a statistically significant (p=0.012) lower incidence of total VTE in the rivaroxaban group (67/965 [6.9%]) than in the enoxaparin group (97/959 [10.1%]) indicating the superiority of rivaroxaban compared with enoxaparin in preventing total VTE. For both analysis populations, the upper limit of the two-sided 95% CI for the Mantel-Haenszel-weighted treatment difference (rivaroxaban minus enoxaparin) was well below 0, thereby establishing not only non-inferiority (based on the non-inferiority margin of 4%) but also superiority of rivaroxaban over enoxaparin.

The results for the primary endpoint and its components in the PP and MITT populations are shown for the RECORD 3 and 4 (TKR) studies in Table 5-9. Supportive analyses of relative risk reduction are also provided and show total VTE reductions for rivaroxaban compared with enoxaparin in the MITT population of 49% [95% CI: 35%; 61%] for RECORD 3 and 31% [95% CI: 8%; 49%] for RECORD 4.

The 30 mg twice daily dose of enoxaparin used in the RECORD 4 study appeared to result in a lower event rate compared to the 40 mg once daily dose used in RECORD 3. However, the rates of total VTE for rivaroxaban were lower than 10% in both studies and significantly lower than for both enoxaparin regimens. As would be expected the most frequently occurring component was asymptomatic DVT, which was reduced consistently in both studies. The number of symptomatic events was infrequent and lower with rivaroxaban in both studies in for all categories.

Table 5-10: RECORD Program TKR Primary Efficacy Endpoint – Total VTE and Components Through the Treatment Phase

STUDY	RECORD 3				RECORD 4			
	RIVA n/N (%)	ENOX n/N (%)	ARD (95% CI) p value	RRR (95% CI) p value	RIVA n/N (%)	ENOX n/N (%)	ARD (95% CI) p value	RRR (95% CI) p value
Dose regimen	10mg once daily	40mg once daily			10 mg once daily	30 mg twice daily		
Total VTE (PP)	74/793 (9.33%)	152/838 (18.14%)	-8.70 (-11.97, -5.44) p<0.001	49% (33%, 60%) p<0.001	58/864 (6.71%)	82/878 (9.34%)	-2.71 (-5.25, -0.17) p=0.036	28% (<1%, 48%) p=0.054
Total VTE (MITT)	79/824 (9.59 %)	166/878 (18.91%)	-9.15% (-12.40, –5.89) p<0.001	49% (35%, 61%) p<0.001	67/965 (6.94%)	97/959 (10.11%)	-3.19 (-5.67, –0.71) p=0.012	31% (8%, 49%) p=0.016
Asymptomatic DVT	73	144			55	78		
Symptomatic DVT	8	20			6	10		
PE	0	4			5	8		
Death	0	2			2	3		

Note: Individual subjects can have more than 1 type of event. All p values are for superiority testing, the noninferiority margin in RECORD 3 and RECORD 4 was 4%. The Treatment Phase is up to Day 17. ENOX = enoxaparin; RIVA = rivaroxaban

For comparison, the results for the primary study endpoint in recently conducted Phase 3 TKR studies are shown in Table 5-11. From these studies it is clear that the incidence of total VTE is higher after TKR than THR surgery. This is likely due to differences in surgical technique, with the use of tourniquets that cause complete obstruction of the distal circulation in TKR surgeries. A similar pattern was seen in the RECORD program (total VTE rates for enoxaparin were 14.3% in the pooled TKR studies compared with 5.7% in the pooled THR studies).

The rates for total VTE for subjects receiving enoxaparin in the RECORD 3 and 4 studies were lower than those observed in most other studies except for the recent ADVANCE-1 study where the rates for the 30 mg twice-daily regimens were similar. The RECORD 3 and 4 study rivaroxaban total VTE rates were both below 10%. indicating the substantial efficacy of rivaroxaban compared with previous studies.

Table 5-11: Primary Endpoint Results in Recent Phase 3 TKR Studies With Thromboprophylactic Agents

Study	Treatment Regimen (Days)		Total VTE (%, n/N)[a,b]	
	Test	Control	Test	Control
PENTAMAKS, (Bauer 2001)	Fondaparinux 2.5 qd (5-9)	Enoxaparin 30 bid (5-9)	12.5 [b] (45/361)	27.8 [b] (101/363)
EXULT A, (Francis, 2003)	Ximelagatran 36 bid (7-12)	Warfarin (7-12)	20.3[a] (128/629)	27.6[a] (168/608)
EXULT B, (Colwell, 2005)	Ximelagatran 36 bid (7-12)	Warfarin (7-12)	22.5[a] (221/982)	31.9[a] (308/967)
PLATINUM –knee[c,] (Francis, 2002)	Ximelagatran 24 bid (7-12)	Warfarin (7-12)	19.2 [b] (53/276)	25.7 [b] (67/261)
RE-MODEL, (Eriksson, 2007b)	Dabigatran 220 qd (6-10)	Enoxaparin 40 od (6-10)	36.4[a] (183/503)	37.7[a] (193/512)
RE-MOBILIZE, (Ginsberg, 2008)	Dabigatran 220 qd (12-15)	Enoxaparin 30 bid (12-15)	31.1 [a,d] (188/857)	25.3 [a] (163/868)
ADVANCE-1 (Lassen 2008)	Apixaban 2.5 mg bid (10-14)	Enoxaparin 30 bid (10-14)	9.0 (104/1157)	8.9 (100/1130)
RECORD 3	Rivaroxaban 10 qd (10-14)	Enoxaparin 40 qd (11-15)	9.6 [a] (79/824)	18.9 [a] (166/878)
RECORD 4	Rivaroxaban 10 qd (10-14)	Enoxaparin 30 bid (10-14)	6.9 [a] (67/965)	10.1 [a] (97/959)
RECORD 3-4	Rivaroxaban 10 qd (10-14)	Enoxaparin 40 qd or 30 bid (10-15)	8.2[a] (146/1789)	14.3[a] (263/1837)

[a] Total VTE endpoint includes death.
[b] Total VTE endpoint excludes death.
[c] unilateral venography
[d] statistically inferior to enoxaparin

The superior efficacy results shown in the RECORD 1, 3 and 4 studies, with an equal postoperative duration of dosing in the rivaroxaban and enoxaparin treatment groups, demonstrate that rivaroxaban 10 mg once daily can prevent more VTE events than enoxaparin. Superior efficacy for rivaroxaban compared with enoxaparin was demonstrated against both approved regimens of enoxaparin (40 mg once daily starting preoperatively and 30mg twice daily starting postoperatively). The results of the RECORD 2 study show that extended dosing with rivaroxaban (35 days) provides substantial reductions in VTE over a short-term standard regimen of enoxaparin (13 days) that is still commonly used in clinical practice.

5.2.2.3. Main Secondary Endpoint: Major VTE

Similarly, statistically significant differences in favor of rivaroxaban were observed in the MITT population for the main secondary efficacy endpoint of major VTE (any proximal DVT, non-fatal PE or VTE related death) in RECORD 1-3 while the difference in RECORD 4 did not reach statistical significance even though a

substantial relative risk reduction (41%) was observed. In RECORD 4, analyses using the PP population showed that the upper limit of the two-sided 95% CI for the Mantel-Haenszel-weighted treatment difference (rivaroxaban minus enoxaparin) was well below the prespecified non-inferiority margin, thereby establishing the non-inferiority of rivaroxaban versus enoxaparin.

The results for major VTE and its components in the MITT population for the RECORD 1 and 2 (THR) studies are shown in Table 5-12. The pattern of the results was consistent with the total VTE results. The rivaroxaban groups had low rates of major VTE in both studies. The shorter duration enoxaparin regimen in RECORD 2 had a higher rate of major VTE than the extended regimen in RECORD 1. The most frequent events were asymptomatic proximal DVT, which were reduced consistently with rivaroxaban in both studies.

Table 5-12: RECORD Program THR Main Secondary Efficacy Endpoint - Major VTE and Components Through The Treatment Phase

	RECORD 1				RECORD 2			
STUDY	RIVA n/N (%)	ENOX n/N (%)	ARD (95% CI) p value	RRR (95% CI) p value	RIVA n/N (%)	ENOX/PBO n/N (%)	ARD (95% CI) p value	RRR (95% CI) p value
Dose regimen	10mg once daily	40mg once daily			10 mg once daily	40mg once daily		
Major VTE (PP)	2/1622 (0.12%)	29/1604 (1.81%)	-1.69% (-2.37, -1.02) p<0.001	93% (71%,98%) p<0.0001	3/898 (0.33%)	41/884 (4.63%)	-4.31% (-5.76, -2.87) p<0.001	93% (77%,98%) p<0.0001
Major VTE (MITT)	4/1686 (0.24 %)	33/1678 (1.97 %)	-1.74% (-2.45, –1.03) p<0.001	88% (66%, 96%) p<0.001	6/961 (0.62%)	49/962 (5.09%)	-4.49% (-5.97, –3.01) p<0.001	88% (72%, 95%) p<0.001
Asymptomatic Proximal DVT	1	27			4	35		
Symptomatic Proximal DVT	0	5			1	9		
Nonfatal PE	4	1			1	4		
VTE related death (fatal PE)	0	1			0	1		

Note: Individual subjects can have more than 1 type of event. All p values are for superiority testing, the noninferiority margin in RECORD 1 was 1.5%. The Treatment Phase is up to Day 42. ENOX = enoxaparin; RIVA = rivaroxaban

For comparison, the results for secondary endpoints in recently conducted Phase 3 THR studies are shown in Table 5-13. Combining RECORD 1-2, the low rates of major VTE observed with extended prophylaxis with rivaroxaban after THR surgery are notable, with only 10 of over 2500 subjects experiencing a major VTE event (0.4%) compared with incidences reported in the literature that are usually over 1%.

Table 5-13: Secondary Endpoint Results in Recent Phase 3 THR Studies With Thromboprophylactic Agents

Study	Treatment Regimen (Days)		Major VTE[a] or Proximal DVT/PE[b] or Proximal DVT[c] (%, n/N)	
	Test	Control	Test	Control
EPHESUS (Lassen, 2002)	Fondaparinux 2.5 od (5-9)	Enoxaparin 40 od (5-9)	0.7[c] (6/922)	2.5[c] (23/927)
PENTATHLON 2000 (Turpie, 2002)	Fondaparinux 2.5 mg od (5-9)	Enoxaparin 30 bid (5-9)	1.7[c] (14/816)	1.2[c] (10/830)
PLATINUM –hip[d] (Colwell, 2003)	Ximelagatran 24 bid (7-12)	Enoxaparin 30 bid (7-12)	3.6[b,e] (28/782)	1.2[b] (9/774)
RE-NOVATE (Eriksson, 2007a)	Dabigatran 220 od (28-35)	Enoxaparin 40 od (28-35)	3.1[a] (28/909)	3.9[a] (36/917)
Extended Rx THR meta-analysis of 6 studies (Hull, 2001)	Enoxaparin/ dalteparin-extended (19-29 additional days)	Enoxaparin /dalteparin-short (6-14 days)	3.0[c] (26/866) lowest 0.9%	11.2[c] (76/678) lowest 4.8%
RECORD 1	Rivaroxaban 10 od (31-39)	Enoxaparin 40 od (32-40)	0.2[a] (4/1686)	2.0[a] (33/1678)
RECORD 2	Rivaroxaban 10 od (31-39)	Enoxaparin 40 od (11-15)	0.6[a] (6/961)	5.1[a] (49/962)
RECORD 1-2	Rivaroxaban 10 od (31-39)	Enoxaparin 40 od (11-15 or 32-40)	0.4[a] (10/2647)	3.1[a] (82/2640)

[a] Major VTE endpoint includes proximal DVT, nonfatal PE and VTE related death.
[b] Proximal DVT/PE
[c] Proximal DVT
[d] Unilateral venography
[e] Statistically inferior to enoxaparin

The results for major VTE and its components in the MITT population for the RECORD 3 and 4 (TKR) studies are shown in Table 5-14 and again were consistent with the primary endpoint results. In both studies the rivaroxaban groups had major VTE rates of about 1%. The most frequent events were asymptomatic proximal DVT, which were reduced consistently with rivaroxaban in both studies. For the other components the numbers of events are small and are not always less with rivaroxaban compared with enoxaparin. For enoxaparin the major VTE rate with the 30 mg twice daily regimen in RECORD 4 was somewhat lower than with the 40 mg once daily regimen in RECORD 3, which may have contributed to the lack of a statistically significant difference for rivaroxaban in RECORD 4.

Table 5-14: RECORD Program TKR Main Secondary Efficacy Endpoint, Major VTE and Components Through The Treatment Phase

STUDY	RECORD 3				RECORD 4			
	RIVA n/N (%)	ENOX n/N (%)	ARD (95% CI) p value	RRR (95% CI) p value	RIVA n/N (%)	ENOX n/N (%)	ARD (95% CI) p value	RRR (95% CI) p value
Dose regimen	10mg once daily	40mg once daily			10 mg once daily	30 mg twice daily		
Major VTE (PP)	9/874 (1.02%)	22/891 (2.47%)	-1.39% (-2.61, -0.17) p=0.025	58% (10%, 81%) p=0.034	11/1011 (1.09%)	15/1020 (1.47%)	-0.37% (-1.34, 0.60) p=0.456	26% (-60%, 66%) p=0.569
Major VTE (MITT)	9/908 (0.99 %)	24/925 (2.59 %)	-1.59% (-2.80, –0.38) p=0.010	62% (18%, 82%) p=0.016	13/1122 (1.16%)	22/1112 (1.98%)	-0.80% (-1.82, 0.22) p=0.124	41% (-16%, 70%) 0.165
Asymptomatic Proximal DVT	6	19			3	13		
Symptomatic Proximal DVT	3	1			5	1		
Nonfatal PE	0	4			5	8		
VTE related death (fatal PE)	0	0			1	0		

Note: Individual subjects can have more than 1 type of event. All p values are for superiority testing, the noninferiority margin in RECORD 3 and RECORD 4 was 1.5%. The Treatment phase is up to Day 17. ENOX = enoxaparin; RIVA = rivaroxaban

For comparison, the results for secondary endpoints in recently conducted Phase 3 TKR studies are shown in Table 5-15. Enoxaparin performed well compared to the previous studies with observed major VTE rates similar to or lower than those of the control and test agents . The rivaroxaban major VTE rates of about 1% are the lowest reported after TKR surgery.

Table 5-15: Secondary Endpoint Results in Recent Phase 3 TKR Studies With Thromboprophylactic Agents

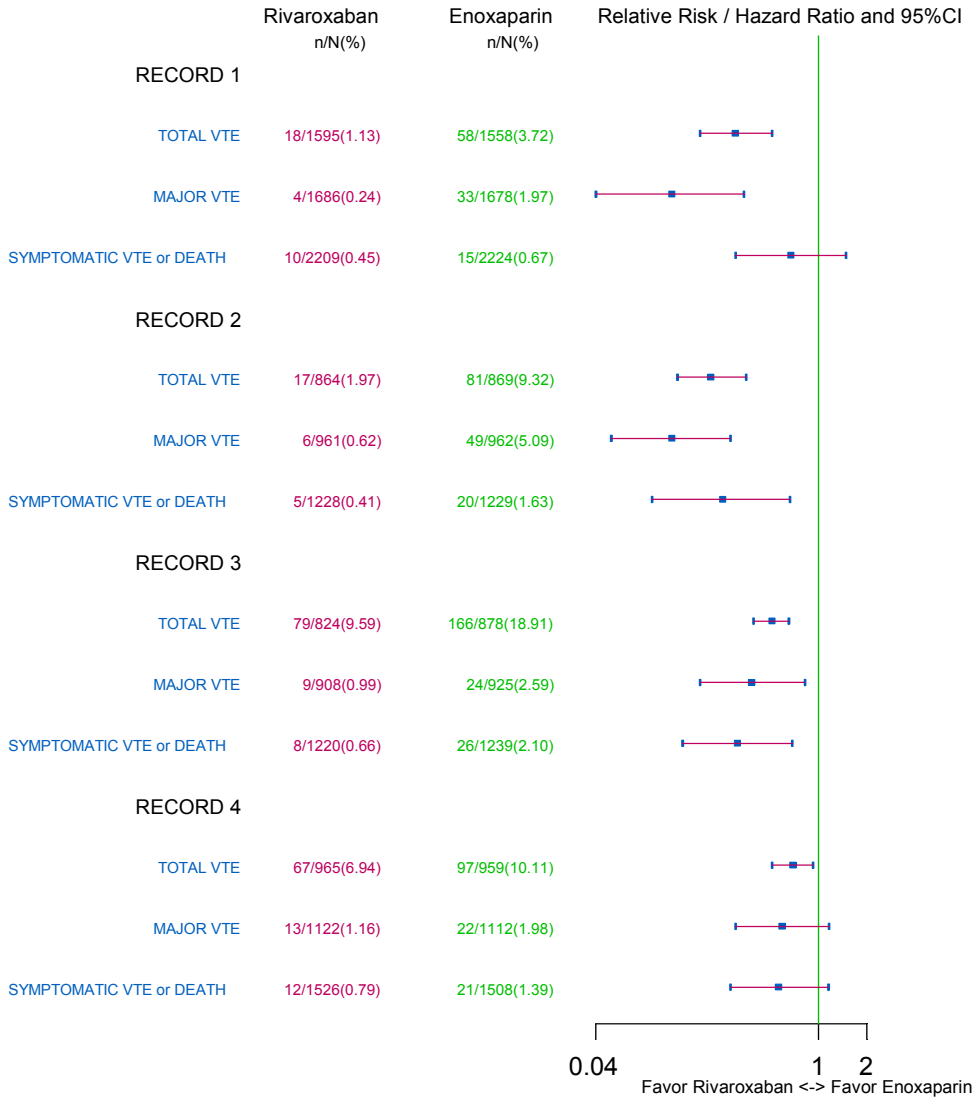
Study	Treatment Regimen (Days)		Major VTEa or Proximal DVT/PE b or Proximal DVTc (%, n/N)	
	Test	Control	Test	Control
Pentamaks (Bauer, 2001)	Fondaparinux 2.5 od (5-9)	Enoxaparin 30 bid (5-9)	2.4[c] (9/368)	5.4[c] (20/372)
Exult A (Francis, 2003)	Ximelagatran 36 bid (7-12)	Warfarin (7-12)	2.7[a] (17/629)	4.1[a] (25/603)
Exult B (Colwell, 2005)	Ximelagatran 36 bid (7-12)	Warfarin (7-12)	3.9[a] (38/976)	4.1[a] (40/964)
Platinum –knee[d] (Francis, 2002)	Ximelagatran 24 bid (7-12)	Warfarin (7-12)	3.3[b] (9/274)	5.0[b] (13/258)
RE-MODEL (Eriksson, 2007b)	Dabigatran 220 od (6-10)	Enoxaparin 40 od (6-10)	2.6[a] (13/506)	3.5[a] (18/511)
ADVANCE-1 (Lassen 2008)	Apixaban 2.5 bid (10-14))	Enoxaparin 30 bid (10-14)	2.0[a] (26/1216)	1.6 [a] (20/1216)
RE-MOBILIZE (Ginsberg, 2008)	Dabigatran 220 od (12-15)	Enoxaparin 30 bid (12-15)	3.4a (21/618)	2.2a (15/668)
RECORD 3	Rivaroxaban 10 od (10-14)	Enoxaparin 40 od (11-15)	1.0[a] (9/908)	2.6[a] (24/925)
RECORD 4	Rivaroxaban 10 od (10-14)	Enoxaparin 30 bid (10-14)	1.2[a] (13/1122)	2.0[a] (22/1112)
RECORD 3-4	Rivaroxaban 10 od (10-14)	Enoxaparin 40 od or 30 bid (11-15)	1.1[a] (22/2030)	2.3[a] (46/2037)

[a] Major VTE endpoint includes proximal DVT, nonfatal PE and VTE related death (except apixaban which includes all deaths).
[b] Proximal DVT/PE
[c] Proximal DVT
[d] Unilateral venography

In summary, considering the data from all four RECORD studies, the enoxaparin results for the total and major VTE endpoints are comparable or better than those in previous studies from the literature indicating that enoxaparin performed well in the RECORD studies and that rivaroxaban provides statistically significant and clinically important further reductions in thromboembolic events after THR and TKR. In this context it is important to note that rivaroxaban was superior to enoxaparin 30 mg twice daily in RECORD 4 for the primary endpoint. Although direct medical literature comparisons of the enoxaparin 40-mg once-daily and 30-mg twice-daily regimens are limited, available data suggest that the higher total daily dose of enoxaparin is more effective.

The reductions in total DVT and especially in proximal DVT (which has higher propensity for pulmonary embolization) observed with rivaroxaban would be expected to translate into a reduction in clinically apparent VTE events since these events all represent a continuum of disease based on a common pathophysiology. This prediction is supported by the data from this clinical program as consistent reductions in symptomatic VTE or death events were observed in all 4 RECORD studies, with the reductions in RECORD 2 and RECORD 3 being statistically significant. Figure 5-6 shows the consistency of the relative scale reductions for all endpoints across the 4 studies (Total VTE, Major VTE, Symptomatic VTE/death). Using a relative scale is more appropriate for comparing endpoints than an absolute scale since the heterogeneity of effect sizes is usually smaller with a relative scale (Deeks 2002). The next section will consider the pooled analyses of symptomatic events in more detail.

Figure 5-6: Efficacy Endpoints - Relative Risks / Hazard Ratios (95% CI) During Treatment Phase (MITT Population Valid for Total VTE and Major VTE, Safety Population Valid for Symptomatic VTE or Death)



Note: Relative Risk was provided for Total VTE and Major VTE; Hazard Ratio was provided for Symptomatic VTE or Death.

5.2.3. Efficacy Results in the Pooled RECORD Studies

5.2.3.1. Symptomatic Events

The pooled efficacy analyses of the RECORD studies are consistent with the individual study results and show the superiority of rivaroxaban over enoxaparin for the prevention of symptomatic thromboembolic events. The pooled analysis across the RECORD program was specifically designed to allow for more precise estimations of rivaroxaban treatment effects for symptomatic events expected to occur at low frequencies in each individual study. The common event definitions, ascertainment procedures and adjudication process support the poolability of the

studies as does the similar frequency of symptomatic events across the studies and the lack of evidence for heterogeneity of results on a relative scale.

The results for the primary endpoint composite of symptomatic VTE or death and its components in the safety population are shown in Table 5-16 and Figure 5-7. The primary endpoint composite showed a statistically significant and clinically important 58% relative risk reduction in the RECORD 1-4 integrated analysis (0.57% rivaroxaban, 1.32% enoxaparin; HR: 0.42, 95% CI: 0.29, 0.63, p value < 0.001). Consistent reductions were observed across all 4 studies (Figure 5-6, p value for test of heterogeneity 0.313) and all components (Figure 5-7). A posthoc analysis showed a 49% relative risk reduction in the composite of symptomatic PE or death for rivaroxaban compared with enoxaparin (0.27% rivaroxaban, 0.53% enoxaparin; HR 0.51, 95% CI: 0.29, 0.92, p=0.025). The separate results for symptomatic PE (HR 0.52, 95% CI: 0.24, 1.13, p=0.098) and all cause death (HR 0.50, 95% CI: 0.21, 1.16, p= 0.108) both contributed to the composite of symptomatic PE or death with similar numbers of events and risk reductions. Similar results were observed for the primary endpoint composite separately for both the pooled RECORD 1 and 2 THR (HR 0.43, 95% CI: 0.23, 0.78, p=0.006; test for heterogeneity p=0.126) and the pooled RECORD 3 and 4 TKR (HR 0.42, 95% CI:0.25, 0.72, p=0.001; test for heterogeneity p=0.270) surgery studies (see Appendix 1 for more detailed presentations of the composite component results by type of surgery).

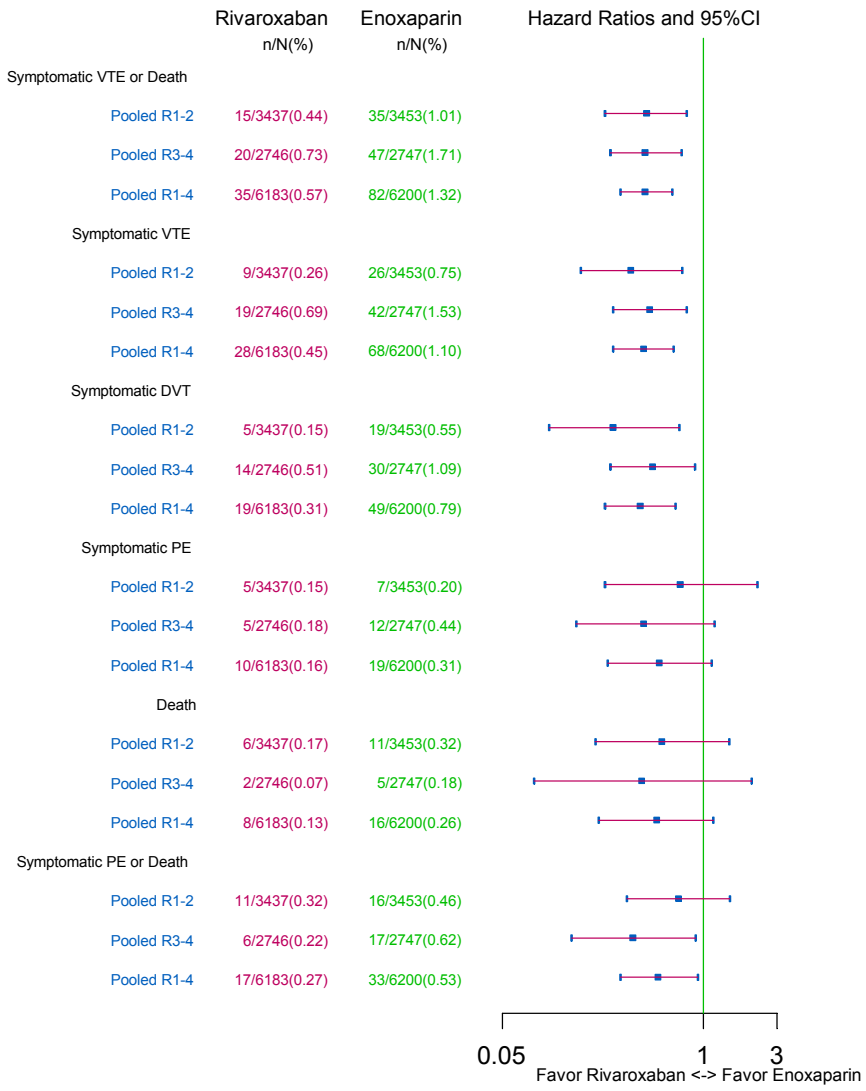
Table 5-16: Composite of Symptomatic VTE or Death and Components During the Treatment Phase: Pooled RECORD 1-4 Results

(Subjects Valid for Safety Analysis in the RECORD Studies)

Endpoint	Rivaroxaban N=6183 n (%)	Enoxaparin N=6200 n (%)	ARD (95% CI)	HR (95%CI)
Symptomatic VTE or death	35 (0.57%)	82 (1.32%)	-0.76% (-1.10, -0.42)	0.42 (0.29, 0.63)
Symptomatic DVT	19 (0.31%)	49 (0.79%)	-0.48% (-0.74, -0.22)	0.39 (0.23,0.66)
Symptomatic PE	10 (0.16%)	19 (0.31%)	-0.15% (-0.32, 0.02)	0.52 (0.24, 1.13)
Death, all causes	8 (0.13%)	16 (0.26%)	-0.13% (-0.28, 0.03)	0.50 (0.21, 1.16)
Symptomatic PE or Death (posthoc)	17 (0.27%)	33 (0.53%)	-0.26% (-0.48, -0.04)	0.51 (0.29, 0.92)

Abbreviations: DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism
Note: Subjects may have more than one type of event

Figure 5-7: Composite of Symptomatic VTE or Death and Components During the Treatment Phase Hazard Ratios (95% CI) (Subjects Valid for Safety Analysis in the Pooled RECORD 1-4 Studies)

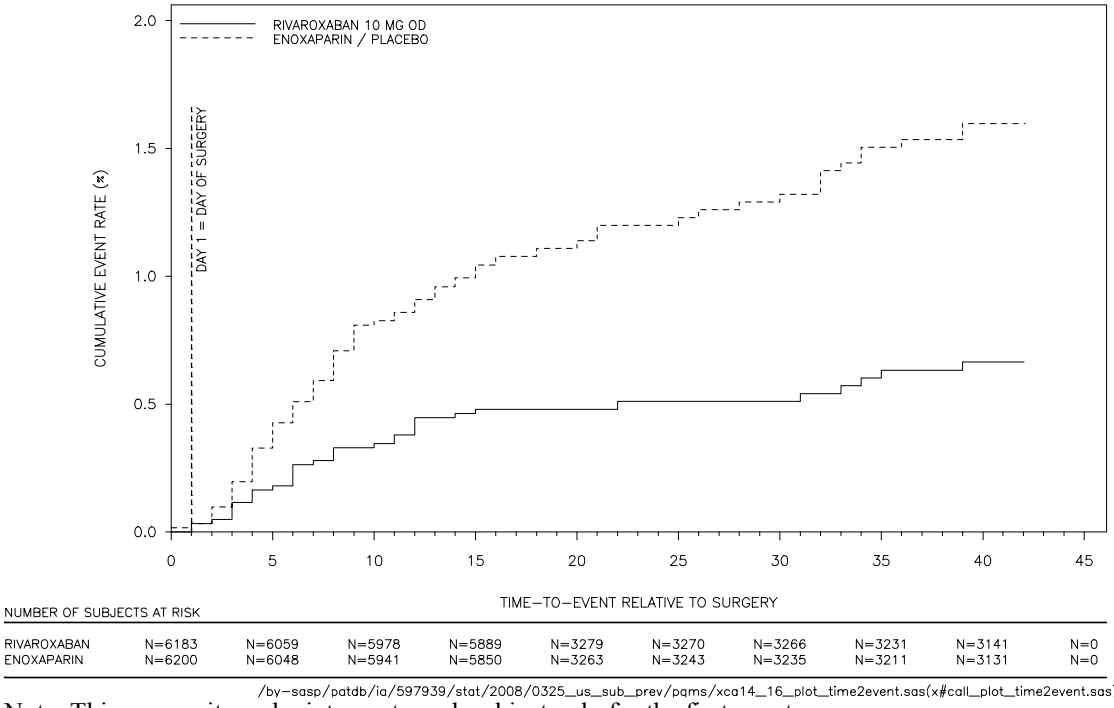


Note: Composite endpoints count each subject only for first event and subjects may have more than one type of event.

The occurrence of symptomatic VTE or death events over time during the treatment phase (Figure 5-8) shows that the rivaroxaban group begins to diverge from the enoxaparin group early after surgery and continues to diverge during the entire treatment phase. The placebo-controlled period in RECORD 2 does contribute to these observations, but is not the major influence since the results of pooled analyses that included events only up to Day 12±2 for each of the 4 RECORD studies, or

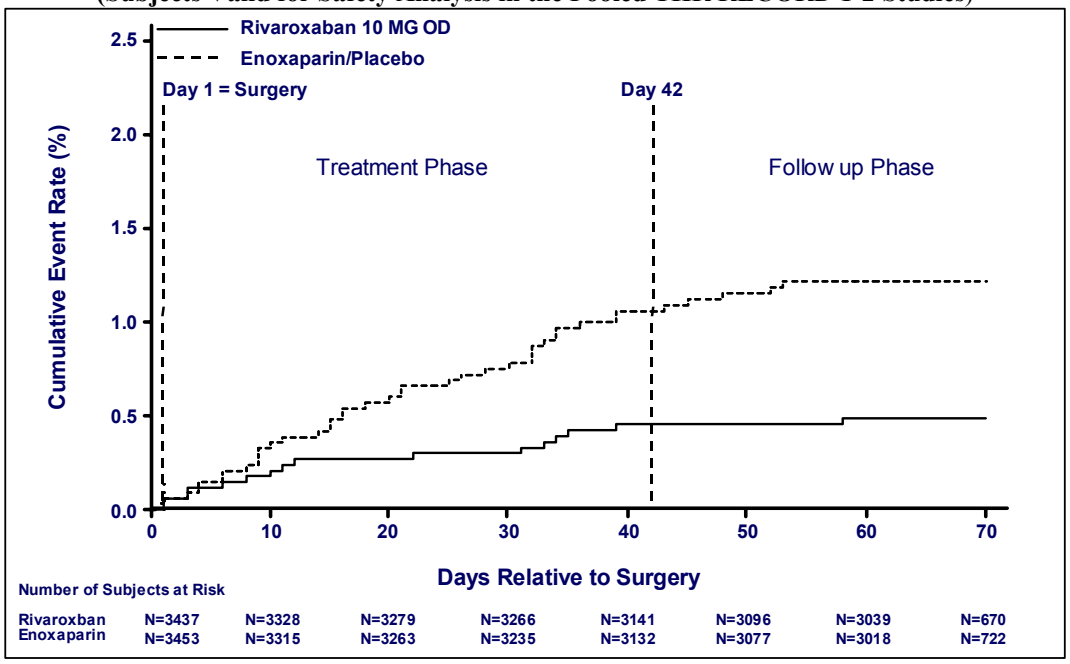
excluded the placebo-controlled period of RECORD 2 were similar to the overall results (See Appendix 1). The number of symptomatic VTE or death events which occurred in the follow-up phase after the time window of planned venography was similar or lower for rivaroxaban compared with enoxaparin (rivaroxaban total 15 events, THR 3, TKR 12; enoxaparin 20 total events: THR 7, TKR 13). This indicates that a rebound excess occurrence of venous thromboembolic events does not occur for rivaroxaban compared with enoxaparin. The continuing separation of the treatment groups during the treatment phase with no loss of the symptomatic VTE or death differences during the follow up phase is shown for the THR and TKR studies separately in Figures 5-9 and 5-10.

Figure 5-8: Cumulative Rate (Kaplan-Meier) of the Composite of Symptomatic VTE or Death During the Treatment Phase
(Subjects Valid for Safety Analysis in the Pooled RECORD 1-4 Studies)



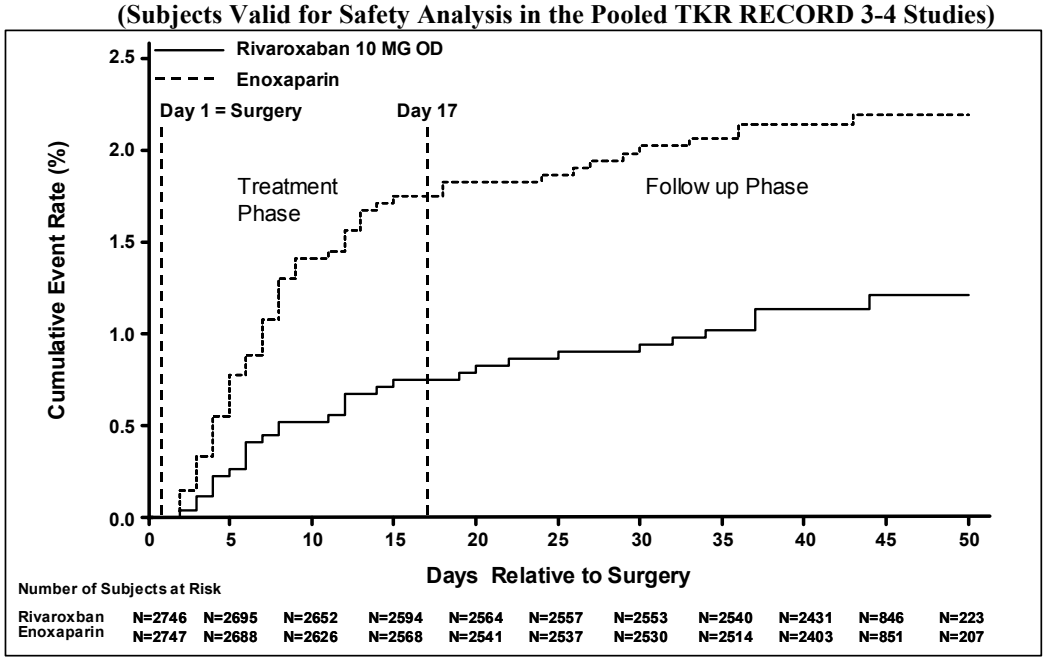
Note: This composite endpoint counts each subject only for the first event

Figure 5-9: Cumulative Rate (Kaplan-Meier) of the Composite of Symptomatic VTE or Death During the Treatment and Follow-Up Phases
(Subjects Valid for Safety Analysis in the Pooled THR RECORD 1-2 Studies)



Note : This composite endpoint counts each subject only for the first event

Figure 5-10: Cumulative Rate (Kaplan-Meier) of the Composite of Symptomatic VTE or Death During the Treatment and Follow-Up Phases
(Subjects Valid for Safety Analysis in the Pooled TKR RECORD 3-4 Studies)



Note : This composite endpoint counts each subject only for the first event

5.2.3.2. Pooled Subgroup Analyses for Total VTE

An additional purpose of the pooled RECORD 1-4 analysis was to examine treatment effects for the total VTE endpoint in prespecified subgroups. Subgroup analyses were

performed for a number of demographic characteristics, surgical characteristics (type of anesthesia and duration of surgery), by timing of first dose of rivaroxaban, and by use of CYP3A4/Pgp inducers. Subgroups for terciles of venogram validity rates of investigative sites were also explored to assess the consistency of treatment effects with respect to different venogram validity rates and are presented in Section 5.2.4.1, Sensitivity Analyses. Since asymptomatic DVT was assessed only at the end of the treatment phase (i.e., by venogram) and not during the entire study phase, as was symptomatic VTE, treatment groups were compared using odds ratios instead of time to event hazard ratios.

The overall odds ratio was 0.43 (95% CI 0.35, 0.51) and the subgroup odds ratios and confidence intervals are graphically depicted in Figure 5-11, where the data points represent the point estimates of the odds ratio of rivaroxaban relative to enoxaparin. The vertical line designates no difference between treatments. If the odds ratio appears to the left of the vertical line, the treatment difference favors rivaroxaban, and if it appears to the right, it favors enoxaparin. The horizontal lines represent the exact 2-sided 95% confidence intervals. For subgroups with less than 5 total events, the numbers of events are shown but the odds ratio and confidence intervals are not displayed.

There were no qualitative interactions observed (i.e. the point estimates for all subgroups favor rivaroxaban over enoxaparin) and for many important subgroups the confidence intervals excluded the line of identity indicating that rivaroxaban is likely to prevent more total VTE events than enoxaparin within that subgroup . Examples of such subgroups include male, female, all age categories, all levels of renal function and fragile subjects. For some subgroups the treatment effects are entirely consistent with the overall treatment effect although the confidence intervals do cross the line of identity due to a smaller number of events in these subgroups (e.g. Hispanic and Asian race , highest and lowest weight categories, lowest BMI category) . Similar findings were observed in the THR or TKR studies separately (see Appendix 1).

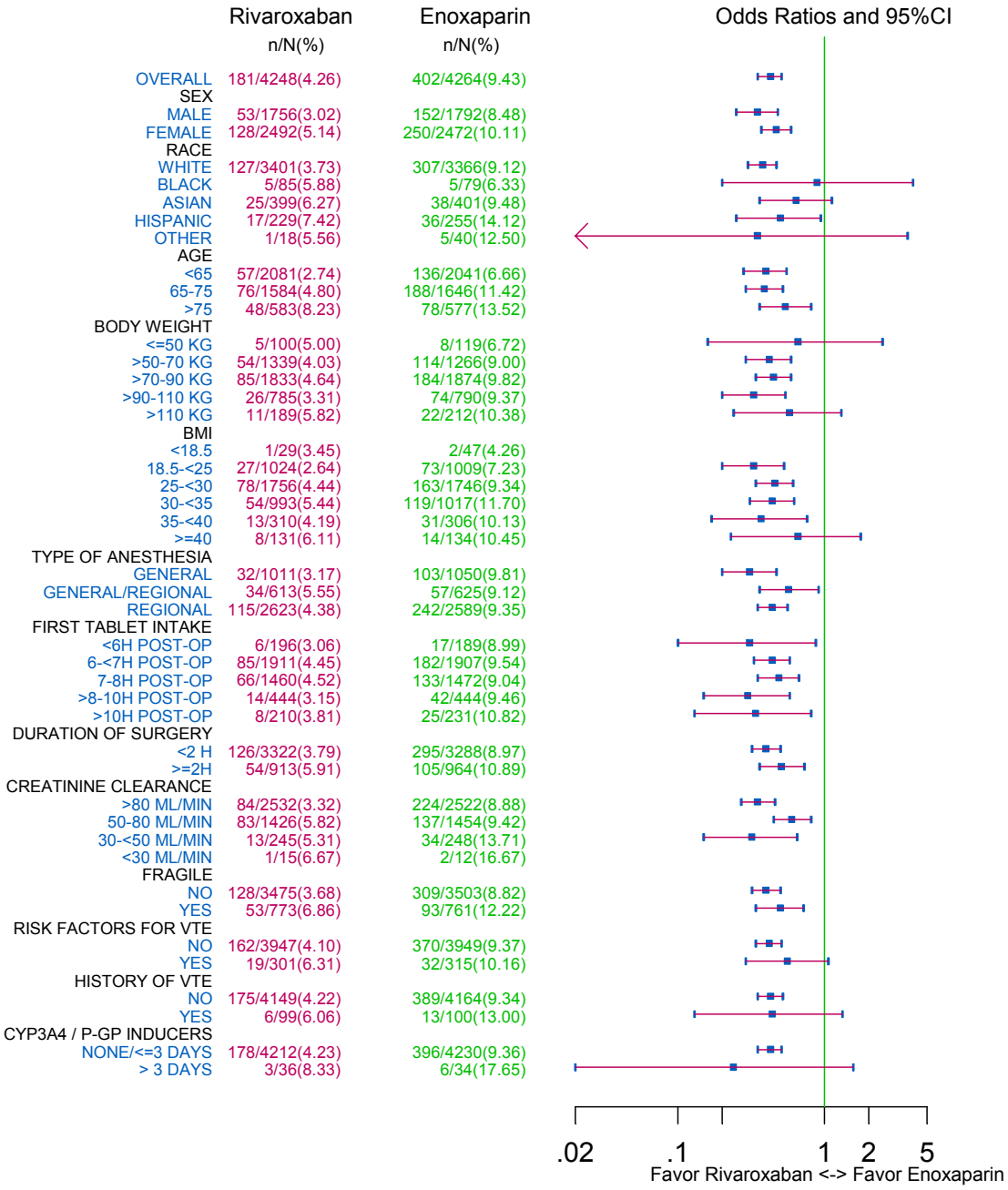
A few subgroups (i.e., Black and Other for the category of race, creatinine clearance < 30 mL/min, and use of CYP3A4/Pgp inducers for >3 days) had few events (10 or less), thus the confidence intervals for their odds ratios are very wide, making it difficult to draw conclusions. For these subgroups the overall treatment effect is likely the best estimate. A limited number of Black subjects participated in these studies and the overall treatment effect slightly favored rivaroxaban (Figure 5-11). Among these subjects in the THR studies, there were fewer events with enoxaparin; based on a small number of events (rivaroxaban 3/29, enoxaparin 0/29) while in the TKR studies with a somewhat larger sample size (rivaroxaban 2/56, enoxaparin 5/50)

there were fewer events with rivaroxaban. Since there are no relevant differences in rivaroxaban pharmacokinetic or pharmacodynamic characteristics between Black and White healthy volunteers (Section 3.5), this difference between the THR and TKR studies probably represents a chance finding. With the concomitant use of CYP3A4/PgP inducers the rivaroxaban total VTE rate was higher with use (3/36 8.33%) than with no use of inducers (178/4212 4.23%) but the odds ratio still favored rivaroxaban compared with enoxaparin in both categories (enoxaparin with inducer 6/34 17.65%, without inducer 396/4230 9.36%). These observations along with the Phase 2 data, which suggest that a 5-mg once daily dose of rivaroxaban has some efficacy indicate that concomitant use of CYP3A4/PgP inducers with rivaroxaban is not likely to lead to loss of the efficacy benefit of rivaroxaban even though exposure is known to be reduced.

Across the subgroups of subjects that received their first dose of rivaroxaban <6, 6-<7, 7-8, >8-10, or >10 hours after surgery, the treatment effect of rivaroxaban versus enoxaparin did not vary, with these subgroups having odds ratios of 0.3, 0.4, 0.5, 0.3, and 0.3, respectively (Figure 5-11). Similar results were observed for bleeding event analyses (Section 6.2.3.1.7). These data support the recommendation to start rivaroxaban dosing within the time window of 6 to 10 hours after surgery. The number of subjects and events for the time window > 10 hours after surgery is too small to make any recommendations for this time period.

Since the treatment effect of rivaroxaban was generally consistent across subgroups for a wide range of patient characteristics, the efficacy of rivaroxaban is expected to be consistent and robust in clinical practice. The effect of demographics and comedications on rivaroxaban pharmacokinetics and pharmacodynamics is discussed in more detail in Section 3.2.2, 3.3.2, and 3.5. The clinical efficacy results are consistent with the clinical pharmacology results.

Figure 5-11: Total VTE Odds Ratios (95% CI) by Subgroup
(MITT Population Valid for Total VTE of the Pooled RECORD 1-4 Studies)



Note: Note: Fragile definition: Age >75 years and/or calculated creatinine clearance <50 ml/min and/or weight ≤50 kg

The results for subjects in the US were consistent with the overall results and primarily represent the findings from the RECORD 4 study as there was no

participation of the US in the RECORD 3 study and limited participation in the RECORD 1 and 2 studies (All US results: OR 0.54, 95% CI 0.32, 0.89; All other country results OR 0.41 95% CI 0.33, 0.50); RECORD 4 US results: OR 0.59, 95% CI 0.34, 0.99; RECORD 4 other country results OR 0.72 95% CI 0.46, 1.14). Appendix 1 provides US and other region efficacy and bleeding event results in more detail.

5.2.4. Sensitivity Analyses

In order to address the issue of the exclusion of approximately one-third of randomized subjects from the MITT population in each RECORD study (the population used for the superiority analysis of the total VTE primary efficacy endpoint [total VTE]) due primarily to an inadequate assessment of thromboembolism for DVT, additional descriptive and sensitivity analyses of total VTE were performed.

It should be noted that symptomatic events, which are already a component of the primary efficacy endpoint, could be separately assessed in the broader valid for safety analysis population in which the patient data are more complete due to the fact that negative confirmatory venograms are not required. Therefore, the robust findings of the symptomatic event analyses represent strong support for the validity of the primary efficacy analysis of total VTE.

5.2.4.1. Assessment of Thromboembolism

For the RECORD studies, the percentage of subjects excluded from the MITT population for total VTE ranged from 31% (RECORD 1 and 2) to 39% (RECORD 4), with the percentage of excluded subjects balanced in the 2 treatment groups for each study (Table 5-17).

Table 5-17: Subjects Excluded From MITT Population for Total VTE (Randomized Population)

Study#	Rivaroxaban n/N (%)	Enoxaparin n/N (%)
RECORD 1		
Excluded From MITT Analysis	671/2266 (29.6)	717/2275 (31.5)
No intake of study medication	57 (2.52)	51 (2.24)
No planned surgery	17 (0.75)	21 (0.92)
No adequate assessment of thromboembolism	588 (25.95)	635(27.91)
Other	9 (0.40)	10 (0.44)
RECORD 2		
Excluded From MITT Analysis	388/1252 (31.0)	388/1257 (30.9)
No intake of study medication	24 (1.92)	28 (2.23)
No planned surgery	16 (1.28)	22 (1.75)
No adequate assessment of thromboembolism	348 (27.80)	338 (26.89)
RECORD 3		
Excluded From MITT Analysis	430/1254 (34.3)	399/1277 (31.3)
No intake of study medication	34 (2.71)	38 (2.98)
No planned surgery	20 (1.59)	22 (1.72)
No adequate assessment of thromboembolism	376 (29.98)	339 (26.55)
RECORD 4		
Excluded From MITT Analysis	619/1584 (39.1)	605/1564 (38.7)
No intake of study medication	58 (3.66)	56 (3.58)
No planned surgery	2 (0.13)	3 (0.19)
No adequate assessment of thromboembolism	559 (35.29)	546 (34.91)

Note: RECORD 1 is Study 11354, RECORD 2 is Study 11357, RECORD 3 is Study 11356 and RECORD 4 is Study 11355.

In all 4 studies the most common reason subjects were excluded from the MITT population for total VTE was an inadequate assessment of thromboembolism. For RECORD 1, 2 and 3, the most common reason for this inadequate assessment was that the bilateral venograms were not done, due to either subject refusal or technical difficulties, while in RECORD 4 the most common reason was a nonevaluable venogram (Table 5-18).

Table 5-18: Inadequate Assessment of Thromboembolism

(Subjects Invalid for MITT Analysis for Total VTE Due to Inadequate Assessment of Thromboembolism)

Study#	Rivaroxaban N (%)	Enoxaparin N (%)
RECORD 1 Total	**588**	**635**
Reasons		
Venography Not Done	319 (54.3)	322 (50.7)
Unilateral Venography	105 (17.9)	105 (16.5)
Nonevaluable Venography	121 (20.6)	164 (25.8)
Venography Too Early/Late	43 (7.3)	44 (6.9)
RECORD 2 Total	**348**	**338**
Reasons		
Venography Not Done	155 (44.5)	159 (47.0)
Unilateral Venography	57 (16.4)	57 (16.9)
Nonevaluable Venography	127 (36.5)	111 (32.8)
Venography Too Early/Late	9 (2.6)	11 (3.3)
RECORD 3 Total	**376**	**339**
Reasons		
Venography Not Done	156 (41.5)	166 (49.0)
Unilateral Venography	82 (21.8)	69 (20.4)
Nonevaluable Venography	131 (34.8)	96 (28.3)
Venography Too Early/Late	7 (1.9)	8 (2.4)
RECORD 4 Total	**559**	**546**
Reasons		
Venography Not Done	189 (33.8)	184 (33.7)
Unilateral Venography	116 (20.8)	105 (19.2)
Nonevaluable Venography	244 (43.7)	253 (46.3)
Venography Too Early/Late	10 (1.8)	4 (0.7)

Note: for subjects with multiple reasons for inadequate venography, the following hierarchy was applied: Unilateral, Nonevaluable, Out of Window
Note: RECORD 1 is Study 11354, RECORD 2 is Study 11357, RECORD 3 is Study 11356 and RECORD 4 is Study 11355.

There was a wide variation in the overall rates and reasons for an inadequate assessment of total VTE across regions, countries and at the individual site level within countries, but this was balanced between the rivaroxaban and enoxaparin treatment groups. The reason for a nonevaluable venogram was almost always poor or no filling of the venous segments by the contrast agent.

For each RECORD study, the MITT evaluability rate by individual site was assessed and ranked from lowest to highest. Sites were then categorized in terciles (lower, middle, upper) based on these evaluability rates. The mean validity rates for the terciles across the 4 RECORD studies varied from 45.8% to 54.3% for the low tercile, 69.7% to 78.8% for the medium tercile, and 82.8% to 93.3% for the high tercile. For each RECORD study, there was a similar validity rate for the 2 treatment groups within each tercile, showing a balance for the rate of invalid venograms in the rivaroxaban and enoxaparin groups. For total VTE, there did not appear to be any

clear relationship between the venogram validity rate and the rivaroxaban treatment effect vs enoxaparin for either the centrally adjudicated or locally assessed results in any study.

The odds ratios for total VTE across the validity terciles were generally consistent with the results for the MITT population of the pooled RECORD 1-4 studies, indicating little change in the response of rivaroxaban vs enoxaparin between validity terciles and no statistical interaction (Table 5-19). Similar results were seen for the separately pooled RECORD 1 and 2 (THR) and pooled RECORD 3 and 4 (TKR) studies. These results indicate that rivaroxaban was statistically significantly more effective than enoxaparin in each subgroup of venogram evaluability.

Table 5-19: Incidence and Odds Ratio for Total VTE Stratified by Venogram Validity Tercile

(MITT Population for Total VTE of the Pooled RECORD Studies)

			Odds Ratio to Enoxaparin		
Validity Tercile Treatment	Study Pool	Incidence (% total VTE)	Point Estimate	95% Confidence Interval	Interaction p value
Lower					
Rivaroxaban	RECORD 1-2	2.18	0.37	[0.20, 0.65]	0.125
	RECORD 3-4	9.56	0.57	[0.40, 0.82]	0.429
	RECORD 1-4	5.28	0.50	[0.37, 0.68]	0.196
Enoxaparin	RECORD 1-2	5.76			
	RECORD 3-4	15.72			
	RECORD 1-4	10.12			
Middle	RECORD 1-2	1.34	0.20	[0.09, 0.39]	
Rivaroxaban	RECORD 3-4	5.98	0.43	[0.27, 0.65]	
	RECORD 1-4	3.31	0.33	[0.23, 0.48]	
Enoxaparin	RECORD 1-2	6.29			
	RECORD 3-4	13.06			
	RECORD 1-4	9.19			
Upper					
Rivaroxaban	RECORD 1-2	0.74	0.14	[0.05, 0.33]	
	RECORD 3-4	8.97	0.60	[0.41, 0.88]	
	RECORD 1-4	4.20	0.44	[0.31, 0.61]	
Enoxaparin	RECORD 1-2	5.10			
	RECORD 3-4	14.11			
	RECORD 1-4	8.94			

Note: RECORD 1 is Study 11354, RECORD 2 is Study 11357, RECORD 3 is Study 11356 and RECORD 4 is Study 11355.

5.2.4.2. Expanded Analysis Populations

For each RECORD study, sensitivity analyses were performed for total VTE by using varying scenarios for the handling of missing responses for subjects without an adequate assessment of thromboembolism. These scenarios used the following assumptions:

- there was the same risk for asymptomatic DVT for subjects without an adequate assessment as there was for subjects with an adequate assessment who belonged to the same treatment group and were within the same geographic region (realistic scenario);
- none of the subjects without adequate assessment were assumed to have a DVT (optimistic scenario); and
- all of the subjects without adequate assessment were assumed to have a DVT (pessimistic scenario)

For each of the RECORD studies, all analyses of total VTE using these assumptions indicated statistical superiority of the rivaroxaban group as compared with the enoxaparin group (i.e., the 95% CI did not contain 0), except in RECORD 3 and 4 for only 1 of the 3 scenarios (pessimistic) that assumed all subjects without an assessment had a DVT.

For each RECORD study, additional sensitivity analyses were performed based on expanded definitions of the MITT population, including the use of investigator reported events, as follows:

- (Population 1) all randomized subjects (including subjects without taking the double-blind study drug or undergoing surgery) who had an evaluable bilateral venography (adjudicated) regardless of whether it was in the time window, or a confirmed symptomatic event/death regardless of whether it was in the time window;
- (Population 2) the same as Population 1 plus subjects with investigator-reported evaluable assessments (i.e., venography/ultrasonography assessments as well as investigator-reported symptomatic events) that were deemed nonevaluable by the adjudication committees; and
- (Population 3) all randomized subjects with evaluable investigator-reported assessments (i.e., including venography/ultrasonography assessments as well as investigator-reported symptomatic events).

Analysis of the treatment difference for total VTE using Populations 1-3 showed results similar to those obtained using the MITT population for each of the 4 Phase 3 studies with all confidence intervals excluding zero except for Population #3 in RECORD 4, where the confidence interval almost excluded zero (Table 5-20).

Table 5-20: Primary Efficacy Results (Total VTE) for the MITT and Other Populations

Endpoint		Mantel-Haenszel-Weighted Difference to Enoxaparin	
Study Populationa	N, Riva/Enox	Point Estimate	95% Confidence Interval
RECORD 1			
Randomized	2266/2275		
MITT Population	1595/1558	-2.62%	[-3.69%, -1.54%]
Population #1	1645/1612	-2.71%	[-3.79%, -1.62%]
Population #2	1798/1813	-2.99%	[-4.13%, -1.85%]
Population #3	1777/1780	-2.54%	[-3.85%, -1.24%]
RECORD 2			
Randomized	1252/1257		
MITT Population	864/869	-7.28%	[-9.41%, -5.15%]
Population #1	875/882	-7.07%	[-9.24%, -4.89%]
Population #2	1011/1012	-6.39%	[-8.51%, -4.27%]
Population #3	996/1006	-5.20%	[-7.45%, -2.94%]
RECORD 3			
Randomized	1254/1277		
MITT Population	824/878	-9.15%	[-12.40%, -5.89%]
Population #1	834/888	-8.86%	[-12.15%, -5.57%]
Population #2	980/1013	-8.05%	[-11.21%, -4.90%]
Population #3	964/997	-7.67%	[-10.96%, -4.38%]
RECORD 4			
Randomized	1584/1564		
MITT Population	965/959	-3.19%	[-5.67%, -0.71%]
Population #1	979/970	-2.87%	[-5.41%, -0.33%]
Population #2	1234/1238	-2.47%	[-4.65%, -0.30%]
Population #3	1196/1213	-2.01%	[-4.06%, 0.04%]

Note: RECORD 1 is Study 11354, RECORD 2 is Study 11357, RECORD 3 is Study 11356 and RECORD 4 is Study 11355.

5.2.4.3. Approaches for Handling Missing Venography Data

An analysis of the primary efficacy endpoint was also performed using the methodology of Quan et al (2007). This approach formally combines asymptomatic venographic assessments of DVT and symptomatic events into a composite endpoint. The methodology derives the probabilities of all possible study outcomes using all available data for both asymptomatic and symptomatic events. Event rates for the composite endpoint are then based on these probabilities. This approach provides an alternative and more formalistic analysis to the primary analysis strategy with the MITT population. The results of this analysis demonstrate the superiority of rivaroxaban to enoxaparin and are very similar to the results of the primary analysis using the MITT population (Table 5-21).

Table 5-21: Supplemental Sensitivity Analysis of the Primary Efficacy Endpoint (Total VTE) Using the Quan Method

Study	Population	Incidence of Total VTE (%)		Unweighted Relative Risk Reduction	
		Rivaroxaban	Enoxaparin	Pt Estimate (%)	95% CI
RECORD 1	MITT (prespecified)	1.13	3.72	70	(49, 82)
	ITT (Quan)	0.94	3.45	73	(53, 84)
RECORD 2	MITT (prespecified)	1.97	9.32	79	(65, 87)
	ITT (Quan)	1.79	8.66	79	(65, 88)
RECORD 3	MITT (prespecified)	9.59	18.91	49	(35, 61)
	ITT (Quan)	9.28	18.13	49	(34, 60)
RECORD 4	MITT (prespecified)	6.94	10.11	31	(8, 49)
	ITT (Quan)	6.49	9.24	30	(5, 48)

Confidence intervals for relative risks were determined using asymptotic methods.
Note: RECORD 1 is Study 11354, RECORD 2 is Study 11357, RECORD 3 is Study 11356 and RECORD 4 is Study 11355.

5.2.4.4. Summary of Sensitivity Analyses

In summary, although about 33% of randomized subjects were not included in the primary endpoint analysis of total VTE in the MITT population, the efficacy results appear robust for the following reasons:

- statistically significant reductions in symptomatic VTE or death events, which are components of the total VTE primary endpoint , were observed in the safety population and ascertainment of these events is not dependent on venography;
- the proportions of subjects excluded were similar between the rivaroxaban and enoxaparin treatment groups in each of the studies (total excluded for all 4 studies; rivaroxaban 33.5%, enoxaparin 33.1%) as were reasons for exclusion;
- the efficacy results do not appear to be dependent on the site's ability to perform venography (i.e., rivaroxaban was more effective than enoxaparin in all 3 terciles of venogram evaluability);and
- sensitivity analyses using expanded populations were consistent with the primary efficacy analyses.

5.2.5. Summary of Efficacy

Endpoints including Venographic Assessments

Each of the 4 RECORD studies individually met or exceeded its primary efficacy objective by showing a greater reduction in the primary efficacy endpoint of total VTE in the rivaroxaban group than in the enoxaparin group that was statistically significant and clinically important. The RECORD 1, RECORD 3, and RECORD 4 studies that had noninferiority comparisons as the first test all showed superiority to

enoxaparin, as did RECORD 2 that had only superiority testing. Results were consistent across studies, populations (PP and MITT), and analysis methods (absolute and relative). The results for the THR and TKR studies were also consistent with each other.

Demographic characteristics, preexisting VTE risk factors, and surgery/anesthesia details, as well as the validity rates of the protocol required venographic assessments were balanced between the rivaroxaban and enoxaparin treatment groups supporting the validity of the efficacy results. The efficacy results from the integrated analysis of the RECORD studies were consistent across all important subgroups in the subject categories of sex, age, race, weight, BMI, and creatinine clearance, with each subgroup that contained a sufficient number of subjects demonstrating statistical superiority of rivaroxaban over enoxaparin. There were also no important differences in results across geographic regions, with the results from the US (about 14% of subjects in the program were from the US [1727/12383], with about 85% of the US subjects from RECORD 4) being well within the range of the overall findings. Most of the subjects in these studies began rivaroxaban treatment between 6-10 hours after surgery (about 90%) with no apparent differences in efficacy observed for either an earlier start (about 5% of subjects) or a later start (about 5% of subjects).

For the prespecified main secondary endpoint of major VTE, clinically important and statistically significant risk reductions were observed for the rivaroxaban group relative to the enoxaparin group in RECORD 1, 2 and 3, while in RECORD 4 a substantial risk reduction (41% relative risk reduction) was observed that did not reach statistical significance. The results were very consistent between the analyses using the per protocol and MITT populations and were independent of analysis method. It should be noted that these analyses included more subjects than the primary efficacy analyses for total VTE since fewer subjects were excluded for an inadequate venographic assessment. As seen for the primary endpoint analyses, the results for major VTE were robust for both the THR and TKR studies, for all important subgroups, and when compared with the results of published studies.

Enoxaparin is the most widely used prophylactic agent following THR and TKR surgery on a worldwide basis, although in the US warfarin is also commonly used. Both agents are effective compared with no therapy and have a Grade 1A recommendation by the American College of Chest Physicians, as does fondaparinux. Enoxaparin performed well in all 4 RECORD studies with efficacy endpoint incidence rates similar to or lower than those reported in the literature. Therefore the further reductions observed with rivaroxaban indicate that rivaroxaban offers

substantial additional protection for both total VTE and major VTE events beyond that provided by enoxaparin.

The basis for the superior efficacy of rivaroxaban compared with enoxaparin is likely multifactorial, but may include its unique mechanism of action (direct factor Xa inhibition), as well as its dose regimen and start time.

In summary, rivaroxaban has demonstrated consistent, clinically important, and statistically significant superior efficacy compared with enoxaparin for the prophylaxis of total VTE and major VTE after both THR and TKR surgery.

Symptomatic Event Endpoints

As screening for asymptomatic DVT is not done in clinical practice, the endpoint that most closely reflects what is seen by the practicing physician is the prevention of symptomatic events. Therefore, symptomatic VTE was a key secondary endpoint in each of the Phase 3 RECORD studies, and a preplanned integrated analysis strategy for symptomatic events across the RECORD studies was prepared prior to the unblinding of the first completed study (RECORD 3). This pooled approach was undertaken since the number of symptomatic events was expected to be low for each individual study, thus requiring pooling across the studies to increase precision. It is important to note that in these integrated analyses there are no exclusions related to venography so that all subjects in the population valid for safety analysis were included.

For the prespecified RECORD 1-4 integrated analysis of symptomatic events, the incidence of the primary composite efficacy endpoint, symptomatic VTE or death from all causes, during the treatment phase was statistically significantly lower in the rivaroxaban group (35 [0.57%]) than in the enoxaparin group (82 [1.32%]) (hazard ratio 0.42, $p<0.001$). This difference was due to an approximately 2 to 3 fold lower incidence in the rivaroxaban group of all components of the endpoint and was consistent for both the THR and TKR studies separately. The cumulative incidence rate curves for rivaroxaban and enoxaparin began to separate shortly after surgery and continued to diverge throughout the entire treatment period with no evidence for any loss of efficacy during the follow-up period.

The incidence of the post-hoc composite of symptomatic PE or death was lower in the rivaroxaban group than in the enoxaparin group (17 [0.27%] and 33 [0.53%], respectively, hazard ratio=0.51, [95% CI: 0.29, 0.92]). The point estimates of the reductions for both symptomatic PE (hazard ratio=0.5, [95% CI [0.24, 1.13]) and all cause death (hazard ratio=0.52, 95% CI [0.21, 1.16]) separately were consistent and

substantial, although due to the limited number of events the confidence intervals did not exclude 1.

The incidence of symptomatic VTE or death observed in the enoxaparin group (overall 1.3% in the RECORD 1-4 dataset, ranging from 0.7% in RECORD 1 to 2.1% in RECORD 3), is similar to what has been reported in the literature from a large database (White 1998) and from previous studies again supporting the efficacy of enoxaparin in the RECORD program and the important additional benefits observed with rivaroxaban.

It is generally accepted that the occurrence of asymptomatic distal (calf) DVT is usually an intermediate step in a progression to proximal DVT, symptomatic DVT, and/or PE. Therefore, the symptomatic event results observed in the RECORD program are entirely consistent with the venographic endpoint results of total VTE and major VTE. Table 5-22 provides results of for all 3 efficacy endpoints using relative scale assessments. These results show that rivaroxaban is the first compound demonstrating statistically significant superior efficacy for both asymptomatic and symptomatic events compared with enoxaparin after both THR and TKR surgery.

Table 5-22: Efficacy Endpoint Relative Risks/Hazard Ratios (95% CI) for Rivaroxaban compared with Enoxaparin During the Treatment Phase

Study or Pool	Total VTE MITT population	Major VTE MITT population	Symptomatic VTE or Death Safety population
RECORD 1	0.30 (0.18, 0.51)	0.12 (0.04,0.34)	0.67 (0.30,1.48)
RECORD 2	0.21 (0.13 0.35)	0.12 (0.05,0.28)	0.25 (0.09,0.66)
RECORD 3	0.51 (0.39, 0.65)	0.38 (0.18,0.82)	0.31 (0.14,0.68)
RECORD 4	0.69 (0.51, 0.92)	0.59 (0.30,1.16)	0.56 (0.28,1.15)
RECORD 1-2	0.25 (0.17,0.36)	0.12 (0.06, 0.23)	0.43 (0.23,0.78)
RECORD 3-4	0.57 (0.47,0.70)	0.48 (0.29,0.80)	0.42 (0.25,0.72)
RECORD 1-4	0.46 (0.39,0.54)	0.25 (0.17,0.37)	0.42 (0.29,0.63)

Note: Relative Risk was provided for Total VTE and Major VTE; Hazard Ratio was provided for Symptomatic VTE or Death

6. SAFETY OF RIVAROXABAN

6.1. Introduction

The safety of rivaroxaban has been demonstrated for use as an anticoagulant for the prophylaxis of DVT and PE in patients undergoing THR or TKR surgery. The overall clinical program includes a total of 17,864 subjects (10,612 rivaroxaban subjects) who participated in 65 completed studies and contribute safety data. Fifty-two of these studies were Phase 1 clinical pharmacology studies in which more than 80% of subjects were exposed to study drug for one day only. There are 13 completed

Phase 2 or 3 studies. Eight of these studies are in subjects receiving rivaroxaban for VTE prophylaxis after THR or TKR surgery. Five of these are Phase 2 studies in subjects receiving rivaroxaban for DVT treatment or in the setting of atrial fibrillation. The majority of the safety exposure comes from four Phase 3 RECORD studies which used enoxaparin as the active control. In Phase 2 THR and TKR studies, a 12-fold dose range of rivaroxaban (2.5 mg po bid to 30 mg po bid) was tested. Most subjects in the safety population of completed studies were exposed to study drug for 35 days or less. Liver safety data from ongoing studies which in some cases involve rivaroxaban doses higher than 10 mg and exposure duration up to 1 year or more are supportive of the liver safety data from the RECORD program and are presented in Section 6.3.

6.2. Phase 3 Studies in THR or TKR

6.2.1. Demographics and Drug Exposure

Demographic data for the pooled safety population of the RECORD studies are provided in Section 5.2.2.1.

The mean duration of exposure to active study medication was similar on rivaroxaban and enoxparin in RECORD 1 (33.4 versus 33.7 days respectively), RECORD 3 (11.9 versus 12.5 days respectively), and RECORD 4 (11.7 versus 11.0 days respectively). In RECORD 2 the mean duration of exposure was 33.5 versus 12.4 days on rivaroxaban and enoxaparin respectively. The mean follow-up period after study drug discontinuation in each of the RECORD studies was approximately 31 days.

6.2.2. Summary of Adverse Events

Adverse events with rivaroxaban were generally similar to or lower than those seen with enoxaparin (Table 6-1). Treatment-emergent events are those that occurred after the first dose of double-blind study medication and up to 2 days after the last dose of of double-blind study medication. A two-day window to define treatment emergent was appropriate given the relatively short (11-13 hour) half-life of rivaroxaban. It is worth noting that any DVT (symptomatic or asymptomatic) and PE events were to be reported as adverse events on the case report form. Adverse events starting more than 2 days after stopping study medication were similar between the two groups (10.14% and 10.02% for rivaroxaban and enoxaparin, respectively).

Table 6-1: Summary of Adverse Events
(Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)

Incidence of:	Rivaroxaban (N=6183) n (%)	Enoxaparin (N=6200) n (%)
Any death[a]	13 (0.21%)	25 (0.40%)
Any serious adverse event[a]	511 (8.26%)	622 (10.03%)
Any adverse event[a]	4365(70.60%)	4497 (72.53%)
Any adverse event starting >2 days after stop of study drug	627 (10.14%)	621 (10.02%)
Any adverse event resulting in permanent discontinuation of study drug	230 (3.72%)	288 (4.65%)
Any treatment-emergent adverse event	4179 (67.59%)	4306 (69.45%)
Any treatment-emergent event excluding bleeding, acute DVT, and PE event[b]	4042 (65.37%)	4066 (65.58%)
Any treatment-emergent acute DVT or PE event[b]	266 (4.30%)	465 (7.50%)
Any treatment-emergent bleeding event[b]	466 (7.54%)	428 (6.90%)
Any serious treatment-emergent event	406 (6.57%)	528 (8.52%)
Any serious treatment-emergent event, excluding bleeding, acute DVT, and PE event[b]	311 (5.03%)	376 (6.06%)
Any serious treatment-emergent acute DVT or PE event[b]	51 (0.82%)	131 (2.11%)
Any serious treatment-emergent bleeding event[a]	65 (1.05%)	50 (0.81%)

[a] Includes events that occur on treatment and during follow-up
[b] as assessed by the investigator
Key: DVT = deep vein thrombosis; PE = pulmonary embolism
Note: Treatment-emergent events are those that occurred after the first dose and up to 2 days after the last dose of study medication.

There were 13 (0.2%) and 25 (0.4%) deaths reported in the safety populations of rivaroxaban and enoxaparin, respectively during treatment and follow-up. One subject randomized to rivaroxaban who died of a hemorrhage did receive study drug (dummy injection) but did not receive active rivaroxaban and is included in the analysis of the safety population. Another rivaroxaban subject died of an upper gastrointestinal bleed on Day 6 of the study. There were 1 and 3 deaths on rivaroxaban and enoxaparin, respectively that were adjudicated as VTE-related. There were 7 and 12 deaths adjudicated as cardiovascular deaths on rivaroxaban and enoxaparin, respectively. (Note: Each subject that died would have 2 classifications of death since there were 2 adjudication committees reviewing deaths, the VTE adjudication committee and the cardiovascular adjudication committee). In the pooled Phase 2 THR or TKR studies, a total of 2232 subjects and 555 subjects were in the safety populations of rivaroxaban and enoxaparin respectively. The mean treatment duration in these studies was approximately 8 days with a 30-day follow-up. The number of deaths observed during both treatment and follow-up was 0.3% (7/2232) for rivaroxaban and none for enoxaparin (0/555). Of the 7 deaths, 3 occurred at the 5 mg dose level with 2 being reported as due to PE by the investigator.

As shown in Table 6-1, the incidence of treatment-emergent adverse events (67.59% vs. 69.45%), treatment-emergent serious adverse events (6.57% vs. 8.52%), or adverse events leading to permanent study drug discontinuation (3.72% vs. 4.65%) was numerically similar or lower in the rivaroxaban group compared to enoxaparin. The incidence of treatment emergent bleeding adverse events (7.54% vs. 6.90%) or treatment emergent serious bleeding adverse events (1.05% vs. 0.81%) was higher in the rivaroxaban group compared to enoxaparin.

A summary of adverse events by the THR and TKR pools separately can be found in Appendix 1. The findings in the THR and TKR pools separately parallel those in RECORD 1-4 pooled.

Tables 6-2, 6-3, and 6-4 summarize the most frequently reported MedDRA preferred terms for treatment-emergent adverse events, treatment-emergent serious adverse events, and adverse events leading to permanent discontinuation of study drug.

Table 6-2 summarizes the most frequently reported treatment-emergent adverse events in the pooled RECORD studies. These events listed in this table are expected after surgery and all occurred at similar rates (< 0.5% difference) in both therapy groups except for DVT which was lower in the rivaroxaban group.

Table 6-2: Most Frequently Reported Treatment-Emergent Adverse Events MedDRA Preferred Terms (POOLED RECORD1-4: Safety Analysis Set)

Preferred Term	Rivaroxaban (N=6183) n (%)	Enoxaparin (N=6200) n (%)
Nausea	788 (12.7)	797 (12.9)
Pyrexia	719 (11.6)	712 (11.5)
Vomiting	605 (9.8)	610 (9.8)
Constipation	573 (9.3)	596 (9.6)
Deep vein thrombosis	258 (4.2)	450 (7.3)
Oedema peripheral	419 (6.8)	409 (6.6)
Anaemia postoperative	352 (5.7)	355 (5.7)
Procedural pain	322 (5.2)	345 (5.6)
Insomnia	307 (5.0)	326 (5.3)
Hypotension	313 (5.1)	315 (5.1)

Table 6-3 summarizes the most frequently reported treatment-emergent, serious adverse event terms (MedDRA preferred terms) in the pooled RECORD studies. In agreement with the adjudicated event results the frequency of investigator reported serious DVT was less in the rivaroxaban group than in the enoxaparin group. PE events were also lower for rivaroxaban. Except for DVT the frequency of these events was low (< 50 events in both groups combined). The incidence of some SAE terms (ALT increased, wound infection, femur fracture) were numerically higher on

rivaroxaban compared to enoxaparin while some other serious adverse event terms (dislocation of joint prosthesis, joint dislocation, pneumonia, hemoglobin decrease) were numerically lower on rivaroxaban likely representing chance findings.

Table 6-3: Most Frequently-Reported Serious Treatment-emergent Adverse Event Preferred Terms (Subjects Valid for Safety Analysis in pooled RECORD 1-4 Studies)

	Rivaroxaban (N=6183)	Enoxaparin (N=6200)
Preferred Term	n (%)	n (%)
ANY EVENT	**406 (6.57%)**	**528 (8.52%)**
Deep vein thrombosis	41 (0.66%)	110 (1.77%)
Dislocation joint prosthesis	14 (0.23%)	28 (0.45%)
Joint dislocation	11 (0.18%)	24 (0.39%)
Pulmonary embolism	12 (0.19%)	22 (0.35%)
Alanine aminotransferase (ALT) increased	17 (0.27%)	11 (0.18%)
Wound infection	14 (0.23%)	9 (0.15%)
Pneumonia	5 (0.08%)	15 (0.24%)
Atrial fibrillation	9 (0.15%)	11 (0.18%)
Hematoma	10 (0.16%)	10 (0.16%)
Femur fracture	13 (0.21%)	6 (0.10%)
Hemoglobin decreased	8 (0.13%)	11 (0.18%)

Table 6-4 summarizes the most frequently reported adverse event terms (MedDRA preferred terms) resulting in permanent discontinuation of study drug in the pooled RECORD studies. Overall the frequency of discontinuations was about 1% lower for rivaroxaban compared with enoxaparin with the largest differences observed for the events of DVT and PE.

Table 6-4: Most Frequently-Reported Adverse Event
Preferred Terms Resulting in Permanent Discontinuation of Study Drug
(Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)

Preferred Term	Rivaroxaban (N=6183)	Enoxaparin (N=6200)
Preferred Term	n (%)	n (%)
ANY EVENT	**230 (3.72%)**	**288 (4.65%)**
Deep vein thrombosis	20 (0.32%)	39 (0.63%)
Pulmonary embolism	11 (0.18%)	23 (0.37%)
Nausea	7 (0.11%)	13 (0.21%)
Atrial fibrillation	5 (0.08%)	12 (0.19%)
Alanine aminotransferase increased	7 (0.11%)	7 (0.11%)
Operative hemorrhage	5 (0.08%)	9 (0.15%)
Myocardial infarction	5 (0.08%)	6 (0.10%)
Vomiting	6 (0.10%)	5 (0.08%)
Peripheral edema	5 (0.08%)	4 (0.06%)
Chest pain	2 (0.03%)	6 (0.10%)
Dyspnea	1 (0.02%)	7 (0.11%)

6.2.3. Adverse Events of Special Interest

Three adverse events of interest were pre-specified and included bleeding events, cardiovascular events, and hepatic disorder events. Each of these 3 events is discussed in more detail below.

6.2.3.1. Bleeding Events

6.2.3.1.1. Methods

The same Bleeding Event Adjudication Committee (AC/BE) adjudicated all bleeding events reported during the RECORD studies in a blinded manner. The assessment of the AC/BE was the basis for the final analysis of all bleeding events. The same AC/BE members assessed all 4 studies, applying standard criteria across all 4 studies.

In all 4 RECORD studies, bleeding events were classified by the AC/BE into 2 categories: Major bleeding events or Non-major bleeding events.

The primary prespecified safety endpoint in each of the RECORD studies was the incidence of treatment-emergent major bleeding events observed no later than 2 days after the last intake of study drug, using absolute risk differences as the primary analysis and hazard ratios as supportive.

The components of major bleeding included:

- Fatal bleeding;
- Bleeding into a critical organ (i.e. retroperitoneal, intracranial, intraocular, or intraspinal bleeding);
- Bleeding that required re-operation;

- Clinically overt extrasurgical site bleeding associated with a ≥2 g/dL decrease in hemoglobin concentration; and
- Clinically overt extrasurgical site bleeding requiring transfusion of ≥2 units of whole blood or packed cells.

The last 2 components of the prespecified definition of major bleeding excluded surgical site bleeding events associated with a ≥ 2 g/dL decrease in hemoglobin concentration or that were associated with a transfusion of ≥ 2units of whole blood or packed cells. The exclusion of surgical site bleeding events meeting these hemoglobin and transfusion criteria was prespecifed in agreement with the external steering committee in order to allow a better assessment of clinically important bleeding events. Hemoglobin decreases and blood transfusions are expected and occur frequently after surgery and usually do not lead to interruption of anticoagulation. However, an analysis of major bleeding was performed that included surgical site bleeding events based upon the investigator's identification of surgical site bleeding and association with a ≥ 2 g/dL decrease in hemoglobin, along with a programmatic determination of transfusions reported by the investigator. The hemoglobin drop criteria and the blood transfusion criteria were programmatically identified. The designation of the site of bleeding as surgical site or extra-surgical site was investigator determined and not formally adjudicated.

Non-major bleeding was further sub-categorized into clinically relevant non-major bleeding and other (non-clinically relevant) non-major bleeding. Non-major clinically relevant bleeding events were defined as overt bleeding events not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life. Clinically relevant non-major bleeding events could include events such as multiple source bleeding, spontaneous hematoma >25 cm^2, excessive wound hematoma, spontaneous nose bleeding lasting for >5 minutes, gingival bleeding >5 minutes, macroscopic hematuria (spontaneous or lasting more than 24 hours, if associated with an intervention), spontaneous rectal bleeding (more than a spot on toilet paper), coughing blood (hemoptysis), hematemesis, prolonged bleeding after venipuncture >5 minutes, surgical site bleeding, intra-articular with trauma, vaginal bleeding, blood in semen, any bleeding event leading to hospitalization or prolongation of rehospitalization.

All other bleeding events that did not fulfill the criteria of major bleeding event or clinically relevant non-major bleeding event were classified as other non-major bleeding events.

6.2.3.1.2. Treatment-Emergent Bleeding Events by Study

The incidence of treatment emergent bleeding events by study, including the primary safety endpoint, major bleeding, is shown in Table 6-5 (RECORD 1-2) and Table 6-6 (RECORD 3-4).

The following bleeding endpoints are presented:

- Major bleeding;
- Major bleeding including surgical site;
- Non-major clinically relevant bleeding;
- Other non-major bleeding;
- Major or non-major, clinically relevant bleeding; and
- Any bleeding (composite of major bleeding, non-major clinically relevant bleeding, and other non-major bleeding).

Table 6-5: Treatment-Emergent Bleeding Events RECORD Program, THR, Safety Population

STUDY	RECORD 1				RECORD 2			
	RIVA	ENOX	ARD (95% CI) p value	HR (95% CI)	RIVA	ENOX	ARD (95% CI) p value	HR (95% CI)
Endpoint	10mg once daily (N = 2209) n (%)	40mg once daily (N = 2224) n (%)			10 mg once daily (N = 1228) n (%)	40mg once daily (N = 1229) n (%)		
Major	6 (0.27%)	2 (0.09%)	0.18% (-0.07, 0.44) p=0.155	3.01 (0.61,14.92)	1 (0.08%)	1 (0.08%)	0.00% (-0.23, 0.22) P=0.980	N/A
Major including surgical site[a]	40 (1.81%)	33 (1.48%)	0.33%	1.22 (0.77,1.93)	23 (1.87%)	19 (1.55%)	0.33%	1.21 (0.66, 2.22)
Non-major clinically relevant	65 (2.94%)	54 (2.43%)	0.51%	1.20 (0.84, 1.73)	40 (3.26%)	33 (2.69%)	0.57%	1.21 (0.76, 1.91)
Other non-major	71 (3.21%)	77 (3.46%)	-0.25%	0.92 (0.67, 1.28)	43 (3.50%)	36 (2.93%)	0.57%	1.19 (0.76, 1.85)
Major or Non-major clinically relevant	70 (3.17%)	56 (2.52%)	0.63% (-0.35%, 1.61%)	1.25 (0.88, 1.78)	41 (3.34%)	34 (2.77%)	0.59 (-0.77%, 1.95%)	1.20 (0.76, 1.89)
Any	133 (6.02%)	131 (5.89%)	0.06% (-1.32%, 1.43%)	1.02 (0.80, 1.29)	81 (6.60%)	68 (5.53%)	1.10% (-0.78%,2.98%)	1.19 (0.86, 1.64)

Treatment emergent major bleeding was the primary prespecified safety endpoint in each of the RECORD studies. Subjects can contribute to more than 1 bleeding event category.

[a]In this alternate major bleeding endpoint definition, the subset of surgical site bleeding events associated with a Hgb drop of 2 or more units or requiring 2 or more units of blood are included.

Riva = rivaroxaban, Enox = enoxaparin, ARD = absolute risk difference, HR = hazard ratio

Table 6-6: Treatment-Emergent Bleeding Evants, RECORD Program, TKR, Safety Population

STUDY	RECORD 3				RECORD 4			
	RIVA	ENOX	ARD (95% CI) p value	HR (95% CI)	RIVA	ENOX	ARD (95% CI) p value	HR (95% CI)
Endpoint	10mg once daily (N = 1220) n (%)	40mg once daily (N = 1239) n (%)			10 mg once daily (N = 1526) n (%)	30 mg twice daily (N = 1508) n (%)		
Major	7 (0.57%)	6 (0.48%)	0.08% (-0.49, 0.66) P=0.774	1.17 (0.39, 3.49)	10 (0.66%)	4 (0.27%)	0.39% (-0.09, 0.88) p=0.110	2.47 (0.77, 7.87)
Major including surgical site [a]	21 (1.72%)	17 (1.37%)	0.35%	1.25 (0.66, 2.37)	27 (1.77%)	16 (1.06%)	0.71%	1.67 (0.90, 3.10)
Non-major clinically relevant	33 (2.70%)	28 (2.26%)	0.45%	1.20 (0.72, 1.98)	39 (2.56%)	30 (1.99%)	0.57%	1.29 (0.80, 2.07)
Other non-major	22 (1.80%)	31 (2.50%)	-0.70%	0.71 (0.41, 1.23)	124 (8.13%)	112 (7.43%)	0.70%	1.10 (0.85, 1.42)
Major or Non-major clinically relevant bleeding	40 (3.28%)	34 (2.74%)	0.53% (-0.81%,1.87%)	1.19 (0.76, 1.88)	46 (3.01%)	34 (2.25%)	0.78% (-0.36%, 1.92%)	1.34 (0.86, 2.09)
Any Bleeding	60 (4.92%)	60 (4.84%)	0.07% (-1.62%, 1.76%)	1.01 (0.71, 1.45)	160 (10.48%)	142 (9.42%)	1.06% (-1.07%, 3.18%)	1.12 (0.90, 1.41)

Treatment emergent major bleeding was the primary prespecified safety endpoint in each of the RECORD studies. Subjects can contribute to more than 1 bleeding event category

[a]In this alternate major bleeding endpoint definition, the subset of surgical site bleeding events associated with a Hgb drop of 2 or more units or requiring 2 or more units of blood are included.

Riva = rivaroxaban, Enox = enoxaparin, ARD = absolute risk difference, HR = hazard ratio

6.2.3.1.3. Pooled Bleeding Event Analysis

Table 6-7 summarizes the incidence of treatment-emergent bleeding event endpoints from the 4 RECORD studies pooled using hazard ratios as primary and absolute risk difference analyses as supportive. Table 6-8 summarizes the data in the THR and TKR pools separately. These tables show data from the total duration pool and include all events that occur while taking double-blind study medication (including events occurring during the placebo period of RECORD 2; refer to Appendix 1 for a description of this pool). The number of bleeding events which occurred in the follow-up period (after discontinuation of study drug) was low and similar for rivaroxaban compared with enoxaparin. Additional analyses based on bleeding events that occur during the treatment and follow-up periods combined, events occurring through Day 12 +/- 2, and the bleeding events in the active control pool (includes on treatment events except those that occur during the placebo period of RECORD 2 (see Appendix 1 for definition). The findings based on these additional analyses (ie. Day 12 +/- 2 pool and Active control pool) are consistent with those from the total duration pool.

In the pooled RECORD analysis, results are presented for the same bleeding endpoints presented earlier in the individual RECORD studies. Pooling all 4 RECORD studies together, each of the bleeding endpoints of any bleeding, major or non-major, clinically relevant bleeding, major bleeding, major including surgical site bleeding were increased for rivaboxaban relative to enoxaparin with absolute risk differences ranging from 0.18% to 0.64%. For the composite endpoint of major or non-major clinically relevant bleeding, a p= 0.04 was observed. The component endpoint of major bleeding was increased by 0.2% (95% CI: -0.01%, 0.37%) absolute risk difference. The results in the THR and TKR studies separately (Table 6-8) are generally similar to those of the pooled RECORD 1-4 analysis.

Table 6-7: Incidence of Treatment-Emergent Bleeding Events
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety,Pooled RECORD 1-4 studies, total duration pool)

Endpoint	Rivaroxaban (N = 6183) n (%)	Enoxaparin (N = 6200) n (%)	Absolute Risk difference[a] (95% CI)	Hazard Ratio[b] (95% CI)	Hazard Ratio P Value
Major	24 (0.39%)	13 (0.21%)	0.18% (-0.01%, 0.37%)	1.84 (0.94, 3.62)	0.076
Major including Surgical site[c]	111 (1.80%)	85 (1.37%)	0.42% (-0.01%, 0.86%)	1.31 (0.99, 1.73)	0.063
Non-major, clinically relevant	177 (2.86%)	145 (2.34%)	0.52% (-0.04%, 1.09%)	1.22 (0.98, 1.52)	0.076
Other, non-major	260 (4.21%)	256 (4.13%)	0.06% (-0.64%, 0.76%)	1.01 (0.85, 1.21)	0.872
Major or non-major clinically relevant (composite)	197 (3.19%)	158 (2.55%)	0.64% (0.05%, 1.23%)	1.25 (1.01, 1.54)	0.039
Any Bleeding (composite)	434 (7.02%)	401 (6.47%)	0.53% (-0.35%, 1.42%)	1.08 (0.94, 1.24)	0.255

[a] Mantel-Haenszel estimate with study as stratum [a]

[b] This is a Cox-regression analysis with study treated as a covariate.

[c] In this alternate major bleeding endpoint definition, the subset of surgical site bleeding events associated with a Hgb drop of 2 or more units or requiring 2 or more units of blood are included.

Key: CI = confidence interval[a] Subjects can contribute to more than 1 bleeding event category.

Table 6-8: Incidence of Treatment-Emergent Bleeding Events
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety in pooled THR (R1-R2) and TKR (R3-R4) Studies, total duration pool)

THR (R1-R2)	Rivaroxaban (N = 3437) n (%)	Enoxaparin (N = 3453) n (%)	Absolute Risk difference[a] (95% CI)	Hazard Ratio[b] (95% CI)	Hazard Ratio P Value
Major	7 (0.20%)	3 (0.09%)	0.12% (-0.06%, 0.30%)	2.34 (0.60, 9.04)	0.219
Major including Surgical site[c]	63 (1.83%)	52 (1.51%)	0.33% (-0.28%, 0.93%)	1.21 (0.84, 1.75)	0.302
Non-major, clinically relevant	105 (3.05%)	87 (2.52%)	0.54% (-0.24%, 1.31%)	1.21 (0.91, 1.60)	0.198
Other, non-major	114 (3.32%)	113 (3.27%)	0.04% (-0.80%, 0.89%)	1.01 (0.78, 1.31)	0.942
Major or non-major clinically relevant (composite)	111 (3.23%)	90 (2.61%)	0.62% (-0.17%, 1.42%)	1.23 (0.93, 1.63)	0.141
Any Bleeding (composite)	214 (6.23%)	199 (5.76%)	0.46% (-0.66%, 1.58%)	1.08 (0.89, 1.30)	0.459

TKR (R3-R4)	Rivaroxaban (N = 2746) n (%)	Enoxaparin (N = 2747) n (%)	Absolute Risk difference (95% CI)	Hazard Ratio[a] (95% CI)	Hazard Ratio P Value
Major	17 (0.62%)	10 (0.36%)	0.26% (-0.11%, 0.63%)	1.70 (0.78, 3.70)	0.185
Major including Surgical site[c]	48 (1.75%)	33 (1.20%)	0.55% (-0.09%, 1.18%)	1.46 (0.94, 2.27)	0.096
Non-major, clinically relevant	72 (2.62%)	58 (2.11%)	0.51% (-0.29%, 1.32%)	1.24 (0.88, 1.76)	0.217
Other, non-major	146 (5.32%)	143 (5.21%)	0.07% (-1.10%, 1.24%)	1.02 (0.81, 1.28)	0.875
Major or non-major clinically relevant (composite)	86 (3.13%)	68 (2.48%)	0.66% (-0.21%, 1.53%)	1.27 (0.92, 1.74)	0.145
Any Bleeding (composite)	220 (8.01%)	202 (7.35%)	0.62% (-0.78%, 2.03%)	1.09 (0.90, 1.32)	0.380

[a] Mantel-Haenszel estimate with study as stratum
[b] This is a Cox-regression analysis with study treated as a covariate.
[c] In this alternate major bleeding endpoint definition, the subset of surgical site bleeding events associated with a Hgb drop of 2 or more units or requiring 2 or more units of blood are included.
Key: CI = confidence interval. Subjects can contribute to more than 1 bleeding event category.

The types of major bleeding events in the pooled RECORD studies are shown in Table 6-9. Most of the bleeding events in both groups were those that either required re-operation or were clinically-overt extrasurgical site bleeding events that were associated with a decrease in hemoglobin (≥ 2 g/dL) or required a blood transfusion (≥ 2 units). There were 8 subjects on rivaroxaban and 1 subject on enoxaparin who experienced a clinically-overt extrasurgical site bleeding associated with a decrease of ≥ 2 g/dL in hemoglobin. These same subjects on rivaroxaban and enoxaparin also required blood transfusions (at least 2 units of blood). All of these events were gastrointestinal tract bleeding events.

There were 2 fatal bleeding events reported in the rivaroxaban group. One of the fatal bleeding events occurred in a RECORD 1 subject who was randomized to study drug but experienced a fatal bleed prior to receiving active rivaroxaban. The subject was a 74-year-old female that experienced surgical site and urogential bleeding that began intraoperatively and continued postoperatively. The subject received 9 units of blood within 7.5 hours on the day of surgery. Disseminated intravascular coagulation syndrome was suspected in this subject and she died from hemorrhage and cardiovascular shock. Active rivaroxaban was never administered in this subject. The second fatal bleed occurred in RECORD 4. A 53-year-old white man who developed a massive upper gastrointestinal bleeding event that led to death on Day 6 of rivaroxaban treatment. Other concomitant medications taken with rivaroxaban before the time of the bleeding event included Goody's powder (containing aspirin), naproxen, and oxaprozin (another NSAID). The subject was on these medications for two weeks prior to surgery. An autopsy revealed multiple benign gastric ulcers. A listing of the major bleeding events shown in Table 6-9 below is located in Appendix 1.

Table 6-9: Components of Treatment-emergent Major Bleeding Event
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety, pooled RECORD 1-4 studies, total duration pool)

Endpoint	Rivaroxaban (N = 6183) n (%)	Enoxaparin (N = 6200) n (%)
Any major bleeding event	24 (0.39%)	13(0.21%)
Fatal bleeding event	2 (0.03%) [a]	0(0%)
Critical organ bleeding event	3(0.05%)	5(0.08%)
Clinically overt extrasurgical site bleeding event (associated with decrease in hemoglobin of 2 g/dL or more)	8 (0.13%)[b]	1 (0.02%) [c]
Clinically overt extrasurgical site bleeding event (requiring blood transfusion)	8 (0.13%)[b]	1 (0.02%) [c]
Bleeding event requiring re-operation	12(0.19%)	7(0.11%)

[a] One of these 2 deaths occurred in a subject who received dummy injection but not active rivaroxaban.
[b] The 8 rivaroxaban subjects in these 2 categories are the same subjects.
[c] The 1 enoxaparin subject in these 2 categories is the same subject..

The types of clinically relevant, non-major bleeding events are shown in Table 6-10. The most frequently reported non-major bleeding events in the 2 treatment groups combined were excessive wound hematomas, surgical site bleedings, macroscopic hematuria, rectal bleeding, and hematemesis. Most of the excess in non-major clinically relevant bleeding events on rivaroxaban relative to enoxaparin appeared to be due to macroscopic hematuria, rectal bleeding, nose bleeding, and vaginal bleeding.

Table 6-10: Components of Treatment-Emergent Non-Major Clinically Relevant Bleeding Events (as Assessed by Central Adjudication Committee) (Subjects Valid for Safety in pooled RECORD 1-4 studies)

	Rivaroxaban (N = 6183)	Enoxaparin (N = 6200)
Endpoint	n (%)	n (%)
Any event	177(2.86%)	145 (2.34%)
Excessive wound hematoma	53 (0.86%)	58(0.94%)
Surgical site bleeding	47(0.76%)	49(0.79%)
Macroscopic hematuriaa	28(0.45%)	8(0.13%)
Rectal bleeding	20(0.32%)	6(0.10%)
Hematemesis	11(0.18%)	14(0.23%)
Nose bleeding (>5 minutes)	8(0.13%)	4(0.06%)
Vaginal bleeding	8(0.13%)	2(0.03%)
Gingival bleeding (>5 minutes)	2(0.03%)	3(0.05%)
Intra-articular with trauma	2(0.03%)	3(0.05%)
Unexpected hematoma (>25 cm2)	2(0.03%)	2(0.03%)
Coughing blood	1(0.02%)	2(0.03%)
Rehospitalization or prolongation of hospitalization	1(0.02%)	1(0.02%)
Blood in semen	1(0.02%)	0(0.00%)
Multiple source bleeding	1(0.02%)	0(0.00%)

[a] Either spontaneous or lasting more than 24 hours if associated with an intervention.

Note: A subject can appear in more than 1 bleeding category but will appear in the "Any" event row only once

Note: Results based on total duration pool.

6.2.3.1.4. Wound complications

Wound compications were identified through a search of the adverse event database using any MedDRA preferred terms possibly related to wound complications. As shown in Table 6-11 below, the incidence of wound complications was 5.37% and 4.52% on rivaroxaban and enoxaparin respectively. The incidence of infectious surgical wound complications was similar on rivaroxaban and enoxaparin. The incidence of non-infectious surgical wound complications was higher on rivaroxaban compared to enoxaparin. The MedDRA preferred term "wound secretion" was the most frequently reported non-infectious wound complication term reported by investigators and occurred in 146 (2.36%) and 106 (1.71%) of subjects on rivaroxaban and enoxaparin respectively, and accounted for most of the excess difference in the incidence of surgical wound complication adverse events. The majority of wound complication adverse events were rated as mild in severity by investigators. Serious treatment-emergent wound complication adverse events were observed in 46 and 47 subjects on rivaroxaban and enoxaparin respectively.

Table 6-11: Treatment-Emergent Wound Complication Adverse Events
(Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)

Preferred Term	Rivaroxaban (N=6183) n (%)	Enoxaparin (N=6200) n (%)
Any Surgical wound complication	**332 (5.37%)**	**280 (4.52%)**
Infectious surgical wound complications	78 (1.26%)	82 (1.32%)
Non-infectious surgical wound complications	269 (4.35%)	206 (3.32%)

Note: Subjects can contribute to more than 1 category

6.2.3.1.5. Timing of Bleeding Events

Figure 6-1 is a Kaplan-Meier curve of time to first treatment-emergent major bleeding event for the pooled RECORD studies. Most of the treatment-emergent major bleeding events occurred by Day 7 in both groups: 15 (63%) in rivaroxaban subjects and 11 (85%) in enoxaparin subjects. A separation in the 2 curves occurs after surgery and persists for the remainder of the study duration. Kaplan-Meier curves of treatment-emergent major bleeding for the THR pool and TKR pool separately are provided in Appendix 1.

Figure 6-2 is a Kaplan-Meier curve of time to first bleeding event for the composite endpoint of major or non-major clinically relevant bleeding events. Most events occurred by Day 7 (137 [69.5%] and 134 [84.8%] in the rivaroxaban and enoxaparin groups respectively). The biggest separation between the 2 curves occurred between Days 8 and 18, with separation maintained thereafter. Kaplan-Meier curves of treatment-emergent major or non-major clinically relevant bleeding for the THR pool and TKR pool separately are provided in Appendix 1.

Figure 6-1: Cumulative Rate (Kaplan Meier) of Treatment-Emergent Major Bleeding Events
(Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)

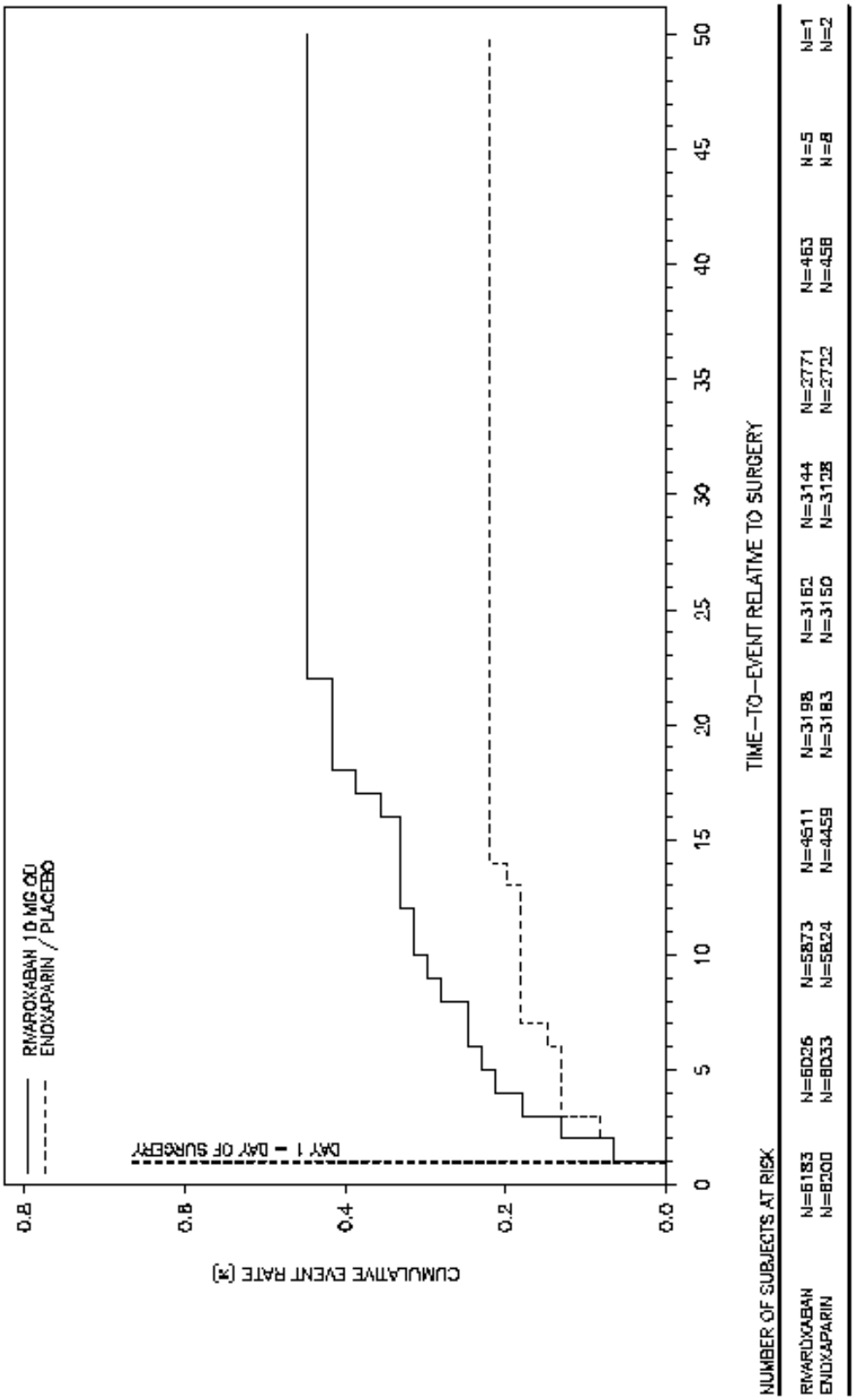
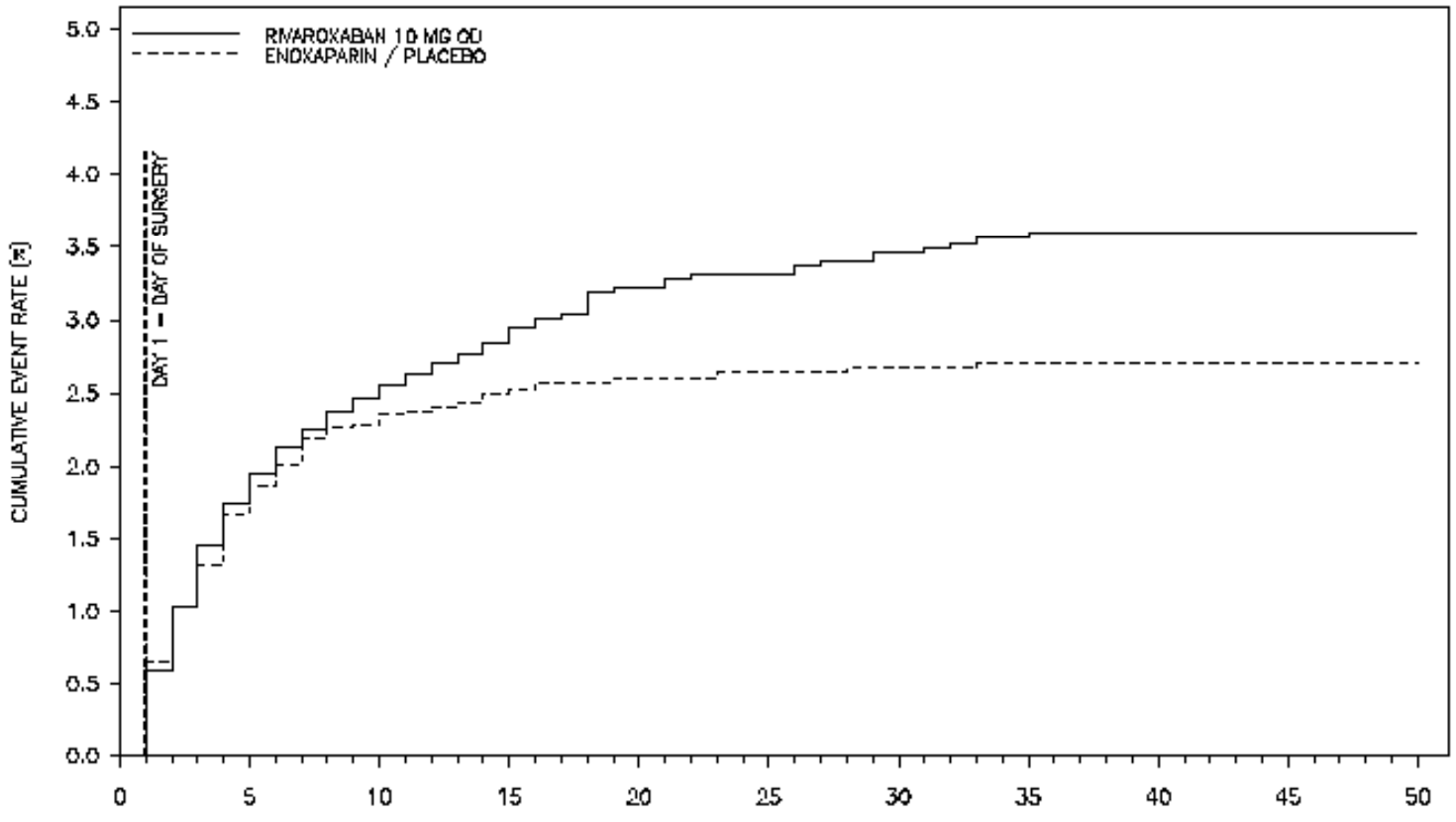


Figure 6-2: Cumulative Rate (Kaplan Meier) of Treatment-Emergent Major or Non-major Clinically Relevant Bleeding Events
(Subjects Valid for Safety Analysis in Pooled RECORD 1-4 Studies)



NUMBER OF SUBJECTS AT RISK

RIVAROXABAN	N=6183	N=5941	N=5758	N=4415	N=3124	N=3089	N=3067	N=2698	N=455	N=5	N=1
ENOXAPARIN	N=6200	N=5943	N=5720	N=4389	N=3116	N=3083	N=3061	N=2884	N=444	N=7	N=2

6.2.3.1.6. Multiple Bleeding Events

An analysis of multiple bleeding events was done in which bleeding events (regardless of site) occurring on the same day were counted as one unique event whereas events occurring on different days were counted as multiple unique events. There were no subjects in the rivaroxaban or enoxaparin groups that experienced two (or more) treatment emergent major bleeding events. This finding is expected because, in almost half of the subjects with major bleeding events, study drug was permanently discontinued. Six subjects on rivaroxaban and seven subjects on enoxaparin experienced two (or more) treatment emergent major or non-major bleeding events. (In this situation, a subject would experience a non-major, clinically relevant bleeding event initially, remain on study drug, then subsequently develop a non-major clinically relevant bleeding event or a major bleeding event).

6.2.3.1.7. Bleeding risk in Subgroups

An analysis of the risk of bleeding events on rivaroxaban relative to enoxaparin was done in various subgroups of the overall RECORD population as specified in the integrated statistical analysis plan. The subgroups evaluated included sex, age, body mass index, type of anesthesia, time of first tablet intake relative to surgery, duration of surgery, calculated creatinine clearance, body weight, race, and fragile subject (subjects with an age > 75 years and/or calculated creatinine clearance < 50 mL/min and/or weight </= 50 kg). There were too few major bleeding events in the pooled RECORD analysis on which to perform a meaningful subgroup analysis. Consequently, Figure 6-3 shows a subgroup analysis of the composite endpoint of major or non-major clinically relevant bleeding events, while Figure 6-4 shows a subgroup analysis of the composite endpoint of any bleeding events (using pooled RECORD 1-4 data). In the figures below are displayed the point estimate of the hazard ratio of rivaroxaban relative to enoxaparin along with the 95% confidence intervals (the hazard ratio and 95% CI were not provided when the number of events in the combined treatment group was less than 5). Subgroup analyses for the THR and TKR studies separately are shown in Appendix 1.

For the composite endpoint of major or non-major clinically relevant bleeding, in the overall RECORD 1-4 population, the hazard ratio was 1.25 (95% CI: 1.01 to 1.54). The effect in most subgroups is consistent with the effect observed in the overall population showing a hazard ratio point estimates > 1.0. In certain subgroups such as subjects over the age of 75 years, creatinine clearance 30 to 50 mL/min, Blacks, or fragile subjects the hazard ratio point estimate of major or non-major clinically relevant bleeding events was <1.0. None of the subgroups evaluated achieved an interaction p-value less than 0.05, supporting that the effects of rivaroxaban in various subgroups were consistent with the effect observed in the overall population. For the composite endpoint of any bleeding event, the findings were similar to that for the composite endpoint major or non-major clinically relevant bleeding except that the 95% confidence intervals within each subgroup were narrower (due to the larger number of events) and the hazard ratio was closer to 1 compared to major or non-major clinically relevant bleeding events.

Figure 6-3: Major or Non-Major Clinically Relevant Treatment-Emergent Bleeding Events and Corresponding Hazard Ratios (95% CI) by Subgroups
(Subjects Valid for Safety Analysis in Pooled RECORD 1-4 Studies)

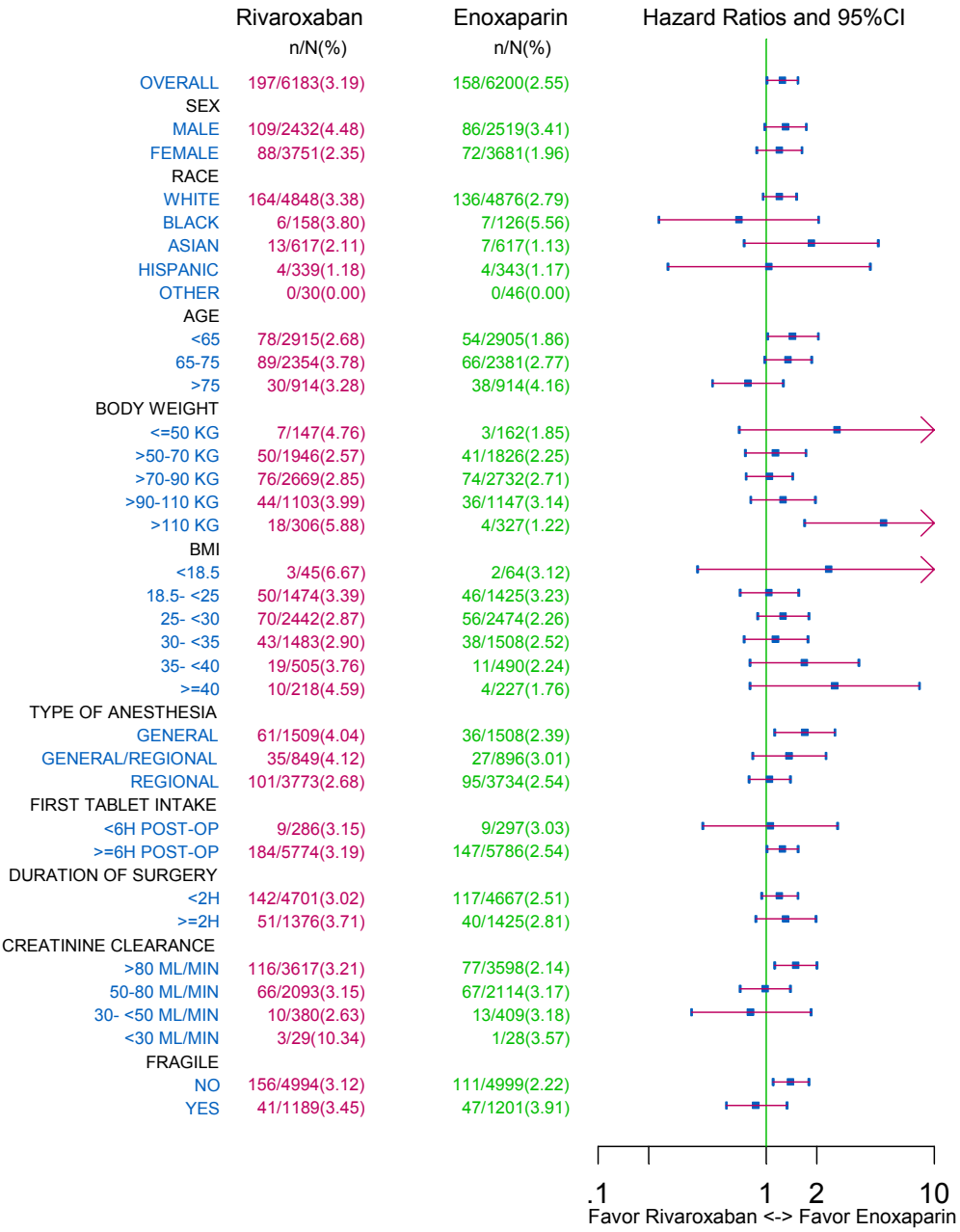
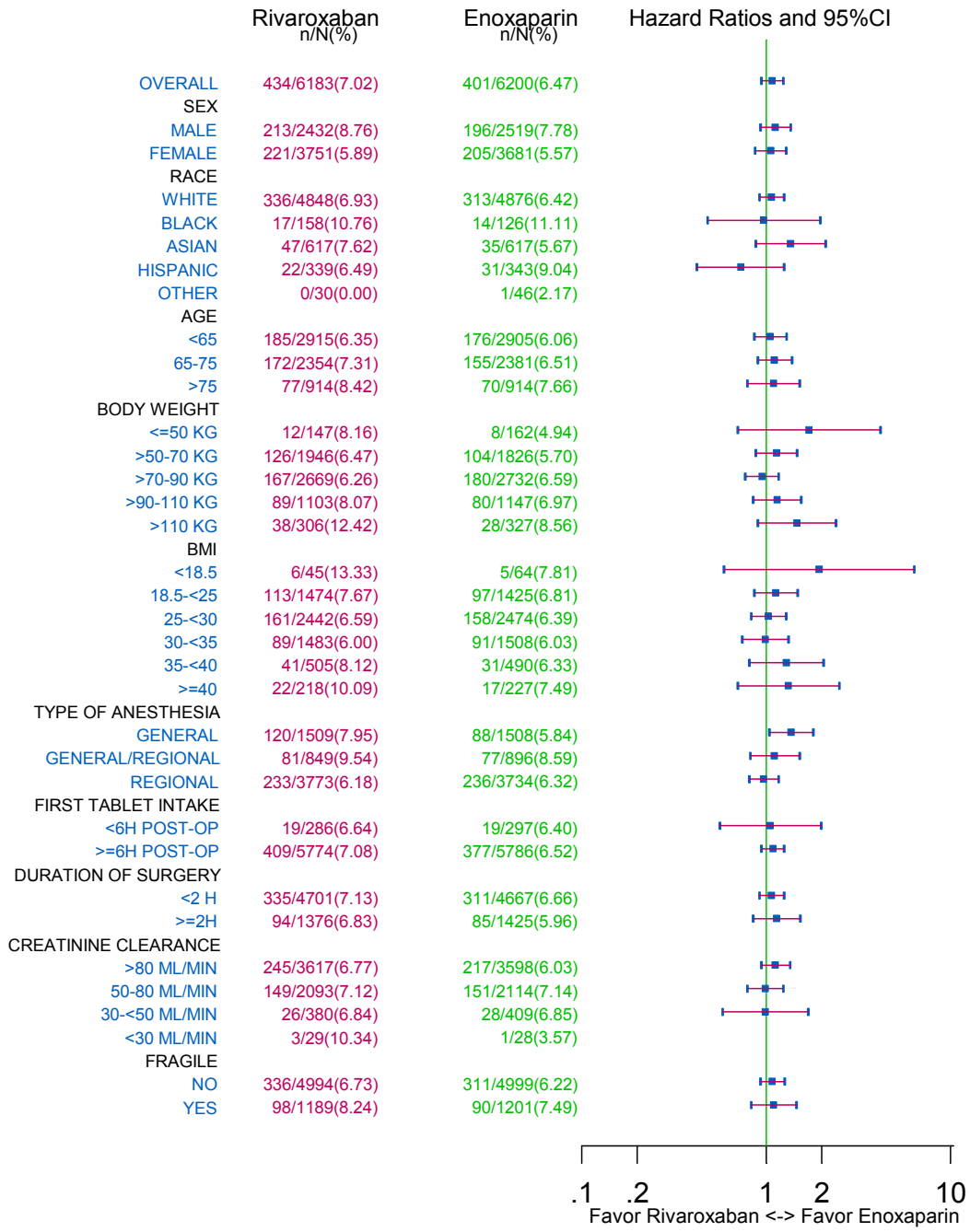


Figure 6-4: Any Treatment-Emergent Bleeding Events and Corresponding Hazard Ratios (95% CI) by Subgroups
(Subjects Valid for Safety Analysis in Pooled RECORD 1-4 Studies)



6.2.3.1.8. Drug Interactions

Approximately 70% of subjects in the RECORD studies received a nonsteroidal anti-inflammatory drug (NSAID) at any time after the start of study drug with NSAID

use being highest in the first 3 days after surgery and declining thereafter. The most commonly used NSAIDS included ketoprofen, diclofenac, ketorolac and ibuprofen. The bleeding rates for both enoxaparin and rivaroxaban were somewhat higher with concomitant NSAID use compared with no use but this observation is difficult to interpret since the bleeding rates are higher close to surgery when most NSAID use occurred.

Based on the pooled RECORD studies, in subjects who underwent surgery and received at least one dose of blinded study drug, the relative risk of major or non-major clinically relevant bleeding events starting after first rivaroxaban or matching placebo intake was 1.33 (1.06, 1.67). Table 6-12 below shows that the point estimate of the relative rates of bleeding (rivaroxaban relative to enoxaparin) with and without concomitant NSAID were similar (1.44 with and 1.22 without), suggesting no increased risk of bleeding for rivaroxaban relative to enoxaparin in users versus non-users of NSAIDS. With respect to any bleeding event, a total of 208 and 194 events were observed with concomitant NSAID use, resulting in a bleeding event rate of 2.67 and 2.51 events per 100 patient weeks on rivaroxaban and enoxaparin respectively. The relative rate of any bleeding was 1.08 (95% CI: 0.89, 1.30) in users and 1.08 (95% CI: 0.88, 1.34) in non-users. Therefore, in the RECORD studies, subjects taking NSAIDS concomitantly with rivaroxaban appeared to be at no greater risk of bleeding compared to the overall RECORD population. This finding is consistent with the Phase 1 data showing a modest pharmacodynamic interaction for bleeding times with the combination of rivaroxaban and naproxen compared to naproxen alone (Section 3.3.2).

Table 6-12: Major or Non-Major, Clinically Relevant Post-Tablet Bleeding Event Rates With and Without Concomitant NSAID Use (RECORD 1-4 Pooled)

NSAID Use	Period of Use		Period of No use	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Patient-weeks at risk	7981	7938	14148	14161
# of first bleeding events	92	64	81	66
Bleeding event rate (per 100 patient-weeks)	1.15	0.81	0.57	0.47
Relative Rate (Riva: Enox)[a]	1.44 (1.05, 1.98)		1.22 (0.89, 1.69)	

[a] Relative rate (rate ratio) estimate stratified by time after surgery (Day 1-3, Day 4-7, and after Day 7).

Approximately 9% of subjects in the RECORD studies received a platelet aggregation inhibitor concomitantly with study drug. The vast majority of subjects receiving platelet aggregation inhibitors (approximately 80%) received aspirin or an aspirin containing formulation. There were a total of 8 and 5 major or non-major, clinically relevant post-tablet bleeding events observed in the rivaroxaban and

enoxaparin groups respectively, among subjects receiving a platelet aggregation inhibitor concomitantly. All 13 events, on rivaroxaban and enoxaparin combined occurred in subjects taking aspirin (or aspirin containing formulation). Less than 0.5% of subjects received clopidogrel concomitantly and there were no bleeding events in subjects receiving clopidogrel concomitantly with rivaroxaban and one bleeding event for the enoxaparin group (this subject also received concomitant aspirin). Concomitant ticlopidine use was reported in very few subjects with no bleeding events under concomitant use. With respect to any bleeding event, there were a total of 20 subjects and 17 subjects that experienced any post-tablet bleeding event in the setting of concomitant platelet aggregation inhibitor use resulting in an event rate of 2.04 and 2.06 events per 100 patient-weeks on rivaroxaban and enoxaparin respectively. The relative rate of any bleeding was 1.01 (95% CI: 0.54, 1.89) in users and 1.08 (95% CI: 0.93, 1.25) in non-users of platelet aggregation inhibitors. In summary, subjects taking platelet aggregation inhibitors (primarily aspirin) concomitantly with rivaroxaban appeared to be at no greater risk of bleeding compared to the overall RECORD population. These RECORD data are consistent with Phase 1 data showing a modest pharmacodynamic interaction for bleeding times with the combination of rivaroxaban and aspirin compared to aspirin alone (Section 3.3.2).

Subjects receiving CYP3A4 and/or Pgp inhibitors were enrolled in the RECORD studies and comprised approximately 8% of the study population. Among the 8% receiving CYP3A4 and/or Pgp inhibitor concomitantly with study drug, cimetidine was the most frequently used (26%), followed by verapamil (22%), and diltiazem (20%). A total of 12 and 2 major or non-major, clinically relevant bleeding events occurred in the rivaroxaban and enoxaparin groups respectively. Of the 12 subjects with bleeding events observed in the rivaroxaban group, 3 subjects received amiodarone, 3 received verapamil, 2 received diltiazem, and 1 each received cyclosporine, clarithromycin, fluoxetine, or quinidine. Of the 2 subjects experiencing bleeding events in the enoxaparin group, the concomitant CYP3A4/Pgp inhibitors used were aprepitant, fluoxetine, and verapamil (1 subject received two of these agents). There were a total of 31 and 17 any bleeding events observed with concomitant CYP3A4/PgP inhibitor use use resulting in an event rate of 3.04 and 1.71 events per 100 patient-weeks on rivaroxaban and enoxaparin respectively. The relative rate of any bleeding was 1.76 (95% CI: 0.98, 3.15) in users and 1.04 (95% CI: 0.90, 1.21) in non-users of platelet aggregation inhibitors. In summary, an analysis based on any post-tablet bleeding events suggests that the risk of bleeding may be increased in users of CYP3A4 and/or Pgp inhibitors relative to non-users although such a conclusion should be interpreted with caution since the number of

bleeding events in the setting of CYP3A4/Pgp inhibitors is small and Phase 1 data show that the rivaroxaban exposure increase with concomitant mild to moderate CYP3A4/Pgp inhibitors is approximately 50% or less .

6.2.3.1.9. Blood Loss and Blood Transfusions

In the pooled THR studies, the intraoperative blood loss was 479.7 ± 337.2 mL and 491.7 ± 357.6 mL in the rivaroxaban and enoxaparin groups, respectively. In the TKR studies, the blood loss volume was lower compared with the THR studies, 203.7 ± 240.4 mL and 196.1 ± 205.1 mL on rivaroxaban and enoxaparin respectively. A total of 1695 (49.3%) and 1763 (51.1%) of subjects on rivaroxaban and enoxaparin respectively received any blood transfusion in the THR studies whereas a total of 1247 (45.4%) and 1172 (42.7%) rivaroxaban and enoxaparin subjects received any blood transfusion in the TKR studies.

6.2.3.2. Cardiovascular Events

As specified in the Cardiovascular Events Adjudication Committee (AC/CV) Manual of Operations, the AC/CV adjudicated cases of death (cardiovascular or non-cardiovascular) and investigator-identified cases of myocardial infarction or stroke. Originally, in RECORD 1 and 2, the AC/CV adjudicated only CV deaths identified by the sponsor medical monitor, but this procedure was later changed to include an evaluation of all deaths. After the databases for RECORD 1 and 2 were unblinded, 14 death events that had not originally been adjudicated by the AC/CV committee underwent a blinded, retrospective adjudication. The AC/CV did not readjudicate or reassess any of the originally adjudicated events.

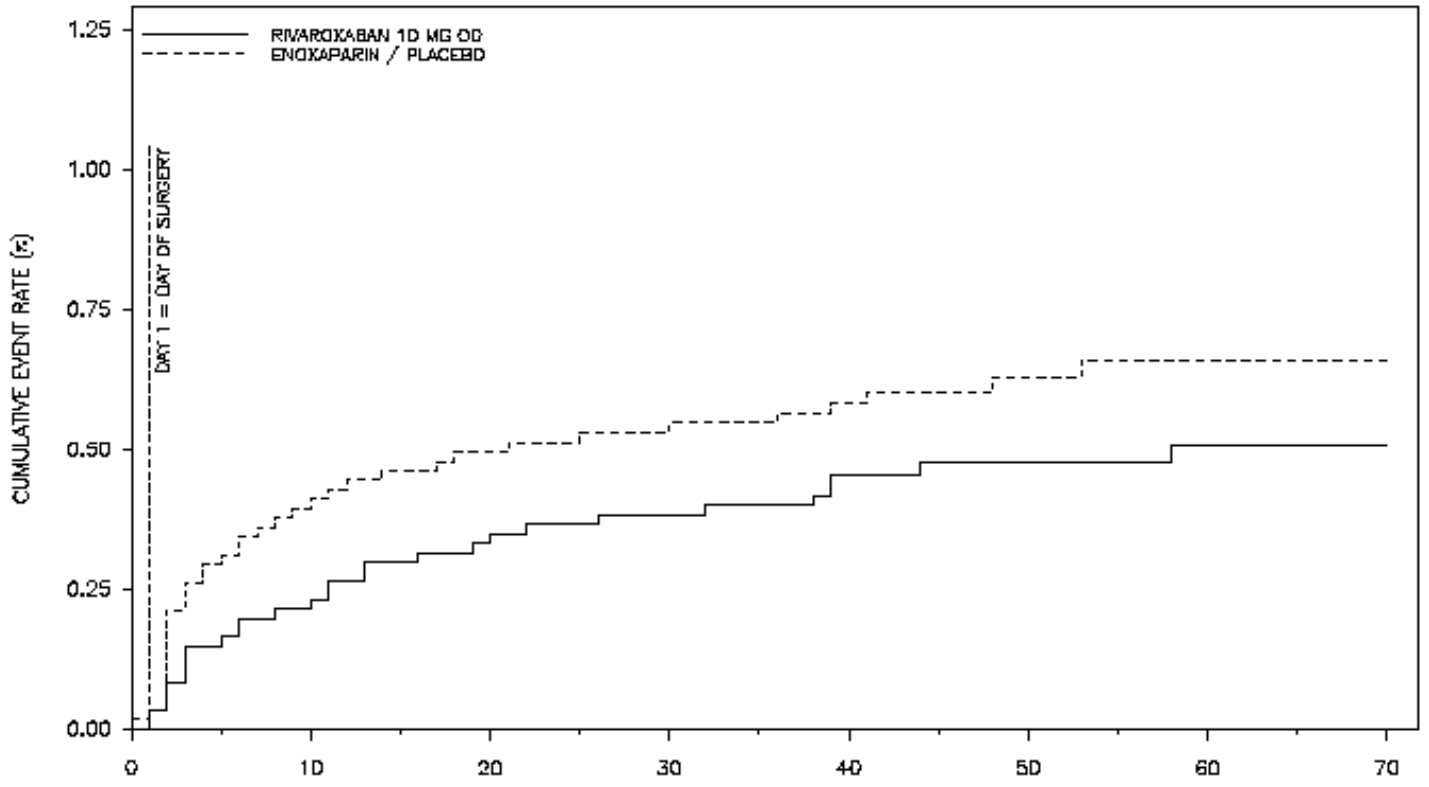
Table 6-13 presents an overall summary of centrally-adjudicated cardiovascular events (including those done retrospectively but in a blinded manner) that occurred in the safety population on treatment and follow-up for the 4 RECORD studies. The incidence of CV events was similar on rivaroxaban and enoxaparin. (Note: There was one subject in the rivaroxaban group with an adjudicated event of ischemic stroke occurring 8 days after the last dose of study drug who was not included in the clinical database because adjudicated results were not available prior to unblinding. This subject is not included in subsequent tables. Inclusion of this subject would not change the conclusions with respect to the cardiovascular events analysis). Figure 6-5 presents a Kaplan-Meier figure of the time to first adjudicated cardiovascular event.

Table 6-13: Incidence of Cardiovascular Events (Retrospective Central Adjudication)
(Subjects Valid for Safety, RECORD 1-4 studies pooled, Treatment plus follow-up)

Endpoint	Rivaroxaban (N =6183)		Enoxaparin (N =6200)	
Preferred Term	n (%)		n (%)	
Cardiovascular events (any)	30	(0.49%)	39	(0.63%)
Myocardial infarction	13	(0.21%)	18	(0.29%)
Ischemic stroke	11	(0.18%)	7	(0.11%)
Cardiovascular death	7	(0.11%)	12	(0.19%)
Unexplained death	1	(0.02%)	4	(0.06%)

Note: Subjects who experienced more than 1 type of cardiovascular event were counted for each category; however, these subjects are counted only once in the "any" cardiovascular event overall category.
One subject in the rivaroxaban group with an adjudicated event of ischemic stroke 8 days after last dose of study drug was not included in the table above because adjudicated results were not available prior to unblinding

Figure 6-5: Cumulative Rate (Kaplan Meier) of Any Adjudicated Cardiovascular Event (After Adjudication of All Deaths)
(Subjects Valid for Safety Analysis in Pooled RECORD 1-4 Studies)



NUMBER OF SUBJECTS AT RISK

RIVAROXABAN	N=6183	N=5966	N=5850	N=5826	N=5582	N=3321	N=3118	N=712
ENOXAPARIN	N=6200	N=5960	N=5825	N=5790	N=5568	N=3307	N=3116	N=771

Note: One additional event of ischemic stroke in the rivaroxaban group is not included.

Table 6-14 is a summary of cardiovascular events subdivided by whether the events occurred while subjects were on or off active treatment. Note that while Table 6-13 shows data on subjects evaluable in the safety population, Table 6-14 shows data on a large subset of the safety population, specifically those that received active study medication since subjects not taking active study medication could not theoretically experience rebound. As described earlier, the start of active rivaroxaban was delayed by approximately 1 day relative to the start of active enoxaparin in RECORD 1, 2, and 3. Events occurring prior to intake of active study medication would not be considered in the table below. Cardiovascular events on active treatment are those that occur after the first intake of active study medication and no later than 1 day after last intake of active study medication. Cardiovascular events off active treatment are those that occur later than 1 day after the last intake of active study medication. The incidence of cardiovascular events occurring off active treatment appear balanced (0.26% versus 0.23% on rivaroxaban and enoxaparin respectively). There does not appear to be an increase of rebound events on rivaroxaban relative to enoxaparin.

Table 6-14: Incidence of Cardiovascular Events (Retrospective Adjudication)
(Subjects Valid for Safety with Active Study Drug in pooled RECORD 1-4 studies)

Endpoint	Rivaroxaban (N =6097)		Enoxaparin (N =6195)	
Cardiovascular events on active treatment	13	(0.21%)	25	(0.40%)
Myocardial infarction	7	(0.11%)	14	(0.23%)
Ischemic stroke	5	(0.08%)	6	(0.10%)
Cardiovascular death	1	(0.02%)	5	(0.08%)
Unexplained death	0	(0%)	0	(0%)
Cardiovascular events off active treatment	16	(0.26%)	14	(0.23%)
Myocardial infarction	5	(0.08%)	4	(0.06%)
Ischemic stroke	5	(0.08%)	1	(0.02%)
Cardiovascular death	6	(0.10%)	6	(0.10%)
Unexplained death	1	(0.02%)	4	(0.06%)

Note: On active treatment events are events starting after intake of first active study medication and not later than 1 day after last intake of active study medication. Off active treatment events are events starting later than 1 day after last intake of active study medication. One subject in the rivaroxaban group with an adjudicated event of ischemic stroke 8 days after last dose of study drug was not included in the table above because adjudicated results were not available prior to unblinding.

An analysis of CV events occurring on and off active treatment by THR and TKR studies separately is located in Appendix 1.

Data from the phase 2, placebo-controlled, ATLAS ACS TIMI 46 study supports the findings from the RECORD studies demonstrating an absence of a cardiovascular rebound effect in association with rivaroxaban use. In the ATLAS study with a 2:1 rivaroxaban: placebo randomization ratio, 20 (0.9%) and 9 (0.8%) on rivaroxaban and placebo respectively experienced death, MI or stroke within 10 days post study drug discontinuation. The number of subjects experiencing death, MI, or stroke events at

any time after study drug discontinuation (including more than 10 days after discontinuation), was 44 (2.0%) and 25 (2.3%) of subjects on rivaroxaban and placebo respectively. The similar incidence of CV events post study drug discontinuation on rivaroxaban and placebo suggest that the potential for rebound CV events with rivaroxaban is low.

6.2.3.3. Hepatic Disorder Events

Perioperative elevations in plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have been reported to occur following orthopedic surgery and also non-orthopedic surgical settings (i.e. abdominal surgery, neurosurgery, cardiac surgery, etc). The causes of such elevations are postulated to include perioperative anesthetic agents (i.e. halothane, isofluarane, sevoflurane), blood transfusion (i.e. autologous, allogeneic, or postoperative shed blood), use of plasma expanders, anesthesia associated hypoperfusion to the liver, anticoagulant (i.e. heparin use) and opiate use. Elevations in AST and ALT most frequently peak during the first few days postoperatively but can be maintained for as long as 1 to 2 weeks post surgery in some subjects. Increases in total bilirubin have also been reported to occur perioperatively, most classically in the cardiac surgical setting. Some reports correlate this finding with the number of blood and plasma transfusions. Elevations in total bilirubin (TB) may persist for 1 to 2 weeks postoperatively. The presence of multiple confounding factors with respect to AST and ALT, in the perioperative, orthopedic surgery setting makes assessment of the potential for drug-induced liver injury challenging and necessitates the use of a well-characterized comparator agent.

6.2.3.3.1. Liver-related Laboratory Abnormalities and Rivaroxaban Dose

Phase 2 VTE prophylaxis studies involving rivaroxaban evaluated a 12-fold dose range from 2.5 mg bid to 30 mg bid. The incidence of ALT or AST abnormalities > 3x ULN did not increase as a function of dose and was lower on rivaroxaban compared to enoxaparin (Table 6-15).

Table 6-15: Incidence of Selected Laboratory Abnormalities After Surgery Start With Presurgery Baseline by Dose of Study Drug in Phase 2 THR and TKR Prophylaxis Studies in Venous Thromboembolism
(Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527– Pooled analysis)

Laboratory Abnormality >3x ULN	Rivaroxaban Total Daily Dose[a]						Total RIVA	ENOX
	5 mg	10 mg	20 mg	30 mg	40 mg	60 mg		
ALT	19/425 (4.5%)	24/439 (5.5%)	16/434 (3.7%)	13/221 (5.9%)	24/432 (5.6%)	11/211 (5.2%)	107/2162 (4.9%)	38/533 (7.1%)
AST	18/425 (4.2%)	24/440 (5.5%)	24/431 (5.6%)	10/218 (4.6%)	21/427 (4.9%)	20/210 (9.5%)	117/2151 (5.4%)	34/ 532 (6.4%)
Total bilirubin	0/350 (0.0%)	1/362 (0.3%)	1/365 (0.3%)	1/131 (0.8%)	2/354 (0.6%)	1/138 (0.7%)	6/1700 (0.4%)	0/379 (0.0%)

[a] Subcutaneous enoxaparin (40 mg od) was administered in Studies 10942, 10944,and 11527; subcutaneous enoxaparin (30 mg bid) was administered in Study 10945.

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

6.2.3.3.2. Schedule of Liver Laboratory assessments in RECORD studies

A schedule of central laboratory assessments specific to the liver is provided in Table 6-16. The liver-related laboratory parameters ALT, AST, TB, alkaline phosphatase (ALK PHOS), and gamma-glutamyltransferase (GGT) were assessed on Days 0, 1, 6, 13, 36, and 65 (follow-up) for RECORD 1 and 2 and on Days 0, 1, 6, 13, and 42 (follow-up) for RECORD 3 and 4. In all 4 studies, Day 1 laboratory assessments were performed after surgery but prior to the administration of the first oral dose of study drug (rivaroxaban or matching dummy tablet).

Table 6-16: Schedule of Liver-Related Laboratory Assessments in Phase 3 Studies (RECORD 1, 2, 3, and 4)

						Follow-up	
Study	Screen Day 0	Surgery Day 1	Day 6 ± 2	Day 13 ± 2	Day 36 ± 4	Day 42 ± 5	Day 65 ± 5
RECORD 1	X	X[a]	X[b]	X	X		X
RECORD 2	X	X[a]	X[b]	X	X		X
RECORD 3	X	X[a]	X	X		X	
RECORD 4	X	X[a]	X	X		X	

[a] After surgery but prior to first administration of oral study drug (active or dummy placebo).
[b] Day 6 ± 2 or on day before discharge (Day 6).
Note: Day 0 assessments could be done up to 14 days prior to the day of surgery (Day 1).

While the testing schedule in Table 6-16 above was a protocol mandated schedule, investigators could also perform additional, non-protocol mandated liver laboratory testing at their discretion via a local laboratory.

6.2.3.3.3. Summary of Liver-related Laboratory abnormalities (Pooled RECORD Study Data)

A pooled analysis of postbaseline liver-related laboratory abnormalities is presented in Table 6-17. A similar analysis in the THR studies and TKR studies separately is located in Appendix 1. Subjects with abnormalities at baseline are included in these tables. A total of 10 (0.16%) rivaroxaban subjects and 10 (0.16%) enoxaparin subjects experienced an ALT >3x ULN along with a total bilirubin >2x ULN regardless of whether the lab tests were from concurrent or non-concurrent samples (or from central or local laboratory tests). Concurrent refers to laboratory analyses drawn on the same day. With respect to concurrent ALT and total bilirubin elevations, 9 subjects (0.15%) and 8 subjects (0.13%) administered rivaroxaban and enoxaparin, respectively, had ALT levels >3x ULN concurrent with a total bilirubin level >2x ULN after the Day 0 baseline. One enoxaparin subject had concurrent ALT>3x ULN and TB>2x ULN elevations based on local labs only. Two

rivaroxaban subjects experienced these elevations on the day of surgery (Day 1) before administration of active rivaroxaban.

Table 6-17: Pooled Incidence Rates of Liver-Related Postbaseline Laboratory Abnormalities – After Day 0 Baseline (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

Laboratory Variable Limit	Rivaroxaban		Enoxaparin	
ALT >3x ULN concurrent or non-concurrent with total bilirubin >2x ULN (central or local labs)				
	10/6131	(0.16%)	10/6131	(0.16%)
ALT >3x ULN concurrent with total bilirubin >2x ULN (central or local labs)				
	9/6131	(0.15%)	8/6131	(0.13%)
ALT >3x ULN concurrent with total bilirubin >2x ULN (central labs only)				
	9/6131	(0.15%)	7/6131	(0.11%)
ALT >3x ULN concurrent with total bilirubin >2x ULN and conjugated bilirubin ≥ 0.5 total bilirubin				
	4/6131	(0.07%)	5/6130	(0.08%)
ALT (central labs only)				
>3x ULN	152/6131	(2.48%)	227/6131	(3.70%)
>5x ULN	56/6131	(0.91%)	78/6131	(1.27%)
>8x ULN	18/6131	(0.29%)	20/6131	(0.33%)
>10x ULN	10/6131	(0.16%)	9/6131	(0.15%)
>20x ULN	2/6131	(0.03%)	1/6131	(0.02%)

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal
Note: All measurements after the start of double-blind study medication are included regardless of onset relative to the last dose.

There were 14 subjects (7 subjects receiving rivaroxaban and 7 subjects receiving enoxaparin) that had ALT>3x ULN concurrent with TB >2x ULN after Day 1 (based on central labs). Many of these cases were temporally associated with surgery occurring within the first week after study drug initiation and could be associated with perioperative anesthetic agents, anesthesia associated hypotension, blood transfusions, use of plasma expanders, or use analgesics (ie. acetaminophen, NSAIDs, or opiates). Three of these 14 subjects had elevations that occurred after Day 13 (2 cases in the rivaroxaban arm and 1 case in enoxaparin). One of these subjects was a RECORD 4 subject that was administered rivaroxaban and experienced liver enzyme elevations 6 weeks after the last dose of study drug. Additional follow-up information showed normalization of ALT levels on Day 72 after the study results were unblinded. A second subject administered rivaroxaban experienced a treatment-emergent acute hepatitis C infection on Day 41. One subject administered enoxaparin had concurrent ALT and total bilirubin elevations on Day 14 that resolved after study drug discontinuation.

As shown in Table 6-17 above, there were fewer subjects with increased laboratory values in the rivaroxaban treatment group compared with the enoxaparin treatment group for thresholds >3x or >5x ULN. Aminotransferase elevations in the setting of heparin use, most classically with unfractionated heparin but also with low molecular

weight heparin use, is a well described phenomenon in the medical literature. At higher thresholds (>8, >10, > 20x ULN), the incidence was similar in the two treatment groups. There were 10 rivaroxaban subjects and 9 enoxaparin subjects with elevations in ALT >10x ULN. In nearly all cases, the liver enzyme elevations returned or were returning to <1x ULN while study drug was continued or after study drug discontinuation. One exception was a subject in RECORD 4 that received rivaroxaban for 10 days and subsequently had an ALT level > 10x ULN approximately 6 weeks (45 days) after the last dose of study drug (Note: This RECORD 4 subject is the same one that was discussed above). As discussed above, additional follow-up received on this subject after study results were unblinded showed normalization of ALT levels. One subject in RECORD 2 that received enoxaparin for 9 days had an ALT > 10x ULN on Day 10. There was incomplete laboratory follow-up on this case.

Forty rivaroxaban subjects [0.7%] and 43 enoxaparin subjects [0.7%]) showed an increase in ALT > 3x ULN on Day 1 after surgery but before administration of active rivaroxaban (likely due to the effects of surgery). The majority of subjects who had increased ALT levels > 3x ULN experienced them in the period between Day 0 until Day 13(108 rivaroxaban subjects [1.8%] versus 169 enoxaparin subjects [2.8%]). The prevalence of ALT levels >3x ULN after Day 13 was low, occurring in 19 (0.3%) and 30 (0.5%) subjects receiving rivaroxaban and enoxaparin, respectively. Appendix 1 shows the cumulative risk of the first occurrence of ALT >3x in RECORD 1-2 and RECORD 3-4.

6.2.3.3.4. Liver-related Adverse Events

For the purpose of the adverse event summary tables in this section, a postbaseline event is defined as any event that occurred after the first dose of any study drug, regardless of the time of event onset relative to the last dose of study drug. Hepatic disorder adverse events were identified from the clinical database using the Maintenance and Support Services Organization (MSSO) Standardized MedDRA Query (SMQ) for hepatic disorders. A total of 290 (4.7%) and 400 (6.5%) of subjects reported a post baseline hepatic disorder adverse event on rivaroxaban and enoxaparin respectively. As shown in Table 6-18 below, the majority of these were liver-related investigations, signs, and symptoms reported as adverse events. The incidence was lower on rivaroxaban compared to enoxaparin and consistent with the lower incidence of laboratory ALT abnormalities >3x ULN on rivaroxaban relative to enoxaparin. The incidence of non-liver related investigations, signs, and symptoms was similar in the two treatment groups.

Table 6-18: Incidence of Hepatic Disorder Adverse Events (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

MSSO-Standardized MedDRA Query	Rivaroxaban (N=6183) n (%)	Enoxaparin (N=6200) n (%)
Any Hepatic disorder adverse event by SMQ	290 (4.69%)	400 (6.45%)
Liver related investigations, signs, and symptoms	278 (4.50%)	395 (6.37%)
ALT increased	144 (2.33%)	200 (3.23%)
GGT increased	126 (2.04%)	183 (2.95%)
Hepatic failure, fibrosis, cirrhosis, and other liver-damage related conditions	6 (0.10%)	5 (0.08%)
Cholestasis and jaundice of hepatic origin	5 (0.08%)	5 (0.08%)
Hepatitis, non-infectious	1 (0.02%)	2 (0.03%)
Possible liver-related coagulation and bleeding disturbances	2 (0.03%)	1 (0.02%)
Liver infection	1 (0.02%)	1 (0.02%)
Liver neoplasms, benign	1 (0.02%)	0

Overall, 12 subjects (0.19%) receiving rivaroxaban and 17 subjects (0.27%) receiving enoxaparin in the RECORD studies experienced a hepatic disorder adverse event that led to permanent discontinuation of study medication (Table 6-19). The majority were discontinuations due to liver-related laboratory abnormalities, occurring in 10 subjects (0.2%) receiving rivaroxaban compared with 16 subjects (0.3%) receiving enoxaparin.

Table 6-19: Incidence of Hepatic Disorder Adverse Events Resulting in Permanent Discontinuation of Study Drug (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

MedDRA Preferred Term	Rivaroxaban (N=6183) n (%)	Enoxaparin (N=6200) n (%)
Any Event	12 (0.19)	17 (0.27)
Alanine aminotransferase increased	7 (0.11)	7 (0.11)
Aspartate aminotransferase increased	3 (0.05)	2 (0.03)
Gamma-glutamyltransferase increased	2 (0.03)	3 (0.05)
Liver function test abnormal	2 (0.03)	2 (0.03)
Bilirubin conjugated increased	1 (0.02)	2 (0.03)
Blood alkaline phosphatase abnormal	1 (0.02)	0
Blood bilirubin increased	1 (0.02)	6 (0.10)
Cytolytic hepatitis	1 (0.02)	0
Gamma-glutamyltransferase abnormal	1 (0.02)	0
Hepatic enzyme increased	1 (0.02)	3 (0.05)
Hepatic failure	1 (0.02)	0
Blood alkaline phosphatase increased	0	1 (0.02)
Blood bilirubin unconjugated increased	0	1 (0.02)
Hepatitis	0	1 (0.02)
Hepatitis B	0	1 (0.02)
Transaminases increased	0	2 (0.03)

A summary of liver safety data from the pooled RECORD 1-4 studies is shown in Table 6-20 below. The list of 7 criteria in Table 6-20 were of interest to the FDA in evaluating the liver safety of rivaroxaban. The first criterion relates to subjects having a combined, concurrent elevation of ALT>3x ULN with a TB >2x ULN (based on central or local labs). The second criterion relates to subjects having ALT >3x ULN and TB >2x ULN on different days (based on central or local labs) – non-concurrent elevations. The third criterion relates to subjects having an ALT > 8x ULN at any time during the study, on treatment or during the post-treatment follow-up period. The fourth criterion relates to subjects having an ALT >3x ULN at any time within 45 days of study drug discontinuation. The fifth criterion relates to subjects having a hepatic disorder adverse event reported as serious by the investigator. The sixth criterion relates to subjects having a hepatic disorder adverse event reported by the investigator leading to permanent study drug discontinuation. Finally, the seventh criterion relates relates to subjects having an ALT >3x ULN at any time within 30 days of death. With respect to these various criteria, the incidence in the rivaroxaban group was similar to the incidence in the enoxaparin group.

Table 6-20: Summary of Subject Selection Criteria
(Study: POOLED RECORD 1-4: Safety Analysis Set)

Criteria	Rivaroxaban n/N(%)	Enoxaparin N/N(%)	Difference %(95% CI)
Combined ALT>3xULN/TB>2xULN[a]	9/6131 (0.15)	8/6131 (0.13)	0.02 (-0.12, 0.15)
Non-concurrent[a]	1/6131 (0.02)	2/6131 (0.03)	-0.02 (-0.07, 0.04)
ALT>8xULN[b]	19/6131 (0.31)	23/6131 (0.38)	-0.07 (-0.27, 0.14)
Discontinuation of ALT>3xULN[b]	19/6131 (0.31)	23/6131 (0.38)	-0.07 (-0.27, 0.14)
Hepatic SAE[c]	36/6183 (0.58)	28/6200 (0.45)	0.13 (-0.12, 0.38)
Hepatic AE discontinuation[c]	12/6183 (0.19)	17/6200 (0.27)	-0.08 (-0.25, 0.09)
ALT>3xULN before death[b]	0/6131 (0.00)	1/6131 (0.02)	-0.02 (-0.05, 0.02)

Note: Visit number greater than 50 is defined as post baseline.
[a] N is based on subjects with at least one post-baseline ALT and TB
[b] N is based on subjects with at least one post-baseline ALT
[c] For criteria (e) and (f), N is based on safety analysis set.

6.3. Studies in Indications Other Than VTE Prophylaxis Post TKR/THR Surgery

Table 6-21 is a summary of the ongoing studies in the rivaroxaban program in indications other than the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing THR or TKR surgery. All of these studies are currently ongoing and several of them involve exposure durations longer than the 35 day exposures observed in the RECORD studies. Overall, there are 9 rivaroxaban

studies that are currently ongoing. The indications being evaluated include stroke prevention in atrial fibrillation, treatment of DVT or PE, treatment of acute coronary syndrome, and prevention of VTE in hospitalized medically ill subjects. The total daily doses evaluated are mostly the same (10 mg) or higher compared to the RECORD studies. Each Phase 2 or 3 study is being monitored by an Independent Data Monitoring Committee or Operations Committee that reviews safety data on a regular basis. For all data presented in this section, a cutoff date of December 5, 2008 was used, except for data from the Japan-ROCKET study (cutoff date October 31, 2008) and the ATLAS ACS TIMI 46 study (database close October 18, 2008).

Table 6-21: Ongoing Studies in the Rivaroxaban Program

Study Name Study Number	Phase	Subject Population	Comparator	Rivaroxaban Total Daily Dose	Study Design	NDA Safety Update Data Presentation	Enrollment Status
ATLAS ACS TIMI 46 [a] 11898	2 (dose ranging)	Recent ACS	Placebo	5 – 20 mg	Double blind	Unblinded	Enrollment complete/ analysis and report ongoing
EINSTEIN DVT/PE [b] 11702	3	Acute DVT/PE	Enoxaparin/ VKA	30 mg for 3 weeks; then 20 mg	Open label	Unblinded	Currently enrolling
ATLAS ACS 2 TIMI 51 13194	3	Recent ACS	Placebo	5 and 10 mg	Double blind	Blinded	Currently enrolling
ROCKET-AF 11630	3	Atrial fibrillation	Warfarin	20 mg/15 mg[c]	Double blind	Blinded	Currently enrolling
J [Japan]-ROCKET-AF 12620	3	Atrial fibrillation	Warfarin	15 mg/10 mg[d]	Double blind	Blinded	Currently enrolling
EINSTEIN Extension 11899	3	DVT/PE after 6 months of standard therapy	Placebo	20 mg	Double blind	Blinded	Currently enrolling
MAGELLaN 12839	3	Hospitalized medically Ill	Enoxaparin/ Placebo	10 mg	Double blind	Blinded	Currently enrolling
CHF 12980	1b	CHF	Enoxaparin/ Placebo	10 mg	Double blind & open label	Blinded	Currently enrolling

[a] All subjects receive low dose aspirin and approximately 80% are also receiving concomitant thienopyridine therapy.
[b] Although these are 2 separate studies, for the purposes of safety, they are presented as 1 study.
[c] In ROCKET-AF, subjects with moderate renal impairment on entry to the study received 15 mg rivaroxaban.
[d] In J-ROCKET-AF, subjects with moderate renal impairment on entry to the study received 10 mg rivaroxaban.
Key: ACS = acute coronary syndrome; CHF = congestive heart failure; DVT = deep vein thrombosis; PE = pulmonary embolism; VKA = vitamin-K antagonist

Rivaroxaban exposures greater than 30 days, 90 days, 180 days, and 360 days from these ongoing studies are summarized in Table 6-22. As discussed above, the doses of rivaroxaban used in these ongoing studies were mostly the same or higher than the doses used in the RECORD studies. More than 5,800 subjects have been exposed to rivaroxaban for 6 months or more, of which 2,220 exposures are from studies for which unblinded results were available. There are a total of 1557 exposures 360 days or more, of which 41 are from unblinded studies.

Table 6-22: Rivaroxaban Exposure Data from Ongoing Studies

	Unblinded studies[a]	Blinded studies[b]	Total
≥30 days	3673	6186	9859
≥90 days	3261	4880	8141
≥180 days	2220	3645	5865
≥360 days	41	1516	1557

[a] The 3 unblinded studies include ATLAS ACS TIMI 46, EINSTEIN DVT, and EINSTEIN PE. ATLAS ACS TIMI 46 was conducted in a double-blind manner but has recently completed all subject visits and was subsequently unblinded. The EINSTEIN DVT/PE studies are being conducted open-label.

[b] Estimated (not actual) exposures since studies are blinded

The focus of this section is to summarize liver safety data from ongoing studies since the duration of exposure to study drug in many of these studies is relatively longer than the 35-day (or less) exposure duration observed in the Phase 3 RECORD studies.

The ATLAS ACS TIMI 46 study was conducted in a double-blind manner while the 2 EINSTEIN DVT/PE treatment studies are being conducted in an open-label manner. The ATLAS ACS TIMI 46 study is an important study for evaluating the safety profile of rivaroxaban because it is one of only 3 Phase 2 or 3 studies in the rivaroxaban program being conducted with a placebo controlled design. More importantly, the scheduled 6-month treatment duration offers a longer exposure duration (relative to the RECORD studies) for assessing liver safety. This study was a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of rivaroxaban in combination with aspirin alone or aspirin and a thienopyridine in subjects with acute coronary syndromes. The protocol-scheduled duration of therapy was 6 months. A total of 2309 and 1153 subjects were randomized and in the safety population of rivaroxaban and placebo respectively. The mean exposure duration was 159 days and 163 days for rivaroxaban and placebo respectively. A total of 1445 subjects and 753 subjects completed 6 months of study drug. ALT and TB levels were assessed monthly during the study period.

Table 6-23, shows the number of subjects in the ATLAS ACS TIMI 46 study experiencing a combined ALT>3x ULN plus total bilirubin>2x ULN abnormality and also the number of subjects experiencing ALT abnormalities at varying thresholds. There were 0 cases of combined ALT >3x ULN and TB > 2x ULN abnormalities observed in the rivaroxaban group versus 3 in the placebo group. Of the 3 placebo cases, 1 was attributed to sepsis and 2 were attributed to pancreatitis. The incidence of postbaseline ALT abnormalities > 3x ULN occurred in 3.7% of rivaroxaban subjects compared with 4.6% of placebo subjects. At higher thresholds, the incidence was generally similar in the 2 groups.

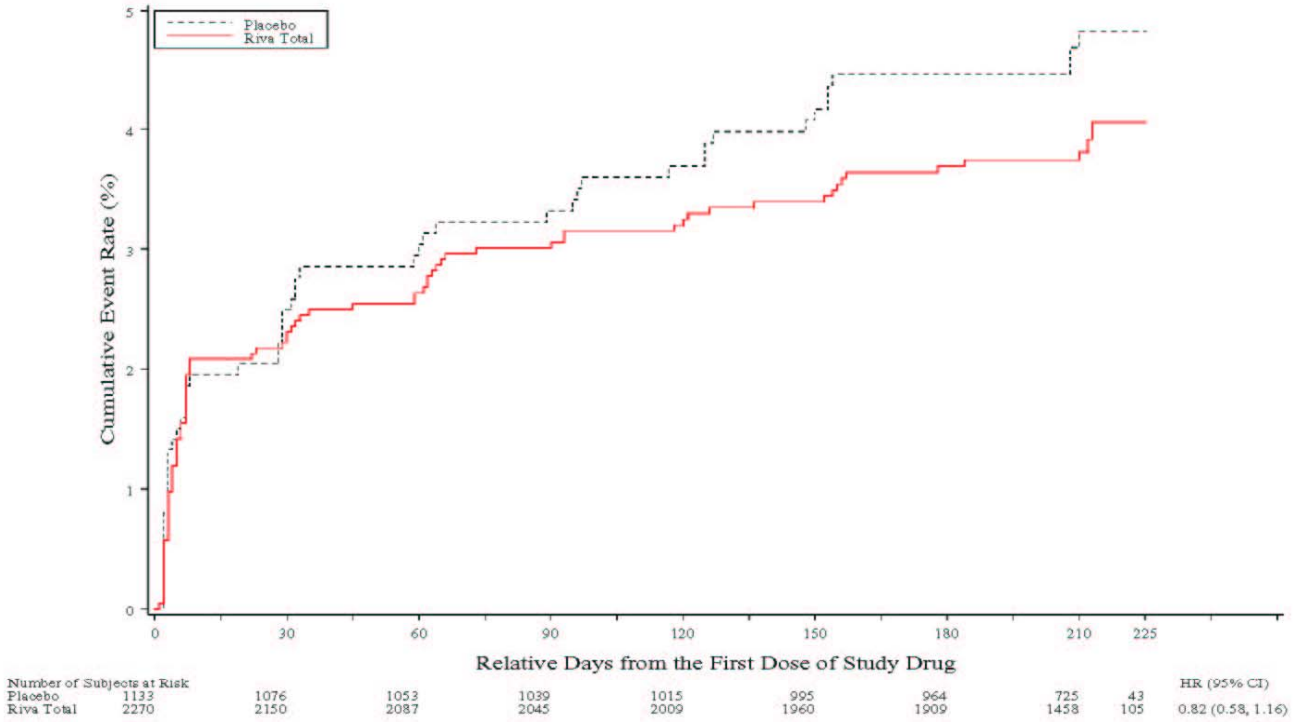
Figure 6-6 shows the Kaplan-Meier estimate of the cumulative risk of first occurrence of postbaseline ALT levels > 3x ULN. The incidence of ALT > 3x ULN was 3.7% and 4.5% (up to Day 180) on rivaroxaban and placebo respectively resulting in a hazard ratio of 0.82 (95% CI: 0.58, 1.16).

Table 6-23: Incidence of Abnormal Liver Function Test Values
(Subjects Available for Safety in ATLAS ACS TIMI 46)

Laboratory Variable **Level of Increase**	Rivaroxaban n/N (%)	Placebo n/N (%)
ALT > 3x ULN combined with TB > 2x ULN (post baseline)	**0/2270 (0.0%)**	**3/1134 (0.3%)**
ALT (post baseline)		
3x ULN	85/2270 (3.7%)	52/1133 (4.6%)
>5x ULN	18/2270 (0.8%)	16/1133 (1.4%)
>8x ULN	4/2270 (0.2%)	4/1133 (0.4%)
>10x ULN	3/2270 (0.1%)	3/1133 (0.3%)
>20x ULN	0/2270 (0.0%)	0/1133 (0.0%)

Key: ALT = alanine aminotransferase; ULN = upper limit of normal
Note: N = number of subjects with non-missing postbaseline lab values

Figure 6-6: Kaplan-Meier Curves for Time to First Postbaseline ALT >3x ULN (Based on Central Laboratory)
(Subjects Available for Safety in ATLAS ACS TIMI 46)



Note: * The Site 972009 has been excluded from the Safety Analysis Set.
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Similarly, the EINSTEIN DVT/PE program also offers a longer exposure duration of 3, 6 or 12 months. The active control in this study is enoxaparin/VKA.

In the EINSTEIN DVT/PE treatment studies, which used enoxaparin/VKA as an active control, a total of 1684 and 1674 subjects were randomized and in the safety population of rivaroxaban and enoxaparin/VKA respectively. ALT, AST, TB, and alkaline phosphatase were measured at Day 15, Day 30 and approximately every 30 days thereafter. The mean treatment duration was 151 days versus 155 days for rivaroxaban and enoxaparin respectively with 775 and 761 subjects respectively having completed at least 6 months of treatment. Table 6-24 shows the number of subjects experiencing a combined ALT>3x ULN plus total bilirubin>2x ULN abnormality and also the number of subjects experiencing ALT abnormalities at varying thresholds. There were 3 cases of combined ALT and TB abnormalities observed on rivaroxaban versus 0 in the enoxaparin/VKA group. Of the 3 rivaroxaban cases, 1 was attributed to ischemic hepatitis, 1 was attributed to heart failure and the last was attributed to gastric cancer with liver metastases. The incidence of postbaseline ALT abnormalities > 3x ULN occurred in 1.41% of rivaroxaban subjects compared with 3.42% of enoxaparin/VKA subjects. At higher thresholds, very few events were reported (i.e. >8, >10,>20x ULN), and the incidence was generally similar in the 2 groups.

Table 6-24: Incidence Abnormal Liver Function Test (EINSTEIN DVT/PE)

Laboratory Variable **Level of Increase**	Rivaroxaban n/N (%)	Enoxaparin/VKA n/N (%)
ALT > 3x ULN concurrent with TB > 2x ULN (post-baseline)	**3/1562 (0.19%)**	**0/1549 (0.0%)**
ALT (post baseline)		
>3x ULN	22/1563 (1.41%)	53/1551(3.42%)
>5x ULN	6/1563 (0.38%)	14/1551 (0.90%)
>8x ULN	3/1563 (0.19%)	5/1551 (0.32%)
>10x ULN	3/1563 (0.19%)	2/1551 (0.13%)
>20x ULN	0/1563 (0.0%)	0/1551 (0.0%)

Key: ALT = alanine aminotransferase; ULN = upper limit of normal
Note: N = number of subjects with non-missing postbaseline lab values

Figures 6-7 and 6-8 show the Kaplan-Meier estimate of the cumulative risk of first occurrence of postbaseline ALT levels > 3x ULN starting from Day 0 and Day 22 respectively. In Figure 6-7, the sharp uptick in the incidence at approximately Day 15 (a protocol scheduled assessment) in the Enoxaparin/VKA group, is attributable to the ALT elevations known to occur with low molecular weight heparins. Figure 6-8 excludes the ALT >3x ULN elevations known to occur during the first 3 weeks following low molecular weight heparin initiation. With these early heparin

associated elevations excluded, the cumulative incidence of ALT >3x ULN on rivaroxaban and control are similar.

Figure 6-7: Kaplan-Meier Curves for Time to First (Post Baseline) ALT >3x ULN (Based on Central Laboratory)(Subjects Available for Safety in EINSTEIN DVT/PE)

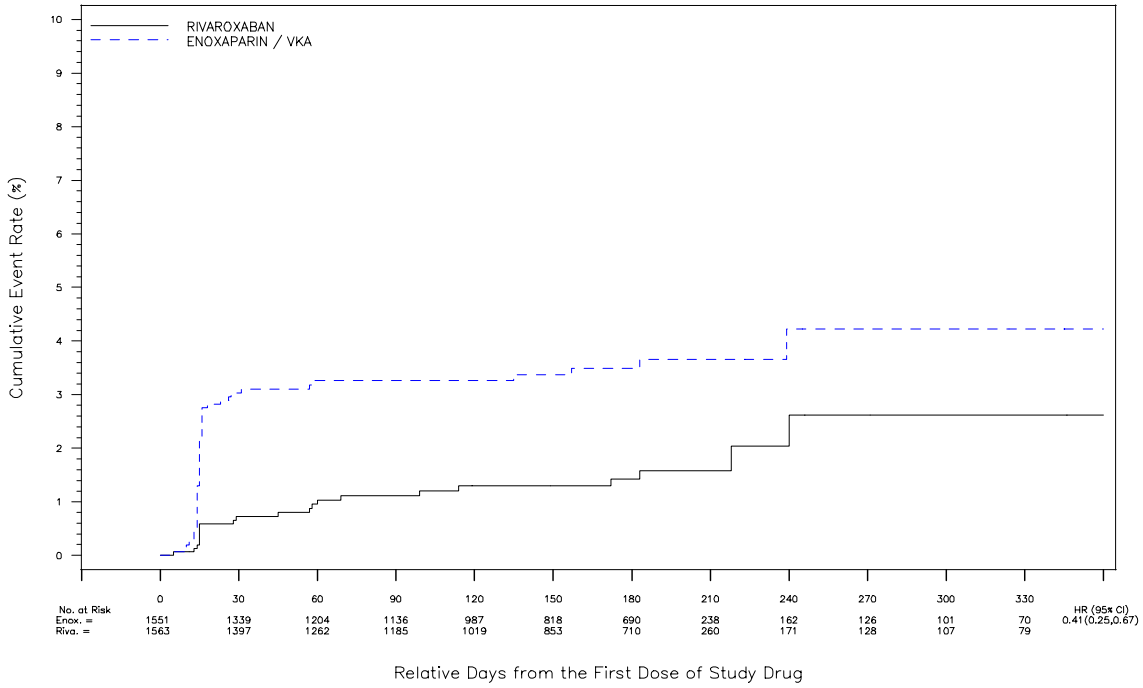
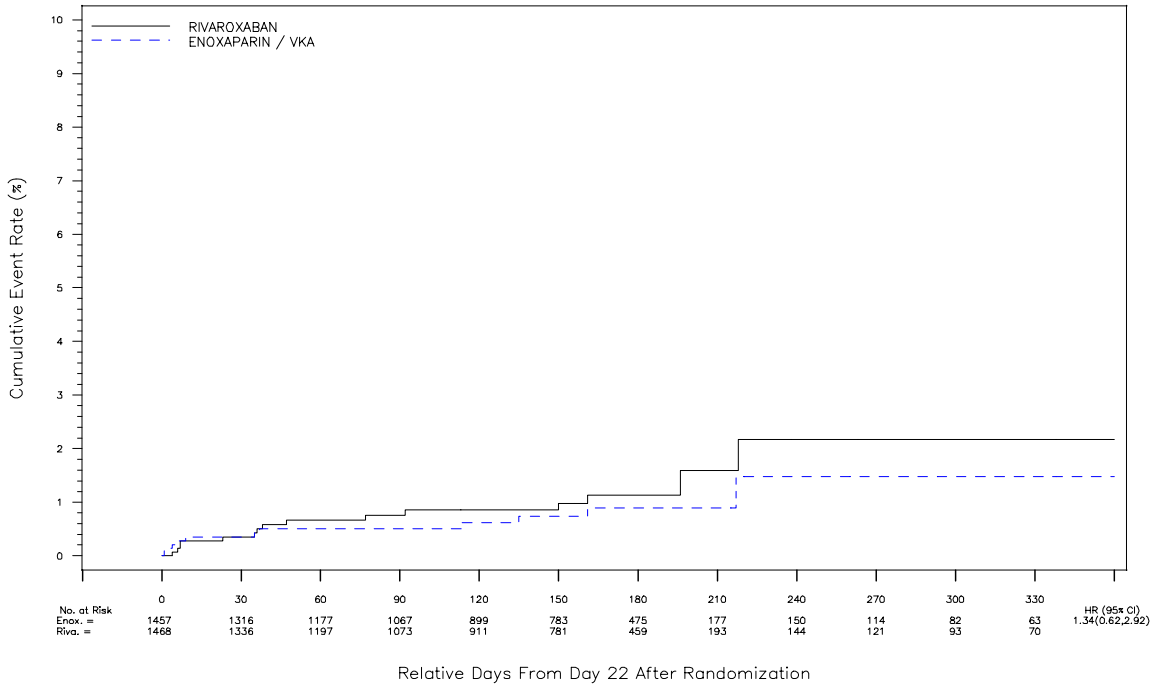


Figure 6-8: Kaplan-Meier Curves for Time to First ALT >3x ULN After Day 22 (Post Baseline) (Based on Central Lab) (Subjects Available for Safety in EINSTEIN DVT/PE)



The ROCKET-AF study remains blinded. Post baseline, ALT and TB are monitored at Week 2, Week 4, then every 4 weeks thereafter through the first year, followed by every 12 weeks thereafter. Sixteen subjects have experienced a combined ALT (>3x ULN)

plus TB (>2x ULN) elevation. Plausible alternate explanations include heart failure (N = 5), viral hepatitis (N = 2), metastatic pancreatic cancer (N = 1), cholecystitis/ bile duct obstruction and/or pancreatitis (N = 3), obstructive hepatitis (N = 1), and cardiogenic shock (N = 2). Two cases do not have clear alternate explanations at this time. One of these subjects had a transient elevation that on repeat testing showed complete normalization and the subject was continued on study medication. In the second subject, additional information is being sought.

The J-ROCKET-AF study also remains blinded. Post baseline, ALT and TB are monitored at Week 2, Week 4, then every 4 weeks thereafter through the first year, followed by every 12 weeks thereafter. Three subjects have experienced a combined ALT (>3x ULN) plus TB (>2x ULN) elevation. Plausible alternate explanations include bile duct stone (N = 1), heart failure (N = 1). In one subject, there does not appear to be a clear alternate etiology, although the investigator suspected the lab findings to be related to telmisartan (a co-administered medication).

The MAGELLAN study remains blinded. Two subjects experienced a combined ALT (>3x ULN) plus TB (>2x ULN). In one subject this finding was attributed to cardiac and renal insufficiency in the setting of Stage 4 esophageal cancer. In the other subject this finding was attributed to cardiac ischemia, heart failure, and hypoperfusion.

The EINSTEIN Extension study, the Phase 1 CHF, and the ATLAS ACS 2 TIMI 51 studies remain blinded. No cases of combined ALT (>3x ULN) plus TB (>2x ULN) have been observed in any of these studies.

6.4. Summary of Cases of Interest and External Expert Liver Assessments

6.4.1. Summary of ALT > 3x ULN with TB > 2x ULN Across Completed and Ongoing Programs

Table 6-25 is a summary of cases of concurrent combined ALT > 3x ULN with total bilirubin > 2x ULN from short-erm, unblinded studies (35 day duration or less). In these short-term studies, the incidence of ALT > 3x ULN with a TB > 2x ULN was low and comparable to comparator. In short-term, ongoing blinded studies, the incidence rate is 0.24% (2/829).

Table 6-25: Summary of Concurrent ALT > 3x ULN with TB > 2x ULN From Short-Term Unblinded Studies (<35 days)

Study	Rivaroxaban	Comparator
Phase 2 THR or TKR surgery (10942, 10944, 10945, 11527)	4/1,700 (0.2%)[a]	2/379 (0.5%)
Phase 2 Japan (11866, 11390, 12024)	0/185 (0%)	0/53 (0%)
RECORD (11354, 11355, 11356, 11357)	9/6131 (0.15%)	7/6131(0.11%)
Combined	13/8016 (0.16%)	9/6563 (0.14%)

Note: The denominators in this table represent subjects in the safety populations of each study with an assessable ALT and TB. This summary table is based on central lab data.
[a]Includes one subject's data that were not in the clinical database because lab values were obtained beyond the 30-day follow-up window.

Table 6-26 is a summary of combined ALT > 3x ULN concurrent with TB > 2x ULN from longer term dosing studies. In these relatively longer term studies, the incidence of ALT > 3x ULN with a TB > 2x ULN was low and comparable to comparator. The incidence rate from ongoing blinded studies is 0.15% (19/12,351). Most cases of ALT > 3x ULN concurrent with TB > 2x ULN come from studies that remain blinded (primarily the ROCKET-AF study).

Table 6-26: Summary of Combined ALT > 3x ULN with TB > 2x ULN From Chronic Dosing Unblinded Studies (>35 days)

Study	Rivaroxaban	Comparator
Phase 2 DVT treatment (11223, 11528)	1/824 (0.1%)	0/235 (0.0%)
ATLAS-ACS TIMI 46 (11898)	0/2,270 (0%)	3/1134 (0.3%)
EINSTEIN DVT/PE (11702)	3/1,562 (0.19%)	0/1,549 (0%)
Combined	4/4,656 (0.08%)	3/2918 (0.10%)

Note: The denominators in this table represent subjects in the safety populations of each study with an assessable ALT and TB.

Since the study duration is variable in each of the chronic dosing studies, correcting for length of study duration gives event rates (per 1000 patient years of follow-up) of 0 and 5.81 events in the rivaroxaban and placebo arms of the ATLAS ACS TIMI 46 study, 4.3 and 0 events in the rivaroxaban and enoxparin/VKA arms of the EINSTEIN DVT/PE study, 2.25 events per 1000 patient years (rivaroxaban plus control pooled) in ongoing, blinded chronic dosing studies.

6.4.2. Liver Advisory Panel (LAP) Summary of Assessments

A Liver Advisory Panel (LAP) was established prior to the initiation of the RECORD studies to evaluate hepatic disorder adverse events of interest. This panel provided the Sponsor with expert subspecialty opinion regarding the etiology of hepatic disorder adverse events. The panel consisted of independent external experts within 2 Subteams (Clinical Subteam and Pathology Subteam) with strong backgrounds in hepatology. The

physicians on the Clinical Subteam were to independently and blindly review single cases based on all available medical records and provide a written assessment. The pathology subteam reviewed cases only in cases where liver tissue was available. The pathology subteam members did not review any cases from the RECORD studies. Cases of hepatic disorder serious adverse events identified by the sponsor were sent for review. Since the LAP was not designed as a formal adjudication committee, individual LAP members did not convene to formulate a unified causality assessment. Not every case was reviewed by each LAP member. Professor Yves Horsmans (University of St. Luc, Brussels, Belgium) reviewed all RECORD cases identified by the sponsor (N = 67). Dr. Willis Maddrey (University of Texas Southwestern Medical Center, Dallas, Texas) reviewed a subset of these cases (N = 28). A summary of the assessments by Professor Yves Horsmans is shown in Table 6-27. The causality classification system was as follows:

> Definite: The drug is considered as the cause, with clear time course, exclusion of other causes and/or histology suggestive of drug-induced livery injury.
>
> Probable: Chronological criteria are suggestive; The etiological work-up reasonably excludes other classical challenging causes; The study drug appears to be the most likely cause even if there is not specific clinical/histological data suggesting the role of study drug.
>
> Possible: Some criteria are missing or there is a challenging diagnosis; Another drug given within a compatible period relative to study drug; Absence of an ultrasound examination in a cholestatic, mixed pattern liver injury; absence of adapted viral screening.
>
> Unlikely (unrelated): Another cause appears more likely or chronology very atypical
>
> Excluded: Another cause is definitiely responsible or time-course not compatible; ALT has already significantly increased before the real onset of study drug; or onset more than 8 weeks after discontinuation of the treatment
>
> Not assessable: available data are too scant to allow a reasonable assessment; not clear chronology; not clear results for liver

The distribution of causality assessments was similar in the rivaroxaban and enoxaparin groups for both Professor Horsmans or Dr. Maddrey. There were no cases identifed as "definite" by either reviewer.

Table 6-27: Summary of Hepatic Disorder Serious Adverse Event Assessments by Professor Horsmans (RECORD 1-4 Pooled)

	Rivaroxaban (N = 36)	Enoxaparin (N = 31)
Unlikely/unrelated/excluded	19 (52.8%)	13 (41.9%)
Possible	16 (44.4%)	17 (54.8%)
Probable	0	1 (3.2%)
Definite	0	0
Not assessable/Need more information	1 (2.8%)	0

A summary of the causality assessments by Dr. Maddrey are shown in the Table 6-28. Dr. Maddrey reviewed a subset of the cases reviewed by Professor Horsmans. The distribution of causality assessments was similar in the rivaroxaban and enoxaparin groups.

Table 6-28: Summary of Hepatic Disorder Serious Adverse Event Assessments by Dr. Maddrey (RECORD 1-4 Pooled)

	Rivaroxaban (N = 16)	Enoxaparin (N = 12)
Unlikely/unrelated/excluded	7 (43.8%)	4 (33.3%)
Possible	5 (31.3%)	5 (41.7%)
Probable	3 (18.8%)	3 (25.0%)
Definite	0	0
Not assessable/Need more information	1 (6.3%)	0

Two additional clinical sub-team LAP members reviewed a total of 4 cases. In two cases, the assessment was unlikely/unrelated/excluded and two other cases were not assessable.

6.4.3. Deaths preceeded by ALT > 3x ULN combined with TB > 2x ULN within 30 days

As of the 05 December 2008 cutoff date, 4 subjects (0.02%) died and had an ALT >3xULN with TB >2x ULN that preceeded death by 30 days out of 20,320 subjects exposed to rivaroxaban from completed or ongoing studies. In comparison, 2 subjects (0.01%) died and had an ALT >3xULN with TB >2x ULN that preceeded death by 30 days out of 16,769 subjects exposed to comparator. Of the 2 deaths in the comparator group, one subject was from the ongoing, double-blind MAGELLAN study (this case was unblinded by the sponsor's Pharmacovigilance department). In each of these cases, there appears to be a plausible alternative explanation for the combined ALT/TB abnormality preceeding death (Table 6-29). Narratives and figures for each of these subjects are provided in Appendix 2.

Table 6-29: Listing of Subjects With Death Preceeded by ALT >3x ULN and TB >2x ULN

Study drug/ Subject number	Study[a]	Key demographics	Day of last dose, Day of ALT/TB elevation, Day of death	Liver laboratory tests (peak)	Alternate etiology for liver enzyme elevations (Sponsor assessment)	Assessment by Liver Experts (LAP)
Rivaroxaban 10944-84008	Phase 2 THR prophylaxis (4:1)	79 y/o German female with a history of cholecystolithiasis and chronic pancreatitis	Day 9, Day 48, Day 127[b]	ALT = 260 U/L (7.4x ULN) TB = 19.8 mg/dL (20x ULN) Alk Phos = 1456 (710x ULN)	Bactrim, deteriorated after ERCP procedure	Not evaluated
Rivaroxaban 11223-506006	Phase 2 VTE treatment (4:1)	72 y/o Czech female with metastatic uterine cancer	Day 23, Day 29, Day 48	ALT = 2142 U/L (87x ULN) TB = 14.5 mg/dL (13x ULN) Alk Phos = 341 U/L (3.3x ULN)	Acute Hepatitis B infection	Maddrey: Unrelated Larrey: Excluded Boitnott: Unrelated Zafrani: Unlikely
Rivaroxaban 160183005	EINSTEIN DVT/PE (1:1)	63 y/o French female with a history of hypertension, asthma and emphysema	Day 18, Day 18, Day 26	ALT = 5371 U/L (149x ULN) TB = 3.9 mg/dL (3.9x ULN) Alk Phos = 151 U/L (1.2x ULN)	Ischemic hepatitis	Consensus committee opinion of Maddrey, Larrey, Horsmans, Rubin, and Zafrani was unlikely
Rivaroxaban 220134004	EINSTEIN DVT/PE (1:1)	71 y/o Italian male with a history of pancreatic cancer and surgery for gastric cancer	Day 56, Day 27, Day 58	ALT = 513 U/L (7.8x ULN) TB = 5.4 mg/dL (4.2x ULN) Alk Phos = 1066 U/L (7.8x ULN)	Gastric cancer with liver metastases	Maddrey: Unlikely Hormans: Unlikely Larrey: Unlikely
Placebo 200039	ATLAS ACS TIMI 46 (2:1)	44 y/o Australian female with a history of folate deficiency, macrocytic anemia and alcohol abuse	Day 91, Day 108, Day 109	ALT = 134 U/L (3.8x ULN) TB = 10.99 mg/dL (9.4x ULN) Alk Phos = 262 U/L (1.9x ULN)	Sepsis, Alcoholic hepatitis	Horsmans: Unlikely
Enoxaparin 280130001	MAGELLAN (1:1)	72 y/o Belgian female with esophageal neoplasia (Stage 4)	Day 28, Day 29 Day 30	ALT = 520 U/L (13x ULN) TB = 3.0 mg/dL (2.5x ULN) Alk Phos = 29 U/L (0.3x ULN)	Cardiac and renal insufficiency; Multi-organ failure	Not yet reviewed by LAP

[a]the ratio reported under each study represents the rivaroxaban:comparator randomization ratio for that study
[b]the ascertainment of death in this case was obtained by the sponsor's pharmacovigilance department beyond the protocol specified follow-up period

6.5. Summary of Safety

The safety of rivaroxaban has been well characterized when used for the prophylaxis of DVT and PE in patients undergoing THR or TKR surgery. Rivaroxaban is well tolerated relative to enoxaparin when administered 10 mg once daily without routine laboratory monitoring.

Rivaroxaban increases the risk of major bleeding by 0.18% (95% CI: -0.01%, 0.37%; absolute risk increase). With respect to major or non-major clinically relevant bleeding, the increase is 0.64% (95%CI: 0.05%, 1.23%; absolute risk increase). The effect in most subgroups is directionally consistent with the effect observed in the overall population showing a hazard ratio point estimate > 1.0. In certain subgroups such as subjects over the age of 75 years, creatinine clearance 30 to 50 mL/min, Blacks, or fragile subjects the hazard ratio point estimate of major or non-major clinically relevant bleeding events was <1.0.

Approximately 70% of subjects in the pooled RECORD studies received an NSAID concomitantly with study drug. Subjects taking NSAIDS concomitantly with rivaroxaban did not appear to be at an increased risk of bleeding compared to non-users. Approximately 9% of subjects in the pooled RECORD studies received a platelet aggregation inhibitor (primarily acetylsalicylic acid) concomitantly with study drug. Users of platelet aggregation inhibitors with rivaroxaban do not appear to be at an increased risk of bleeding compared to non-users. Approximately 8% of subjects received a CYP3A4 and/or Pgp inhibitor concomitantly with study drug. The risk of bleeding may be increased in users of CYP3A4 and/or Pgp inhibitors relative to non-users. The bleeding event data with concomitant CYP3A4 and/or Pgp inhibitor use should be interpreted with caution due to the small number of bleeding events and Phase 1 data showing a 50% or less increase in exposure with the use of such inhibitors concomitantly with rivaroxaban.

The incidence of cardiovascular events during treatment and follow-up was similar in rivaroxaban group and the enoxaparin group. There was no evidence of a rebound cardiovascular phenomenon relative to enoxaparin after rivaroxaban discontinuation. The placebo-controlled ATLAS ACS TIMI 46 study provides additional support with respect to the absence of cardiovascular events. The incidence of ALT > 3x ULN was lower in the rivaroxaban group (2.48%) compared to enoxaparin (3.70%) in the RECORD studies, which is expected given the well described phenomenon of aminotransferase elevations in association with heparin use.

The incidence of the combined ALT > 3x ULN with TB > 2x ULN abnormality was similar on rivaroxaban (0.15%) and enoxaparin (0.11%) in the RECORD studies. In ongoing, longer term studies in indications other than the prophylaxis of DVT and PE in patients undergoing THR or TKR surgery, the potential for drug-induced liver injury involving rivaroxaban appears to be low. Specifically, in the unblinded study ATLAS ACS TIMI 46 the incidence of ALT > 3x ULN on rivaroxaban (3.7%) was similar to placebo (4.6%). In the ongoing EINSTEIN DVT/PE studies, the incidence of ALT > 3x ULN was lower with rivaroxaban (1.41%) compared to enoxaparin/VKA (3.42%). With respect to combined, concurrent cases of ALT>3x ULN with TB>2x ULN, the incidence was balanced in unblinded studies of short term and long term duration. Based on the totality of data, that includes the shorter duration RECORD studies and the longer duration, ongoing studies, the potential for drug induced liver injury with rivaroxaban appears to be low.

6.6. Therapeutic Drug Monitoring

The first anticoagulants that were introduced into clinical practice were unfractionated heparin and warfarin (a vitamin K antagonist). Both are classic examples of narrow therapeutic index drugs for which small changes in the dose can cause serious bleeding events or loss of efficacy. Because of its narrow therapeutic index, warfarin requires laboratory monitoring and dose adjustment in all clinical settings including for the prophylaxis of VTE after THR or TKR. The efficacy of warfarin declines steeply at INRs below 2.0 and the bleeding risk increases exponentially at INRs of 4.0 and above (Hylek 1994, 1996) The current standard target therapeutic range— an INR between 2.0 and 3.0 — was established by consensus on the basis of the results of randomized trials (Laupacis 1995). Since there is considerable variability both between patients and within patients over time in response to warfarin, INR monitoring is necessary both during the initiation of therapy to get to the target range and routinely during treatment to maintain the patient within the therapeutic range. Given the well-known interactions of warfarin with diet and many other drugs as well as its intrinsic variability, dose adjustments are frequently required during therapy and maintaining patients within the target INR interval is challenging.

Enoxaparin and other LMWHs were the first anticoagulants approved for clinical use that do not require therapeutic effect monitoring or dose adjustment for most patients. Enoxaparin is the most widely used LMWH for prophylaxis of VTE after THR and TKR, with approved dose regimens of 40 mg once daily for THR or 30 mg twice daily for THR and TKR without any laboratory monitoring. Fondaparinux, a pentasaccharide with specific, indirect inhibition of FXa, has been more recently developed for use after orthopedic surgery at a fixed subcutaneous dose of 2.5 mg once daily.

The RECORD program provides a comprehensive evaluation of the efficacy and safety of a 10 mg once daily dose of rivaroxaban for the prophylaxis of DVT and PE after THR or TKR. The overall results of this program show that this rivaroxaban dosing regimen is highly effective and well tolerated compared with standard regimens of enoxaparin. These results were consistent across all major subgroups of patients examined including age, weight and renal function categories that would be expected to be associated with differences in rivaroxaban exposures based on the clinical pharmacology data. Although pharmacodynamic measurements were obtained on Day 6 of dosing primarily for the purposes of assessing exposure (e.g., PT values measured via a central laboratory for analysis) the results were not available at the investigative site and the protocols did not include any routine coagulation test monitoring or mechanism for making dose adjustments. Administration of a 10 mg dose in the RECORD studies resulted in a prothrombin time of between 13 seconds and 26 seconds (median 18 seconds) in 90% of study subjects at Day 6 (Figure 3-14). There was significant overlap in the range of PT values in subjects not experiencing any bleeding events compared to subjects experiencing any bleeding event (including major bleeding events) suggesting that no threshold for bleeding events could be established for rivaroxaban exposure.

In summary, the development strategy for orally administered rivaroxaban has paralleled those for the parenteral anticoagulants currently approved for prophylaxis of DVT and PE after THR or TKR surgery and the results provide strong evidence that rivaroxaban can be administered as a 10 mg dose without laboratory monitoring or dose adjustment in this indication.

6.7. Overdose

While there have been no reports of accidental or intential overdose in the rivaroxaban clinical study program, an overdose of rivaroxaban could lead to hemorrhagic complications. There is no antidote to immediately reverse the anticoagulant effects of rivaroxaban. Doses of up to 30 mg twice daily (total daily dose of 60 mg) and 40 mg once daily have been studied in Phase 2 studies. Due to limited solubility, rivaroxaban absorption plateaus at higher doses limiting exposures.

In suspected cases of rivaroxaban overdose or with a serious bleeding event, the following steps should be considered:

- Delay or discontinue rivaroxaban treatment;
- Administer activated charcoal to help reduce absorption (if within 8 hours of injestion); and

- Supportive treatment (ie. mechanical compression, fluid treatment, hemodynamic support, blood transfusion).

If none of the measures above are successful, consideration should be given to administration of Activated prothrombin complex concentrate, PCC (prothrombin complex concentrate), or recombinant factor VIIa. While no clinical experience currently exists with any of these potential treatments, the recommendations are based on non-clinical data showing partial reversal of rivaroxaban anticoagulant effect. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.

7. RIVAROXABAN SAFETY SURVEILLANCE PLAN

7.1. Overview

According to the FDA final guidance's on risk management published in March 2005 (Guidance for Industry: Development and Use of Risk Minimization Action Plans) risk management is an iterative process of (1) assessing a product's risk-benefit balance; (2) developing and implementing tools to minimize its risks while preserving its benefits; (3) evaluating tool effectiveness and reassessing the risk-benefit balance; and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the risk-benefit balance.

Risk assessment consists of identifying and characterizing the nature, frequency, and severity of the risks associated with the use of the product. Risk assessment occurs throughout the product's lifecycle from early identification of a potential product, through the pre-marketing development process, and after approval.

J&J is committed to developing and proposing a safety surveillance plan encompassing risk management with the goal of minimizing risks and preserving/maximizing benefits to improve the overall balance of risks and benefits in the intended target patient population in the post –approval setting.

Following a rigorous and thorough review of the clinical trial safety database, a comphrehensive pre-marketing risk assessment has identified the following risks: 1) Identified Risk - bleeding and 2) Potential Risk - perioperative transient elevation of liver laboratory tests.

Additionally, it was determined that rivaroxaban would have the potential for chronic off-label use for non-approved indications, due to its a once daily fixed dose oral dosing regimen formulation that does not require laboratory monitoring.

7.2. Risk Assessment and Minimization Strategies

To ensure that rivaroxaban has the optimal benefit-risk balance for the intended population and use, J&J PRD is proposing, in addition to routine risk minimization measures, the utilization of a variety of additional tools to further assess and mitigate the identified and potential risks when rivaroaxaban is used for the prophylaxis of DVT and PE in patients undergoing THR or TKR. These tools are intended to communicate information regarding product risk and facilitate proper use to ensure appropriate patient selection and to minimize off-label use for indications where the benefit-risk ratio has not yet been established.

The choice of proposed risk minimization tools (processes or systems intended to enhance safe product use by reducing risk) listed below carefully takes into consideration the ability to maintain access to the product, which is intended for prophylaxis therapy, with the least burden to the healthcare system (healthcare practitioner-patient, pharmacist-patient, and/or other healthcare relationships) that is compatible with acceptable risk minimization. The following tools are proposed:

- US Package Labeling
- Patient Package Insert
- Routine Pharmacovigilance Practices
- Enhanced Pharmacovigilance Activities for specific adverse events of interest (AEOIs)
- Drug Packaging Strategies
- Commercialization Strategies
- Education and Outreach Programs
- Post-Marketing Utilization Study
- Post-Marketing Observational Study – Ex US.

The following outlines the set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks related to the use of rivaroxaban in the post-marketing setting (Table 7-1).

Table 7-1: Pharmacovigilance Activities and Interventions to Identify, Characterize, Prevent or Minimize Risks

	Identified Risk: Bleeding	Potential Risk: Perioperative Transient elevation of liver laboratory tests	Potential for Off-label Use:
Risk Minimization			
U.S. Product Labeling	√	NA	√
Patient Package Insert	√	NA	√
Pharmacovigilance Practices:			
Routine	√	√	√
Enhanced	√	√	√
Commercialization Strategies	√	NA	√
Education and Outreach Programs	√	NA	√
Drug Packaging Strategies	NA	NA	√
Risk Assessment			
Post-Marketing Drug Utilization Study	√	√	√
Post-Marketing Observational Cohort Study	√	√	NA

NA=Not Applicable

7.2.1. US Package Labeling

The aim of the warnings and information contained within the proposed labeling is to ensure appropriate use of the product for the approved indication. It should further reduce the probability of an adverse reaction occurring or minimize its severity and any related clinical outcomes should it occur.

The proposed indication for rivaroxaban is:

> prophylaxis of DVT and PE in patients undergoing Total Hip Replacement (THR)or Total Knee Replacement. (TKR) surgery.

For patients undergoing THR, treatment duration of 35 days is recommended. For patients undergoing TKR, treatment duration of 14 days is recommended.

Outlined is a summary of the cautionary information to be included in the proposed USPI.

- Black Box Warning: Anticoagulant use in patients undergoing spinal/epidural anesthesia or spinal puncture increases the risk of spinal or epidural hematoma, which may cause long-term or permanent paralysis.
- Section 4. Contraindications:
  - Patients with clinically significant active bleeding;
  - Patients with hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk;
  - Pregnant or breast-feeding women

- Section 5 Warnings and Precautions:
  - Use with caution in patients with concomitant medical conditions with an increased bleeding risk such as congenital or acquired bleeding disorders, active ulcerative gastrointestinal disease, recent intracranial or intracerebral hemorrhage, shortly after brain, spinal or ophthalmological surgery, intraspinal or intracerebral vascular abnormalities, uncontrolled severe arterial hypertension, recent gastrointestinal ulcerations and vascular retinopathy,
  - Concomitant use not recommended with strong inhibitors of both CYP3A4 and P-glycoprotein
  - Other than for required transitions in therapy, it is not recommended to concurrently use rivaroxaban with any other anticoagulant, due to increased bleeding risk
  - Use with caution in patients treated concomitantly with drugs affecting hemostasis (such as non-steroidal anti-inflammatory drugs (NSAIDs; including acetylsalicylic acid), platelet aggregation inhibitors or fibrinolytics
  - Use with caution in patients with moderate renal impairment (creatinine clearance 30 to<50 mL/min) who are also receiving certain specific concomitant medications (e.g., strong CYP3A4 inhibitors)
  - Use with caution in patients with severe renal impairment (creatinine clearance 15 to<30 mL/min)
  - Not recommended for patients with kidney failure (creatinine clearance <15 mL/min)

7.2.2. Patient Package Insert

The Patient Package Insert (PPI) will be included within the US Package Labeling and will state the approved indication for use, the recommended duration of therapy and the recommended dose. Additionally the PPI will identify in patient-friendly terms, the contraindications for use of rivaroxaban as well as warnings and precautions for using rivaroxaban with specific comorbid conditions and concomitant medications which can increase the risk of bleeding.

7.2.3. Routine Pharmacovigilance Practices

The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for ***routine*** risk assessment and risk minimization (e.g., FDA requirements for professional labeling and adverse event monitoring and reporting) - Safety Reporting Regulations (21 CFR 310.305, 314.80, 314.98, and 600.80) and Labeling Regulations (21 CFR 201, 314, and 601).

The objective of the routine pharmacovigilance practices is to systematically collect adverse events from multiple sources and to conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals. Early detection of safety signals enables the development and implementation of an appropriate

risk management strategy. Unlisted serious adverse event cases shall be expedited as 15 day reports to the Agency and aggregate data will be presented in the US Periodic Adverse Drug Experience Reports (PADER) and Periodic Safety Update Reports (PSURS).

7.2.4. Enhanced Pharmacovigilance Activities

Enhanced pharmacovigilance activities will be used to investigate reports for specific AEOI, including serious bleeding events and serious liver-related events.

In addition to routine surveillance activities described above,

1) enhanced surveillance of bleeding events will include:

   - Safety data collection for bleeding–related adverse events from ongoing clinical trials and SAE targeted bleeding questionnaires
   - Bleeding events reported from clinical trials will be adjudicated by Clinical Events Committee;

2) enhanced surveillance for liver disorder adverse events will include:

   - Safety Data collection for liver–related adverse events from ongoing clinical trials and SAE targeted liver questionnaires;
   - Targeted liver questionnaires will be used in the post-marketing setting for spontaneous liver-related adverse event reports, including site visits when necessary;
   - Ongoing review of selected single case serious liver-related events will be sent to an established external Liver Advisory Panel for further individual evaluation and assessment.

7.2.5. Drug Packaging Strategies

Specific drug packaging strategies can be used, in addition to education and outreach programs, to assist healthcare providers in following appropriate prescribing practices and to reinforce key messages about approved indications and appropriate duration of therapy.

The total knee replacement (TKR)/total hip replacement (THR) surgery market involves many possible permutations of dosing length and distribution, to net 14 days for TKR and 35 days for THR (per labeling):

   - While the patient is in the hospital: approximately 2-4 doses are provided via Hospital Unit Dose dispensing

- When the patient is out of the hospital: additional doses for TKR or THR are provided by the Skilled Nursing Facility (SNF)/Long Term Care site (LTC); or obtained by the patient at a retail pharmacy via prescription).

Pharmacies in all settings of care (in-hospital, in-SNF/LTC, and retail) will need available stock to accommodate dispensing these different permutatons of dosing length: therefore rivaroxaban will be available in special packaging for hip and knee replacement procedures, with sufficient tablets available for the prescribed dosing duration for the approved indication. These packages will include the US Package Label (including the Patient Package Insert). Specifically in the hospital and SNF/LTC settings, Hospital Unit Dose blister card and 30 count bottles will be available to accommodate varying durations of stay. In the retail setting, rivaroxaban will only be distributed in blister packs dispensed in two different carton configurations - one for TKR, the other for THR - with suitable numbers of blister cards for the indication by procedure (TKR, THR).

7.2.6. Commercialization Strategies

In the hospital setting, there are several important stakeholders involved in anticoagulant strategy for THR/TKR surgery patients. Orthopedic Surgeons are the primary drivers of the choice of specific perioperative VTE prophylaxis medication, in concert with other health care providers (HCPs) such as hospitalists, hematologists and the hospital Pharmacy and Therapeutics (P&T) committee, which determine what pharmaceutical agents are available in the hospital.

In the out-patient setting, similarly, there are several important stakeholders involved in ongoing patient management. Orthpedic surgery patients are discharged to SNF/LTC or directly to home (with or without Home Healthcare), therefore the SNF/LTC personnel and/or Primary Care Physicians/General Practitioners/Internists play a central role in ensuring appropriate medication usage. Also in this outpatient setting, private insurers and government payers are gatekeepers for access to VTE prophylaxis medication.

As such, rivaroxaban Marketing and Promotional efforts will predominantly focus on hospitals and payers, while Educational and Outreach Programs will span all groups, including outpatient stakeholders, as they interact with the patient for the majority of anticoagulant treatment days.

7.2.6.1. Launch Information Sheet

At the time of product availability, a Launch Information Sheet will be mailed to hospital-based HCPs, including orthopedic surgeons, hospitalists, pharmacists, anesthesiologists, selected nurses, and hematologists. This Information Sheet will provide education on proper use of rivaroxaban for the labeled indication and the recommended

duration of therapy. A copy of the rivaroxaban US package label, including PPI, will also be provided.

7.2.6.2. Formulary Kit Callouts for Payers

To educate payer organizations and formulary stakeholders on the labeled indication and proper use of rivaroxaban, an educational kit will be developed for Medical Directors and Pharmacy Directors. Specific language will be employed, describing appropriate use and labeled duration of therapy.

7.2.6.3. Compendia and Formulary References

Rivaroxaban will be entered into appropriate reference publications, compendia, and formularies serving HCPs who prescribe, dispense, administer, or care for patients being treated with rivaroxaban.

7.2.6.4. Rivaroxaban Product Monograph

A product specific monograph will be developed to educate pharmacists and others HCPs on prophylaxis of DVT and PE in patients undergoing THR or TKR. The Monograph will serve as a primary reference on rivaroxaban for pharmacists.

7.2.6.5. Other Professional and Promotional Medical Education

Other educational vehicles to continue educating and updating HCPs on the appropropriate use and risk/benefit of rivaroxaban include:

- Attending annual meetings of major professional societies, which allows interaction between Medical Information personnel and HCPs in attendance;
- Training a professional Speaker's Bureau, which will schedule local and regional thought leader symposia.

7.2.6.6. Promotional Programs

Promotional programs are vehicles for branded within-label communications. All promotional communications will include specific information regarding the approved indications, dosing, and length of prophylaxis recommended in the rivaroxaban label.

7.2.6.7. Personal Selling

Personal selling resources for rivaroxaban will focus on orthopaedic surgeons and other hospital-based stakeholders involved in the administration of VTE prophylaxis following TKR and THR surgery (e.g. nursing staff, pharmacists, case managers, hospitalists, Pharmacy and Therapeutics Committees, and members of Protocol Committees).

There will be no personal selling resources directed at cardiologists, general surgeons or emergency room physicians until the time in which rivaroxaban has approved indications

appropriate for those specialties. . There will be no personal selling resources directed at office-based HCPs in the out-patient setting during the time in which rivaroxaban will only have the indication for VTE prophylaxis in TKR and THR patients.

Sales force training is an important method of ensuring communication regarding appropriate product utilization to the prescribing HCP. Each sales representative will undergo extensive training and be required to successfully show competency on the package label and promotional materials, and will receive separate instruction on health care compliance practices. All questions posed by HCPs, regarding use of rivaroxaban in non approved indications will be directed to the Ortho-McNeil-Janssen Scientific Affairs medical information department. Information regarding the application of rivaroxaban outside of approved indications, and other ongoing development programs, will only be provided in medical-to-medical exchange, as permitted, and only upon receipt of unprompted inquires from HCPs. These communications will include language indicating that the sponsor has no efficacy data for any other indication or for any other dose and thus rivaroxaban should not be used outside of the approved indication and dosing regimen.

7.2.7. Education and Outreach Programs

Education and Outreach Programs are vehicles to communicate appropriate usage (indications, patient populations, and dosing regimen) and benefits and risks of usage. These programs will also define inappropriate use (e.g., unapproved indications, patient populations, and duration of therapy). Although Orthopedic Surgeons are the primary prescribers of VTE prophylaxis following TKR/THR surgery, target stakeholders for Education and Outreach also include hematologists and hospitalists, nurses, rehabilitation specialists (physiatrists and rheumatologists) and pharmacists. In addition, institutions systems (guidelines/policy committees, formulary committees) and payers (private and government) will be important audiences for these Education and Outreach Programs.

Key educational messages for all audiences are:

- Rivaroxaban is indicated for the prophylaxis of DVT and PE in patients undergoing THR or TKR surgery.
- For patients undergoing THR, treatment duration of 35 days is recommended.
- For patients undergoing TKR, treatment duration of 14 days is recommended.

As a result of these Education and Outreach Programs, payers (private and government), hospital-specific policies/guidelines, and hospital Pharmacy and Therapeutics (P&T) committees are likely to restrict payment/reimbursement for rivaroxaban to the approved indication and to institute quantity limits, which will enforce appropriate length of therapy and support appropriate use.

7.2.8. Post-Marketing Utilization Study

Rivaroxaban represents a new therapeutic option for the prevention of DVT and PE after THR or TKR and offers advantages over currently available therapies (including oral route of administration, once daily dosing, no routine laboratory monitoring, and fewer potential drug-drug interactions). It will be important to characterize the patterns of use of this new drug in clinical practice and the extent to which clinicians prescribe this drug according to the labelled instructions. In particular, the areas of main interest would be: 1) to assess the duration of use of the drug; and 2) to assess the patient populations in which the medication is being dispensed and used. Because the efficacy and safety of rivaroxaban for extended use, and for additional indications, are currently under investigation, these measures will provide important information on appropriate use.

The Sponsor proposes to conduct a post-marketing utilization study to investigate and quantify the duration of use, and the populations under treatment. This will permit an assessment of the extent of use within and outside the label. In addition, because some specific, clinically important adverse events can be captured in the course of conducting the proposed utilization study, rates of these events will also be evaluated.

The primary objective of the study is to describe the usage patterns of rivaroxaban in clinical practice in the United States. The study will capture patient demographics (i.e., age, race, and sex), prescribed dose and duration of use, use of concomitant prescription medications (particularly anti-platelet drugs), and underlying conditions, and indication for treatment.

The secondary objectives of this study are to document:

- the extent and duration of use outside the intended population, including use in groups with safety warnings/contraindications, or use for indications other than the prevention of DVT and PE in adult patients undergoing elective hip or knee replacement surgery;
- selected features of the usage pattern, which include, but will not be limited to, concomitant prescriptions of CYP450 3A4 inhibiting drugs, recent and current history of renal and liver diseases, concomitant use of antithrombotic therapies, and history of conditions associated with an increasing risk of bleeding; and

- rates of adverse events (AEs) of interest, such as severe liver injury and major bleeding (will be further assessed and defined in a feasibility study)

Enoxaparin, the active comparator in all clinical studies, will be examined in a similar fashion, in order to provide context for interpreting the AE reports in patients treated with rivaroxaban. No statistical comparisons will be made between the two medications.

Because of the multiple indications approved for enoxaparin, its utilization, *per se*, will not be of interest, except to help in understanding the context for AE rates.

Study Design, Rationale, and Intended Use of the Study Results

The existing commercially available databases (e.g., PharMetrics, Premier, and MarketScan databases) offer the opportunity to examine the above parameters in the context of actual clinical practice. To achieve the objectives, this study will retrospectively identify all patients with at least 6 months or one year of medical history or membership (depending upon the feasibility study) in the database whose records indicate they received at least one dispensing of rivaroxaban after the launch date in the United States. Once these patients are identified, the analysis will provide a comprehensive description of the demographics of those patients, along with other relevant clinical information that is available in the database.

The study period will begin following the identification of the first post-launch dispensing of rivaroxaban in the database (index date) and is considered completed when the last patient has been identified or the study end date has been reached (see below). Two analyses will be generated in a sequential manner: 1) The initial report will be based on the data from first six months following the index date or from the first 3,000 patients exposed to rivaroxaban, whichever comes later; and 2) the final report will be based on the data from one year following the index date or a total of 6,000 patients (cumulative) exposed to rivaroxaban, whichever comes later. In addition, if deemed necessary, additional analyses (by time-period or an equally-divided number of patients) will be conducted to assess whether the usage pattern changed over time. As noted, patients exposed to enoxaparin will be accrued in a similar manner, although the number of patients included in the study may eventually depend on the time of the analysis and how often this drug is prescribed in clinical practice. Note that a sample of 6,000 allows an estimate of use outside the label of 5% with a precision of +/- 0.55%. Final sample size or study duration will be determined based on the feasibility study.

Several commercial databases are under evaluation for the purposes of this study (e.g., PharMetrics, Premier, and MarketScan, etc). The strengths and limitations of the available databases will be examined to identify the most suitable database(s). A feasibility study will be conducted prior to implementing the entire study protocol as it is

expected that more than one database will be required to fully characterize the post-marketing clinical experience with rivaroxaban as utilization will cross hospitals, skilled nursing facilities, and other long term care facilities as well as retail outlets.

The proposed study is primarily descriptive in nature. The sample size (or study duration) is determined to provide a comprehensive understanding about the usage pattern of rivaroxaban in clinical practice, rather than testing any particular hypothesis. Because the study may also include capture of potential adverse events, it is worth noting that from a safety perspective a sample size of 6,000 produces a 95% confidence interval of 2.75% to 3.66% when the event rate is estimated to be 3.19% (e.g., the risk of major and clinically relevant, non-major bleeding in the clinical trials), and the study will have at least an 80% probability of observing at least one event, even if the risk of that event is as low as 0.027%.

In the context of postmarketing surveillance, this study will also support hypothesis generation in a study population with a defined (and known) denominator. If rare and serious unusual adverse events are reported in patients taking rivaroxaban or rates of the adverse events of interest (e.g., major bleeding) in rivaroxaban-exposed patients are substantially higher than what was observed in the clinical trials program, further actions will be discussed with the Agency. The emphasis on hypothesis generation, rather than hypothesis testing, is consistent with the limitations of any observational study conducted in the context of claims or other electronic health records databases. In particular, lack of ability to control for several important confounders (e.g., over-the-counter NSAIDS for bleeding risk), and lack of clinical detail of adverse events of interest, dictate that formal statistical comparisons should not be made between the drugs in this study.

For transparency, the investigational effort will be either done jointly, or reviewed and validated by an independent organization. The information gathered from this study will help the Sponsor better understand any issues associated with usage patterns or potentially serious safety concerns, and form a strategic plan to mitigate any identified risks.

7.2.9. Post-Marketing Observational Study

XAMOS (Xarelto in the prophylaxis of post surgical venous thromboembolism after elective Major Orthopedic Surgery of hip or knee) is a post-marketing observational cohort study designed to obtain data on the use of rivaroxaban and other pharmacologic agents in the prevention of venous thromboembolism (VTE) in elective hip or knee arthroplasty in clinical practice that will be conducted ex US by Bayer HealthCare. The study will be conducted in cooperation with physicians who will conduct the surgery and/or are responsible for perioperative thromboprophylaxis. Where necessary, general

practioners (GPs) and physicians in rehabilitation clinics will also be involved in the data collection. Up to 15,000 patients worldwide who are undergoing elective hip or knee arthroplasty and who are receiving pharmacologic treatment for the prevention of VTE will be enrolled at 200 sites. It is planned to collect data from 7,500 patients receiving current standard of care drug therapy, and from 7,500 patients receiving rivaroxaban.

This international non-interventional study is mainly considered to be hypothesis generating, and may lead to further research in this area. Following the findings of the clinical trials in drug development, this study will pursue the use of rivaroxaban under real-life treatment conditions in comparison with pharmacological current standard VTE-prevention treatment. Data will be collected on the use of rivaroxaban in comparison with other pharmacologic agents in the prophylaxis of VTE in a large sample of patients who undergo elective hip or knee arthroplasty.

The main objectives of the study are to collect data on:

- Bleeding events reported as serious or non-serious adverse events;
- Symptomatic thromboembolic events (DVT, PE) reported as adverse events;
- Uncommon adverse events (incidence rate between 0.1 % and 1 %);
- All cause mortality.

The main focus of the analyses is the comparison between the group of subjects treated with rivaroxaban and the group treated with any standard VTE prevention therapy, as well as, the comparison of the rivaroxaban group and the group of subjects treated with any LMWH.

8. QUANTITATIVE BENEFIT-RISK ASSESSMENT OF RIVAROXABAN FOR DVT AND PE PROPHYLAXIS AFTER THR OR TKR

8.1. Introduction

Benefit

Each of the 4 RECORD studies individually met or exceeded their primary efficacy objectives. The absolute and relative reductions in the primary efficacy endpoint of total VTE for rivaroxaban compared with enoxaparin were highly statistically significant and clinically meaningful. Robust and consistent results were obtained for the THR and TKR studies separately, as well as for all important subgroups of subjects, and for various sensitivity analyses with imputation of missing venographic data. It is important to note that rivaroxaban demonstrated superior efficacy for the primary endpoint against both of the currently approved US regimens of enoxaparin (40 mg once daily for THR and 30 mg twice daily for THR and TKR). The reductions for the composite of symptomatic VTE or death are also highly statistically significant (HR 0.42; 95% CI 0.29,0.63;p< 0.001) in

the pooled RECORD 1-4 analysis and were consistent for both THR (HR 0.43; 95% CI 0.23,0.78; p=0.006) and TKR (HR 0.42; 95%CI 0.25,0.72; p=0.001).

Risk

At the same time, there were modest increases in most bleeding event categories for rivaroxaban when compared with enoxaparin. In the pooled analysis of the 4 RECORD studies, an absolute increase of 0.18% was observed for major bleeding events with rivaroxaban compared to enoxaparin. Most of the increase was due to the differences in the categories of extrasurgical site bleeds with hemoglobin drops or transfusions, or surgical site events leading to reoperation. For the composite endpoint of major or non-major clinically relevant bleeding events, an absolute increase of 0.64% was observed with rivaroxaban compared with enoxaparin. Most of the increase was due to clinically relevant non-major bleeding events in the non-surgical categories of hematuria, rectal bleeding, nosebleed and vaginal bleeding. These modest increases with rivaroxaban were not unexpected since the efficacy and bleeding risks of anticoagulant drugs are probably mechanistically linked.

A summary of key efficacy and safety measures is included in Table 8-1:

Table 8-1: Pooled Incidence Rates of Key Efficacy and Bleeding Measures
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies, Unless Otherwise Noted)

	Rivaroxaban (N=6183)		Enoxaparin (N=6200)	
Efficacy events [a]				
Total VTE (MITT population)	181 (N=4248)	(4.26%)	402 (N=4264)	(9.43%)
Major VTE (MITT population valid for major VTE)	32 (N=4677)	(0.68%)	128 (N=4677)	(2.74%)
Symptomatic VTE/death	35	(0.57%)	82	(1.32%)
Symptomatic DVT	19	(0.31%)	49	(0.79%)
Symptomatic Non-fatal PE	10	(0.16%)	17	(0.27%)
Death, all causes	8	(0.13%)	16	(0.26%)
VTE-related	1	(0.02%)	2	(0.03%)
not VTE-related	3	(0.05%)	8	(0.13%)
Unexplained	4	(0.06%)	6	(0.10%)
Bleeding events [b]				
Any major bleeding event	24	(0.39%)	13	(0.21%)
Fatal	2[c]	(0.03%)	0	(0%)
Critical organ	3	(0.05%)	5	(0.08%)
Extrasurgical site, associated with decrease in hb of 2 g/dL or more/ requiring blood transfusion	8	(0.13%)	1	(0.02%)
Requiring re-operation	12	(0.19%)	7	(0.11%)
Any major bleeding/non-major, clinically relevant bleeding event	197	(3.19%)	158	(2.55%)
Non-major, clinically relevant	177	(2.86%)	145	(2.34%)
Surgical site [d]	98	(1.58%)	98	(1.58%)
Extra-surgical site [d]	82	(1.33%)	49	(0.79%)
Other, non-major	260	(4.21%)	256	(4.13%)

Note: Individual subjects can have more than 1 type of event.
[a] Efficacy events are given for the planned treatment phase (pre-specified time period).
[b] Bleeding events are given for the treatment-emergent period.
[c] One of these 2 deaths occurred in a subject who received enoxaparin placebo but not active rivaroxaban
[d] Site of bleeding based upon investigator determination.

Benefit-Risk Assessment

There are currently no analysis guidelines for quantifying pharmaceutical benefit-risk, and virtually no consensus on which methodologies are optimal. NNT/NNH (number needed to treat/harm) approaches are gaining increasing attention in the benefit-risk literature. A closely related approach involves calculating the excess number of beneficial or harmful events in a hypothetical population of a specified size. This is an intuitively appealing approach for assessing the public health implications of the results of a clinical trial program. While both methods are different representations of the same absolute risk difference between treatments, the excess number of events is more amenable to the calculation of confidence intervals. These methods are sometimes supplemented by the use of "utility" scores that reflect the degree to which patients weight the different benefit and risk outcomes they may experience.

8.2. Methods

In this analysis of the benefit-risk for rivaroxaban in the prevention of DVT and PE in THR and TKR, the excess number of events approach is utilized. The excess number of events is defined as the additional number of patients, out of a hypothetical population, who would experience a particular event when using one treatment compared to another treatment. In this analysis of rivaroxaban data, the excess number of events is defined as the number of events in a population of 10,000 patients treated with enoxaparin minus the number of events in a population of 10,000 patients treated with rivaroxaban. A positive value indicates that more events occur in the population treated with enoxaparin. In these analyses, all events are weighted equally.

In addition, an analysis describing the context and clinical import of symptomatic VTE and clinically relevant bleeding endpoints is presented. Finally, a utility-weighted analysis of the excess number of beneficial/harmful events was also performed, in which the outcomes are weighted by patient preferences for different health states. This analysis supports the primary analyses, and can be found in Appendix 3.

The pooled RECORD 1-4 data set was chosen for the benefit-risk analyses, given that each of the RECORD studies, taken alone, met its primary endpoint, that the treatment effects were consistent across studies, and that the study designs had many features in common. Use of the pooled data set, by virtue of its greater size and event numbers, allows for greater precision in estimates of overall treatment effects and benefit-risk ratios.

8.3. Results

8.3.1. Excess Number of Event Results

Table 8-2 shows the excess number of events for several outcomes pooled over the 4 RECORD studies. The table also includes the number of events for each treatment in a population of 10,000 patients along with the relevant confidence intervals.

Table 8-2: Pooled 1 – 4 RECORD Program treatment phase number of events for a hypothetical population of 10,000 patients and excess number of events, shown for several end points and with 95% confidence intervals (CIs).*

	Number of Events (in 10,000 patients)				Excess # of Events (Enox - Riva)		Difference Between Excess # of Events	
	Riva		Enox					
Outcome	N	95% CI	N	95% CI	N	95% CI	N	95% CI
Total VTE	426	(364 to 488)	943	(853 to 1032)	504	(399 to 608)	440	(320 to 560)
Major & Clin-Rel/non-Major Bleeds	319	(274 to 363)	255	(215 to 295)	-64	(-123 to -5)		
Major VTE	68	(44 to 93)	274	(226 to 321)	205	(153 to 257)	187	(132 to 243)
Major Bleeding	39	(23 to 55)	21	(9 to 33)	-18	(-37 to 1)		
Symptomatic VTE & All-Cause Mortality	57	(38 to 77)	132	(103 to 161)	76	(42 to 110)	58	(19 to 97)
Major Bleeding	39	(23 to 55)	21	(9 to 33)	-18	(-37 to 1)		
Any treatment-emergent serious AE	657	(594 to 720)	852	(781 to 923)	194	(101 to 287)		

There are several comparisons that are made in this table:

8.3.1.1. Total VTE and Major / Clinically Relevant, Non-Major Bleeding

Total VTE is a prespecified primary endpoint in the individual RECORD studies. It is a composite of any DVT (symptomatic or asymptomatic), nonfatal PE or death from all causes. Major and clinically relevant non-major bleedings comprise all bleeding events deemed clinically relevant. This might be viewed as a balanced benefit-risk comparison, as a key clinical need is to reduce the Total VTE events while not elevating the risk for clinically meaningful bleeding.

As shown in Table 8-2, enoxaparin would be associated with 504 more total VTE events in a population of 10,000 patients than would rivaroxaban, while rivaroxaban would result in 64 more bleeding events than enoxaparin. In a population of 10,000 patients, treatment with rivaroxaban would result in a net of 440 fewer events than with enoxaparin treatment, suggesting that the benefit exceeds the risk in favor of rivaroxaban.

8.3.1.2. Major VTE (key secondary endpoint) and Major Bleeding

Another comparison can be performed with the more severe outcomes within the composite outcomes examined above. The comparison of major VTE to major bleeding was prespecified as the benefit-risk comparison of specific interest within the individual RECORD studies. In a population of 10,000 patients, treatment with enoxaparin would be associated with 205 more major VTE events than rivaroxaban, while rivaroxaban would result in 18 more major bleeding events, a net of 187 fewer events for rivaroxaban than for enoxaparin (Table 8-2).

8.3.1.3. Symptomatic VTE/All Cause Mortality and Major Bleeding

Symptomatic VTE (DVT or PE) or death is the prespecified primary efficacy endpoint for the pooled analysis. This is an important composite endpoint for patients and health care providers, since asymptomatic VTEs will generally not be identified without special testing, which is generally not conducted in routine clinical practice. Again, for the comparison with major bleeding, the excess number of Symptomatic VTE or death events minus that for Major bleeding events yields a net of 58 fewer events with rivaroxaban treatment.

It is worth noting that, in all three scenarios, benefit exceeds risk even when using the excess number of events on the low end of the confidence intervals for the VTE composite outcomes and on the high end for the bleeding outcomes (e.g., a net difference

276 (399 – 123) for Total VTE and major/clinically-relevant, non-major bleeding). This observation can be considered a sensitivity analysis, indicating the consistency of the conclusion that benefit exceeds risk for rivaroxaban compared with enoxaparin.

In each of the above comparisons, thrombotic and bleeding events are composite endpoints of heterogeneous events, but each event is essentially weighted equally, which may not accurately reflect their overall clinical importance. In THR and TKR patients, most bleeding events occur early after surgery, during the time when the patient is hospitalized and under close medical supervision for what are infrequent, but anticipated postoperative occurrences. These bleeding events are usually transient in nature, are usually manageable with supportive care, and are usually without long-term sequelae. In contrast, most symptomatic VTE events occur after hospital discharge, require rehospitalization, prolonged anticoagulant therapy, may result in long-term disability, and can have an appreciable mortality risk.

Table 8-3 illustrates these points. Across the RECORD program, all symptomatic VTE events, major bleeding events, and clinically relevant non-major bleeding events were assessed for the criteria listed. Symptomatic VTE events were longer in duration, and were more likely than either major or non-major clinically relevant bleeds to be considered serious, require remedial treatment, persist at the time of study end, and occur remotely from the immediate perioperative period. They were also more likely than clinically relevant non-major bleeds to be severe, and require hospitalization. All of these taken together support the tenet that symptomatic VTE events are of greater clinical import than both non-major and major bleeds.

Table 8-3: Clinical Impact Comparison of Symptomatic VTE Events vs. Bleeding Events Pooled RECORD 1-4 – Treatment Period

Parameter[a]	Symptomatic VTE	Major Bleeding	Clinically-relevant, non-major bleeding
	N=97	N=37	N=349
Severe intensity	26.8%	27.0%	8.0%
Serious event	99.0%	70.3%	21.5%
Hospitalization	53.6%	54.1%	13.5%
Event unresolved	50.5%	13.5%	9.5%
Transfusion	NA	73.0%	38.4%
Action – permanent d/c	71.1%	45.9%	16.3%
Action- remedial Rx	85.6%	29.7%	24.9%
Duration of event – median days	29.0	2.0	4.0
Onset time from surgery- median days	7.0	2.0	3.0

[a] As identified by the investigator in case report forms and adverse event reports.

Consistent with the above assessment is the overall comparison of serious adverse events across the RECORD program. Serious AEs are events identified by the investigator that:

- result in death
- are life-threatening
- require inpatient hospitalization or prolong hospitalization
- result in persistent or significant disability
- result in a congenital anomaly
- or are an otherwise important medical event

By definition, SAEs include only *serious* events, or events of clinical import. SAEs capture both efficacy and safety events, and represent the investigator perspective without filtering according to adjudication criteria. In a comparison of SAEs in the RECORD program, rivaroxaban treatment again results in a favorable benefit-risk profile. Table 8-2 shows that, in a population of 10,000 patients, rivaroxaban treatment would result in 194 fewer treatment-emergent serious AEs than enoxaparin.

Finally, as noted above, a utility-weighted analysis of the excess number of beneficial/harmful events was also performed, in which the outcomes are weighted by patient preferences for different health states. Consistent with the analyses presented above, the weighted utility analysis results demonstrate a strongly favorable benefit-risk profile for rivaroxaban treatment. Details of this analysis can be found in Appendix 3.

8.4. Summary and Conclusions

Each of the four RECORD studies independently demonstrated superiority in reducing the incidence of total VTE vs. the comparator, either enoxaparin, or, in the case of RECORD 2, an enoxaparin-placebo combination. In three of the studies (RECORD 1, RECORD 3, and RECORD 4), the first objective was to demonstrate comparable efficacy (non-inferiority) in total VTE, but in each case, statistically significant and clinically meaningful reductions in events were achieved with rivaroxaban treatment. Consistent reductions were also seen in Major and Symptomatic VTE. These occurred at the expense of a modest increase in bleeding events, most of which had relatively lesser clinical impact than the VTE events.

Comparisons of key efficacy and safety composites across the pooled data set demonstrate similar outcomes. In each comparison, rivaroxaban consistently demonstrated an excess of benefit over risk compared with enoxaparin. This conclusion applies to a variety of definitions of the endpoint examined (total VTE, major VTE, symptomatic VTE and all-cause mortality) and the AEs considered. Furthermore, analyses of the the clinical import of the symptomatic VTE events versus bleeding events indicate that the events prevented by rivaroxaban are of greater clinical impact than the bleeding events that occur as a result of treatment, further solidifying the favorable

benefit-risk profile of rivaroxaban. Keeping in mind that enoxaparin is an accepted part of standard therapy in the proposed setting of THR/TKR, the results present a compelling argument that the benefit-risk balance of rivaroxaban is favorable. Considering the number of THR and TKR surgeries, the potential public health benefit is substantial.

In conclusion, data from the RECORD program, consisting of four pivotal phase 3 studies, consistently demonstrate that rivaroxaban is highly efficacious vs. an active comparator in the prevention of DVT and PE in patients undergoing THR or TKR, is well tolerated with only a modest increase in bleeding, and has a highly favorable benefit-risk ratio. Furthermore, rivaroxaban is administered orally, once daily, has limited potential for significant drug-drug interactions, and requires no laboratory monitoring. As such, rivaroxaban represents an important advance in the treatment of patients undergoing THR or TKR, with the potential to significantly reduce the burden of thrombotic complications in this large patient population.

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APPENDICES

APPENDIX 1

SUPPORTIVE BASELINE, EFFICACY , AND SAFETY ANALYSES

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Advisory Committee Briefing Book – Appendix 1

Rivaroxaban for the Prophylaxis of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) in Patients Undergoing Hip or Knee Replacement Surgery

JNJ-39039039 (BAY 59-7939, rivaroxaban)

Issue/Report Date: 10 FEBRUARY 2009
Document No.: EDMS-PSDB-9380584:2.0

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1. DEMOGRAPHIC AND STUDY COMPLETION RESULTS BY TREATMENT GROUP

Table 1 and Table 2 show the demographic characteristics of the safety population by treatment group for the THR (RECORD 1 and 2) and TKR (RECORD 3 and 4) studies. There were no clinically important differences between the treatment groups for any parameter.

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Table 1: Demographics and Baseline Characteristics
(Subjects Valid for Safety Analysis in Pooled THR RECORD 1-2 studies)

	Rivaroxaban (N=3437)	Enoxaparin (N=3453)	Total (N=6890)
Sex N (%)			
Male	1550 (45.10%)	1560 (45.18%)	3110 (45.14%)
Female	1887 (54.90%)	1893 (54.82%)	3780 (54.86%)
Race N (%)			
White	2840 (82.63%)	2847 (82.45%)	5687 (82.54%)
Black	55 (1.60%)	48 (1.39%)	103 (1.49%)
Asian	252 (7.33%)	246 (7.12%)	498 (7.23%)
American Indian	2 (0.06%)	1 (0.03%)	3 (0.04%)
Hispanic	156 (4.54%)	173 (5.01%)	329 (4.78%)
Uncodable	17 (0.49%)	23 (0.67%)	40 (0.58%)
Missing	115 (3.35%)	115 (3.33%)	230 (3.34%)
Age (yrs.) Mean±SD	62.5 ±12.2	62.7 ±12.2	62.6 ±12.2
Age (categorized) N (%)			
<65 yrs	1762 (51.27%)	1770 (51.26%)	3532 (51.26%)
65-75 yrs	1243 (36.17%)	1217 (35.24%)	2460 (35.70%)
>75 yrs	432 (12.57%)	466 (13.50%)	898 (13.03%)
Weight (kg) Mean±SD	76.8 ± 16.0	77.2 ±16.4	77.0 ±16.2
Weight (categorized) N (%)			
<=50 kg	106 (3.08%)	122 (3.53%)	228 (3.31%)
>50-70 kg	1240 (36.08%)	1165 (33.74%)	2405 (34.91%)
>70-90 kg	1457 (42.39%)	1499 (43.41%)	2956 (42.90%)
>90-110 kg	540 (15.71%)	551 (15.96%)	1091 (15.83%)
>110 kg	86 (2.50%)	112 (3.24%)	198 (2.87%)
Missing	8 (0.23%)	4 (0.12%)	12 (0.17%)
BMI (kg/m^2) Mean±SD	27.5 ±4.8	27.6 ± 4.9	27.5 ±4.9
BMI (categorized) N (%)			
<18.5	36 (1.05%)	56 (1.62%)	92 (1.34%)
18.5 - <25	1053 (30.64%)	1038 (30.06%)	2091 (30.35%)
25 - <30	1422 (41.37%)	1378 (39.91%)	2800 (40.64%)
30 - <40	851 (24.76%)	913 (26.44%)	1764 (25.60%)
>=40	64 (1.86%)	59 (1.71%)	123 (1.79%)
Missing	11 (0.32%)	9 (0.26%)	20 (0.29%)
Creatinine clearance (ml/min) Mean±SD	90.2 ± 30.7	90.1 ± 31.1	90.2 ± 30.9
Creatinine clearance (categorized) N (%)			
>80 ml/min	2003 (58.28%)	2012 (58.27%)	4015 (58.27%)
50-80 ml/min	1177 (34.24%)	1156 (33.48%)	2333 (33.86%)
30-<50 ml/min	206 (5.99%)	241 (6.98%)	447 (6.49%)
<30 ml/min	16 (0.47%)	19 (0.55%)	35 (0.51%)
Missing	35 (1.02%)	25 (0.72%)	60 (0.87%)
Fragile subject[a] N (%)			
No	2837 (82.54%)	2796 (80.97%)	5633 (81.76%)
Yes	600 (17.46%)	657 (19.03%)	1257 (18.24%)

BMI=Body Mass Index
Note: Percentages are calculated including missing values.
[a] Fragile definition: Age >75 years and/or calculated creatinine clearance <50 ml/min and/or weight ≤50 kg

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Table 2: Demographics and Baseline Characteristics
(Subjects Valid for Safety Analysis in Pooled TKR RECORD 3-4 studies)

	Rivaroxaban (N=2746)	Enoxaparin (N=2747)	Total (N=5493)
Sex N (%)			
Male	882 (32.12%)	959 (34.91%)	1841 (33.52%)
Female	1864 (67.88%)	1788 (65.09%)	3652 (66.48%)
Race N (%)			
White	2008 (73.12%)	2029 (73.86%)	4037 (73.49%)
Black	103 (3.75%)	78 (2.84%)	181 (3.30%)
Asian	365 (13.29%)	371 (13.51%)	736 (13.40%)
American Indian	1 (0.04%)	4 (0.15%)	5 (0.09%)
Hispanic	183 (6.66%)	170 (6.19%)	353 (6.43%)
Uncodable	10 (0.36%)	18 (0.66%)	28 (0.51%)
Missing	76 (2.77%)	77 (2.80%)	153 (2.79%)
Age (yrs.) Mean±SD	65.8 ±9.6	66.0 ±9.4	65.9 ±9.5
Age (categorized) N (%)			
<65 yrs	1153 (41.99%)	1135 (41.32%)	2288 (41.65%)
65-75 yrs	1111 (40.46%)	1164 (42.37%)	2275 (41.42%)
>75 yrs	482 (17.55%)	448 (16.31%)	930 (16.93%)
Weight (kg) Mean±SD	82.6 ± 18.3	83.0 ± 18.2	82.8 ± 18.2
Weight (categorized) N (%)			
<=50 kg	41 (1.49%)	40 (1.46%)	81 (1.47%)
>50-70 kg	706 (25.71%)	661 (24.06%)	1367 (24.89%)
>70-90 kg	1212 (44.14%)	1233 (44.89%)	2445 (44.51%)
>90-110 kg	563 (20.50%)	596 (21.70%)	1159 (21.10%)
>110 kg	220 (8.01%)	215 (7.83%)	435 (7.92%)
Missing	4 (0.15%)	2 (0.07%)	6 (0.11%)
BMI (kg/m^2) Mean±SD	30.3 ± 5.7	30.3 ± 5.6	30.3 ± 5.6
BMI (categorized) N (%)			
<18.5	9 (0.33%)	8 (0.29%)	17 (0.31%)
18.5 - <25	421 (15.33%)	387 (14.09%)	808 (14.71%)
25 - <30	1020 (37.14%)	1096 (39.90%)	2116 (38.52%)
30 - <40	1137 (41.41%)	1085 (39.50%)	2222 (40.45%)
>=40	154 (5.61%)	168 (6.12%)	322 (5.86%)
Missing	5 (0.18%)	3 (0.11%)	8 (0.15%)
Creatinine clearance (ml/min) Mean±SD	91.5 ± 32.8	91.6 ± 33.7	91.6 ± 33.2
Creatinine clearance (categorized) N (%)			
>80 ml/min	1614 (58.78%)	1586 (57.74%)	3200 (58.26%)
50-80 ml/min	916 (33.36%)	958 (34.87%)	1874 (34.12%)
30-<50 ml/min	174 (6.34%)	168 (6.12%)	342 (6.23%)
<30 ml/min	13 (0.47%)	9 (0.33%)	22 (0.40%)
Missing	29 (1.06%)	26 (0.95%)	55 (1.00%)
Fragile subject[a] N (%)			
No	2157 (78.55%)	2203 (80.20%)	4360 (79.37%)
Yes	589 (21.45%)	544 (19.80%)	1133 (20.63%)

BMI=Body Mass Index
Note: Percentages are calculated including missing values.
[a] Fragile definition: Age >75 years and/or calculated creatinine clearance <50 ml/min and/or weight ≤50 kg

The overall rates of study medication treatment completion and the reasons for premature termination of study medication by treatment group are shown in Table 3. The overall rate of premature terminations was about 1% lower for rivaroxaban compared with enoxaparin with the largest difference in the category of " reached clinical endpoint."

Table 3: Subject Study Medication Completion/Withdrawal Information
(Randomized Population in the Pooled RECORD 1-4 studies)

	Rivaroxaban (N=6356)	Enoxaparin (N=6373)	Total (N=12729)
Completed Treatment	**5679 (89.35%)**	**5638 (88.47%)**	**11371 (88.91%)**
Premature Termination	**677 (10.65%)**	**735 (11.53%)**	**1412 (11.09%)**
Adverse Event	224 (3.52%)	244 (3.03%)	468 (3.68%)
Clinical Endpoint Reached	23 (0.36%)	59 (0.93%)	82 (0.64%)
Consent Withdrawn	289 (4.55%)	273 (4.28%)	562 (4.42%)
Investigator Decision, Not Protocol Driven	10 (0.16%)	15 (0.24%)	25 (0.20%)
Lost to Follow-up	8 (0.13%)	15 (0.24%)	23 (0.18%)
Non-compliant With Study Medication	40 (0.63%)	28 (0.44%)	68 (0.53%)
Protocol Violation	78 (1.23%)	91 (1.43%)	169 (1.33%)
Other	5 (0.08%)	10 (0.16%)	15 (0.12%)

2. ADDITIONAL EFFICACY ANALYSES

2.1. Description and Definitions

This section provides the results for additional analyses that were conducted to support the prespecified pooled primary analysis of symptomatic VTE or death for the total treatment duration pool across all 4 RECORD studies. These analyses included looking at the components of the primary endpoint and also the results for the THR and TKR studies separately. Subgroup analyses of the total VTE endpoint for the THR and TKR studies separately are also presented.

Additional treatment duration pools examined were:

- Until Day 12 ± 2 pool (this pool includes events occurring during the double-blind treatment period until Day 12±2, which represents the period of active study medication treatment that was common to all 4 RECORD studies);
- Active control pool (this pool includes all events occurring during the active treatment periods for each study, excluding the placebo treatment period after Day 12 ±2 in RECORD 2); and
- Treatment plus follow-up period pool (this pool includes all events occurring during the treatment period and through the follow-up period after blinded study medication discontinuation).

The analyses that were conducted are outlined in Table 4 and the different treatment duration pools are illustrated in Figure 1.

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Table 4: Analyses (Cox Regression) of Symptomatic VTE or Death for the Pooled RECORD Studies

Treatment Phase
Composite of Symptomatic VTE or Death (primary endpoint), Composite of Symptomatic PE or Death, Symptomatic VTE, Symptomatic DVT, Symptomatic PE, and Death for:

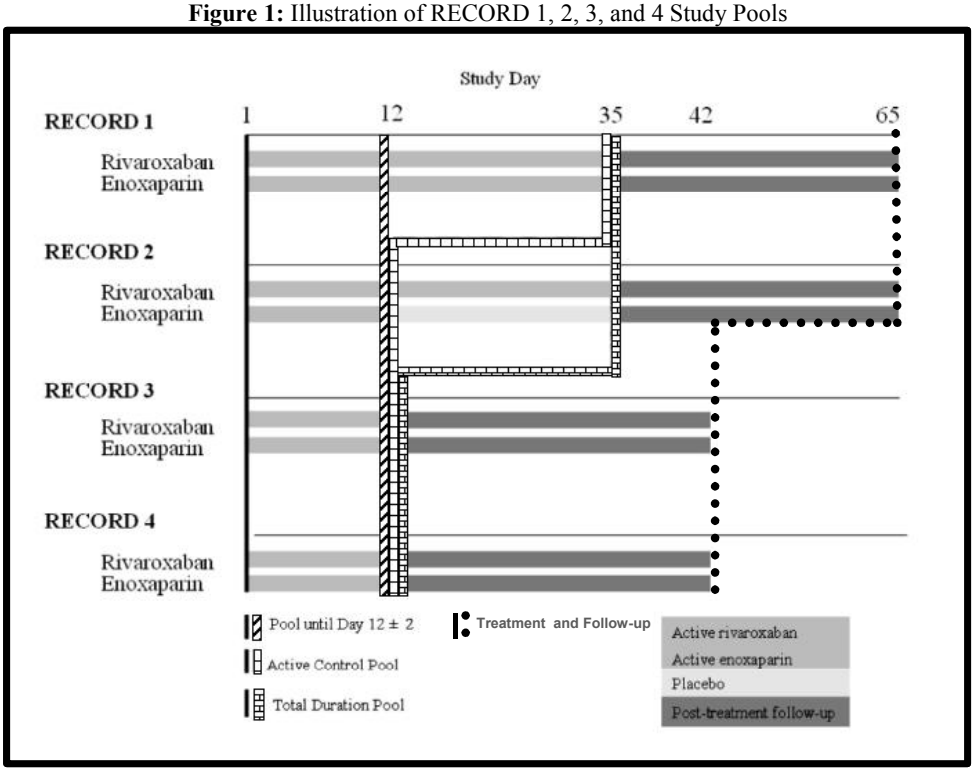
- the RECORD 1-4 total duration pool (primary study pool)
- the RECORD 1-2 (THR) pool
- the RECORD 3-4 (TKR) pool
- the RECORD 1-4 treatment phase until Day 12±2 pool
- the RECORD 1-4 active control pool.

Treatment and Follow-Up Phases Combined
Composite of Symptomatic VTE or Death, Composite of Symptomatic PE or Death ,Symptomatic VTE , Symptomatic DVT, Symptomatic PE and Death for:

- the RECORD 1-4 pool
- the RECORD 1-2 (THR) pool
- the RECORD 3-4 (TKR) pool.

Note: Population was valid for safety analysis.

Figure 1: Illustration of RECORD 1, 2, 3, and 4 Study Pools



2.2. Symptomatic Event Endpoint Components by THR or TKR

Table 5 shows the incidence and corresponding hazard ratio for symptomatic event endpoints during the treatment period for all 4 RECORD studies combined and for the THR and TKR studies separately. As already discussed in the main briefing document the primary endpoint of symptomatic VTE or death was statistically significantly reduced in

all 4 studies combined (p< 0.001) and in the THR (p=0.006) and TKR (p=0.001) studies separately. All the components of this endpoint were directionally consistent with point estimates favoring rivaroxaban in both the THR and TKR studies. Kaplan Meier curves for the THR and TKR studies for the symptomatic PE or death composite endpoint are provided in Figures 2 and 3. These curves show that the event rate separation between the treatment groups begins early and continues during the active treatment period with no loss of separation during the follow-up period.

Table 5: Composite of Symptomatic VTE or Death and Components During the Treatment Phase Pooled Results
(Subjects Valid for Safety Analysis in the RECORD Studies)

Study	Rivaroxaban n (%)	Enoxaparin n (%)	HR (95%CI)
Symptomatic VTE or death			
Pooled R 1-2	15/3437 (0.44)	35/3453 (1.01)	0.43(0.23, 0.78)
Pooled R 3-4	20/2746 (0.73)	47/2747 (1.71)	0.42(0.25, 0.72)
Pooled R 1-4	35/6183 (0.57)	82/6200 (1.32)	0.42(0.29, 0.63)
Symptomatic VTE			
Pooled R 1-2	9/3437 (0.26)	26/3453 (0.75)	0.34(0.16, 0.73)
Pooled R 3-4	19/2746 (0.69)	42/2747 (1.53)	0.45(0.26, 0.78)
Pooled R 1-4	28/6183 (0.45)	68/6200 (1.10)	0.41(0.26, 0.64)
Symptomatic DVT, all			
Pooled R 1-2	5/3437 (0.15)	19/3453 (0.55)	0.26(0.10,0.70)
Pooled R 3-4	14/2746 (0.51)	30/2747 (1.09)	0.47(0.25,0.88)
Pooled R 1-4	19/6183 (0.31)	49/6200 (0.79)	0.39(0.23,0.66)
Symptomatic PE			
Pooled R 1-2	5/3437 (0.15)	7/3453 (0.20)	0.71(0.23, 2.24)
Pooled R 3-4	5/2746 (0.18)	12/2747 (0.44)	0.41(0.15, 1.18)
Pooled R 1-4	10/6183 (0.16)	19/6200 (0.31)	0.52(0.24, 1.13)
Death, all causes			
Pooled R 1-2	6/3437 (0.17)	11/3453 (0.32)	0.54(0.20, 1.47)
Pooled R 3-4	2/2746 (0.07)	5/2747 (0.18)	0.40(0.08, 2.05)
Pooled R 1-4	8/6183 (0.13)	16/6200 (0.26)	0.50(0.21, 1.16)
Symptomatic PE or Death			
Pooled R 1-2	11/3437 (0.32)	16/3453 (0.46)	0.69(0.32, 1.48)
Pooled R 3-4	6/2746 (0.22)	17/2747 (0.62)	0.35(0.14, 0.89)
Pooled R 1-4	17/6183 (0.27)	33/6200 (0.53)	0.51(0.29, 0.92)

Abbreviations: DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism.

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Figure 2: Kaplan Meier Curve for the THR (RECORD 1-2) Studies for the Symptomatic PE or Death Composite Endpoint for Treatment and Follow-up Periods

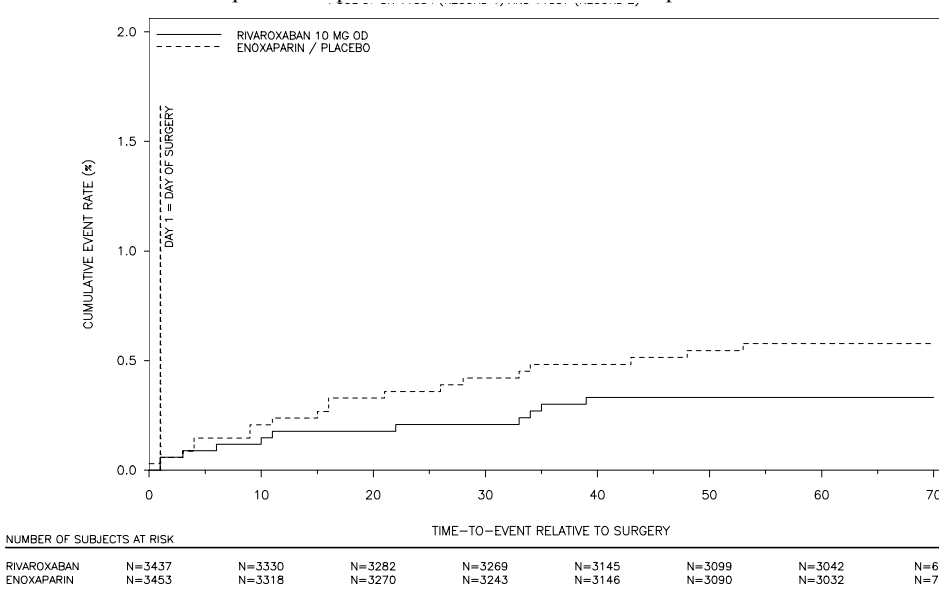
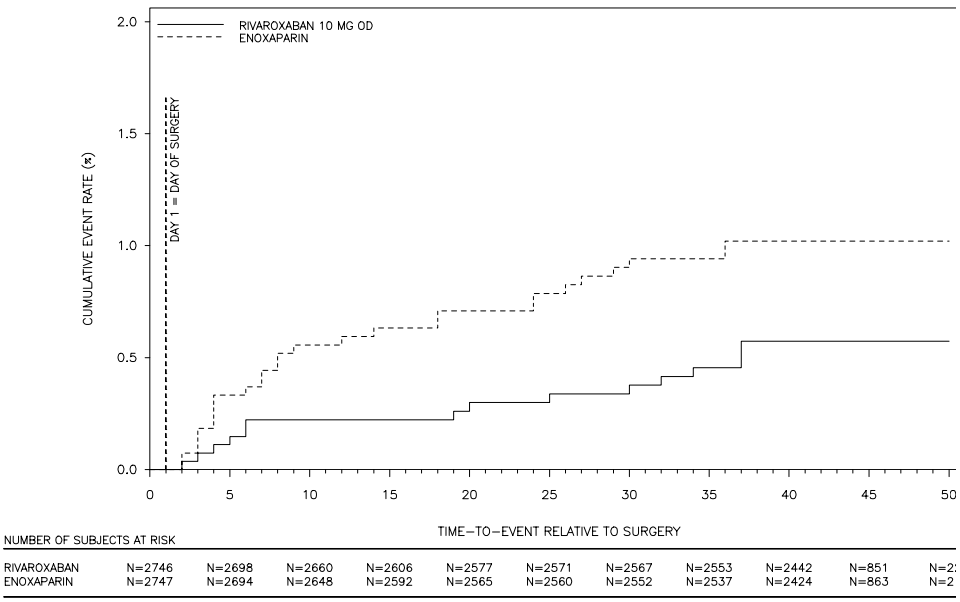


Figure 3: Kaplan Meier Curve for the TKR (RECORD 3-4) Studies for the Symptomatic PE or Death Composite Endpoint for the Treatment and Follow-up Periods.



2.3. Symptomatic Event Endpoint Analyses for Additional Treatment Duration pools

Analyses for the 4 studies combined for the up to Day 12 ±2, active control and treatment plus follow-up period pools are shown in Table 6. These analyses are consistent with those for the total treatment duration pool. For the primary endpoint of symptomatic VTE or death the results were statistically significantly different in favor of rivaroxaban for all 3 pools (Day 12 ±2 p=0.001, active control p<0.001, treatment and follow-up p<0.001) and all component point estimates favored rivaroxaban.

Table 6: Composite of Symptomatic VTE or Death and Components During the Treatment Phase Until Day 12±2, Active Control and Treatment Plus Follow-up Period Pools

(Subjects Valid for Safety Analysis in the pooled RECORD 1-4 Studies)

	Rivaroxaban	Enoxaparin	Hazard Ratio	
Event	n (%) N=6183	n (%) N=6200	Point Estimate	95% CI
Symptomatic VTE or Death				
Day 12±2	29 (0.47)	60 (0.97)	0.48	0.31, 0.75
Active control	32 (0.52)	67 (1.08)	0.48	0.31, 0.73
Treatment and Follow-up	50 (0.81)	101 (1.63)	0.49	0.35, 0.69
Symptomatic VTE				
Day 12 ±2	24 (0.39)	52 (0.84)	0.46	0.28, 0.75
Active control	26 (0.42)	57 (0.92)	0.45	0.29,0.72
Treatment and Follow-up	38 (0.61)	79 (1.27)	0.48	0.32, 0.70
Symptomatic DVT				
Day 12 ±2	17 (0.27)	36 (0.58)	0.47	0.27, 0.84
Active control	18 (0.29)	41 (0.66)	0.44	0.25, 0.76
Treatment and Follow-up	22 (0.36)	56 (0.90)	0.39	0.24, 0.64
Symptomatic PE				
Day 12 ±2	7 (0.11)	16 (0.26)	0.44	0.18, 1.06
Active control	9 (0.15)	16 (0.26)	0.56	0.25,1.27
Treatment and Follow-up	17 (0.27)	25 (0.40)	0.67	0.36,1.25
Death				
Day 12 ±2	6 (0.10)	10 (0.16)	0.60	0.22, 1.65
Active control	7 (0.11)	12 (0.19)	0.58	0.23,1.48
Treatment and Follow-up	13 (0.21)	25 (0.40)	0.52	0.27, 1.01
Symptomatic PE or Death				
Day 12 ±2	12 (0.19)	24 (0.39)	0.50	0.25, 1.00
Active control	15 (0.24)	26 (0.42)	0.57	0.30,1.08
Treatment and Follow-up	29 (0.47)	47 (0.76)	0.61	0.39, 0.98

Abbreviations: CI=confidence interval, DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism

Pooled p value from two-sided Wald test, H_0: HR=1.0

2.4. Total VTE Endpoint Subgroup Results by THR or TKR

A summary of the total VTE endpoint subgroup results in the THR and TKR studies separately is provided in Figures 4 and 5. Overall the results were similar in both the THR and TKR studies with almost all of the odds ratio point estimates favoring rivaroxaban. The only exceptions were in subgroups with very few events (e.g. black race

and creatinine clearance <30 mL/min in THR and other race in TKR) with the ratios calculated using median unbiased estimators due to zero cell counts.

Figure 4: Total VTE: Odds Ratios (95% CI) by THR Subgroup
(MITT Population Valid for Total VTE of the Pooled RECORD 1-2 Studies)

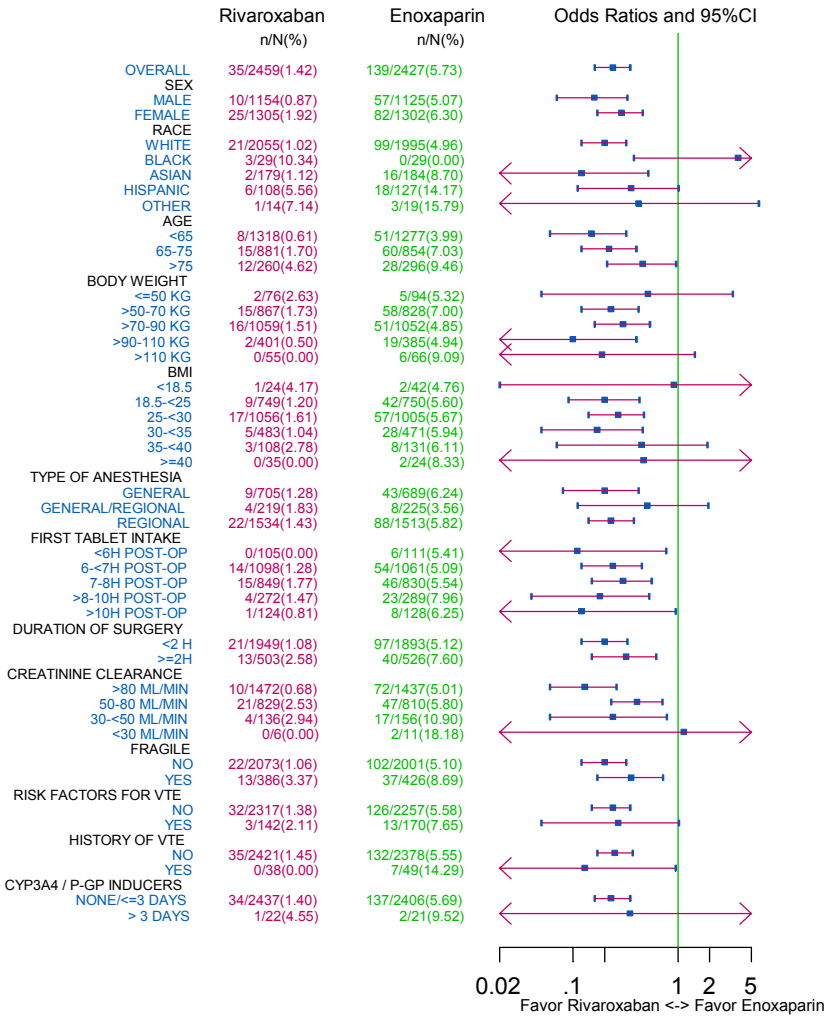
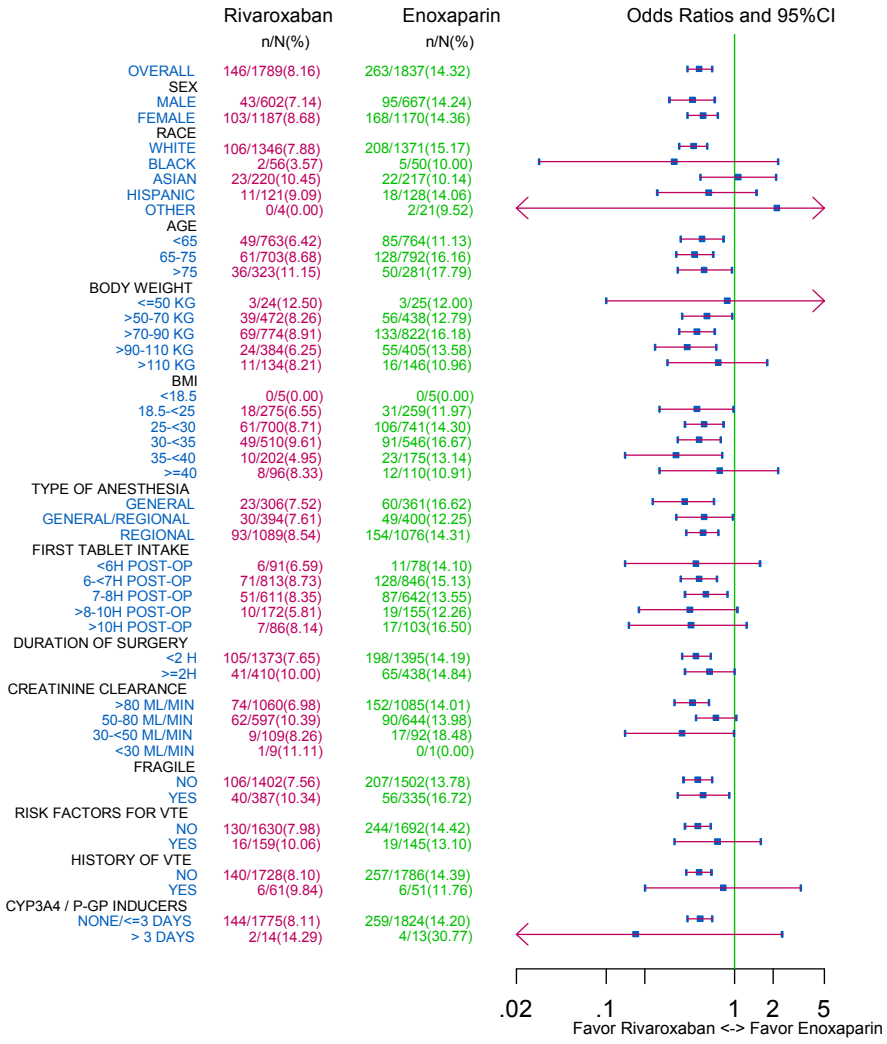


Figure 5: Total VTE: Odds Ratios (95% CI) by TKR Subgroup
(MITT Population Valid for Total VTE of the Pooled RECORD 3-4 Studies)



3. ADDITIONAL SAFETY ANALYSES

Additional safety analyses for the THR and TKR studies separately and for the different treatment duration pools are provided in this section.

3.1. Adverse Events Summary by THR or TKR

Tables 7 and 8 summarize adverse events from the THR (RECORD 1-2) and TKR (RECORD 3-4) studies respectively. In both the THR and TKR studies, the incidence of

treatment-emergent adverse events, treatment-emergent serious adverse events, or adverse events leading to permanent study drug discontinuation were similar or lower on rivaroxaban compared to enoxaparin.

Table 7: Summary of Adverse Events THR
(Subjects Valid for Safety Analysis in Pooled RECORD 1-2 Studies)

Incidence of:	Rivaroxaban (N= 3437)	Enoxaparin (N= 3453)
Any death	7 (0.20%)	13 (0.38%)
Any serious adverse event	278 (8.09%)	347 (10.05%)
Any adverse event	2243 (65.26%)	2303 (66.70%)
Any adverse event starting >2 days after stop of study drug	254 (7.39%)	234 (6.78%)
Any adverse event resulting in permanent discontinuation of study drug	131 (3.81%)	164 (4.75%)
Any treatment-emergent adverse event	2181 (63.46%)	2246 (65.04%)
Any treatment-emergent event excluding bleeding, acute DVT, and PE event[a]	2111 (61.42%)	2128 (61.63%)
Any treatment-emergent acute DVT or PE event[a]	79 (2.30%)	173 (5.01%)
Any treatment-emergent bleeding event[a]	231 (6.72%)	214 (6.20%)
Any serious treatment-emergent event	236 (6.87%)	312 (9.04%)
Any serious treatment-emergent event, excluding bleeding, acute DVT, and PE event[a]	201 (5.85%)	241 (6.98%)
Any serious treatment-emergent acute DVT or PE event[a]	14 (0.41%)	58 (1.68%)
Any serious treatment-emergent bleeding event[a]	27 (0.79%)	25 (0.72%)

[a] as assessed by the investigator
Key: DVT = deep vein thrombosis; PE = pulmonary embolism
Note: Treatment-emergent events are those that occurred after the first dose and up to 2 days after the last dose of study medication.

Table 8: Summary of Adverse Events TKR
(Subjects Valid for Safety Analysis in Pooled RECORD 3-4 Studies)

Incidence of:	Rivaroxaban (N=2746)	Enoxaparin (N=2747)
Any death	6 (0.22%)	12 (0.44%)
Any serious adverse event	233 (8.49%)	275 (10.01%)
Any adverse event	2122 (77.28%)	2194 (79.87%)
Any adverse event starting >2 days after stop of study drug	373 (13.58%)	387 (14.09%)
Any adverse event resulting in permanent discontinuation of study drug	99 (3.61%)	124 (4.51%)
Any treatment-emergent adverse event	1998 (72.76%)	2060 (74.99%)
Any treatment-emergent event excluding bleeding, acute DVT, and PE event[a]	1931 (70.32%)	1938 (70.55%)
Any treatment-emergent acute DVT or PE event[a]	187 (6.81%)	292 (10.63%)
Any treatment-emergent bleeding event[a]	235 (8.56%)	214 (7.79%)
Any serious treatment-emergent event	170 (6.19%)	216 (7.86%)
Any serious treatment-emergent event, excluding bleeding, acute DVT, and PE event[a]	110 (4.01%)	135 (4.91%)
Any serious treatment-emergent acute DVT or PE event[a]	37 (1.35%)	73 (2.66%)
Any serious treatment-emergent bleeding event[a]	38 (1.38%)	25 (0.91%)

[a] as assessed by the investigator
Key: DVT = deep vein thrombosis; PE = pulmonary embolism
Note: Treatment-emergent events are those that occurred after the first dose and up to 2 days after the last dose of study medication.

3.2. Bleeding Events Analyses for Additional Treatment Duration Pools

Table 9 summarizes results for postbaseline bleeding event endpoints (includes events that occurred during treatment and follow-up). The number of additional bleeding events occurring during follow-up (more than 2 days after study drug discontinuation) was small and the estimates of absolute risk differences and hazard ratios obtained from this post baseline analysis are very similar to those based on the treatment emergent bleeding event analysis presented in the main body of the briefing document.

Table 10 presents bleeding event endpoint data based on the Day 12 +/- 2 pool which includes events that occurred while taking double-blind study medication until Day 12 +/- 2, since active rivaroxaban and active enoxaparin were administered at least through Day 12 in each of the RECORD studies. Table 10 also includes data from the active control pool which includes events occurring during the active control phase from each study, but excludes events in both treatment groups occurring during the placebo period from RECORD 2.

Table 9: Incidence of Postbaseline Bleeding Events
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety in pooled RECORD 1-4 studies)

Endpoint	Rivaroxaban (N = 6183)	Enoxaparin (N = 6200)	Absolute Risk difference (95% CI)	Hazard Ratio[a] (95% CI)	Hazard Ratio P Value
Major[b]	27 (0.44%)	17 (0.27%)	0,16% (-0.05%, 0.37%)	1.59 (0.87, 2.92)	0.135
Major including Surgical site[c]	115 (1.86%)	92 (1.48%)	0.38% (-0.08, 0.83%)	1.25 (0.95, 1.65)	0.108
Non-major, clinically relevant	184 (2.98%)	154 (2.48%)	0.49% (-0.08, 1.07%)	1.19 (0.96, 1.48)	0.104
Other, non-major	269 (4.35%)	260 (4.19%)	0.14% (-0.57%, 0.85%)	1.03 (0.87, 1.23)	0.702
Major or non-major clinically relevant bleeding	207 (3.35%)	171 (2.76%)	0.59% (-0.02%, 1.20%)	1.21 (0.99, 1.48)	0.064
Any Bleeding	452 ((7.31%)	415 (6.69%)	0.60% (-0.30%, 1.49%)	1.09 (0.95, 1.24)	0.207

[a]This is a Cox-regression analysis with study treated as a covariate.
[b] The protocol pre-specified definition of major bleeding restricted events to those that were extrasurgical for clinically overt bleeding events leading to a decrease in hemoglobin or requiring a blood transfusion.
[c] In this alternate major bleeding endpoint definition, the subset of surgical site bleeding events associated with a Hgb drop of 2 or more units or requiring 2 or more units of blood are included.
Note: Post Baseline includes all bleeding events observed during the study including those occurring more than 2 days after study drug discontinuation
Key: CI = confidence interval

Table 10: Incidence of Treatment-Emergent Bleeding Events in the Day 12±2 and Active Control Pools
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety in pooled RECORD 1-4 studies)

Endpoint	Rivaroxaban (N = 6183)	Enoxaparin (N = 6200)	Absolute Risk difference (95% CI)	Hazard Ratio[a] (95% CI)	Hazard Ratio P Value
Day 12±2 Pool					
Major[b]	21 (0.34%)	13 (0.21%)	0.13% (-0.05%, 0.31%)	1.61 (0.81, 3.22)	0.175
Major including Surgical site[c]	108 (1.75%)	84 (1.35%)	0.39% (-0.04%, 0.83%)	1.29 (0.97, 1.71)	0.082
Non-major, clinically relevant	159 (2.57%)	139 (2.24%)	0.33% (-0.21%, 0.87%)	1.14 (0.91, 1.44)	0.249
Other, non-major	251 (4.06%)	245 (3.95%)	0.09% (-0.60%, 0.78%)	1.02 (0.86, 1.22)	0.797
Major or non-major clinically relevant bleeding	176 (2.85%)	152 (2.45%)	0.40% (-0.17%, 0.96%)	1.16 (0.93, 1.44)	0.186
Any Bleeding	409 (6.61%)	384 (6.19%)	0.40% (-0.46%, 1.26%)	1.06 (0.93, 1.22)	0.376
Active Control Pool					
Major[b]	23 (0.37%)	13 (0.21%)	0.16% (-0.03%, 0.35%)	1.77 (0.90, 3.49)	0.101
Major including Surgical site[c]	110 (1.78%)	84 (1.35%)	0.42% (-0.01%, 0.86%)	1.31 (0.99, 1.74)	0.061
Non-major, clinically relevant	171 (2.77%)	143 (2.31%)	0.46% (-0.09%, 1.01%)	1.20 (0.96, 1.49)	0.116
Other, non-major	256 (4.14%)	254 (4.10%)	0.02% (-0.67%, 0.72%)	1.01 (0.85, 1.20)	0.941
Major or non-major clinically relevant bleeding	190 (3.07%)	156 (2.52%)	0.56% (-0.02%, 1.14%)	1.22 (0.99, 1.51)	0.068
Any Bleeding	424 (6.86%)	397 (6.40%)	0.44% (-0.44%, 1.31%)	1.07 (0.93, 1.22)	0.348

[a] This is a Cox-regression analysis with study treated as a covariate.
[b] The protocol pre-specified definition of major bleeding restricted events to those that were extrasurgical for clinically overt bleeding events leading to a decrease in hemoglobin or requiring a blood transfusion.
[c] In this alternate major bleeding endpoint definition, the subset of surgical site bleeding events associated with a Hgb drop of 2 or more units or requiring 2 or more units of blood are included.
Key: CI = confidence interval

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3.3. Bleeding Events Time Course by THR or TKR

Figures 6 and 7 show Kaplan-Meier figures for the time to first major bleeding event in the THR and TKR pools separately. The incidence of bleeding was lower in the THR pool relative to the TKR pool. Separation of the rivaroxaban and enoxaparin curves occurs relatively early in both the hip and knee studies and persist for the remainder of the treatment duration.

Figure 6: Cumulative Rate (Kaplan-Meier) of Treatment-Emergent Major Bleeding Events (Subjects Valid for Safety Analysis in R1-R2, THR Pool)

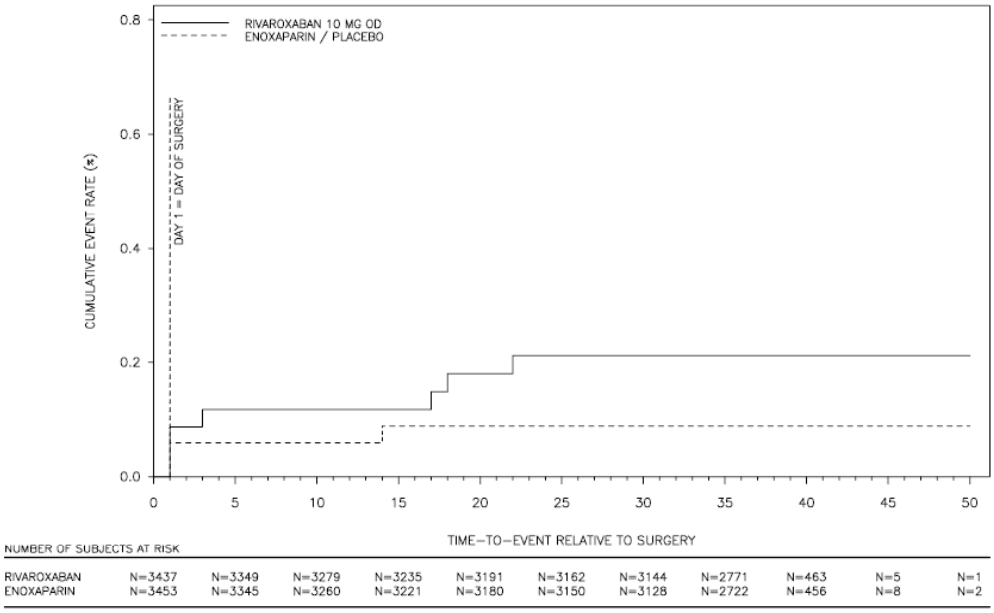

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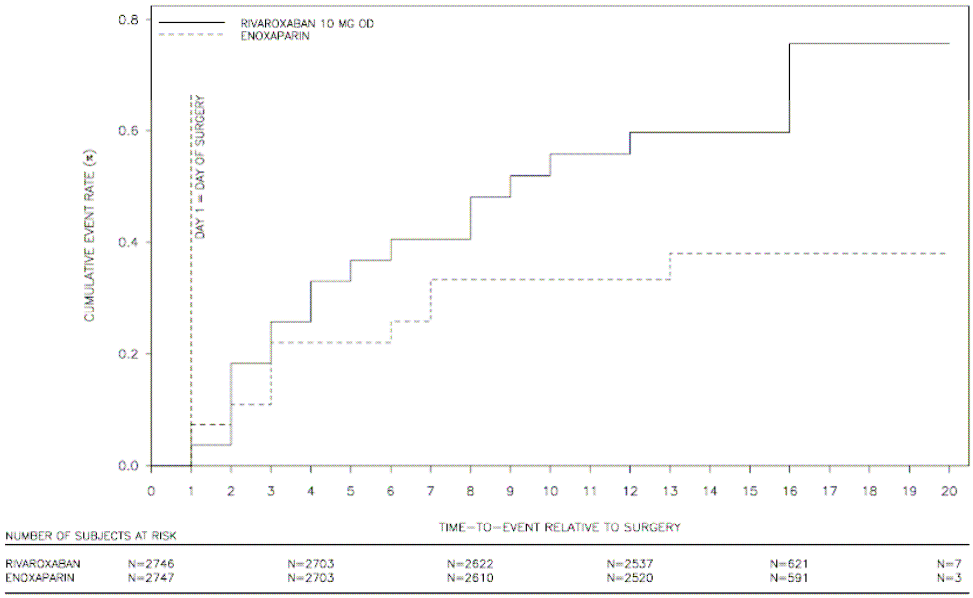
Figure 7: Cumulative Rate (Kaplan-Meier) of Treatment-Emergent Major Bleeding Events (Subjects Valid for Safety Analysis in R3-R4, TKR Pool)



Figures 8 and 9 show Kaplan-Meier figures for the time to first major or non-major clinically relevant bleeding event in the THR and TKR pools separately. The incidence of bleeding was generally similar in the THR and TKR pools. Separation of the rivaroxaban and enoxaparin curves occurred after Day 13 in the THR studies and after Day 8 in the TKR studies.

Figure 8: Cumulative Rate (Kaplan-Meier) of Treatment-Emergent Major or Non-Major Bleeding Events (Subjects Valid for Safety Analysis in R1-R2, THR Pool)

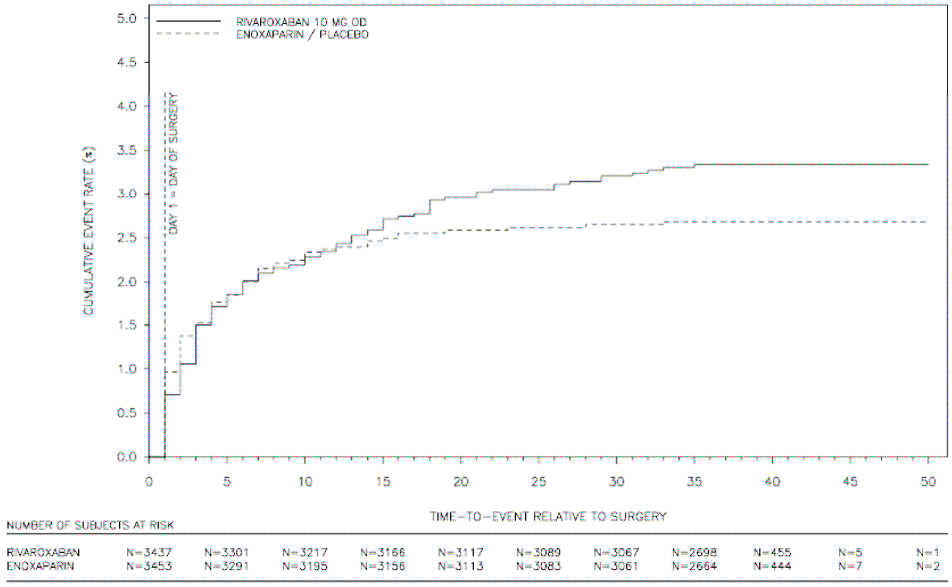


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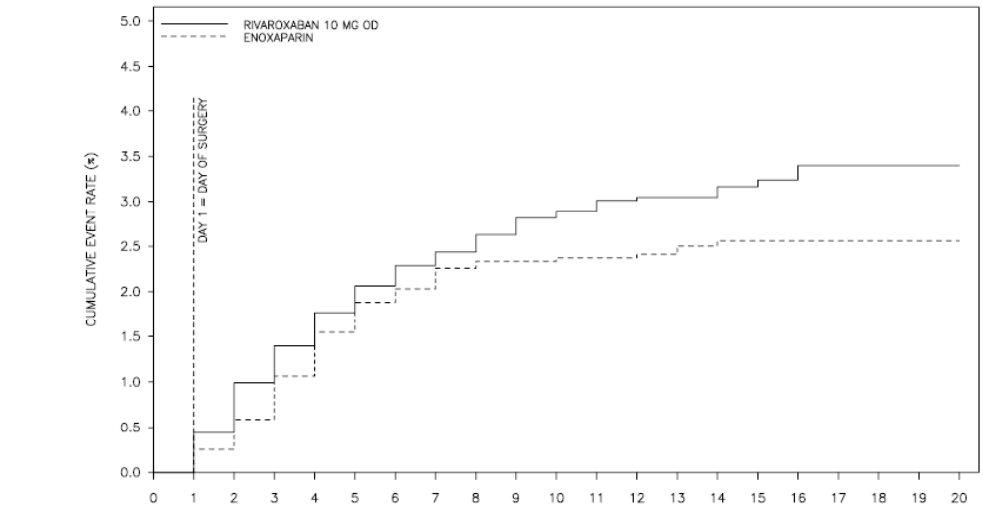
Figure 9: Cumulative Rate (Kaplan-Meier) of Treatment-Emergent Major or Non-Major Clinically Relevant Bleeding Events (Subjects Valid for Safety Analysis in R3-R4, TKR Pool)



3.4. Listing of Subjects With Major Bleeding Events

Subjects with major bleeding events are listed in Table 11. This listing provides information on the nature of the event, when it occurred and its outcome. This listing includes events that occurred on treatment and during the follow-up period. An "*" indicates events that were not treatment-emergent (occurring more than 2 days after study drug discontinuation).

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Table 11: Major Bleeding Events (Central Adjudication)
(Subjects Valid for Safety Analysis in Pooled RECORD 1-4 Studies)

Study Medication **Study-Subject Number**	Age, Sex	Type of Event	MedDRA Preferred Term (Intensity)	Date of Last ASM	Day of Bleeding Relative to Surgery/ASM Start	Outcome
Rivaroxaban 10 mg od						
Study 11354						
11354-100104016	67, M	Re-operation	Hematoma evacuation (moderate)	34	18/18	Resolved
11354-160084031	74, F	Fatal bleeding	Hemorrhage (Severe)	Subject did not receive active study drug		Death
11354-180154011	78, F	Extrasurgical Hgb drop/Transfusion	Gastrointestinal hemorrhage (moderate); hematemesis (moderate)	3	3/3	Resolved
11354-220014003	51, M	Critical organ (Intraocular)	Retinal hemorrhage (moderate)	40	1/1	Improved
11354-240054006	66, M	Extrasurgical Hgb drop/Transfusion	Gastrointestinal hemorrhage (moderate)	35	22/21	Resolved
11354-350024032	64, M	Re-operation	Wound hemorrhage (mild)	31	1/1	Resolved
Study 11357						
11357-120037006	54, F	Extrasurgical Hgb drop/Transfusion	Hematemesis (moderate); hemorrhagic diarrhea (moderate)	17	17/17	Improved
Study 11356						
11356-160016021	65, M	Re-operation	Operative hemorrhage (severe)	15	16/16	Resolved
11356-240036002	65, M	Re-operation	Post-procedural hemorrhage (moderate)	14	2/2	Resolved
11356-240036020	78, F	Critical Organ (Intraspinal/hemorrhagic puncture)	Post-procedural hematoma (mild)	Subject did not receive active study drug		Resolved
11356-300026006*	49, M	Re-operation	Hematoma (severe)	13	17/17	Resolved
11356-300026031	67, M	Re-operation	Hematoma (moderate)	14	4/4	Resolved
11356-370056009	67, M	Extrasurgical Hgb drop/Transfusion	Rectal hemorrhage (severe)	13	12/12	Resolved
11356-370106010	54, M	Re-operation	Hemorrhage (severe)	14	2/2	Resolved
11356-370106022	60, M	Re-operation	Hemarthrosis (moderate)	14	3/3	Resolved
11355-140045071*	80, F	Critical Organ (Retroperitoneal)	Adrenal hemorrhage (moderate)	8	8/8	Resolved
			Hemorrhagic stroke (mild)	8	32	Resolved

Table 11: Major Bleeding Events (Central Adjudication)
(Subjects Valid for Safety Analysis in Pooled RECORD 1-4 Studies)(Continued)

Study Medication **Study-Subject Number**	Age, Sex	Type of Event	MedDRA Preferred Term (Intensity)	Date of Last ASM	Day of Bleeding Relative to Surgery/ASM Start	Outcome
Study 11355						
11355-140105018*	56, F	Re-operation	Subcutaneous hematoma (mild)	11	23/23	Resolved
11355-140105153	53, M	Fatal Bleeding	Upper GI hemorrhage (severe)	6	6/6	Death
11355-140115004	78, F	Re-operation	Hemarthrosis (moderate)	11	10/10	Resolved
11355-140115016	69, F	Extrasurgical Hgb drop/Transfusion	Hematemesis (moderate)	2	2/2	Resolved
11355-140205041*	69, F	Re-operation	Hemarthrosis (moderate)	3	29/28	Resolved
11355-140225061	68, M	Re-operation	Incision site hemorrhage (moderate)	1	2/2	Resolved
11355-140455077	59, M	Re-operation	Post-procedural hematoma (moderate)	4	5/5	Resolved
11355-140705004	47, M	Re-operation	Hematoma (moderate)	4	5/5	Resolved
11355-260135015	76, M	Extrasurgical Hgb drop/Transfusion	Gastrointestinal hemorrhage (moderate)	2	3/3	Resolved
11355-350065008	63, F	Re-operation	Hemarthrosis (moderate)	9	9/9	Resolved
11355-600015092*	60, M	Critical organ: (Intraspinal/hemorrhagic puncture)	Catheter site hemorrhage (moderate)	12	1/1*	Resolved
11355-900015002	71, F	Extrasurgical Hgb drop/Transfusion	Gastroduodenal hemorrhage (severe)	7	8	Resolved
Enoxaparin 40 mg od						
Study 11354						
11354-100024030	69, M	Re-operation	Arterial hemorrhage (moderate)	9	1/2	Resolved
11354-180214023*	78, F	Extrasurgical Hgb drop	Feces discolored (moderate)	7	12/13	Resolved
11354-260054017	76, M	Extrasurgical Hgb drop/Transfusion	Gastrointestinal hemorrhage (moderate)	14	14/15	Resolved
Study 11357						
11357-340017005	78, F	Critical organ (Intraspinal; Hemorrhagic puncture)	Spinal epidural hemorrhage (mild)	1	1/2	Resolved
Study 11356						
11356-100056012*	65, M	Re-operation	Subcutaneous hematoma (moderate)	10	27/28	Resolved
11356-100106003	74, F	Critical organ (Intraspinal; Hemorrhagic puncture)	Extradural hematoma (severe)	2	2/3	Resolved

Table 11: Major Bleeding Events (Central Adjudication)
(Subjects Valid for Safety Analysis in Pooled RECORD 1-4 Studies)(Continued)

Study Medication **Study-Subject Number**	Age, Sex	Type of Event	MedDRA Preferred Term (Intensity)	Date of Last ASM	Day of Bleeding Relative to Surgery/ASM Start	Outcome
11356-180036023	74, F		Post-procedural hemorrhage (mild)	11	7	Resolved
11356-180106016	77, F	Crtical organ (Intraspinal; hemorrhagic puncture)	Catheter-related complication (mild)	11	1/2	Resolved
11356-300026018	81, M	Re-operation	Hematoma (moderate)	6	7/8	Resolved
11356-350016024	81, M	Re-operation	Post-procedural hemorrhage (severe)	12	3/4	Resolved
11356-370106015	71, F	Re-operation	Wound hemorrhage (severe)	14	3/4	Resolved
11356-440046019*	74, M	Re-operation	Hemarthrosis (severe)	5	8/9	Resolved
Enoxaparin 30 mg twice daily Study 11355						
11355-140105112	47, F	Re-operation	Subcutaneous hematoma (mild)	12	13/12	Resolved
11355-140295094	67, M	Re-operation	Hematoma (moderate)	Did not receive active study drug		Resolved
11355-320075009*	86, F	Extrasurgical Hgb drop/Transfusion	Gastrointestinal hemorrhage (moderate)	4	10/10	Resolved
11355-600015098	66, F	Critical organ (Intraspinal/Hemorrhagic puncture)	Catheter site hemorrhage (mild)	11	1/1	Resolved
11355-600105031	78, M	Critical organ (Subdural hemorrhage)	Subdural hemorrhage (severe)	6	7/6	Improved

Key: ASM = active study medication; F = female; GI = gastrointestinal; M = male; MedDRA = Medical Dictionary of Regulatory Activities

* Next to subject ID number indicates that the bleeding event was not treatment emergent.

Note: RECORD 1 is Study 11354 (THR), RECORD 2 is Study 11357 (THR), RECORD 3 is Study 11356 (TKR), and RECORD 4 is Study 11355 (TKR).

Note: "Extrasurgical Hgb drop/Transfusion" means that the bleeding event was associated with a drop in hemoglobin of at least 2 g/dL or associated with a blood transfusion of at least 2 units of packed red cells or whole blood.

Note: Subject 11355-140045071 had 2 bleeding events. The event adrenal hemorrhage was considered treatment-emergent but the event of hemorrhagic stroke was not considered treatment-emergent.

Note: Subject 11355-600015092 was not considered treatment-emergent because the event started before study medication intake.

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3.5. Treatment-Emergent Bleeding Events By THR or TKR

A summary of major or non-major clinically relevant treatment-emergent bleeding events in the THR and TKR studies separately is provided in Figures 10 and 11. A summary of any treatment-emergent bleeding event in the THR and TKR studies separately is provided in Figures 12 and 13. The results for each joint were similar to the overall results with most subgroups slightly favoring enoxaparin.

Figure 10: Major or Non-Major Clinically Relevant Treatment-Emergent Bleeding Events: Hazard Ratios (95% CI) by THR Subgroups (Subjects Valid for Safety Analysis in Pooled RECORD 1-2 Studies)

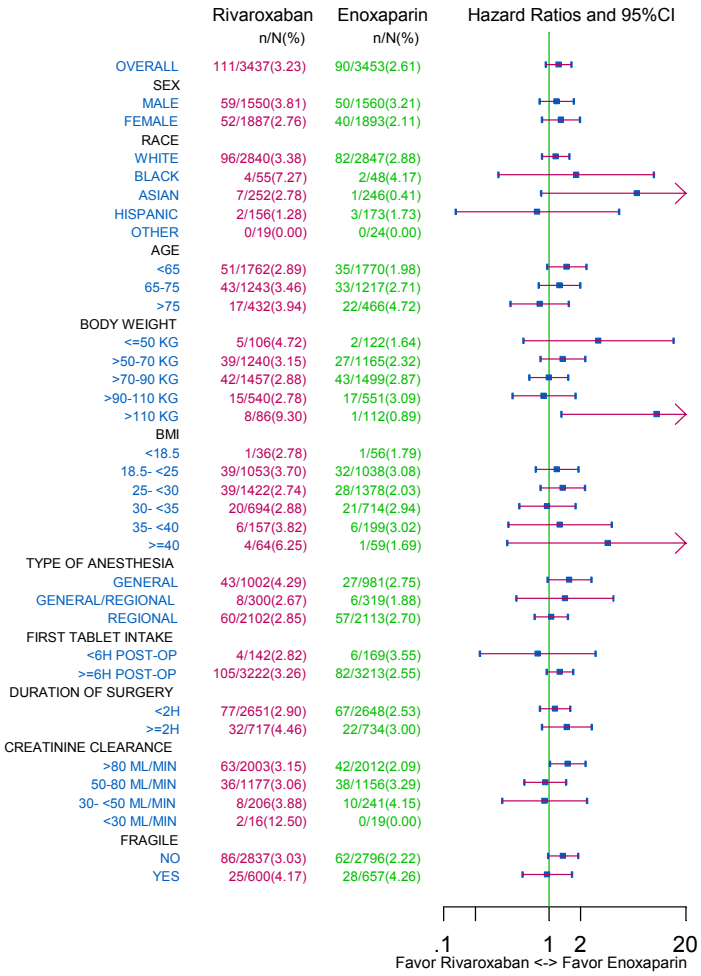

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Figure 11: Major or Non-Major Clinically Relevant Treatment-Emergent Bleeding Events: Hazard Ratios (95% CI) by TKR Subgroups (Subjects Valid for Safety Analysis in Pooled RECORD 3-4 Studies)

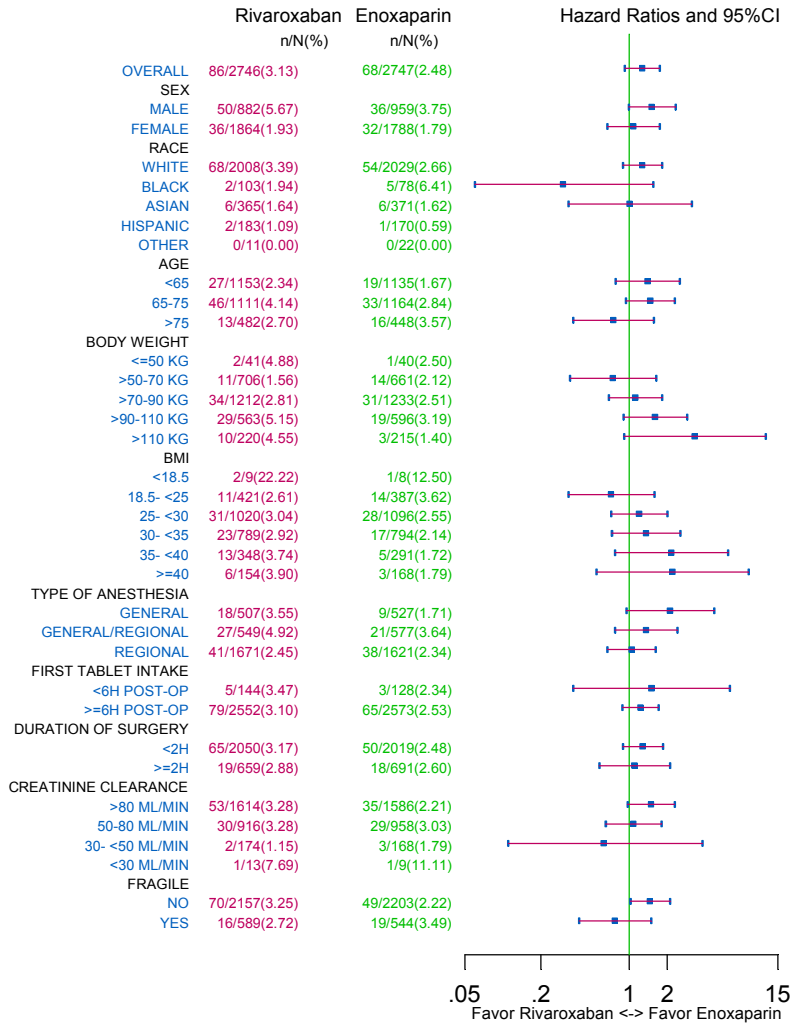

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Figure 12: Any Treatment-Emergent Bleeding Events: Hazard Ratios (95% CI) by THR Subgroups (Subjects Valid for Safety Analysis in pooled RECORD 1-2 Studies)

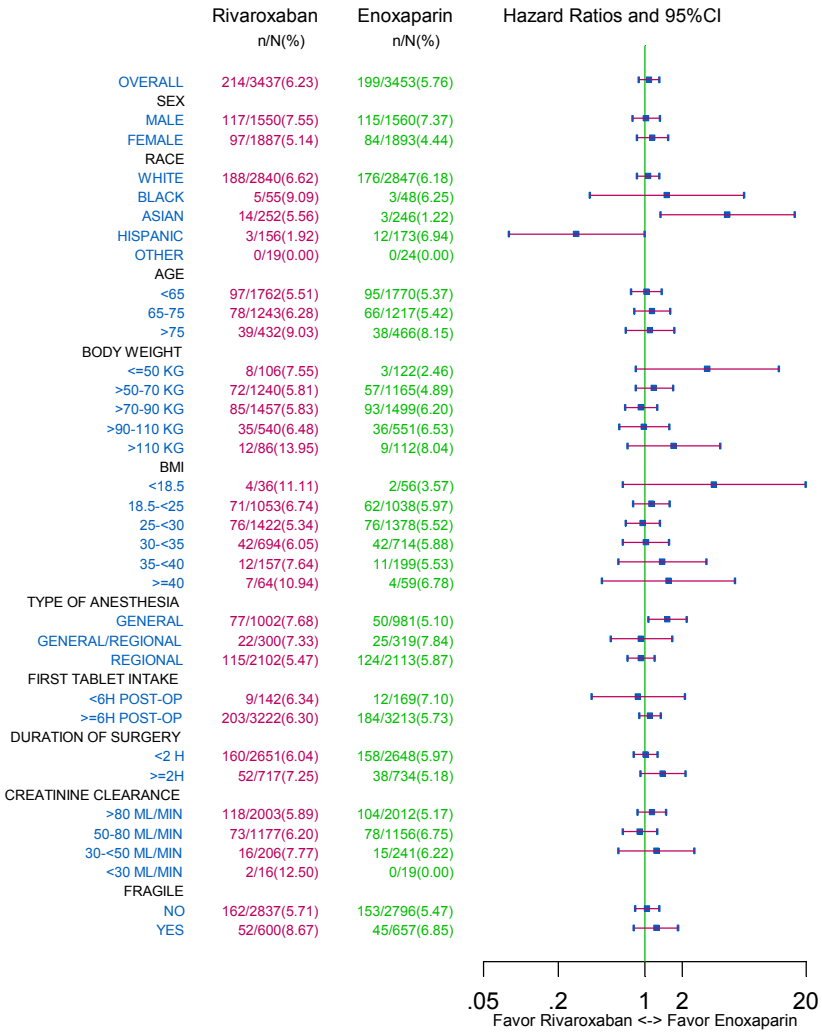

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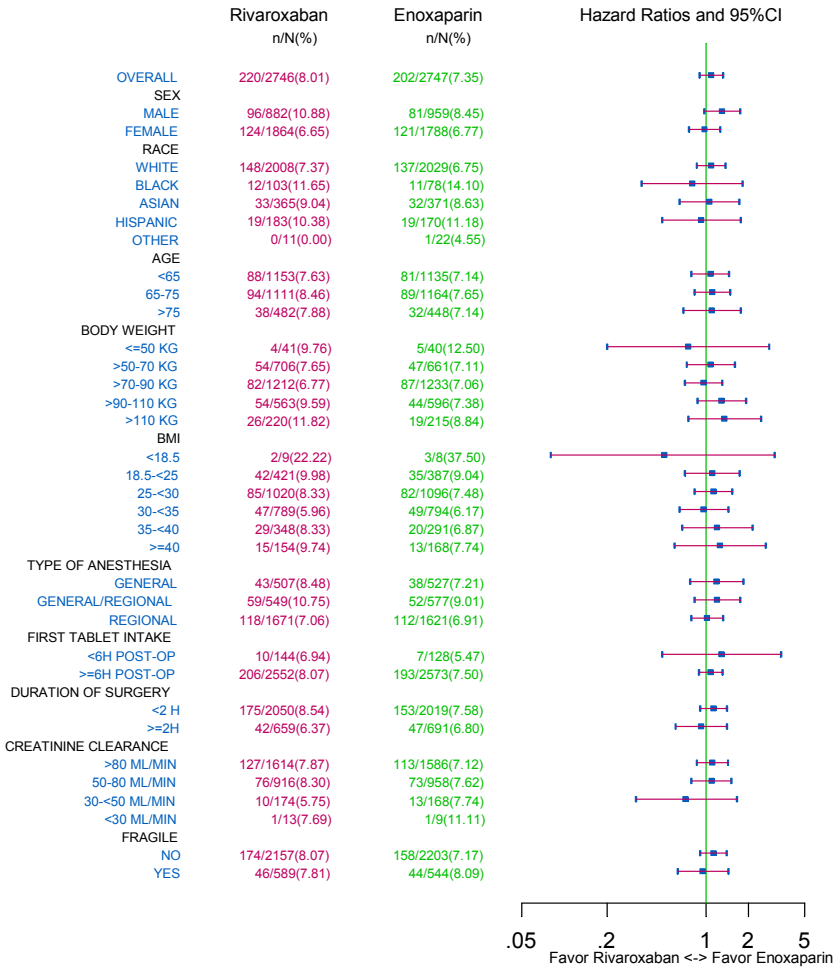
Figure 13: Any Treatment-Emergent Bleeding Events: Hazard Ratios (95% CI) by TKR Subgroups (Subjects Valid for Safety Analysis in pooled RECORD 3-4 Studies)



3.6. Cardiovascular Events by THR or TKR

Tables 12 and 13 summarize the incidence of CV events occurring on active treatment and off active treatment in the THR (RECORD1-2) and TKR (RECORD 3-4) studies separately. On active treatment events include those that occur after the first intake of active study medication but no later than 1 day after the last intake of active study medication. Note that subjects that received dummy placebo (inactive study medication) but that never took active study medication would not be included in this analysis. Events occurring more than 1 day after the last intake of active study medication would be counted in the off active treatment category. In the THR studies, the incidence of on and off active treatment events was balanced on rivaroxaban and enoxparin. There were

numerically fewer on active treatment events and numerically more off active treatment events on rivaroxaban compared to enoxaparin likely a chance finding due to the small number of events. In the TKR studies the incidence of CV events on and off active treatment was similar on rivaroxaban and enoxaparin. There were numerically fewer on and off active treatment events on rivaroxaban compared to enoxaparin likely representing a chance finding due to the small number of observed events.

Table 12: Incidence of Cardiovascular Events (Retrospective Adjudication)
(Subjects Valid for Safety with Active Study Drug in pooled THR RECORD 1-2 studies)

Endpoint	Rivaroxaban (N =3380)		Enoxaparin (N = 3452)	
Cardiovascular events on active treatment	8	0.24%	15	0.43%
Myocardial infarction	5	0.15%	9	0.26%
Ischemic stroke	2	0.06%	4	0.12%
Cardiovascular death	1	0.03%	2	0.06%
Unexplained death	0	0.00%	0	0.00%
Cardiovascular events off active treatment	11	0.33%	5	0.14%
Myocardial infarction	5	0.15%	0	0.00%
Ischemic stroke	3	0.09%	0	0.00%
Cardiovascular death	4	0.12%	4	0.12%
Unexplained death	0	0.00%	1	0.03%

Table 13: Incidence of Cardiovascular Events (Retrospective Adjudication)
(Subjects Valid for Safety with Active Study Drug in pooled TKR RECORD 3-4 studies)

Endpoint	Rivaroxaban (N =2717)		Enoxaparin (N = 2743)	
Cardiovascular events on active treatment	5	0.18%	10	0.36%
Myocardial infarction	2	0.07%	5	0.18%
Ischemic stroke	3	0.11%	2	0.07%
Cardiovascular death	0	0.00%	3	0.11%
Unexplained death	0	0.00%	0	0.00%
Cardiovascular events off active treatment	5	0.18%	9	0.33%
Myocardial infarction	0	0.00%	4	0.15%
Ischemic stroke	2	0.07%	1	0.04%
Cardiovascular death	2	0.07%	2	0.07%
Unexplained death	1	0.04%	3	0.11%

3.7. Liver Related Laboratory Abnormalities by THR or TKR

Tables 14 and 15 summarize the incidence of postbaseline ALT abnormalities at various thresholds in the THR and TKR pools separately. The incidence of ALT abnormalities > 3x ULN and > 5x ULN was lower on rivaroxaban compared to enoxaparin in both the hip and knee studies. The incidence of ALT abnormalities at higher thresholds (>8, > 10, and > 20x ULN) was similar in the two treatment groups.

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Table 14: Pooled Incidence Rates of Postbaseline ALT Abnormalities – After Day 0 Baseline (Subjects Valid for Safety, Pooled THR RECORD 1-2 Studies)

Laboratory Variable **Limit**	Rivaroxaban		Enoxaparin	
>3x ULN	88/3408	2.58%	134/3406	3.93%
>5x ULN	32/3408	0.94%	46/3406	1.35%
>8x ULN	10/3408	0.29%	11/3406	0.32%
>10x ULN	5/3408	0.15%	5/3406	0.15%
>20x ULN	1/3408	0.03%	1/3406	0.03%

Key: ALT = alanine aminotransferase.
Note: All measurements after the start of double-blind study medication are included regardless of onset relative to the last dose.

Table 15: Pooled Incidence Rates of Postbaseline ALT Abnormalities – After Day 0 Baseline (Subjects Valid for Safety, Pooled TKR RECORD 3-4 Studies)

Laboratory Variable **Limit**	Rivaroxaban		Enoxaparin	
>3x ULN	64/2723	2.35%	93/2725	3.41%
>5x ULN	24/2723	0.88%	32/2725	1.17%
>8x ULN	8/2723	0.29%	9/2725	0.33%
>10x ULN	5/2723	0.18%	4/2725	0.15%
>20x ULN	1/2723	0.04%	0/2725	0.00%

Key: ALT = alanine aminotransferase
Note: All measurements after the start of double-blind study medication are included regardless of onset relative to the last dose.

Figures 14 and 15 below show the cumulative risk of the first occurrence of postbaseline ALT >3x ULN in the THR and TKR studies respectively.

Figure 14: Crude Cumulative Risk of the First Occurrence of Postbaseline ALT > 3x ULN (THR RECORD 1-2)

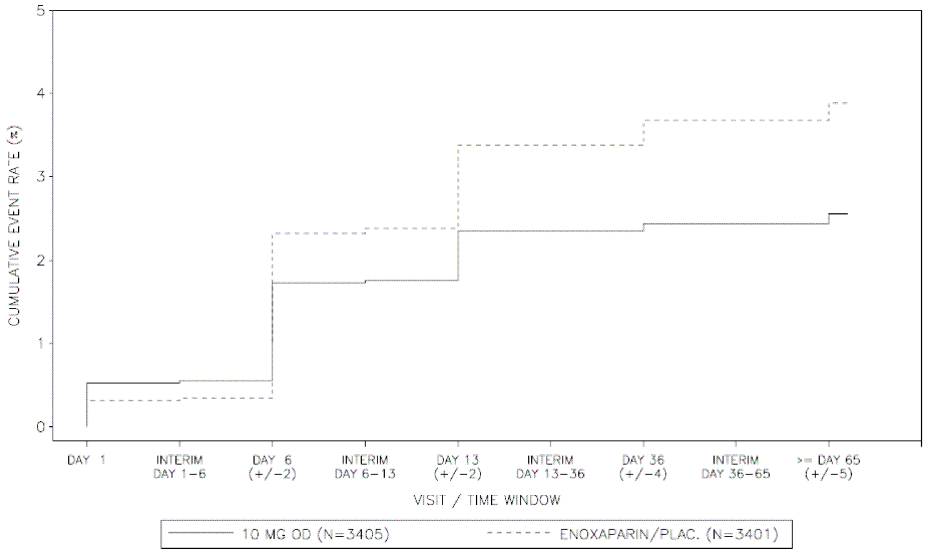
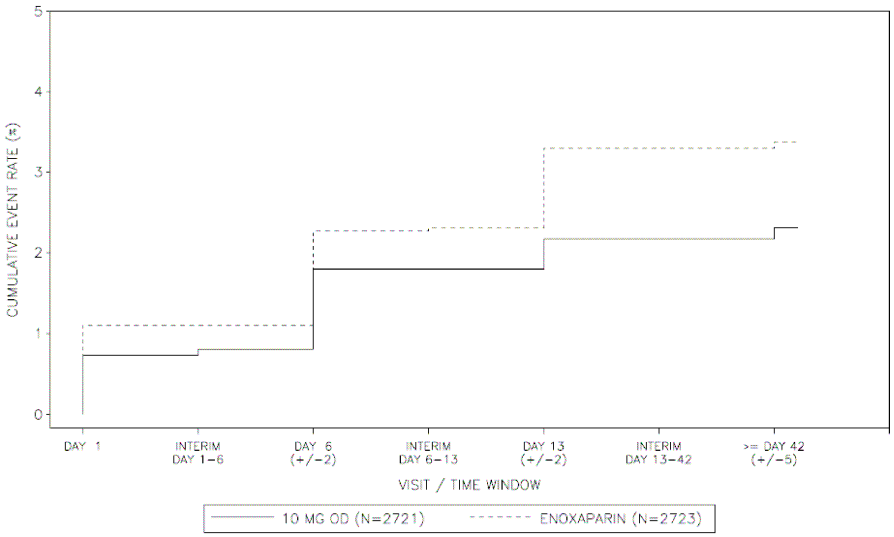


Figure 15: Crude Cumulative Risk of the First Occurrence of Postbaseline ALT>3x ULN (TKR RECORD 3-4)



4. EFFICACY AND SAFETY BY GEOGRAPHIC REGION

4.1. US Participation in the RECORD Studies and Baseline/Surgical Characteristics

Forty-one countries participated in the RECORD program with some countries participating in only one study and some in all four. The RECORD 4 study was the only study enrolling a substantial number of subjects from the US and the number of US subjects was comparable to the number of subjects from the other participating countries (Table 16). There was no participation of US centers in the RECORD 3 study and limited participation in the RECORD 1 and 2 studies. Overall 14% of the subjects in the program were from the US.

Table 16: US Subjects in the RECORD Studies- Safety Population

Study	Rivaroxaban		Enoxaparin	
	US N/N(%)	other than US n/N(%l)	US n/N(%)	other than US n/N(%)
RECORD 1	80/2209 (3.62)	2129/2209 (96.38)	79/2224 (3.55)	2145/2224 (96.45)
RECORD 2	37/1228 (3.01)	1191/1228 (96.99)	39/1229 (3.17)	1190/1229 (96.83)
RECORD 3	0/1220 (0.00)	1220/1220 (100)	0/1239 (0.00)	1239/1239 (100)
RECORD 4	749/1526 (49.08)	777/1526 (50.92)	743/1508 (49.27)	765/1508 (50.73)
Total	866/6183 (14.01)	5317/6183 (85.99)	861/6200 (13.89)	5339/6200 (86.11)

Since RECORD 4 had the majority of the US subjects the demographic, surgical, anesthetic and duration of hospital admission characteristics were compared between the US and other country subjects in this study. Summaries of these analyses are shown in Tables 17-18.

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Table 17: Demographics and Baseline Characteristics for US and Other Countries (Subjects Valid for Safety Analysis in the RECORD 4 Study)

	US		Other than US	
	Rivaroxaban (N=749)	Enoxaparin (N=743)	Rivaroxaban (N=777)	Enoxaparin (N=765)
Sex N (%)				
Male	295 (39.39%)	296 (39.84%)	224 (28.83%)	245 (32.03%)
Female	454 (60.61%)	447 (60.16%)	553 (71.17%)	520 (67.97%)
Race N (%)				
White	612 (81.71%)	642 (86.41%)	396 (50.97%)	390 (50.98%)
Black	86 (11.48%)	63 (8.48%)	2 (0.26%)	2 (0.26%)
Asian	4 (0.53%)	4 (0.54%)	285 (36.68%)	285 (37.25%)
American Indian	1 (0.13%)	3 (0.40%)	0 (0.0%)	1 (0.13%)
Hispanic	43 (5.74%)	31 (4.17%)	94 (12.10%)	85 (11.11%)
Uncodable	2 (0.27%)	0 (0.0%)	0 (0.0%)	2 (0.26%)
Missing	1 (0.13%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age (yrs.) Mean±SD	64.1 (10.0)	64.0 (9.8)	64.6 (9.5)	65.3 (9.6)
Age (categorized) N (%)				
<65 yrs	371 (49.53%)	377 (50.74%)	373 (48.01%)	329 (43.01%)
65-75 yrs	265 (35.38%)	270 (36.34%)	297 (38.22%)	332 (43.40%)
>75 yrs	113 (15.09%)	96 (12.92%)	107 (13.77%)	104 (13.59%)
Weight (kg) Mean±SD	92.3 (21.2)	91.6 (20.6)	77.3 (16.4)	77.5 (16.8)
Weight (categorized) N (%)				
<=50 kg	4 (0.53%)	3 (0.40%)	18 (2.32%)	25 (3.27%)
>50-70 kg	99 (13.22%)	100 (13.46%)	268 (34.49%)	258 (33.73%)
>70-90 kg	271 (36.18%)	279 (37.55%)	358 (46.07%)	337 (44.05%)
>90-110 kg	220 (29.37%)	231 (31.09%)	102 (13.13%)	112 (14.64%)
>110 kg	155 (20.69%)	130 (17.50%)	30 (3.86%)	32 (4.18%)
Missing	0	0	1 (0.13%)	1 (0.13%)
BMI (kg/m^2) Mean±SD	32.1 (6.7)	31.9 (6.5)	29.7 (5.3)	29.6 (5.3)
BMI (categorized) N (%)				
<18.5	1 (0.13%)	1 (0.13%)	1 (0.13%)	4 (0.52%)
18.5 - <25	83 (11.08%)	82 (11.04%)	143 (18.40%)	130 (16.99%)
25 - <30	236 (31.51%)	246 (33.11%)	282 (36.29%)	317 (41.44%)
30 - <40	338 (45.13%)	327 (44.01%)	317 (40.80%)	282 (36.86%)
>=40	91 (12.15%)	87 (11.71%)	33 (4.25%)	31 (4.05%)
Missing	0	0	1 (0.13%)	1 (0.13%)
Creatinine clearance (ml/min) Mean±SD	103.1 (39.7)	103.2 (39.7)	89.7 (29.3)	88.8 (31.3)
Creatinine clearance (categorized) N (%)				
>80 ml/min	512 (68.36%)	513 (69.04%)	460 (59.20%)	413 (53.99%)
50-80 ml/min	187 (24.97%)	187 (25.17%)	261 (33.59%)	288 (37.65%)
30-<50 ml/min	38 (5.07%)	36 (4.85%)	44 (5.66%)	49 (6.41%)
<30 ml/min	1 (0.13%)	2 (0.27%)	3 (0.39%)	4 (0.52%)
Missing	11 (1.47%)	5 (0.67%)	9 (1.16%)	11 (1.44%)
Fragile subject[a] N (%)				
No	615 (82.11%)	634 (85.33%)	631 (81.21%)	613 (80.13%)
Yes	134 (17.89%)	109 (14.67%)	146 (18.79%)	152 (19.87%)

BMI=Body Mass Index

Note: Percentages are calculated including missing values.

[a] Fragile definition: Age >75 years and/or calculated creatinine clearance <50 ml/min and/or weight ≤50 kg

Table 18: Surgery and Anesthesia Details for the US and Other Countries (Subjects Valid for Safety Analysis in the RECORD 4 Study

Parameter	US		Other than US	
	Rivaroxaban N=749	Enoxaparin N=743	Rivaroxaban N=777	Enoxaparin N=765
Osteoarthritis as reason for surgery (%)	98.53	98.52	93.05	94.90
Unilateral, primary (%)	94.26	95.69	89.45	88.10
Unilateral, revision (%)	3.07	2.42	1.80	1.31
Bilateral (%)	2.40	1.62	8.62	10.46
Duration of surgery (mean min)	92.2	90.9	108.4	109.3
Duration of anesthesia (mean min)	143.4	141.3	167.5	169.8
General anesthesia	30.57	30.69	6.56	7.45
General with femoral block (%)	40.45	42.40	0.77	1.43
Spinal anesthesia (%)	16.82	16.55	50.06	47.58
Spinal with epidural (%)	0.13	0.13	19.56	20.13
Time to mobilization (median/mean days)	1.0/0.9	1.0/0.9	1.0/1.9	1.0/1.7
Duration of initial hospital stay (median days)	4.0	4.0	9.0	9.0

Many features are similar for the US and other than US subjects such as their ages and reason for surgery. However, as would be expected, there are some differences in weight, BMI, length of hospital stay, and the types of anesthesia.

4.2. US and Other Region Efficacy and Safety Results

The elements of the THR or TKR surgery are similar across all centers (e.g. bone and soft tissue trauma, similar prosthesis materials, tourniquet use in TKR) and these factors are the primary determinants of VTE and bleeding event risk. Also, in subgroup analyses for many of the baseline factors with regional differences (e.g. weight and type of anesthesia) the efficacy and safety treatment effects for rivaroxaban compared to enoxaparin were consistent in magnitude. (see sections 5.2.3.2 and 6.2.3.1.7 of main briefing document). Therefore, the regional differences observed for these factors would not contribute to any differences in treatment effects.

Total VTE and major VTE incidence rates and odds ratios for the pooled RECORD 1-4 studies for 4 geographic regions (US, Western Europe, Eastern Europe, all other countries) are shown in Table 19.

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Table 19: Total VTE and Major VTE for the US and Other Regions – Pooled RECORD 1-4 MITT Populations

Endpoint	Rivaroxaban	Enoxaparin	Odds Ratio (95% CI)
Total VTE			
US	27/565 (4.78%)	49/572 (8.57%)	0.54 (0.32, 0.89)
Western Europe	48/1498 (3.20%)	122/1502 (8.12%)	0.37 (0.25, 0.53)
Eastern Europe	34/954 (3.56%)	88/927 (9.49%)	0.32 (0.20, 0.49)
All other countries	72/1231 (5.85%)	143/1263 (11.32%)	0.50 (0.36, 0.68)
Major VTE			
US	7/620 (1.13%)	16/617 (2.59%)	0.43 (0.15, 1.12)
Western Europe	9/1591 (0.57%)	40/1595 (2.51%)	0.22 (0.09, 0.46)
Eastern Europe	4/1023 (0.39%)	19/1000 (1.90%)	0.20 (0.05, 0.62)
All other countries	12 /1443 (0.83%)	53/1465 (3.62%)	0.22 (0.11, 0.42)

The odds ratios for total VTE and major VTE consistently favor rivaroxaban in all 4 regions. Similarly, the hazard ratio for symptomatic VTE or death during the treatment phase for the US (0.53 95% CI 0.22, 1.25) was comparable to that for the other regions combined (0.40 95% CI 0.26, 0.63). The incidence of total VTE and the odds ratios for each participating country in the RECORD program are provided in Figure 16.

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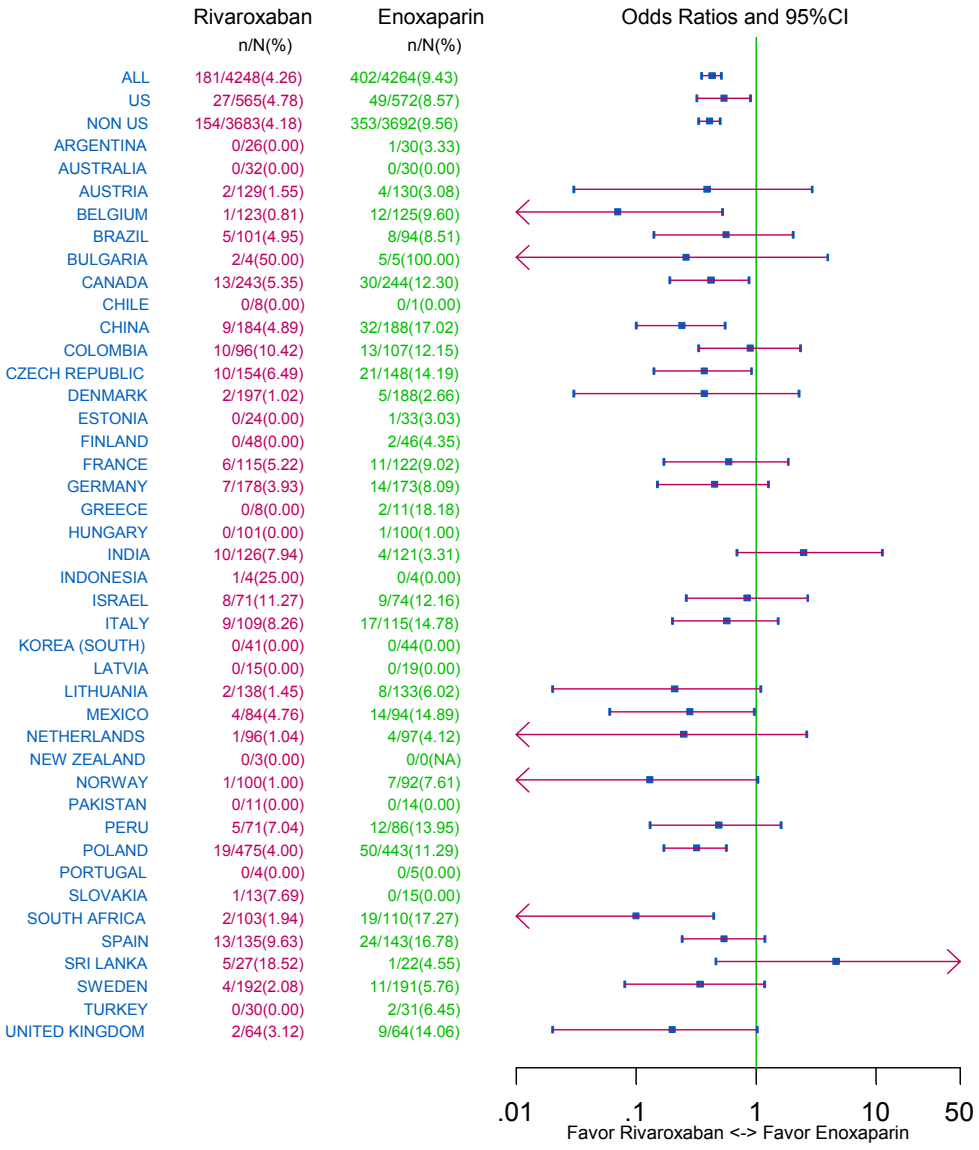
Figure 16: Total VTE Odds Ratios (95% CI) by Country
(MITT Population Valid for Total VTE of the Pooled RECORD 1-4 Studies)



For most countries, including the US, the odds ratio was comparable with that of the overall MITT population for RECORD 1-4 indicating results favoring rivaroxaban over enoxaparin. Of the countries with small numbers of subjects (<100 total) 6 had no events in either treatment group (e.g. Australia), 5 had fewer events with rivaroxaban (e.g. Argentina) and 2 had more events with rivaroxaban (e.g. Indonesia). Only India had more than 100 total subjects with an odds ratio greater than 1.0 but the confidence intervals were wide due to the small number of events observed. The results for subjects in the United States are consistent with the overall results and primarily represent the findings from the RECORD 4 study as there was no participation of the United States in the RECORD 3 study and limited participation in the RECORD 1 and 2 studies (Table 17). In RECORD 4, the total VTE odds ratio for the US was 0.59 (95% CI 0.34, 0.99) compared with 0.72 (95% CI 0.46, 1.14) for the other countries combined. For major VTE the odds ratios were 0.50 (95%CI 0.17, 1.32) and 0.73 (95%CI 0.21, 2.42), respectively.

Similarly for bleeding events, the primary risk is from the surgical procedure itself and the associated postoperative therapies. The results by region for the major or non-major clinically relevant bleeding and any bleeding events endpoints are shown in Table 20.

Table 20: Treatment-Emergent Bleeding Event Endpoints in the US and Other Regions- Pooled RECORD 1-4 Safety Population

Endpoint	Rivaroxaban	Enoxaparin	Hazard Ratio (95% CI)
Major or non-major clinically relevant bleeding			
US	38/866 (4.39)	23/861 (2.67)	1.65 (0.98, 2.77)
Western Europe	86/2193 (3.92)	71/2204 (3.22)	1.22 (0.89, 1.66)
Eastern Europe	24/1274 (1.88)	28/1272 (2.20)	0.85 (0.49, 1.46)
All other countries	49/1850 (2.65)	36/1863 (1.93)	1.37 (0.89, 2.10)
Any bleeding			
US	113/866 (13.05)	91/861 (10.57)	1.25 (0.95, 1.65)
Western Europe	144/2193 (6.57)	147/2204 (6.67)	0.98 (0.78, 1.23)
Eastern Europe	42/1274 (3.30)	48/1272 (3.77)	0.86 (0.57, 1.31)
All other countries	135/1850 (7.30)	115/1863 (6.17)	1.18 (0.92,1.52)

In RECORD 4 the hazard ratio for major or non-major clinically relevant bleeding was 1.42 (95%CI 0.81, 2.48) for the US and 1.21 (95% CI 0.58, 2.52) for the other countries combined. For any bleeding event the hazard ratios were 1.15 (95%CI 0.85, 1.54) and 1.09 (95%CI 0.77, 1.54), respectively. These results do not show clear differences between the US and the other regions although the reported bleeding event rates and hazard ratios for the US tend to be higher.

4.3. Summary

Although there are some regional variations in baseline demographic and surgical management characteristics between the US and other geographic regions, the efficacy of rivaroxaban is robust across all geographic regions for both the total VTE and major VTE endpoints, with the results in the U.S consistent with the overall program results. There is some variation for the bleeding event endpoint comparisons across regions (i..e. some hazard ratios are less than 1 and some greater than 1), as might be expected with overall results that have modestly increased hazard ratios. In the RECORD 4 study, which has the majority of the US subjects and provides the most direct comparison, the US bleeding event endpoint hazard ratios appear similar to those from the other countries combined. Overall, these data support a favorable benefit to risk ratio for rivaroxaban compared with enoxaparin in the US and in all other regions.

APPENDIX 2

SUBJECT NARRATIVES FOR LIVER-RELATED DEATH

Appendix 2.1

Phase 2 VTE Prophylaxis Study Subject 10944-84008

BAY 59-7939 /010944 1 - 786
03 March 2005

Patient identifier	10944-84008
Date of birth	18 Apr 1925
Sex	F
Height (cm)	143
Baseline weight (kg)	52
Race	White
Study drug	Bay 59-7939 10mg bid
Start/stop dates of study drug	18 Jun 2004 – 25 Jun 2004
Event	1. Liver impairment (Investigator term term) - Liver disorder (MedDRA term) 2. Pancreatitis (Investigator term) - Pancreatitis (MedDRA term)
Severity	1. Severe 2. Severe
Serious (yes/no)	1. Yes 2. Yes
Start/stop date of event	1. 03 Aug 2004 - N/A 2. 03 Sep 2004 - N/A
Date of last dose of study drug before event	1. 25 Jun 2004 07:30 2. 25 Jun 2004 07:30
Action taken	1. Other 2. Other
Outcome of event	1. Death 2. Death
Date of death (if applicable)	1. 22 Oct 2004 2. 22 Oct 2004
Relationship to study drug	1. Yes 2. Yes

Narrative:
This 79 year old female postmenopausal patient had medical history of hypertension, heart insufficiency, compensated renal insufficiency, hyperuricemia, varicosis, coxarthrosis left side, cholecystolithiasis, hyperlipidemia and Parkinson's disease. Concomitant medication included analgesics, anesthetics, volume substitution, Pantozol® (pantoprazole), Lasix® (furosemide), Dytide® (triamteren/ hydrochlorothiazid), Catapressan® (clonidin hydrochlorid), Indometacin® (indometacin), Novalgin® (metamizol), Sifrol® (pramipexole), Vioxx® (rofecoxib), Dipidolor® (piritramid), Tramal® (tramadol-HCL), Cotrim Forte® (trimethoprim/ sulfamethoxazol), Mono Embolex® (certoparin-sodium), Eryfer® (ironsulfate), Lactulose® (lactulose) and Cefazolin® (cephazolin-sodium) during the first hospital stay.

From 16 June 2004 to 08 July 2004 the patient was hospitalized for elective total hip

Patient identifier	10944-84008

replacement. During this hospital stay the patient was included in the study and received BAY 59-7939 10mg bid from 18 June to 25 June 2004.
From 08 July to 29 July 2004 the patient was hospitalized in a rehabilitation center.
On 03 August 2004 (39 days after last intake of BAY 59-7939) the patient was again hospitalized to clarify reason for icterus.

The elective hip replacement was performed on 18 June 2004. In the evening the patient got 1 unit heterologous packed cells. The patient took BAY 59-7939 10mg bid from 18 June to 25 June 2004. The patient suffered urinary tract infection on 25 June 2004 which was treated with Cotrim forte® and resolved on 03 July 2004. From 08 July 2004 to 29 July 2004 the patient went to a rehabilitation hospital for mobilization and stabilization after elective hip replacement. During rehabilitation tremor of right leg and right hand and mild distal edema of lower legs were reported. The patient was in reduced general condition and normal nutritional condition (weight 48.8 kg, height 139 cm). The patient received physiotherapy, ferrum, Lasix® (furosemid), Sifrol® (pramipexol), Clexane® 0.4 mL once daily (enoxaparin) and lactulose. After the application of furosemid edema improved and creatinine (at admission: 1.29 mg/dL) decreased (no second creatinine value available) according to the discharge letter of the rehabilitation center. On 03 August 2004 (39 days after the last intake of BAY 59-7939) the patient went to her family doctor due to loss of appetite, weight loss and brown urine. The patient reported of frequent nausea and vomiting if food was seen. No pain was reported. There the icterus was seen and the patient was hospitalized. On admisssion increased liver enzymes (ALT 190, ASAT 504, GGT 566 U/L) and bilirubin (18.3 mg/dL) were found. Icterus of the sclerae and integrum was seen. The abdomen was free of pain on pressure and there were no resistences palpable. Marked edema of lower legs and feet and tremor at rest were seen. No other pathological findings were reported. Sonography of abdomen and ERCP with papillotomy, due to the fact that papillitis stenosans could not be excluded, were performed on 06 August 2004. Except cholecystolithiasis no other abnormalities were found. On 06 August 2004 after ERCP increased lipase (928 U/L) and amylase (151 U/L) was measured. During the hospital course cholestasis parameter (ALT up to 639, ASAT to 550, GGT to 1987, AP to 2764 U/L on 14 Sep 2004), bilirubin (highest value 54.6 mg/dL on 20 August 2004) and inflammation parameter (CRP up to 12.4 mg/dL on 06 September 2004 – normal range < 0.5) increased further. According to the investigator the relationship to study drug was possible for liver impairment and pancreatitis.
In the hepatitis serology (ELISA) only positiv CMV-IgG- and EBV-IgG-antibodies were found. On 10 August 2004 APTT was prolonged to 40.2 sec. and on 06 September 2004 to 180 sec., on 07 September 2004 APTT decreased to 29.8 sec.. Prothrombin time related coagulation tests were in normal range until death. Ammonia was 59 µg/dL (normal range 19-87) on 06 September 2004.
The patient got several blood transfusions: 2 units on 04 September, 1 unit on 09 September, 2 units on 16 September, 4 units on 27 September and 2 units on 02 October 2004. During the hospital course the patient suffered pneumothorax right side after a.subclavia punction attempt which resolved on 13 August 2004. The condition of the patient worsened, the patient became somnolent. A cerebral CT to exclude ischemia,

Patient identifier 10944-84008

tumour or bleeding on 06 September 2004 showed marked cerebral atrophy and arteriosclerosis. The lipase improved on 09 September 2004 to 59 U/L. The condition of the patient worsened and for sufficient food intake parenteral nutrition became necessary. The liver biopsy on 16 August 2004 showed mild to moderate fatty degeration and lipofuscin enrichment, but no signs of inflammation. On 23 September 2004 reflux esophagitis, hiatus hernia and antrum- and bulbus ulcers were found. Phlegmonic cholecystitis with cholangitis was found in the sonography on 12 October 2004, which was resistant to antibiotic therapy. Additionally bronchopneumonia developed. The patient received intensive therapy: infusions, furosemid, pantoprazol, metoclopramide, hydrochlorothiazide plus triamteren, pramipexol, clonidine, tramadol, enoxaparin, lactulose, neomycin, corticosteroid, insulin, fresh frozen plasma, dopamin, ciprofloxacin, ursodexoxycholic acid, vitamine B12, metronidazole, amoxicillin and clavulanic acid. The patient died on 22 October 2004. According to the autopsy the reasons for death was septic-cholemic cardiovascular insufficiency with bronchopneumonia, acute cholecystitis and acute necrotizing pancreatitis. The histology of the liver showed autolytic hepatocytes, no increased portal area and no intrahepatic signs of cholestasis.

Comment: First signs of liver impairment became obvious 39 days after last intake of BAY 59-7939. Liver enzyme values are available until 13 days after stop of BAY 59-7939, ASAT and ALT were in normal range. In the liver biopsy no signs of toxic liver damage were seen. µIn the medical history cholelithiasis was reported and in the examinations cholecystolithiasis was confirmed. A relationship to BAY 59-7939 seems to be unlikely also in the view of the time window the event occurred after stop of BAY 59-7939.
The lipase and amylase values increased after ERCP with papillotomy was performed. Pancreatitis is a known complication after ERCP with papillotomy. The reason for death was septic-cholemic cardiovascular insufficiency according to the autopsy report. Bronchopneumonia, acute cholecystitis and necrotizing pancreatitis contributed to the death. The death is seen as consequences of the events and is considered not related to BAY 59-7939 intake.

Laboratory values measured by central laboratory during the study:

Normal ranges:
ALT 5-31 U/L
ASAT 5-31 U/L
AP 35-104 U/L
Bilirubin 5.1-18.8 µmol/L
Lipase 0-60 U/L
Amylase 28-100 U/L

	17 06 04	18 06 04	19 06 04	21 06 04	24 06 04
ALT (U/L)	15	13	18	27	26
AST (U/L)	18	16	34	29	24
GGT (U/L)	16	9	14	51	46
AP (U/L)	68	39	51	86	76

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03 March 2005

Patient identifier	10944-84008				
Bilirubin (µmol/L)	6.6	6.3	7.9	4.4	6.1
Lipase (U/L)	69	32	37	28	24
Amylase (U/L)	67	58	114	58	35

Laboratory values measured in the hospital laboratory after study treatment:

Normal ranges:
ALT 10-35 U/L
AST 10-35 U/L
LDH 135-214 U/L
AP < 141 U/L
Bilirubin <1.0 mg/dL
Bilirubin (direct) <0.2 mg/dL
Lipase <60 U/L
Amylase 28-100 U/L

	28 06 04	29 06 04	01 07 04	07 07 04		03 08 04	04 08 04	05 08 04
ALT (U/L)	38	33	31	26		190	452	435
ASAT (U/L)	29	31	27	29		504	178	215
LDH (U/L)	248	294	261	202		274		
GGT (U/L)						566	538	566
AP (U/L)							566	588
Bilirubin (mg/dL)						18.3	23.0	25.4
Bilirubin (direct)							14.8	
Lipase (U/L)						57	39	
Amylase (U/L)						59		
	06 08 04	07 08 04	08 08 04	09 08 04	10 08 04	11 08 04	12 08 04	13 08 04
ALT (U/L)	418	438			404	456	558	450
ASAT (U/L)	234	272			272	385	543	267
LDH (U/L)	206	217	213	227		261	261	204
GGT (U/L)	549	571	601	636	690	651		565
AP (U/L)	586			1055	1077	948	962	969
Bilirubin (mg/dL)	23.7	28.3			43.5	43.9	41.5	37
Bilirubin (direct)								
Lipase (U/L)	928	6763	383	102	139	137	98	
Amylase (U/L)	151	1862			54	50	44	
	14 08 04	16 08 04	17 08 04	18 08 04	19 08 04	20 08 04	23 08 04	24 08 04
ALT (U/L)	456	576	584	628	653	919	610	489
AST (U/L)	283	390	300	293	369	314	336	217
LDH (U/L)	226	322					319	
GGT (U/L)	604	750	800	873	907	979	1723	1806
AP (U/L)	924	866	949	990	907	785	1118	

BAY 59-7939 /010944 1 - 790
03 March 2005

Patient identifier	10944-84008							
Bilirubin (mg/dL)	35.4	39.5	40.7	45.1	45.4	54.6	49.3	44.9
Bilirubin (direct)								
Lipase (U/L)			106	136	186	236	212	171
Amylase (U/L)			51	58	84	97	108	90
	26 08 04	30 08 04	01 09 04	03 09 04	04 09 04	05 09 04	06 09 04 12:00	06 09 04 14:00
ALT (U/L)	336	191	148	167	239	228	359	357
AST (U/L)	139	73	51	130	270	248	402	399
LDH (U/L)			174					
GGT (U/L)	1757	1556	1325	1997	1409	1394	1500	1502
AP (U/L)	1234	1170	1129	1429	986	1064	1775	1777
Bilirubin (mg/dL)	41.7	36.4	34.1		26.6	26.5		26.6
Bilirubin (direct)								
Lipase (U/L)	130	75	97	9500	3857	1333	518	519
Amylase (U/L)	79	60	77	1697	1587	471	157	159
	07 09 04	08 09 04	09 09 04	10 09 04	13 09 04	14 09 04	15 09 04	
ALT (U/L)	356	464	560	552	549	639	490	
AST (U/L)	482	616	680	424	400	550	433	
LDH (U/L)	606	607	578	471		445	430	
GGT (U/L)	1700	1893	1743	1626	1769	1987	1642	
AP (U/L)	2682	3195	3382	3231	2742	2764	2327	
Bilirubin (mg/dL)	28.1		27	29.9	32.6	33.7	31.7	
Bilirubin (direct)								
Lipase (U/L)	176	122	59	63	56	50	52	
Amylase (U/L)	78				27	26	28	
	16.09.04	17.09.04	20.09.04	22.09.04	23.09.04	27.09.04	30.09.04	01.10.04
ALT (U/L)	551	498	477	399	314	175	100	87
AST (U/L)	557	514	494	353	226	123	83	67
LDH (U/L)	477	453	410		279	274	248	
GGT (U/L)	1642	1570	1469	1134	995	816	666	562
AP (U/L)	2360	2310	2550	2028	1736	1470	1039	895
Bilirubin (mg/dL)	33.9	33.2	35.9	31.3	28.8	26.8	19.3	16.5
Bilirubin (direct)								
Lipase (U/L)	55	49	87	79	72	73	77	70
Amylase (U/L)	29	26	33	34	34	31	33	30
	06.10.04	08 10 04	09 10 04	12.10.04	14.10.04	18.10.04	20.10.04	22.10.04
ALT (U/L)	106	94	99	185	212	159	221	260
AST (U/L)	93	96	88	153	175	123	195	254
LDH (U/L)	288	231		293	284	243	358	492

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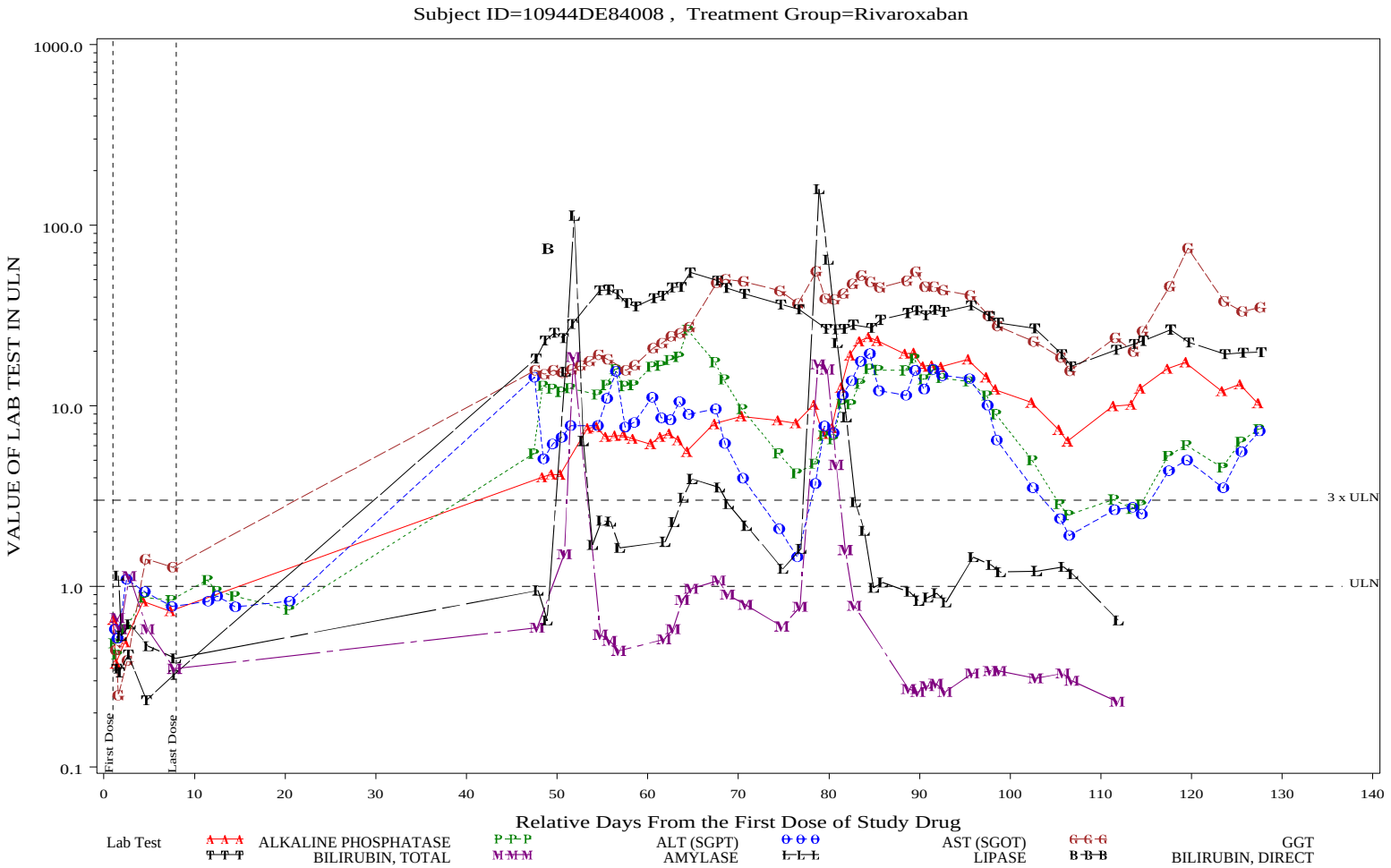
03 March 2005

Patient identifier	10944-84008							
GGT (U/L)	856	719	930	1648	2681	1362	1198	1261
AP (U/L)	1405	1428	1751	2261	2456	1698	1852	1456
Bilirubin (mg/dL)	20.4	22	22.9	26.4	22.4	19.3	19.7	19.8
Bilirubin (direct)								
Lipase (U/L)	39							
Amylase (U/L)	23							

Figure: Time Course of Liver Enzyme for Subjects of Special Interest (Based on the Data from the Narratives)
(Phase 2 VTE PREVENTION (Study 10944): SAFETY Analysis Set)



Note: VALUE OF LAB TEST IN ULN was calculated as the ratio of the actual lab value and the corresponding upper limit of normal. The Y-axis is on the log-scale.

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Appendix 2.2

Phase 2 VTE Treatment Study Subject 11223-506006

BAY 59-7939/011223/MRR-00150 1 - 1211
03 August 2006

Subject identifier	11223-506-006
Date of birth	09 Mar 1933
Sex	F
Height (cm)	166
Baseline weight (kg)	74
Race	White
Study drug	BAY 59-7939 40mg od
Start/stop dates of study drug	05 May 2005 to 27 May 2005
Event	Acute hepatitis B (Investigator term) Hepatits B (MedRA term)
Severity	Severe
Serious (yes/no)	Yes
Start/stop date of event	30 May 2005 to 21 Jun 2005
Date of last dose of study drug before event	27 May 2005
Action taken	Study drug discontinued permanently, remedial drug therapy
Outcome of event	Death
Date of death (if applicable)	21 Jun 2005
Relationship to study drug	No

Narrative:
This 72 year old female subject had a medical history of hypertension, diabetes mellitus, blood transfusions, in addtition deep venous thrombosis in Apr 2004 (treated with warfarin until Oct 2003), uterine malignancy (uterine sarcoma stabilized) with lung and mediastinal metastases (Oct 2004), hysterectomy with bilateral adnectomy due to uterine sarcoma (18 Oct 2004) and thereafter 6 cycles palliative chemotherapy from Nov 2005 until Apr 2005 [Doxolem® (doxorubicin hydrochloride), dacarbazine, Holoxan® (ifosfamide) concurrently with Uromitexan® (mesna)]. During the chemotherapy in Apr 2005 the subject got two transfusions on 08 and 09 Apr 2005.
On 14 Apr 2005 no liver metastases, but cyst or pseudocyst of pancreas up to 20 mm of size, were seen in ultrasound.
She got following concomitant medication: Fraxiparin® (nadroparin 0.6 mL on 05 May 2005, 0.3mL from 28 May 2005 to 21 Jun 2005), Amaryl® (glimepiride) since 2001 for diabetes mellitus, Siofor® (metformin hydrochloride) since 2001 for diabetes mellitus, Cardilan® (magnesium, potassium) from 05 May 2005 to 27 May 2005 because of hypopotassemia, Agen® (amlodipine) since 2004 for hypertension, Ramil® (ramipril) since 07 May 2005 for hypertension, Helicid® (omeprazole) from 10 May 2005 to 27 May 2005, potassium from 26 Apr to 12 May 2005 for hypopotassemia, Enelbin R® (heparin plus salicylic acid ointment), Essentiale® (phospholipide, vitamin B1, B2, B6, B12, vitamin E, nicotinamid), Transmetil® (ademetionine butanedisulfonate), Dalacin® (clindamycin), Ciprinol® (ciprofloxacine), Nutramin Vli® (amino acids), glucose with minerals, Plasmalyte® (electrolyte infusion) Aspegic® (acetylsalicylic acid) and Venuroton® (oxerutins).
Start of intake of study drug was 05 May 2005 due to femoropopliteal thrombosis.

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03 August 2006

Subject identifier 11223-506-006

On 24 May 2005 increase of ALAT, ASAT, gamma GT, bilirubin and AP was found. In addition the subject was febrile and slight icterus was seen. In ultrasound no abnormalities were found. Acute hepatitis B was diagnosed. Hepatitis serology from 30 May 2005: S-anti HAV IgM negative, S-anti HAV total 96.65 (normal<50), HBsAg 216.21 (normal <2), anti HBs negative, HBeAg negative, anti-HCV negative. The study drug was stopped on 27 May 2005.
Serology on 03 Jun 2005: anti HBc IgM 3.2, anti HBe 65.34, on 08 Jun 2005 HBs Ag was 315.09, HBe Ag negative and anti-HBe 69.74 (normal <60). The diagnosis of acute hepatitis B was made – increase of HBs Ag titer, 3fold increase of anti HBc IgM and negative HBeAg with only discrete increase of anti HBe antibodies.
In central laboratory the hepatitis serology was as following:

	05 May 2005 (day 1)	24 May 2005 (day 21)
HBs Ag	positive	positive
HBs Ab	0 UI/mL	0 UI/mL
HBc Ab (total)	negative	positive
HBc Ab IgM	NA	positive
HBe Ag	negative	negative
HBe AB	negative	negative

The subject had positive HBs antigen before start of study medication.
Serum protein electrophoresis on 27 May 2005: Albumin was 0.43 (normal range 0.53-0.65), alpha-1-globulin 0.069 (normal range 0.02-0.04), alpha-2-globulin 0.091 (normal range: 0.08-0.13), Beta-globulin 0.134 (normal range 0.09-0.16), gamma-globulin 0.163 (normal range 0.115-0.19) and albumin globulin 1.2. Alpha-1-globulin, acute phase protein was elevated; this is in agreement with acute inflammation.
Ultrasound on 30 May 2005: liver no detectable lesions, gallbladder thickened wall, probable chronic cholecystitis, tumour can not be ruled out, intrahepatic bile ducts not enlarged, commen bile duct slightly dilated, pancreas not enlarged, two round hypoechogenic structures of 10 and 21 mm size, similar structure at cauda of pancreas of 11 mm size (retroperitoneal lymph nodes or pseudocysts?), 11 mm hypoechogenic structure of 1mm diameter at pancreas caput.
CT on 31 May 2005: Liver no focal changes, no signs of dilatation of intra- and extrahepatic bile ducts. Gallbladder: low filling, suspected thickened wall, chronic cholecystitis can be ruled out. Pancreas: thin in all parts, distinct borders, no signs of expansion. No pathological enlarged lymph nodes in peripancreatic region or porta hepatic. In right subphrenic region calcified lymph node of 10mm diameter. Normal spleen and kidneys. Abdominal aorta: artherosclerotic changes. Spondylosis of thoracic and lumbar spine. Conclusion: no signs of cholelithiasis, suspected chronic cholecystitis, no signs of retroperitoneal lymphadenopathy.
The subject was transferred to the infection ward on 03 Jun 2005. Progression of icterus and development of liver failue was reported. No signs of encephalopathy were seen.
The subject got following remedial therapy: Antibiotics because of fever accompanied with shivering, Essentiale® (essential phospholipids, vitamins), Transmetil® (ademetionine butanedisulfonate), Helicid® (omeprazole) and Aspegic® (acetylsalicylic acid). In addition

BAY 59-7939/011223/MRR-00150 1 - 1213
03 August 2006

Subject identifier 11223-506-006

following infusion solutions were given Nutramin® (aminoacid infusion solution), Plasmalyte® (electrolyte infusion) and glucose. As prophylaxis Dalacin® (clindamycin) and Ciprinol® (ciprofloxacin) from 29 May 2005 to 06 Jun 2005 were given. She got Fraxiparin® (nadroparin 0.3 mL) from 28 May 2005 to 21 Jun 2005.
Serum protein electrophoresis on 04 Jun 2005: albumin 0.445, alpha-1-globulin 0.055, alpha-2-globulin 0.078, beta-globulin 0.091, gamma-globulin 0.331 and albumin-globulin 0.8. Albumin and alpha-2-globulin were slightly decreased and alpha-1-globulin and gamma-globulin increased.
On 18 Jun 2005 aminotranferases decreased, considered by the investigator as sign of liver failure. Icterus progressed and the subject died on 21 Jun 2005 due to acute liver failure during acute hepatitis B. Autopsy was performed. According to the investigator the event was not related to study drug.

Central Laboratory

	05 May 2005	**11 May 2005**	**24 May 2005**	**02 Jun 2005**	**13 Jun 2005**
ALAT	27	35	2477+	2142+	644+
ASAT	20	34	1544+	2700+	414+
gamma GT	50+	40	537+	813+	251+
LDH	474	681+	1498+	1860+	548+
Bilirubin	6.7	8.5	34.5+	247.9+	471.6+
AP	74	57	304+	341+	190+
Lipase	33	47	35	36	148+
Albumin	43	40	35	28+	27+

Normal range:
ALAT: 5-31 U/L
ASAT: 5-36 U/L
gamma GT: 5-46 U/L
LDH: 240-480 U/L
Bilirubin: 5.1-18.8 umol/L
AP: 35-104 U/L
Lipase: 0-60 U/L
Albumin: 34-48 g/L
+out of normal range

BAY 59-7939/011223/MRR-00150 1 - 1214
03 August 2006

Subject identifier	11223-506-006								
Local laboratory									
	27 May 2005 10:33	**27 May 2005 15:44**	**30 May 2005**	**01 Jun 2005**	**04 Jun 2005**	**08 Jun 2005**	**13 Jun 2005**	**16 Jun 2005**	**18 Jun 2005**
ALAT	51.83 +	48.35 +	36.37 +	43.51 +	42.71 +	48.52 +	12.89 +	6.29+	4.21+
ASAT	37.12 +	31.9+	24.89 +	39.7+	60+	60+	7.22+	3.5+	2.42+
Bilirubin	136+	131+	166+	263+	339+	421+	473+	494+	458+
Bilirubin, conj.	98.4+								
Albumin		36.5			25.5+		26.2+	21.3+	22.1+
PT INR		1.8		1.4	1.9	3.4	3	3.2	
APTT		35.4			32.5	50.6+	55+	68+	

Normal range:
ALAT: 0.1-0.67 ukat/L
ASAT: 0.1-0.67 ukat/L
Bilirubin, total: 3-22 umol/L
Bilirubin, conj.< 5 umol/L
Albumin 35-52 g/L
+out of normal range

Autopsy Report

Month: June Year**:** 2005
Name: xxxxxxxxxx
Age: 72 years, xxxx, female
Occupation: 906/05
Hospital file number: .xxxx

Address: xxxx

Number of Autopsy Report: xxxx
From Department: INF – EIIB
Date of death: 21 June 2005, 13:28
Date of the autopsy: 22 June 2005
Autopsy performed by: Dr.Kopřivová Miroslava
Revised by: prim.Dr.Mukenšnabl Petr

CLINICAL DIAGNOSIS:

Liver failure

ANATOMIC DIAGNOSIS:

(I.Main diseases, II.Complications, III. Immediate cause of death, IV.Secondary findings)

I. Main diseases

General atherosclerosis grade III, obesity, diabetes mellitus type II treated by oral

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03 August 2006

Subject identifier	11223-506-006

antidiabetics according to the clinician. Undifferenced stromal uterine sarcoma treated by total abdominal hysterectomy and bilateral adnexectomy 8 months before the death and palliative chemotherapy (11/04 – 1/05), generalized (vide inv. Biopt. No. 86382/04 – Biopt.labor.s.r.o.). C54.1 – 8930/33. Deep vein thrombosis of the right leg during palliative chemotherapy according to the clinician. Viral hepatitis B according to the clinical data, histologically not confirmed during the autopsy. Subacute liver necrosis most probably due to toxic damage without acute inflammatory changes found during the histological examination.

II. Complications

General icterus. Metastases of undifferenced stromal uterine sarcoma in lungs and intraabdominal lymphatic nodes,
Excentric hypertonic hypertrophy of the left heart ventricle. Intraalveolar lung edema. Ascites (volume of 2000 ml). Arteriolosclerotic nephrosclerosis. Multiple erosions of stomach body mucosa. Melaena of small and large intestine. Edema of calf and ankle region bilaterally.

III. Immediate cause of death

Acute liver failure according to clinical data.

IV.Secondary findings

Anthracosis of lungs and mediastinal lymphatic nodes. Lipomatous pancreatic atrophy. Submucosal haemorrhage of urinary bladder, most probably after catheter.
Body weight: Weight of organs:

brain: 1280, heart: 310, right lung: 760, left lung: 710, spleen: 100, kidney: 310, liver: 1420, thymus:…., thyroid gland: ……, pancreas:……, suprarenal gland:…….. .

Kidney: some glomerulae hyalinized, advanced autolysis of tubular epithelium, biliary cylinders in the lumen of some canaliculi, pelvis without inflammation. Lungs: anthracosis of mild degree, venostasis with penetration of erythrocytes to alveoli. Intraalveolar edema, metastases of undifferenced stromal uterine sarcoma. Heart: hypertrophy of cardiomyocytes. Stomach: a few erosions of the stomach body mucosa. Pancreas: Significantly advanced autolysis, lymphatic nodes with metastases of undifferenced stromal uterine sarcoma are adjacent to the pancreatic parenchyma. Vagina: excision covered by pavement epithelium without dysplasia, focus of unspecific granular tissue in subepithelial stroma. Liver: advanced autolysis. Pronounced postnecrotic fibrosis of liver lobulae, where solitary two-row hepatocyte trabeculae and hyperplastic nodulae of parenchyma are present, especially at the periphery of the lobulae. In the preserved parenchyma, there is significant canalicular and intracelular cholestasis; infrequent biliary cylinders are in ductulae. Steatosis can not be judged in the autolyzed tissue. Marked hemosiderosis is in hyperplastic parenchyma at the periphery of lobulae, in

Subject identifier	11223-506-006

the epithelium of some ductulae and in Kupffer cells. Portobiliary spaces are slightly fibrously enlarged with reactive ductular prolipheration at the borders. In the surroundings of some ductulae there is slight mixed inflammatory infiltration (due to ductal cholestasis). Portobiliary spaces are without inflammatory changes, there is only scarce round-cell infiltration in the centre of two fields. There are no inflammatory changes in the portobiliary spaces or in lobulae, which would indicate the presence of acute exacerbation of chronic hepatitis B (it is not possible to judge the presence of ground-glass cells due to autolysis). **Conclusion**: Postnecrotic fibrosis of the liver tissue with compensatory hyperplasia of the preserved parenchyma, corresponding to so call subacute necrosis (hepatodystrophy) – protracted liver damage without acute inflammatory changes (and parenchyma necroses). Toxic origin of the changes is probable. The cause of hemosiderosis of the liver tissue is not clear, might be associated with the treatment (transfusion?).

Dg. MKN-O: 8930/33
Dg.MKN10: C541 K729 B169

7 July 2005

Biopsy and cytology:
86382/04
0:00:00

Report from Professor Botnott, Department of Pathology Johns Hopkins Medical Institutions, Baltimore

November 22, 2005

I have examined slides prepared from a single paraffin block of liver tissue obtained at autopsy from BAYer case ID numbers 11223-506-006 (clinical database), 200511782GDS (safety database). Slides stained with hemotoxin and eosin, Masson trichrome, Ki-67, Hepatitis B core antigen and Hepatitis B surface antigen were examined. My diagnosis is acute hepatitis B hepatitis with submassive hepatic necrosis, and possible partial regenerative failure.

The H&E stained slide shows evidence of extensive recent hepatocellular loss (necrosis) with small regenerative hepatocellular nodules. Marked bile stasis and autolysis somewhat complicate histologic interpretation, but while the liver can now be described as cirrhotic there is relatively little actual fibrosis (confirmed by Masson stain). The changes are thus quite consistent with the 4 week duration of the reported clinical illness and there is nothing to suggest underlying liver disease of longer duration.

BAY 59-7939/011223/MRR-00150 1 - 1217
03 August 2006

Subject identifier	11223-506-006

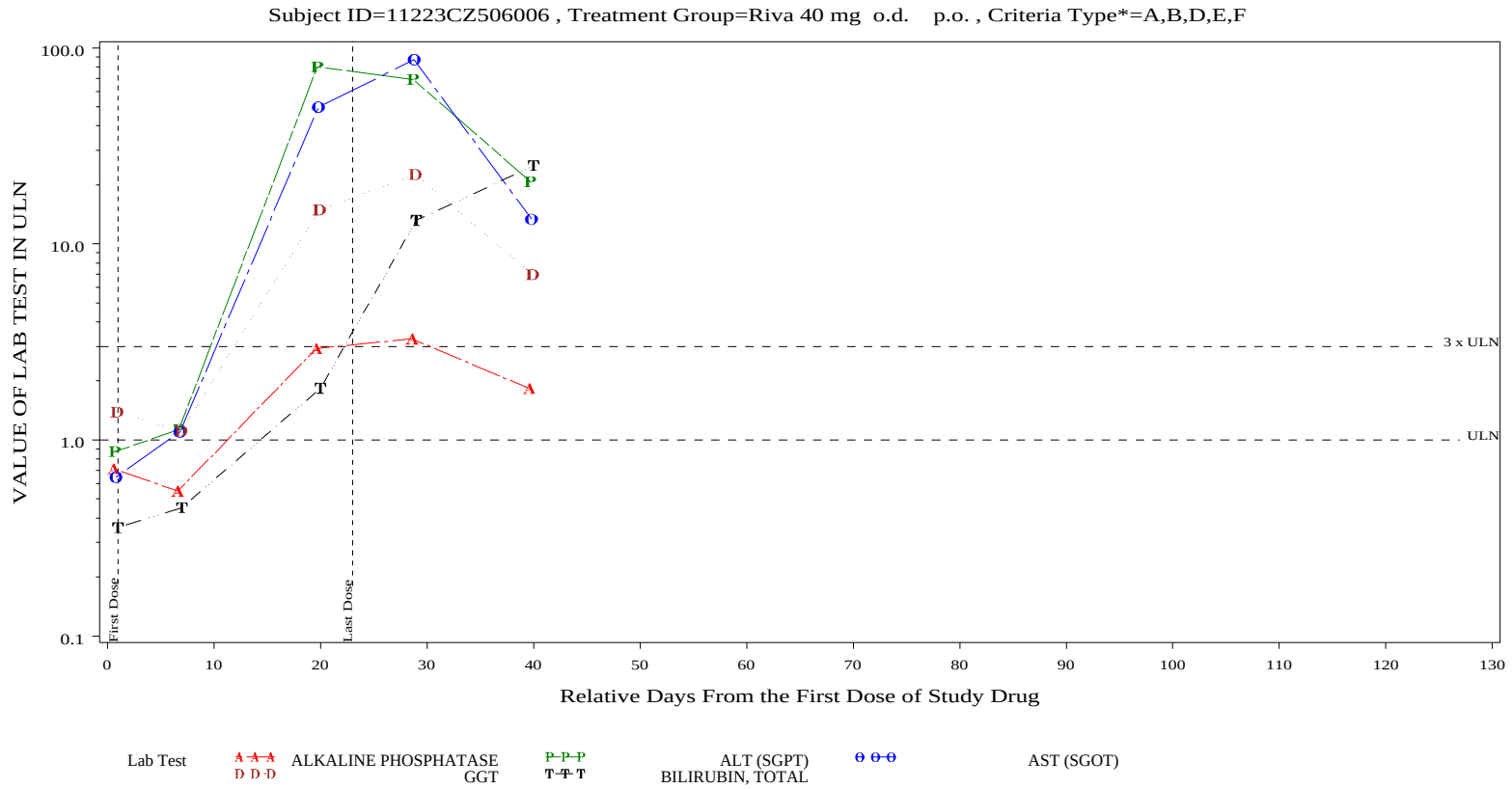
The stain for Hepatitis B core antigen is positive in occasional hepacyte nuclei while a stain for Hepatitis B surface antigen is negative. This is the expected pattern for acute Hepatitis B hepatitis and the absence of staining for surface antigen detracts from the possibility of acute hepatitis of another cause superimposed on symptomatic chronic Hepatitis B virus infection (as do the reported serum serologic studies and clinical history).

The stain for Ki-67 (a cell proliferative marker) shows very little hepatocellular nuclear staining suggesting impaired regeneration as a factor in the rapid clinical progression to death in hepatic failure. Regerative failure is uncommon in subjects with acute hepatitis, but when seen is generally in elderly subjects who often chronic non-hepatic diseases (as was certainly true in this case).

Signed John K. Boitnott, M.D., Professor, Department of Pathology

Figure FLS130-TR: Time Course of Liver Enzyme for Subjects of Special Interest (Based on Central Labs)

(Study Phase 2 VTE TREATMENT: Safety Analysis Set)



Note: VALUE OF LAB TEST IN ULN was calculated as the ratio of the actual lab value and the corresponding upper limit of normal. The Y-axis is on the log-scale.
* CRITERIA TYPE:
[A] ALT>3xULN within 30 days prior to death.
[B] Hepatic disorder serious adverse event.
[C] Discontinued and had an ALT>3xULN within 45 days prior to or after last dose.
[D] Hepatic disorder adverse event resulting in permanent discontinuation.
[E] ALT> 8xULN
[F] Combined ALT>3xULN/TB>2xULN

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Appendix 2.3

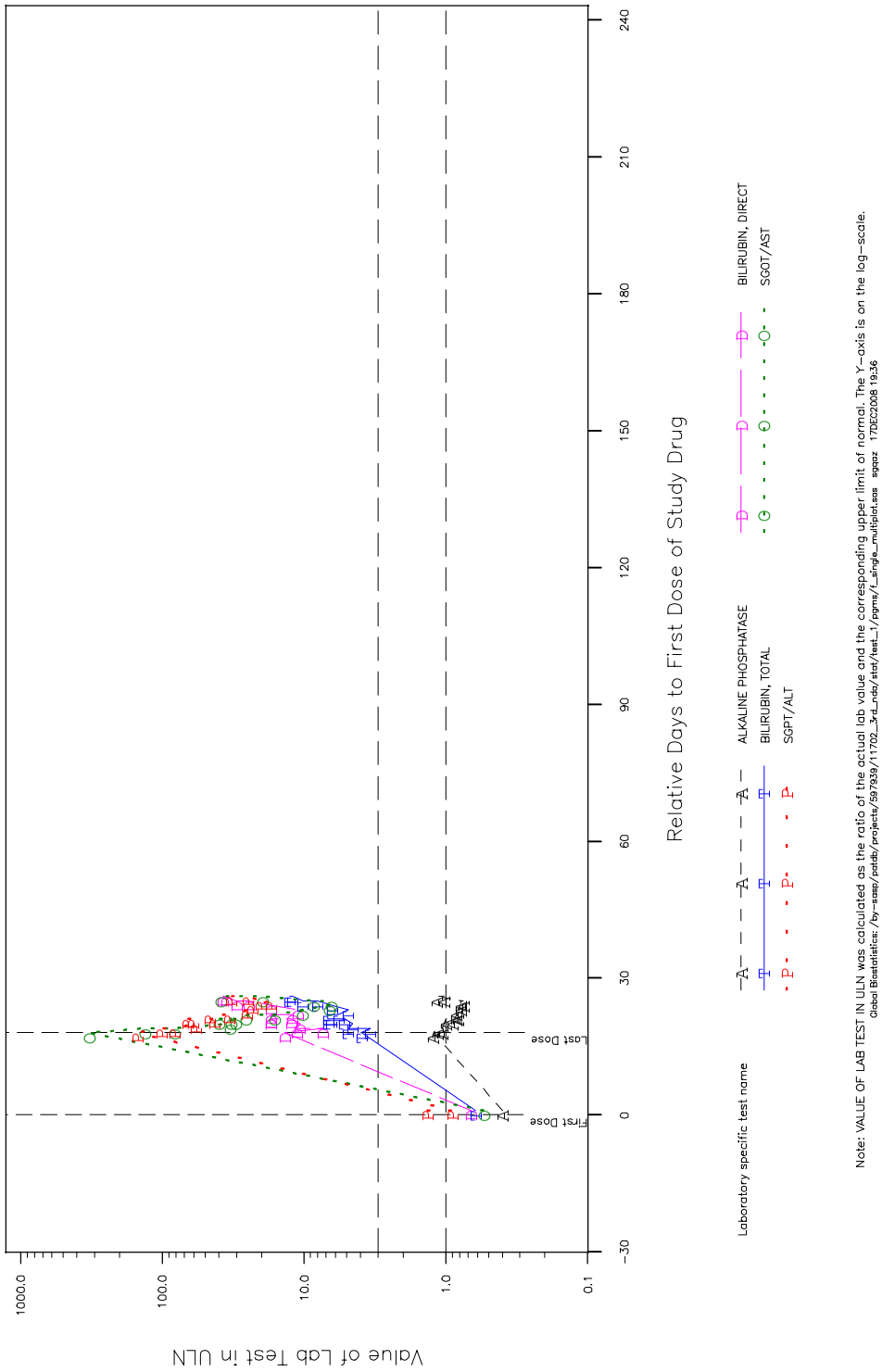
Einstein DVT/PE Study Subject 11702-160183005

Subject #160181005 [also known as #160183005] (serious adverse event: Severe Acute Hepatitis)

A 63-year-old female patient was enrolled in EINSTEIN VTE Treatment phase III trial after being diagnosed via CT scan with a multi-segmental pulmonary embolism in the right lower lobe on 27-December-2007. Study drug (rivaroxaban 15 mg twice daily) was taken for 17 days between 28-December-2007 through 14-January-2008. The patient's past medical history included systemic arterial hypertension (since 1994), severe asthma which had been treated with oral cortisteroids for 10 years and required tracheal intubation in 1997 as well as pulmonary emphysema. An echocardiography in December 1996 showed normal left and right chambers, normal cardiac valves, left ventricular relaxation dysfunction, and a non-significant pericardial effusion of 5 mm. She had no past medical history of liver disease or alcohol use but did have a history of smoking cigarettes (34 pack years) which she discontinued one year ago. Prior to initiation of study drug, in Jan/Feb 2007, the patient had experienced two episodes of acute respiratory decompensation (one with a superinfection with P. aeruginosa). In November 2007, the patient's dyspnea worsened despite of corticosteroid and antibiotic treatment. On 17 Dec 2007 she was hospitalized due to exacerbation of her asthma and respiratory decompensation. She had received prednisone, amoxicillin 3 g/day, terbutaline, ipratropium, oxygen and prophylactic enoxaparin (40 mg sc /day) without any significant improvement. Baseline liver tests on 28-December-2007 showed normal AST, alkaline phosphatase and bilirubin. The ALT was 49 U/L and the GGTP was 421 U/L. After starting study drug on 28-December-2007, the subject showed clinical improvement and was discharged home on 7-January-2008. Between 7-January-2008 and 12-January-2008, the patient was reported to have episodes of disorientation and increased dyspnea according to the patient's daughter. She was re-admitted on 12-January-2008 due to increased dyspnea and asthenia. Upon admission, was noted to be tachycardiac with a blood pressure of 110/80 mmHg. Treatment included an increase of her regular therapy with salbutamol and ipratropium; moreover, Therapy with amoxicillin-clavulanic acid (Augmentin®) started on 12 Jan 2008, in addition, insulin and oxygen. On 14 Jan 2007 laboratory findings showed an AST of 10,506 U/L, ALT of 5,371 U/L, Factor V level less than 10%, D-dimer > 4,000, B-type natriuretic peptide of 1610 (normal < 100 pg/mL), and serum creatinine 180 micromol/L (increased from 113 micromol/L on 12-January-2008). Study drug was discontinued on 14-Janauary-2008 and subject was transferred to another hospital on 15-Janauary-2008 for consideration of liver transplant. The subject was noted to have a Blood pressure of 100/70, heart rate of 107 along with conjunctival icterus. At the new hospital work-up that included a thoracoabdominal CT showed a 6 cm tumoral mass, suspicious for malignancy. The patient also had several transthoracic echocardiograms done between 15-January and 21-January-2008 that showed hypokinetic left ventricle with a reduced EF in the range of 30-40%, evidence of dilated cardiomyopathy. On 21-January-2008, the subject had a cardiac arrest and died due to multiple organ failure. An autopsy was done and showed massive dilatation of the right ventricle and left ventricular hypertrophy. In addition, there was evidence of hemorrhagic necrosis of the liver, especially in the centrilobular areas with minimal inflammation. In addition, there was evidence of ischemic type tubular necrosis of the

kidney. This case was reviewed in detail by all members of the Liver Advisory Panel – 3 clinicians and 2 pathologists. The 3 clinicians reviewing this case (Drs. Larrey, Horsmans, and Maddrey) each thought the role of rivaroxaban was unlikely. One of the pathologists (Dr. Zafrani) thought the role of rivaroxaban was unlikely. The second pathologist (Dr. Rubin) initially suspected ischemic hepatitis based on a review of tissue slides but subsequently diagnosed drug-induced liver injury after reviewing the clinical records which revealed an absence of any documented clinical episodes of hypotension. A group meeting of all 5 LAP members was convened at a later date to re-examine the case. At the conclusion of that meeting, it was thought that ischemic injury leading to hepatocellular necrosis in a setting of multi-organ failure was the most likely explanation for this subjects liver injury.

Figure 2: Liver Tests Time Course by Subject With ALT > 3xULN and Total Bilirubin > 2xULN (Based on Central and Local Labs)
(Bay 59-7939 (Rivaroxaban) Study 11702 Data Cut-off Date: 05DEC08: Safety Analysis Set)
Treatment = Rivaroxaban Subject Identifier for the study = 160183005



Note: VALUE OF LAB TEST IN ULN was calculated as the ratio of the actual lab value and the corresponding upper limit of normal. The Y-axis is on the log-scale.
Global Biostatistics: /by-sasp/patdb/projects/597939/11702_3rd_rdb/stat/last_1/pgms/f_single_multiplot.sas sgaaz 17DEC2008 19:36

Appendix 2.4

Einstein DVT/PE Study Subject 11702-220134004

Subject #220131004 [also known as #220134004] (serious adverse events: High liver enzymes, high bilirubin; adverse event: hematuria)

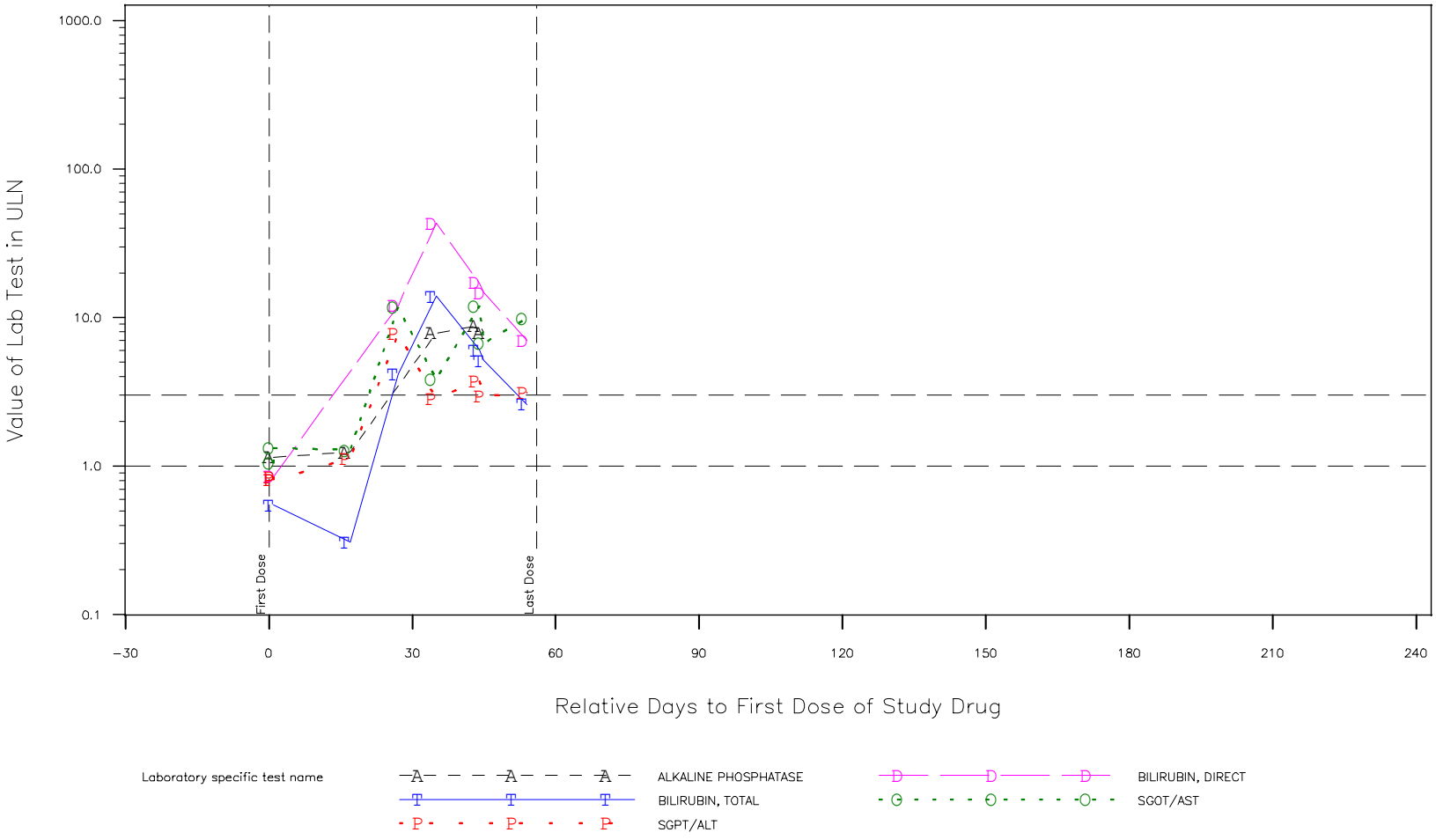
Subject #220131004, a 71-year-old white man, was enrolled in the EINSTEIN DVT/PE study after being diagnosed with a deep vein thrombosis. The subject received rivaroxaban 30 mg daily from 11 October 2007 to 01 November 2007 and then 20 mg daily from 01 November 2007 until 15 November 2007. The subject had a past medical history of pancreatic cancer (2007) and underwent surgery for gastric cancer (Billroth II) on 18 June 2007. Enoxaparin was taken for 2 days just prior to study entry from 10-11 October 2007. No other medications were reported before the start of study medication. The subject did not receive any chemotherapy. Baseline BMI was 18.1 kg/m^2.

On 15 October 2007 (Day 5), the subject experienced mild hematuria that was considered non-serious. On 6 November 2007 (Day 27), the subject had high liver enzymes (ALT 513 U/L, AST 537 U/L) and high bilirubin levels (total bilirubin 5.4 mg/dL, direct bilirubin 4.8 mg/dL). These events were considered serious due to hospitalization. An abdominal ultrasound on 7 November 2007 (Day 28) showed liver parenchyma deranged by metastases and enlarged biliary tree at the liver ileum. The subject was found to have concomitant gastric cancer with liver metastases. On 20 November 2007 (Day 41), a biliary stent was placed for a neoplastic stenosis of the biliary tree and three days later the subject developed deep vein thrombosis and was treated with enoxaparin. The last dose of study medication was on 15 November 2007. The subject was discharged from the hospital on 24 November 2007 (Day 45) and the events of high liver enzymes and bilirubin were considered resolved on 27 November 2007 (Day 48). The investigator considered the elevated liver enzymes and bilirubin not to be related to study medication but instead to gastric cancer with liver metastases. The subject received various concomitant medications including tramadol (for pain); kayexalate, lasix and insulin (for blood potassium), rocefin (antimicrobial after biliary stent implantation), metoclopramide (for vomiting) and enoxaparin (for DVT developed during hospitalization). The subject's last study visit was 5 December 2007 (Day 54) and the subject died on 7 December 2007. Although an autopsy was not performed and the cause of death was unknown, it was presumed to be from metastatic gastric cancer. [Bayer Case ID: 200716255GDS]

Study Day	ALT (U/L)		AST (U/L)		Total Bilirubin (mg/dL)		Direct Bilirubin (mg/dL)		AP (U/L)	
	Value	Ratio	Value	Ratio	Value	Ratio	Value	Ratio	Value	Ratio
1	53	0.80	61	1.33	0.7	0.55	0.3	0.85		
1	38	0.84	41	1.05					141	1.15
17	51	1.13	50	1.28	0.4	0.31			153	1.24
27	513	7.77	537	11.67	5.4	4.17	4.8	12.00		
35#	189	2.86	177	3.85	18.1	13.92	17.3	43.15	1066	7.84
44	248	3.76	550	11.96	7.9	6.07	6.9	17.15	1204	8.85
45	195	2.95	311	6.76	6.7	5.15	5.9	14.75	1081	7.95
54	206	3.12	455	9.89	3.4	2.61	2.8	7.00		

Ratio = lab value divided by the corresponding ULN. Ratio provided when ULN available.
# Last dose of study medication 15 November 2007 [Day 36].

Figure 2: Liver Tests Time Course by Subject With ALT > 3xULN and Total Bilirubin > 2xULN (Based on Central and Local Labs)
(Bay 59–7939 (Rivaroxaban) Study 11702 Data Cut–off Date: 05DEC08: Safety Analysis Set)
Treatment = Rivaroxaban Subject Identifier for the study = 220134004



Note: VALUE OF LAB TEST IN ULN was calculated as the ratio of the actual lab value and the corresponding upper limit of normal. The Y–axis is on the log–scale.
Global Biostatistics: /by–sasp/patdb/projects/597939/11702_3rd_nda/stat/test_1/pgms/f_single_multiplot.sas sgqaz 17DEC2008 19:36

Appendix 2.5

ATLAS ACS TIMI 46 Study Subject 11898-200039

Subject 200039 (serious adverse event: sepsis, worsening liver failure, cause of death: liver failure) – This 44-year-old white woman was enrolled in the ATLAS ACS TIMI 46 trial following an index event of STEMI and randomized to receive placebo.

The subject had a history of severe folate deficiency, macrocytic anemia, alcohol abuse and was a current smoker at the time of randomization. In addition, she had a 2-week history of rhinorrhea with a productive cough and weight loss of 14 kg in the 2 months prior to her adverse event of sepsis. Baseline BMI was 22.4 Kg/m^2.

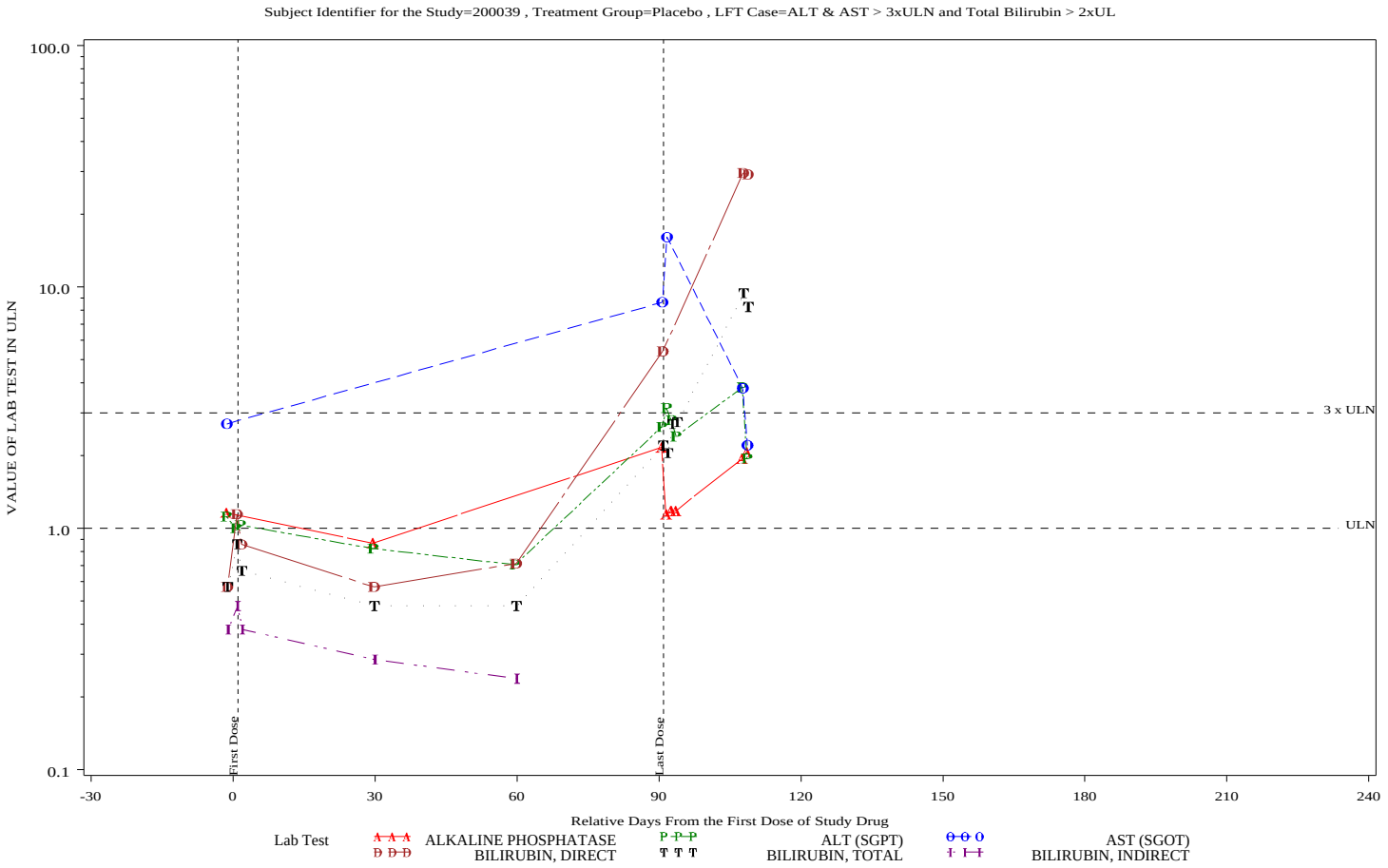
Concomitant medications include low dose aspirin, clopidogrel, ramipril, metoprolol, atorvastatin, pantoprazole and diazepam.

On 11 June 2007 (Day 91), the subject was hospitalized with blurred vision, headache and hypotension (78/50) and diagnosed with sepsis and abnormal liver function. Ultrasound of the abdomen showed changes consistent with fatty liver, without evidence of cholelithiasis. The subject recovered from sepsis 3 days later, and her liver function tests improved without intervention. Study medication was discontinued on 11 June 2007 (Day 91) because of the abnormal liver function tests. On 28 June 2007 (Day 108) the subject was readmitted to the hospital with worsening liver function. Blood tests taken on 29 June 2007 (Day 109) were positive for CMV IgG and negative for CMV IgM. On the same day the subject developed bradycardia, hypotension, and multi-organ failure resulting in death. The cause of death was multi-organ failure including liver failure and lower respiratory tract infection. An autopsy was not performed. The investigator considered sepsis to be unrelated to study medication and worsening liver failure to be related to study medication.
[Bayer Case ID: 200713254GDS]

Study Day	ALT (U/L)		AST (U/L)		Total Bilirubin (mg/dL)		Direct Bilirubin (mg/dL)		AP (U/L)	
	Value	Ratio	Value	Ratio	Value	Ratio	Value	Ratio	Value	Ratio
0	38	1.12	92	2.71	0.70	0.57	0.23	0.57	123	1.16
0	34	1.00			1.05	0.86	0.47	1.14		
2	35	1.03			0.82	0.67	0.35	0.86		
30	28	0.82			0.58	0.48	0.23	0.57	92	0.87
60	24	0.71			0.58	0.48	0.29	0.71		
91					2.51	2.05			229	2.16
91#	92	2.63	302	8.63	2.57	2.20	1.58	5.40	241	1.79
92	110	3.14	562	16.06	2.40	2.05			154	1.14
93	98	2.80			3.16	2.70			159	1.18
94	84	2.40			3.22	2.75			159	1.18
108	134	3.83	133	3.80	10.99	9.40	8.65	29.60	262	1.94
109	66	1.94	75	2.21	9.65	7.86			219	2.07
109	68	1.94			9.65	8.25	8.54	29.20	212	1.57

Ratio = lab value divided by the corresponding ULN. Ratio provided when ULN available.
#Study medication permanently discontinued on Day 91

Figure FLABL20V: (Figure 2) Liver Tests Time Course by Subject With ALT/AST > 3xULN and Total Bilirubin > 2xULN (Based on Central and Local Labs)
(Bay 59-7939 (Rivaroxaban) Study ATLAS-11898 Data Base Lock Date: 18OCT2008: Safety * Analysis Set)



Note: VALUE OF LAB TEST IN ULN was calculated as the ratio of the actual lab value and the corresponding upper limit of normal. The Y-axis is on the log-scale. * The Site 972009 has been excluded.

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Appendix 2.6

Magellan Study Subject 28013-0001

Subject #280130001 (serious adverse events: Thrombocytopenia, fever of unknown origin, septic shock, cardiac insufficiency, atrial fibrillation, agranulocytosis, increased transaminases, renal insufficiency, pulmonary hypertension with suspicion of pulmonary embolic event, fatal multiple organ failure, increased bilirubin, hypokalemia, arterial hypertension)

Subject #280130001, a 72-year-old white female, was enrolled in the MAGELLAN study after being hospitalized for stage IV esophageal neoplasia. The subject received study drug from 13 August 2008 until 9 September 2008. The treatment code for the subject was broken by Bayer Global Pharmacovigilance and revealed that the subject received enoxaparin 40 mg subcutaneously. Relevant medical history included arterial hypertension, lumbodiscarthrosis, scoliosis, calcifying atheromatosis, chronic venous insufficiency, rheumatism, splenectomy, proximal DVT, arterial and carotid bypass for arteriosclerosis, esophageal stenosis and esophageal neoplasia stage IV. The subject had a history of smoking (1 pack/day from 16 to 45 years of age). Prior medications included aspirin, indapamide, metoprolol, ramipril, tramadol and triazolam. Baseline BMI was 29.6 kg/m^2.

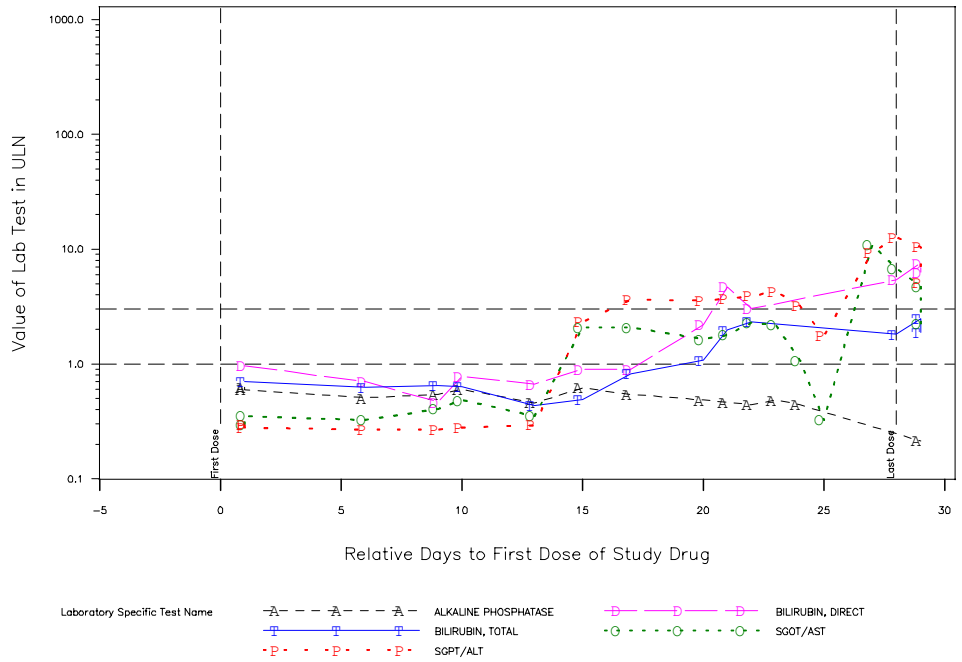
Esophageal neoplasia was diagnosed on 1 August 2008 by endoscopy; biopsy showed moderately differentiated epidermoid cancer. Diagnostic work-up between 1 August 2008 and 22 August 2008 showed no suspect secondary lesions either intra-abdominal or in the brain. PET scan showed lesion of right superior pulmonary lobe; however, pathohistology for pulmonary metastases was negative. The subject was hospitalized on 12 August 2008 and started study drug the next day. On 22 August 2008 (Day 11), it was determined that the subject was a candidate for surgery and radio-chemotherapy was planned. On 25 August 2008 (Day 13) the subject received the following chemotherapeutic agents: 5-fluorouracil, cis-platin, dexamethasone and odansetron. She also received aprepitant for vomiting and fluconazole for erythema. Increased transaminases were noted on 27 August 2008. Cis-platin and 5-fluorouracil were stopped on 29 August 2008 and increased bilirubin levels were noted on 1 September 2008 (Day 20). On 3 September 2008 (Day 22), the subject was hypokalemic (due to diarrhea and cis-platin) and was diagnosed with thrombocytopenia [platelet values decreased from 90 Giga/L on 2 September 2008 (Day 21) to 14 Giga/L on 8 September 2008 (Day 27)]. The laboratory elevations on this day showed ALT>3xULN and total bilirubin >2xULN. One day later, on 4 September 2008 (Day 23), the subject was hospitalized with fever, agranulocytosis, septic shock, cardiac insufficiency and atrial fibrillation and was treated with Meronem, Amukin, Lanoxin, Targocid, Perfusalgan, Glazidim, Lasix, Corvaton, and Dobutamine. Study medication was temporarily discontinued on this day. Despite remedial therapy, the subject's condition worsened. On 5 September 2008 (Day 24), the subject was diagnosed with renal insufficiency and had severe arterial hypertension (200/100). The subject received amiodarone, paracetamol, Neupogen, and Lasix and required resuscitation. Two days later (on 7 September 2008, Day 26), the subject was still in atrial fibrillation and had severe hypokalemia. Her condition deteriorated further, the doses of antibiotics and Meronem were increased, and study medication was restarted. In addition, during this time, the subject received platelet transfusions 4 times between 4 September 2008 and 10 September 2008 as well as other miscellaneous medications. On

9 September 2008 (Day 28) the subject experienced respiratory degradation and hypoxia, an echocardiogram showed pulmonary hypertension and the following laboratory values were obtained: ALT 12.7xULN, AST 6.8xULN and total bilirubin 1.8xULN. Clexane was administered from 9 September 2008 to 10 September 2008 for suspected pulmonary embolism. One day later, on 10 September 2008 (Day 29), the subject had cardiac degradation with bradycardia, hypotension, and respiratory arrest and died several hours later from multiple organ failure and pulmonary hypertension. The last dose of study medication was administered on 9 September 2008. The investigator considered the increased transaminases and increased bilirubin related to study medication and all other events were considered not related to study drug. [Bayer Case ID: 200826131GPV]

Study Day	ALT (U/L)		AST (U/L)		Total Bilirubin (mg/dL)		Direct Bilirubin (mg/dL)		AP (U/L)	
	Value	Ratio	Value	Ratio	Value	Ratio	Value	Ratio	Value	Ratio
1	12	0.28	13	0.35					70	0.59
1	12	0.29	11	0.30	0.8	0.70	0.3	0.97	85	0.63
6	11	0.27	12	0.32	0.8	0.63	0.2	0.70	69	0.51
9	11	0.27	15	0.41	0.8	0.65	0.1	0.47	74	0.54
10	12	0.28	18	0.49	0.8	0.63	0.3	0.78	71	0.60
13	12	0.29	13	0.35	0.5	0.43	0.2	0.67	62	0.46
15	95	2.32	77	2.08	0.6	0.49	0.3	0.90	84	0.62
17	149	3.63	77	2.08	1.0	0.82	0.3	0.90	74	0.54
20	146	3.56	61	1.65	1.3	1.08	0.7	2.20	66	0.49
21	152	3.71	66	1.78	2.4	1.98	1.4	4.67	63	0.46
22	160	3.90	85	2.30	2.8	2.33	0.9	3.03	60	0.44
23	176	4.29	81	2.19					66	0.49
24	132	3.22	40	1.08					60	0.44
25	72	1.76	12	0.32						
26	40		7							
27	384	9.37	405	10.95						
28#	520	12.68	252	6.81	2.2	1.83	1.6	5.4		
29	429	10.46	176	4.76	3.0	2.47	2.3	7.5		
29	211	5.15	83	2.24	2.3	1.88	1.9	6.3	29	0.21

Ratio = lab value divided by the corresponding ULN. Ratio provided when ULN available.
# Last dose of study medication 9 September 2008 [Day 28].

Figure 2: Liver Tests Time Course by Subject With ALT > 3xULN and Total Bilirubin > 2xULN
(Based on Central and Local Labs)
(Bay 59-7939 (Rivaroxaban) Study 12839: Safety Analysis Set)
Treatment = Blinded Subject Identifier for the study = 280130001



Note: VALUE OF LAB TEST IN ULN was calculated as the ratio of the actual lab value and the corresponding upper limit of normal. The Y-axis is on the log-scale.
Global Biostatistics: /by-sasp/patdb/projects/597939/12839/stat/test_sgavg_safe_up_2/pgms/1_single_multiplot.sas sgavg 17DEC2008 3:55

APPENDIX 3

WEIGHTED QUANTITATIVE BENEFIT-RISK ASSESSMENT

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Advisory Committee Briefing Book – Appendix 3

Rivaroxaban for the Prophylaxis of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) in Patients Undergoing Hip or Knee Replacement Surgery

JNJ-39039039 (BAY 59-7939, rivaroxaban)

Issue/Report Date: 10 FEBRUARY 2009
Document No.: EDMS-PSDB-9449651:2.0

Rivaroxaban: Advisory Committee Briefing Book, Appendix 3

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1. INTRODUCTION

When patients regard a particular beneficial event and particular adverse event (AE) as equally important, the benefit-risk assessment is readily apparent: If the excess number of beneficial events resulting from a treatment exceeds the excess number of AEs resulting from that treatment, benefit exceeds risk. However, patients often regard different outcomes and AEs very differently. One measure often used to reflect patient preference is "utility," which measures patient preferences or a particular outcome or health state. Utility-based approaches are a crucial part of cost-effectiveness analysis and value-based medicine[1] and are available for numerous medical conditions[2,3]. The use of these measures in the current context is not intended to make any value-or cost-related claims, but simply to serve as a tool to facilitate accounting for patient preferences.

In the Methods section below, we provide background on how utility is measured and applied to excess number of event calculations. Because utilities for an outcome often span a range yielding noticeable uncertainty, we also conducted multiple sensitivity analyses for the utility-weighted assessment.

2. METHODS

2.1. Utility Scores

Utilities measure patient preferences for a particular health outcome or health state. A health state is a description of mental, physical and/or functional measures for a patient at a given point in time. While there are numerous means to elicit utilities, they are generally normalized to a 0–1 scale, with 1 corresponding to perfect health and 0 corresponding to immediate death.

There is a large and growing body of literature with utilities for numerous medical conditions[2, 3]. Unfortunately, there is a broad variation in the manner and the populations in which utilities are assessed, and published literature does not always specify complete details of the health states studied. For these reasons, applying results to novel situations requires considerable care.

Utilities are measured in a variety of ways including methods based on patient-reported outcomes or structured interviews that assess specific aspects of "quality of life."

- Preference-based instruments are commonly used to obtain utilities and include:
    - Time-tradeoff: A patient is given choice between, e.g., 10 years in his/her current health state and x ($x \leq 10$) years in perfect health. Variable x is varied until the patient is indifferent between choices. The utility is derived from x.

- Standard Gamble: A patient is given a hypothetical choice between continuing in his/her current health state vs. an experimental treatment, both for a given period of time. The treatment has x% chance of complete cure and (100 – x)% chance of immediate death. Variable x is varied until the patient is indifferent between the choices. The utility is derived from x.
- Rating scale: Patient directly indicates utility on a visual scale

- Functional quality of life instruments such as the Medical Outcomes Study Short Form Surveys (SF-36, SF-12) and Quality-of-Well-Being Scale are also used to assess patient self-reported outcomes, after which the responses can be converted into utilities. These instruments can apply to health conditions in general or be geared towards specific conditions[4].

To assess benefit-risk balance of Rivaroxaban, we reviewed utilities from numerous sources and developed the low/typical/high values based on assessing the range of health states under each outcome and the particulars of the health states examined in each article.

Weighted excess number of events

Since utility changes are measured per person, the change in utility for a given number of events is the product of the utility change and the excess number of events. For example, patients who experience a non-fatal pulmonary embolism (PE) have a drop in utility from 1.0 to 0.63 (Table 1), as all these calculations are normalized to starting with a healthy population. Preventing 11 non-fatal PE events within a population of 10,000 would then correspond to preventing a drop in population utility of 11 x (1.0 – 0.63) ≈ 4. Since death corresponds to a drop in utility to 0, this 4 is equivalent at the population level to the utility of preventing death in 4 of the 10,000 patients.

2.2. Results

2.2.1. Weighted Excess Number of Event Results

Weighted analyses are performed with distinct endpoints, rather than composite endpoints, since utilities differ for each specific health state. Table 1 shows the utilities for the RECORD study endpoints used in the weighted excess number of events analyses. These values were obtained from review of literature collected in the Tufts Medical Center Cost-Effectiveness Analysis (CEA) Registry, a comprehensive database of cost-utility analyses on a wide variety of diseases and treatments.[2]

Rivaroxaban: Advisory Committee Briefing Book, Appendix 3

Table 1: Utilities Used in Weighted Excess Number of Event Analyses.

	Typical	Low	High
Efficacy Clinical Outcome			
Symptomatic non-fatal DVT	0.80	0.60	0.90
Non-fatal PE	0.63	0.35	0.80
Death from all causes	0.00	0.00	0.00
Safety Clinical Outcome			
Bleeding			
Major Bleeding	0.80	0.65	0.87
Clinically relevant, not major	0.87	0.80	0.98
Other Non-major Bleeding	0.98	0.97	1.00
Cardiovascular			
Acute MI	0.82	0.64	0.93
Ischemic stroke	0.60	0.30	0.80

Some RECORD study outcomes encompass a wide range of health states. For example, non-major, clinically-relevant bleeding includes 12 types of events such as coughing blood and prolonged bleeding after venipuncture, for which patients will have different preferences. With the understanding that the present analysis is a post hoc analysis, the low, typical and high values reflect our best attempt to capture these sources of variability.

Published literature suggests that the utility for VTE (DVT and PE collectively) is lower than that for major bleeding, which in turn is lower than that for clinically-relevant, non-major bleeding. This aligns qualitatively with the clinical impact measures observed in the RECORD studies (Table 8-3 of Benefit-Risk Section of the Advisory Committee Briefing Book). Major and symptomatic VTE events require chronic anticoagulation, and can be associated with long-term morbidity. Pulmonary embolism requires hospitalization, chronic anticoagulation, and poses a risk of severe hemodynamic compromise and death. On the other hand, while some major bleeding events had serious sequelae, approximately 25% were not considered serious by the investigator, and over 85% of the major bleeding events were judged as resolved by the investigator by study completion.

Table 2 shows the number of excess events for all efficacy and safety outcomes from Table 1, both unweighted and weighted by utility. The unweighted score of 48 for symptomatic non-fatal DVT indicates that, in a hypothetical population of 10,000 patients treated with enoxaparin for either total hip or total knee replacement surgery, 48 more patients would have non-fatal DVTs than the same population would experience when treated with rivaroxaban. The weighted value of 10 is the 48 multiplied by the 0.2 change in utility associated with going from perfect health (utility = 1.0) to having a DVT (typical utility of 0.8). Positive values indicate an unweighted or weighted excess number of events in favor of rivaroxaban.

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Table 2: Unweighted and Weighted Excess # of Events for RECORD Studies (10,000 Patient Hypothetical Population)*

	Excess Number of Events	
	Unweighted	Utility-weighted
Efficacy Clinical Outcome		
Symptomatic non-fatal DVT	48	10
Non-fatal PE	11	4
Death from all causes	13	13
Safety Clinical Outcome		
Major Bleeding	-18	-3.6
Clinically relevant, not major	-52	-6.8
Other Non-major Bleeding	-6	-0.1
Acute MI	8	1.4
Ischemic stroke	-6	-2.4
Total Excess Efficacy Events	72	26.7
Total Excess Safety Events	-74	-11.4
Total Excess Events	-2	15

*Non-cardiovascular Outcomes based on safety population through the double blind treatment period. Acute MI and ischemic stroke outcomes based on treatment plus follow-up period.

The benefit-risk utility difference for the population as a whole is the sum of the utility-weighted excess number of events for each outcome. For the pooled RECORD studies, the unweighted utility difference is –2. Since this number regards minor bleeds, PEs and death as equivalent events, it is difficult to interpret. Using the weighted method, however, the net gain in efficacy events is 26.7 (in favor of rivaroxaban), while the net loss in safety events is –11.4 (in favor of enoxaparin). Thus, the net difference is 15, which indicates a net benefit to rivaroxaban. The total weighted excess number of events can be interpreted as the utility equivalent to preventing the death of 15 out of 10,000 patients when they are treated with rivaroxaban as compared to being treated with enoxaparin.

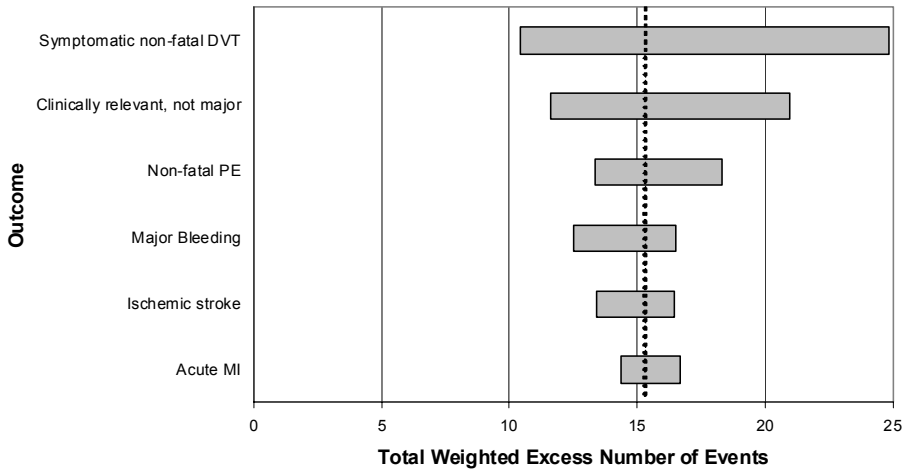
Uncertainty and Sensitivity Analysis Results

The results shown above are subject to uncertainty related to measurement of both the excess number of events and the utility scores. This section demonstrates that the total weighted excess number of events remains positive despite wide variation in the utilities, uncertainty in the absolute rate differences for each outcome, and when approximating the variation of utilities in the target population.

(1) Utility uncertainty for each outcome considered individually

Figure 1 shows a tornado plot reflecting the degree to which variation in each individual utility alters the total weighted excess number of events. Each bar represents how changing the utility for one outcome from its low to high value changes the total weighted excess number of events. For example, changing the utility of symptomatic non-fatal DVTs from its typical value of 0.8 to its high value of 0.9 reduces the total weighted benefit from its base case of 15 (Table 2) to 11. This reduction occurs since rivaroxaban causes fewer DVTs than enoxaparin, and a higher utility reflects less patient impact for each DVT. A key observation is that the outcomes are roughly in order of decreasing magnitude of unweighted excess number of events, indicating that the primary driver for the result is absolute risk difference, rather than the uncertainty in utilities. A more critical key observation is that none of the bars approach 0, reflecting that benefit continues to exceed risk in each case.

Figure 1: Sensitivity Analysis for Weighted Excess Number of Events as Utilities are Varied Individually. The Dotted Line is the Total Weighted Excess Number of Events Using the Typical Utilities. Each bar Reflects the Change Caused by Changing Each Utility From its low to High Value. The Values in or Next to the bars are the low, Typical and High Utilities Assessed. Outcomes are Shown in Order of Decreasing Influence.



Because the total weighted excess number of events is a simple sum of separate weighted components, the effect of changing the utilities for more than one outcome can also be inferred from Figure 1. Consider the case in which two outcomes have their utilities set to their "worst case" values; i.e., to whichever of their low or high values would most favor enoxaparin in the benefit-risk balance. The total weighted excess number of events is then 15 minus the sum of the deviations to the left of the dotted line for the two individual bars. For example, picking worst case utilities for both symptomatic non-fatal DVT (deviation ~4.5 from dotted line) and clinically-relevant, non-major bleeding

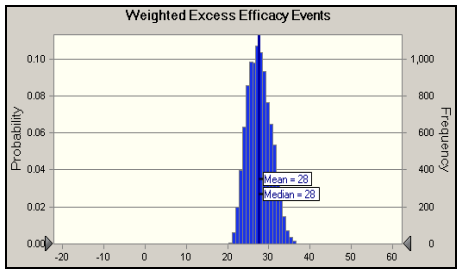
(deviation ~3.5) would result in a total weighted excess number of events of about 7. This type of sensitivity analysis can also be viewed as a way of taking into account preferences of individual patients, rather than relying on a single value derived from a population. Visual inspection of the bars show that, even for patients who have strong preferences regarding several events that favor enoxaparin, the benefit-risk calculations favor rivaroxaban.

(2) Utility uncertainty for outcome considered collectively

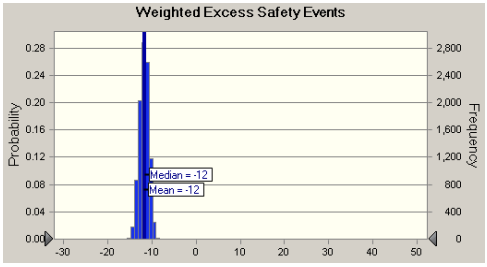
To determine the effect of all the utility uncertainties simultaneously on the benefit-risk balance, a Monte Carlo simulation was performed for the total weighted excess number of events. The simulation reproduces the calculation shown in Table 2, but with random variables underlying the utilities. This is essentially a kind of simulation study, roughly mimicking the variability that would be observed in the above calculations in different samples from a large population with heterogeneous utilities.

Figure 2: Distribution of Weighted Excess Number of Events (Benefit and Risk) Using Uncertainties in Utilities for a Hypothetical Population of 10,000 THR and TKR Patients.
Data is for RECORD Studies 1-4 Pooled. (a) Probability Density Function (pdf) for Weighed Efficacy Outcomes; (b) pdf for Weighted Safety Outcomes; (c) pdf for all Outcomes – 100% of the Probability Mass is Above Zero (Benefit Outweighs Risk)

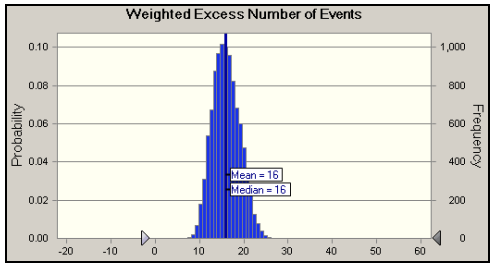
(a)



(b)



(c)



Utilities for each outcome were represented by beta distributions anchored at the low and high utilities and with the typical utility as the mode. The simulation was performed with Oracle Crystal Ball ver. 11 within Microsoft Excel ver. 2000. Distributions are based on simulations of 10,000 runs.

Figure 2 shows the Monte Carlo results for the efficacy, safety and all events separately. As can be seen by comparison with Table 2, there were very small changes in the mean weighted number of events; however, the probability density functions now span a range of total weighted excess number of events. Figures 2(a) and 2(b) show that the uncertainty in weighted efficacy outcomes drives considerably more of the spread in benefit-risk than do the weighted safety outcomes.

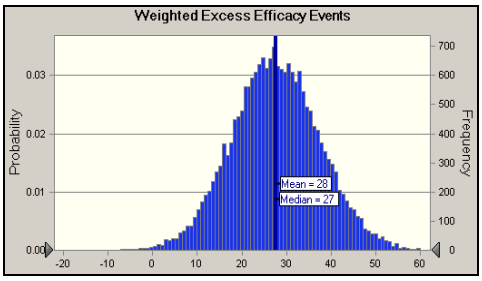
Figure 2(c) shows the distribution of weighted excess number of events for all outcomes. The distribution has its entire probability mass well above zero, indicating that the benefit-risk balance favors rivaroxaban over the heterogeneity of utilities found in a population.

(3) Combined event rate and utility uncertainties

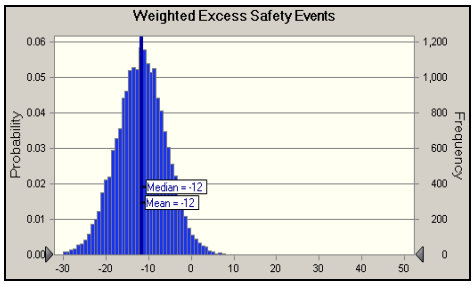
Finally, the effect of event rate uncertainty on the benefit-risk balance in the simulation population was also considered (Figure 3). In addition to the utility uncertainty, the Monte Carlo was augmented to represent absolute risk differences with normal distributions, with the variance determined by the 95% confidence intervals. This simulation accounts for all uncertainty in the total weighted excess number of events calculation. As shown in Figure 3(c), over 93% of the probability mass is above zero, indicating that the benefit-risk balance still highly favors rivaroxaban over enoxaparin.

Figure 3: Distribution of Weighted Excess Number of Events (Benefit and Risk) Using Uncertainties in Both Utilities and Event Rates for a Hypothetical Population of 10,000 THR and TKR Patients. Data is for RECORD Studies 1 – 4 Pooled, see Figure 3 for Details. (a) Efficacy Outcomes; (b) Safety Outcomes; (c) All Outcomes – the Positive Region (in Which Benefit Exceeds Risk) Contains Over 93% of the Probability Mass.

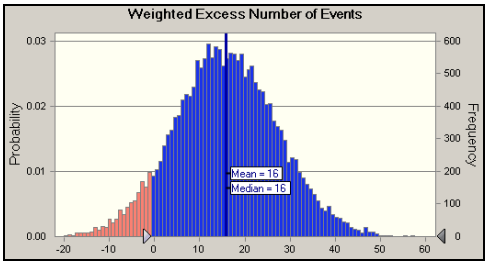
(a)



(b)



(c)



3. SUMMARY AND CONCLUSIONS

To account for the differences in how patients regard different outcomes and adverse events, we extended the benefit-risk assessment of rivaroxaban by weighting each efficacy and safety event with the corresponding change in patient-assessed utility. "Utility" scores measure patient preference for a particular outcome or health state and were obtained from published literature. Because of the uncertainties in the estimation of event rates, and the variability in estimates of utilities, the robustness of the results of these analyses was evaluated in a series of sensitivity analyses.

For results pooled over all four RECORD studies, the weighted analysis showed that benefits outweigh risk for rivaroxaban relative to enoxaparin. In sensitivity analyses that varied patient preferences across a wide range of plausible alternative values, or that incorporated uncertainties in event rates, the results consistently showed that benefits outweigh risks. This weighted utility analysis provides additional evidence that rixaroxaban has a favorable benefit-risk relative to enoxaparin.

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