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FDA Advisory Committee Briefing Document

Cardiovascular and Renal Drugs Advisory Committee

March 19, 2009

Prepared by the Division of Medical Imaging and Hematology Products/Office of
Oncology Drug Products/Office of New Drugs
Consultative assistance from the Office of Clinical Pharmacology, Office of Biostatistics
and Office of Surveillance and Epidemiology (OSE)

**New Drug Application (NDA) 22-406: Rivaroxaban oral tablets (10 milligrams),
Johnson & Johnson Pharmaceutical Research & Development, L.L.C., for the
prophylaxis of deep vein thrombosis and pulmonary embolism in patients
undergoing hip replacement or knee replacement surgery**

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Abbreviations

ACCP	American College of Chest Physicians
AAOS	American Academy of Orthopaedic Surgeons
ACS	acute coronary syndrome
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CHF	congestive heart failure
DVT	deep vein thrombosis
Enox	enoxaparin
IPC	intermittent pneumatic compression
ITT	intent to treat
mITT	modified intent to treat
NDA	new drug application
NSAID	non-steroidal anti-inflammatory drug
PE	pulmonary embolus
RECORD	REgulation of Coagulation in ORthopedic Surgery to prevent DVT and PE
SAE	serious adverse event
TE	thromboembolism
Tx	treatment
ULN	upper limit of normal
VKA	vitamin K antagonist
VTE	venous thromboembolism

Topics for Questions

FDA anticipates questions and discussions pertaining to the topics outlined below. Each topic is followed by a summary of major background points.

1. The robustness and clinical meaningfulness of the efficacy data, considering the following items:

- In four randomized clinical studies that examined a total of approximately 12,000 patients who were undergoing hip or knee replacement surgery, the occurrence of "total VTE" (proximal or distal DVT by venography or pulmonary embolus or death) was statistically lower for patients receiving rivaroxaban, compared to patients who received enoxaparin.
- The predominant rivaroxaban treatment effect within each of the RECORD studies related to a reduction in the venographic detection of proximal and/or distal VTE. Symptomatic DVT and/or PE were very uncommon events within each study.
- In integrated analyses across the four RECORD studies, the occurrence of "Symptomatic VTE" (symptomatic VTE or death) was statistically lower for patients receiving rivaroxaban, compared to enoxaparin (0.6% for the rivaroxaban group versus 1.3% for the enoxaparin group).
- The planned use of intermittent pneumatic compression (IPC) during the perioperative period was an exclusion criterion for all RECORD studies. IPC has been shown to reduce the risk for VTE in certain clinical studies. Data are unavailable to describe the VTE-prevention effect of rivaroxaban in the setting of IPC use.
- Approximately 85% of the patients enrolled in the RECORD studies were from non-USA sites. Data are not available to fully assess the extent to which USA and non-USA sites may differ in concomitant medication usage (particularly for drugs that increase the risk for bleeding) and operative/perioperative management techniques.

2. The clinical importance of the bleeding risks associated with rivaroxaban, considering the following items:

- All categories of bleeding (e.g., "major" or "any bleeding") were numerically higher for patients receiving rivaroxaban in the RECORD studies, compared to enoxaparin. In the integrated analyses of the RECORD studies, "any major bleeding" event occurred in 0.39% of the rivaroxaban group and 0.21% of the enoxaparin group.

- In the RECORD studies, one patient who received rivaroxaban along with NSAIDs developed gastric bleeding that resulted in death. No fatal bleeding events occurred among patients receiving enoxaparin in the RECORD studies.
- Rivaroxaban was approved for marketing in Europe in September, 2008. As of December 5, 2008, adverse event reports (two patients) have pertained to bleeding events (non-fatal).
- Clinical pharmacology analyses show that increased exposure to rivaroxaban may importantly increase the risk for major bleeding events. A dose ranging study indicated that a two fold increase in rivaroxaban exposure resulted in a five fold increase in the risk of major bleeding.
- Two clinical pharmacology studies showed a "clinically relevant" prolongation of bleeding time when rivaroxaban was administered together with clopidogrel.
- Clinical pharmacology analyses suggest that clinically relevant increases in rivaroxaban exposure (and the risk for bleeding) may occur in patients with moderate to severe renal or hepatic impairment and/or when rivaroxaban is administered concomitantly with many drugs that may alter its metabolism and transport.
- The FDA has requested the sponsor to develop a lower dose rivaroxaban tablet or a scored 10 mg tablet to permit downward dose titration in the special populations at risk for clinically relevant higher rivaroxaban drug exposure (compared to the proposed dose). To date, the sponsor has regarded this modification as unnecessary.

3. The sufficiency of the available data to characterize any risks for liver injury or toxicity, considering the following items:

- In FDA's review of another oral anticoagulant (ximelagatran), liver toxicity was not readily evident in the submitted "short term VTE" prophylaxis studies. The drug was approved for use in Europe and was subsequently withdrawn from marketing because of liver toxicity.
- Clinical studies of "long term" rivaroxaban use are currently on-going. These studies generally use rivaroxaban doses higher than those proposed for use in the VTE prophylactic indication.
- In the RECORD studies, the liver test abnormalities of particular concern (ALT > 3X ULN combined with total bilirubin > 2X ULN) occurred at a rate of 0.15% in the rivaroxaban group and a rate of 0.11% in the enoxaparin group. Various other comparisons of liver test abnormalities generally showed similar outcomes between the rivaroxaban and the enoxaparin groups.

- Within the full pool of available data, four patients (0.02%) who received rivaroxaban died within 30 days after detection of an ALT > 3X ULN combined with a total bilirubin > 2X ULN. In comparison, two patients (0.01%) in a comparator group died with these liver test abnormalities/criteria.

4. The importance, if any, of obtaining the final clinical data from the on-going clinical studies that examine the effects of prolonged rivaroxaban administration, considering the following items:

- The risks are unknown for prolonged administration of rivaroxaban for potential "off label" uses (e.g, anticoagulation among patients with atrial fibrillation).
- Generally routine measures are proposed by the sponsor to manage risks. The sponsor notes, "...a Risk Minimization Action Plan is not needed for rivaroxaban because routine risk assessment and risk minimization measures, targeted educational activities and outreach programs can adequately address all the potential safety risks."

5. The overall risks and benefits associated with the use of rivaroxaban for the proposed marketing indication. The following items are of note for this topic:

- Approximately 800,000 patients in the USA underwent hip or knee replacement surgery in 2005 (AAOS press release). If approved, rivaroxaban may be widely used due to the convenience of oral administration and the absence of need for anticoagulant test monitoring.
- Several products are currently marketed for use in the prophylaxis of VTE among patients undergoing hip or knee replacement surgery.
- The proposed label generally refers to using "caution" when administering rivaroxaban to patients with renal insufficiency or patients who are concomitantly receiving drugs that may affect hemostasis (e.g., NSAIDs).
- The proposed label notes that rivaroxaban is "not recommended" for use in patients who are receiving certain medications that interfere with the drug's metabolism; additionally, the drug is "not recommended" for use in patients with kidney failure. The proposed label contraindicates the use of rivaroxaban among patients with hepatic disease associated with a coagulopathy leading to a clinically relevant bleeding risk.
- In addition to the risks cited above, the following imbalances were evident within the RECORD study database (integrated across the studies):
 - a) an isolated signal for potentially increased risk of cardiovascular events following rivaroxaban therapy. During this "off treatment" period, the overall rate of cardiovascular events (myocardial infarction, ischemic stroke, cardiovascular

or unexplained death) was similar between the two study groups. However, ischemic stroke was reported in five rivaroxaban group patients and one enoxaparin group patient. Additionally, most cardiovascular events in the rivaroxaban group occurred shortly following the drug's discontinuation, whereas the events in the enoxaparin group were not concentrated in this period.

b) a small imbalance in the occurrence of abnormal creatinine values (10% for rivaroxaban group patients versus 8% for enoxaparin group patients) and blood urea (9% for the rivaroxaban group patients versus 8% for the enoxaparin group patients), during the active study treatment period. These abnormalities were predominantly related to values 1X to 2X ULN.

- A Risk Evaluation and Mitigation Strategy (REMS) is not proposed by the sponsor for use with rivaroxaban. A REMS can be required if FDA determines that additional measures (beyond routine labeling and pharmacovigilance) are necessary to ensure that the benefits of a product outweigh the risks. A REMS generally consists of three potential components (all or only one component may be required):
 - a Medication Guide
 - specific education/communication to healthcare providers
 - "elements to assure safe use" (e.g., require training or certification of prescribers, dispensers; limit administration to certain healthcare settings; document certain "safe use" activities prior to dispensing; require patient monitoring; and/or require patient enrollment in a program).
- FDA anticipates obtaining opinions from this Advisory Committee regarding the importance of the evidenced and possible risks associated with rivaroxaban, particularly with respect to approvability and the potential need, if any, for additional risk management measures. FDA's preliminary review finds the clinical data most solid for a risk of bleeding (including potential fatal bleeding) with rivaroxaban. The risks for liver injury/hepatotoxicity and other toxicities are less clear. FDA's Office of Surveillance and Epidemiology notes that, without more fully characterized signals, the effectiveness of most risk mitigation strategies is limited.

Executive Summary

1. Introduction

This advisory committee is convened to assist in the on-going review of the clinical data within the NDA for rivaroxaban, a new molecular entity. Rivaroxaban is proposed for use in the prophylaxis of DVT and PE in patients undergoing hip or knee replacement surgery. Consistent with Good Review Management Practices, this committee's discussion will assist FDA in completing the review of the application. The presentations by the FDA, including the materials in this document, are preliminary comments and analyses. FDA opinions expressed in this document and at the upcoming presentation are based upon preliminary observations, particularly for individual reviewers, and should not be regarded as FDA's final perspective regarding the outcome of the NDA review.

Importantly, new information has been submitted to this NDA throughout the review cycle, including shortly prior to the preparation of this background document. In general, this background document relies upon the information originally submitted with the NDA. Given the recent and on-going submissions to the NDA, some of this background information maybe outdated. Updates will be provided at the Committee presentation.

2. Product Background:

Rivaroxaban is proposed for marketing with the following clinical indication:

"XARELTO™ (rivaroxaban) is indicated for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing:

- hip replacement surgery
- knee replacement surgery."

Rivaroxaban is a chemically synthesized, small molecular weight drug which is proposed to act as an anticoagulant by direct Factor Xa inhibition and subsequent lessening of thrombin production. Rivaroxaban, administered as a 10 mg daily dose, prolongs the prothrombin time (generally from 13 to 26 seconds) and no specific antidote is available for reversal of the anticoagulant effect. Rivaroxaban, as originally described in the NDA, was to be supplied as 10 mg tablets available to pharmacists in bottles of 30 tablets or a blister pack that contains 10 tablets.

The rivaroxaban clinical development program has focused upon the use of the drug in five specific areas. Listed below are the program areas and the acronyms for the major clinical studies:

1. Prophylaxis of DVT and PE in patients undergoing elective total hip replacement (THR) or total knee replacement (TKR): the 4 "RECORD" studies (completed);
2. Secondary prevention and long-term treatment of patients who have experienced DVT/PE: the "EINSTEIN and EINSTEIN extension" studies (on-going);

3. Prophylaxis of DVT and PE in hospitalized medically ill patients: the "MAGELLaN" study (on-going);
4. Prevention of stroke and non-central nervous system systemic embolism in subjects with non-valvular atrial fibrillation: the "ROCKET-AF and J-ROCKET-AF" studies (on-going);
5. Secondary prevention of cardiovascular events after an acute coronary syndrome: the "ATLAS" study (on-going).

2. Clinical Background

Thromboembolism has long been recognized as a major complication of orthopedic surgery. Publications have generally cited venographic rates of DVT as approximately 40 to 60% among patients undergoing major orthopedic surgery, in the absence of thromboprophylaxis. In general, the rates are reported as higher for knee surgery compared to hip surgery although the period for increased DVT risk is generally regarded as longer for patients undergoing hip surgery. Importantly, proximal DVT is widely recognized as having greater clinical importance than distal DVT and venographic outcomes in studies are generally analyzed based upon the occurrence of proximal versus distal DVT.

Two major professional groups have developed guidelines for the prophylaxis of DVT/PE in hip and knee surgery. The 2008 guidelines from the American College of Chest Physicians (ACCP) provide recommendations that modestly differ from those of the 2007 guidelines from the American Academy of Orthopedic Surgeons (AAOS). Examples of the differences in these two guidelines are illustrated by the following:

- The AAOS guideline particularly focuses upon the prevention of PE balanced against the risk for major bleeding and perioperative complications (such as post-operative bleeding that requires reoperation). The guideline emphasizes the relative rarity of symptomatic PE, fatal PE and death in clinical studies (generally rates of < 1%) and generally concluded that available studies have not shown important differences among the various chemoprophylaxis regimens (such as low molecular weight heparin) and mechanical prophylaxis (such as pneumatic compression) alone or mechanical prophylaxis with aspirin.
- The AAOS guideline recommends surgeons/physicians to tailor PE prophylaxis based upon patient risks for PE as well as risks for major bleeding. For example, the guideline notes that the recommended chemoprophylaxis for patients at "standard risk of both PE and major bleeding" consists of the option of aspirin alone as well as the use of low molecular weight heparin, synthetic pentasaccharide or adjusted dose warfarin. Regardless of the chosen chemoprophylactic regimen, the guideline notes that all patients should be considered for intra-operative and/or immediate postoperative mechanical prophylaxis.

- The ACCP guidelines are detailed based upon the specific type of hip or knee surgery. In general, the guideline recognizes pneumatic compression as useful in thrombo-prophylaxis for patients undergoing elective hip replacement or elective knee replacement surgery but it also cites the difficulties with compliance and the generally more limited clinical data supporting use of mechanical prophylaxis.
- The ACCP guidelines recommend the "routine" use of certain chemoprophylaxis regimens (such as low molecular weight heparin) for patients undergoing elective hip or knee surgery, unless the patients are at high risk for bleeding. For patients with a high risk for bleeding, the guideline recommends mechanical prophylaxis (e.g., pneumatic compression) without chemoprophylaxis.
- The ACCP guideline recommends against the use of aspirin as the sole method of thromboprophylaxis in patients undergoing elective hip or knee replacement surgery.

These guidelines are relevant to the review of the rivaroxaban data because the RECORD studies compared rivaroxaban to enoxaparin (a low molecular weight heparin) and did not incorporate the use of intermittent pneumatic compression. Indeed, patients planned for pneumatic compression therapy were actively excluded from enrollment in the RECORD studies. Of additional note, the RECORD studies were international studies, in which approximately 85% of the patients were studied at sites outside of the USA. The extent to which surgical procedures or perioperative care varies between the USA and non-USA sites is unknown. Nevertheless, the randomized and double blind nature of the RECORD studies provides important controls upon potential bias due to variations in site-specific operative and peri-operative care. Additionally, the relatively large recruitment goals of the RECORD studies resulted in approximately 1800 USA patients receiving either rivaroxaban or enoxaparin.

3. Regulatory Background:

Several pertinent background considerations pertain to this application, as follows:

- The four major clinical studies (the "RECORD" studies) were reviewed under the Special Protocol Assessment program and, during the program development, FDA concurred that the study designs were sufficient to assess the study objectives.
- The primary endpoints in the RECORD studies incorporated venographic assessments, as well as other outcomes. FDA generally recognizes venographic outcomes as "accepted surrogates" for the diagnosis of deep vein thrombosis and these assessments have formed, in large part, the basis for prior anticoagulant drug approvals.
- Clinical outcomes, such as death, symptomatic deep vein thrombosis and/or pulmonary embolism were also assessed in the RECORD studies.

- If approved, rivaroxaban would be the first oral anticoagulant approved by the FDA since approval of warfarin in 1954. Warfarin is generally regarded as a drug with relatively wide public usage, particularly in situations where "long term" (including life-long) anticoagulation is necessary. No restricted distribution or unique packaging was originally proposed for rivaroxaban, such that, if marketed, physicians may prescribe rivaroxaban "off label" for longer than the recommended short term treatment duration.
- The available rivaroxaban clinical data are predominantly from studies that examine a "short term" (no more than 35 days) usage. The long term data for rivaroxaban will derive from on-going studies that examine dosage regimens that generally differ from those proposed for short term use (10 mg daily in the short term studies versus higher doses in the long term studies—generally 15 to 30 mg daily).
- In 2004, the Cardiovascular and Renal Drugs Advisory Committee reviewed another oral anticoagulant, ximelagatran, for use in the prophylaxis of deep vein thrombosis in knee replacement surgery, secondary prevention of venous thromboemboli after an acute venous thromboembolus as well as prevention of stroke and other thromboembolic complications associated with atrial fibrillation. That application contained data from short term as well as long term clinical studies and the advisory committee did not recommend approval, based in large part upon signals of liver toxicity (predominantly in the long term studies), signals of cardiovascular risks (such as myocardial infarction) as well as questionable efficacy in the short term studies. Ximelagatran was not marketed in the USA but was marketed in Europe until the sponsor detected further evidence of liver toxicity in a clinical study of ximelagatran usage during hip surgery. Following identification of this toxicity, the sponsor withdrew ximelagatran from marketing.
- The ximelagatran experience illustrates some of the challenges of developing an oral anticoagulant, particularly the detection of liver toxicity, a generally uncommon event. Importantly, ximelagatran was a direct thrombin inhibitor and the clinical development program importantly differed from that for rivaroxaban. For example, at the time of the ximelagatran application submission, approximately 3,000 patients had been exposed for the short term usage (knee surgery), generally 12 days or less. In contrast, the rivaroxaban short term usage (knee and hip surgery) consists of exposure to approximately 6,200 patients.

Four drugs are currently marketed with FDA-approved indications for prophylaxis of DVT/PE in orthopedic surgery. These drugs consist of:

1) Enoxaparin (Lovenox™) indicated for prophylaxis of deep vein thrombosis (DVT) in hip replacement surgery or knee replacement surgery. The recommended doses are initiated 12 to 24 hours post-surgery, as follows:

-for knee replacement: 30 mg subcutaneously every 12 hours for 1 to 2 weeks;

-for hip replacement: 30 mg subcutaneously every 12 hours or 40 mg subcutaneously once daily, each regimen for 3 weeks.

2) Fondaparinux (Arixtra™) indicated for prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- in patients undergoing hip fracture surgery, including extended prophylaxis
- in patients undergoing hip replacement surgery
- in patients undergoing knee replacement surgery.

The recommended fondaparinux dose regimen is 2.5 mg subcutaneously once daily given 8 hrs post-operatively with a usual duration of 5 to 9 days although "up to 11 days has been tolerated." The label also notes that, "In patients undergoing hip fracture an extended prophylaxis course of up to 24 additional days is recommended."

3) Dalteparin (Fragmin™) indicated for prophylaxis of DVT which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery. The recommended dose is subcutaneous administration of 5,000 units 10 hours before surgery or started as 5,000 units 8 hours post-operatively, then 5,000 units once daily. The label notes the usual duration of administration is 5 to 10 days after surgery; "up to 14 days has been well tolerated in trials."

4) Heparin sodium (unfractionated) is indicated for anticoagulant therapy in prophylaxis and treatment of venous thromboembolism and its extension. The recommended dose is 5,000 units administered subcutaneously 2 hrs prior to surgery and 5,000 units every 12 hrs after surgery. The duration of therapy is not explicitly stated in the drug label.

Warfarin (Coumadin™) is not FDA-approved for prophylaxis of DVT/PE although ACCP and AAOS refer to the use of adjusted dose warfarin as a form of chemoprophylaxis in orthopedic surgery.

4. Efficacy:

a. Overview:

Overall, 64 completed clinical studies that enrolled approximately 18,000 subjects have assessed rivaroxaban effects. Fifty-one of these studies were phase 1 clinical studies focused predominantly upon clinical pharmacology and exploratory safety. As previously mentioned, rivaroxaban is under development for five unique indications and only one of these indications (DVT/PE prophylaxis in total hip or knee replacement) has a completed portfolio of studies. This "VTE prevention portfolio" consists of four phase 2 studies (2,232 subjects receiving rivaroxaban) and four phase 3 studies (the "RECORD" studies, 6,183 subjects receiving rivaroxaban).

This summary will focus upon the four RECORD studies. The major features of these studies are highlighted in Table 1.

Table 1. Major Design Features for the Four RECORD Studies

RECORD Study	Dose		Tx Duration (post-op days)		V'graphy Day*	Final Follow-up Day*
	Riva	Enox	Riva	Enox		
1 (Hip)	10 mg daily	40 mg daily	35	35	36	66
2 (Hip)	10 mg daily	40 mg daily	35	12	36	66
3 (Knee)	10 mg daily	40 mg daily**	12	12	13	43
4 (Knee)	10 mg daily	30 mg twice daily	12	12	13	43

*day 1 = day of surgery, the final follow-up day occurred ~ 30 days after last active study drug dose

**this enoxaparin dose is not FDA-approved for DVT/PE prevention therapy in knee surgery

As shown in Table 1, the RECORD 2 study importantly differed from the RECORD 1 study in that the enoxaparin dosing duration was only 12 days in RECORD 2. This shorter duration of enoxaparin administration is notable because the duration of active study drug treatment is different between the two study arms. Also as shown in Table 1, the RECORD 3 study used an enoxaparin dose regimen that is not FDA-approved. This regimen is, however, approved in certain foreign countries.

Multiple study design features were the same in the RECORD studies (see Table 2), with only a few notable differences.

Table 2. Comparison of Design Features Across RECORD Studies

Same or Very Similar Features	Notable Divergent Features
Parallel group, randomized (1:1, rivaroxaban to enoxaparin)	no divergence
Double dummy design	no divergence
Rivaroxaban 10 mg daily orally, initiated 6 to 8 hours post-operatively	no divergence
Enoxaparin administered subcutaneously	Enoxaparin initiated preoperatively in RECORD 1, 2 and 3; Enoxaparin initiated post-operatively in RECORD 4.
Multicenter, international	no divergence
Central adjudication of major study outcomes	no divergence
Bilateral venography at end of active study drug treatment	no divergence
~30 day follow-up "off treatment"	no divergence
Primary and secondary endpoint definitions	Primary endpoint ("total VTE") tested for non-inferiority followed by superiority in RECORD 1, 3 and 4; Primary endpoint ("Total VTE") tested only for superiority in RECORD 2.
Exclusion of patients who were to undergo IPC; also excluded patients with any of the following characteristics: "significant liver disease;" severe renal failure; receiving HIV-protease medications; as well as women of child-bearing potential who were not using birth control methods.	no divergence

IPC = intermittent pneumatic compression

The major efficacy endpoints are summarized below:

Primary endpoints:

- "Total VTE" defined as the composite of: any DVT (proximal and/or distal) or non-fatal PE or death for any reason analyzed among the per-protocol population for non-inferiority and the modified ITT population for superiority. Because all primary endpoints ultimately met the non-inferiority tests, in this summary we highlight only the superiority tests of the primary endpoint.
- Analysis for superiority was tested among the modified ITT population which was defined as the group of subjects who received at least one dose of study drug, underwent the surgery and had an adequate assessment of thromboembolism. The superiority test was a test of the hypothesis of equal Total VTE rates between the two groups, analyzed using Mantel-Haenszel comparison of rates with adjustment

by geographic site (country); the hypothesis was rejected in favor of superiority if the upper limit of the 95% CI for the treatment difference was below zero.

Secondary endpoints:

- "Major VTE" was identified as the "main" secondary endpoint and was defined as a composite of a proximal DVT or a non-fatal PE or a VTE-related death; it was analyzed among the "per protocol population" for non-inferiority and the modified ITT population for superiority (similar to the primary endpoint);
- Multiple other secondary endpoints consisted of various iterations of composite endpoints;
- Secondary endpoints were analyzed predominantly among the modified ITT population.

Safety endpoints (e.g., "major bleeding events", deaths, adverse events, etc.) were analyzed among the population of patients who received at least one dose of study drug.

The sponsor also developed a plan for integrated analyses of the RECORD studies. This plan was finalized prior to the unblinding of RECORD 1, 2 and 3. The plan was modified to incorporate RECORD 4, prior to the unblinding of RECORD 4. The primary endpoint in this integrated plan was a comparison of the rates of symptomatic venous thromboembolism (VTE, defined as DVT and/or PE) or death from any cause, analyzed among the population of patients who received at least one dose of study drug.

b. Subject Disposition and Baseline Characteristics

Overall, subjects were enrolled from 41 countries. Approximately 85% of the subjects were enrolled from non-USA sites. This is an important consideration since concomitant medication use and perioperative therapy may vary across countries. Nevertheless, with respect to the number of subjects contributed by any single country, the USA provided the most subjects. The subset of the primary endpoint by country (Figure 1) illustrates the international nature of the data.

Subject disposition in the RECORD studies is summarized below.

Table 3. Subject Disposition in RECORD Studies

Group	RECORD 1		RECORD 2		RECORD 3		RECORD 4	
	Riva	Enox	Riva	Enox	Riva	Enox	Riva	Enox
Randomized	2266	2275	1252	1257	1254	1277	1584	1564
Completed treatment	89%	88%	89%	87%	90%	89%	90%	90%
Premature termination	11%	12%	11%	13%	10%	12%	10%	10%
Terminated due to AE	4%	4%	4%	4%	3%	3%	4%	4%
Terminated consent	5%	5%	4%	4%	5%	5%	3%	3%

Baseline characteristics were generally well-balanced between the rivaroxaban and enoxaparin groups in the RECORD studies. Table 4 summarizes the major characteristics.

Table 4. Major Baseline Characteristics in RECORD Studies

Characteristic	RECORD 1 and 2 (hip)	RECORD 3 and 4 (knee)
Male	45%	34%
Race:		
-white	83%	73%
-black	1%	3%
-Asian	7%	13%
Average age, years	63 years	66 years
Age > 75 years	14%	17%
Average weight	77 kg	83 kg
Weight < 50 kg	3%	1%
Weight > 110 kg	3%	8%

The modified ITT (mITT) population was the group applicable to most efficacy outcome analyses. Table 5 summarizes the major reasons for exclusion from the mITT population.

Table 5. Summary of Exclusions from the mITT RECORD Study Populations

Group	RECORD 1		RECORD 2		RECORD 3		RECORD 4	
	Riva	Enox	Riva	Enox	Riva	Enox	Riva	Enox
Randomized	2266	2275	1252	1257	1254	1277	1584	1564
Excluded from mITT	671 (30%)	717 (32%)	388 (31%)	388 (31%)	430 (34%)	399 (31%)	619 (39%)	605 (39%)
<i>Reason:</i>								
Inadequate TE assessment	588 (26%)	635 (28%)	348 (28%)	338 (27%)	376 (30%)	339 (27%)	559 (35%)	546 (35%)
no venog	319 (14%)	322 (14%)	155 (12%)	159 (13%)	156 (12%)	166 (13%)	189 (12%)	184 (12%)
unilateral venography	105 (5%)	105 (5%)	57 (5%)	57 (5%)	82 (7%)	69 (5%)	116 (7%)	105 (7%)
unevaluable venography	121 (5%)	164 (7%)	127 (10%)	111 (9%)	131 (10%)	96 (8%)	244 (15%)	253 (16%)
venography early/late	43 (2%)	44 (2%)	9 (1%)	11 (1%)	7 (1%)	8 (1%)	10 (1%)	4 ($< 1\%$)
No study drug	57 (3%)	51 (2%)	24 (2%)	28 (2%)	34 (3%)	38 (3%)	58 (4%)	56 (4%)
No surgery	17 (1%)	21 (1%)	16 (1%)	22 (2%)	20 (2%)	22 (2%)	2 ($< 1\%$)	3 ($< 1\%$)

TE = thromboembolism; venog = venography

c. Primary Endpoint Results:

The primary endpoint in all four studies was a comparison of "Total VTE" rates, defined as the occurrence of: any DVT (proximal and/or distal), non-fatal PE or death due to any cause. In RECORD 1, 3 and 4 the primary endpoint was analyzed initially using a non-inferiority approach. Subsequently, the primary endpoint in these studies was analyzed using a test of superiority. Because rivaroxaban was assessed as non-inferior in all the step-wise analyses, shown below are the superiority test results. All primary endpoint results showed statistically superior results for rivaroxaban ($p < 0.05$), compared to enoxaparin. These results are summarized in Table 6 (using the mITT populations).

Table 6. Primary Endpoint ("Total VTE") in RECORD Studies

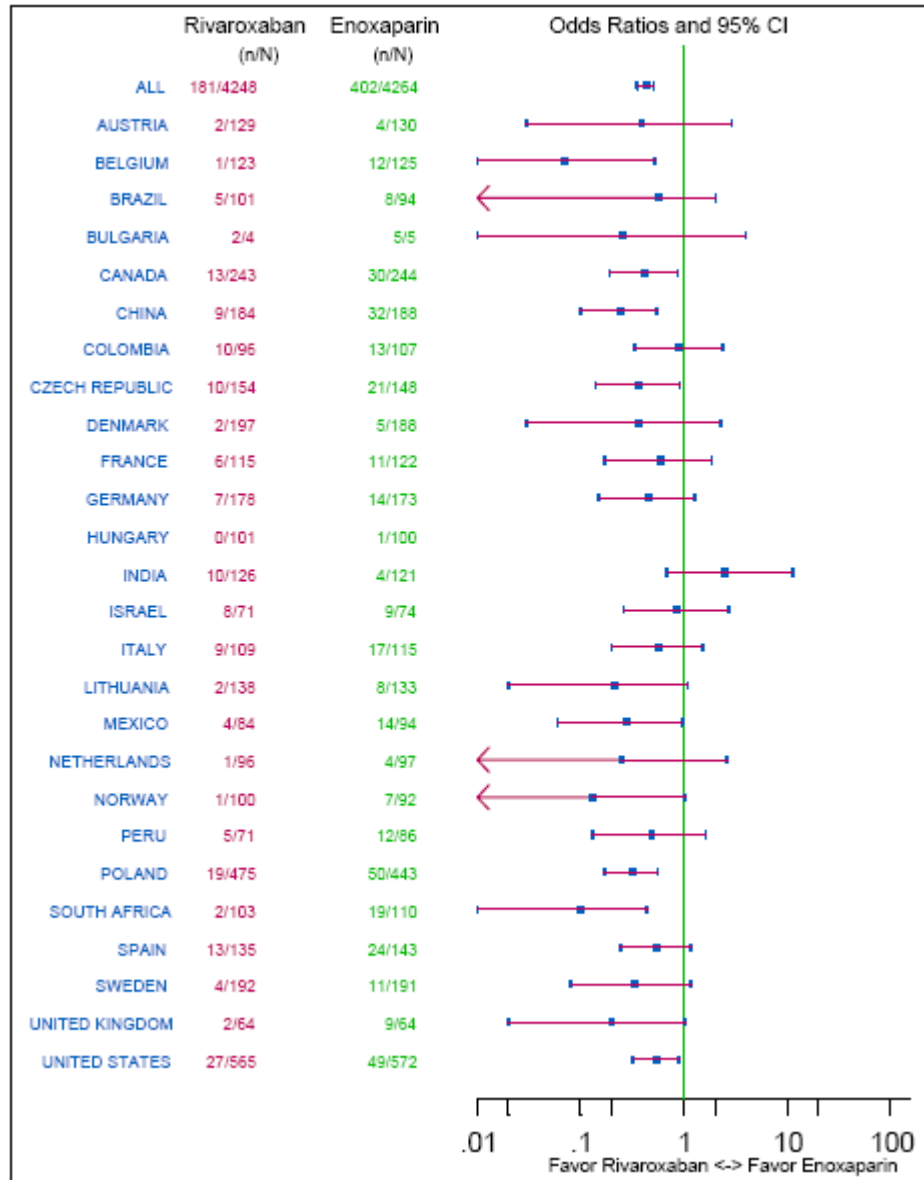
Outcome	RECORD 1 (hip)		RECORD 2 (hip)		RECORD 3 (knee)		RECORD 4 (knee)	
	Riva n = 1595	Enox n = 1558	Riva n = 864	Enox n = 869	Riva n = 824	Enox n = 878	Riva n = 965	Enox n = 959
Total VTE*	18 (1.1%)	58 (3.7%)	17 (2.0%)	81 (9.3%)	79 (9.6%)	166 (18.9%)	67 (6.9%)	97 (10.1%)
<i>"Total VTE" components</i>								
DVT, all	12 (0.8%)	53 (3.4%)	14 (1.6%)	71 (8.2%)	79 (9.6%)	160 (18.2%)	61 (6.3%)	86 (9.0%)
Nonfatal PE	4 (0.3%)	1 ($< 0.1\%$)	1 (0.1%)	4 (0.5%)	0	4 (0.5%)	5 (0.5%)	8 (0.8%)
Death	4 (0.3%)	4 (0.3%)	2 (0.2%)	6 (0.7%)	0	2 (0.2%)	2 (0.2%)	3 (0.3%)
<i>Components of "DVT, all" (some patients had both proximal and distal DVT)</i>								
Prox DVT	1 ($< 0.1\%$)	31 (2.0%)	5 (0.6%)	44 (5.1%)	9 (1.1%)	20 (2.3%)	8 (0.8%)	14 (1.5%)
Distal DVT	12 (0.8%)	27 (1.7%)	11 (1.3%)	49 (5.6%)	74 (9.0%)	156 (17.8%)	57 (5.9%)	82 (8.6%)

*all p-values for comparison of rates < 0.05 (Mantel-Haenszel-weighted difference)

Table 6 shows that, within the individual studies, the rivaroxaban treatment effect was mainly due to differences in the venographic outcomes, with a reduction in the rates of both proximal and distal DVT.

Figure 1 (next page) provides an exploratory summary of the primary endpoint that illustrates the international nature of the RECORD studies. In this summary, the primary endpoint results are pooled across the RECORD studies and the results shown by country.

Figure 1. Total VTE and Corresponding Odds Ratio (95% CI) by Country (mITT population of pooled RECORD studies)



d. Secondary Endpoint Results:

The "main" secondary endpoint was "Major VTE" which was defined as a composite of: proximal DVT, non-fatal PE or VTE-related death. In RECORD 1, 3 and 4, this endpoint was analyzed in a step down procedure (non-inferiority/ followed by superiority), similar to the primary endpoint. For this main secondary endpoint, superiority for rivaroxaban was shown in RECORD 1, 2 and 3 but not in RECORD 4 (mITT population). However, in RECORD 4, the rivaroxaban rate was below the treatment difference non-inferiority limit of 1.5%, suggesting non-inferiority.

Overall, the main secondary endpoint suggested that the major rivaroxaban treatment effect related to a reduction in proximal DVT detected on venography (Table 7).

Table 7. Main Secondary Endpoint ("Major VTE") in RECORD Studies

Outcome	RECORD 1 (hip)		RECORD 2 (hip)		RECORD 3 (knee)		RECORD 4 (knee)	
	Riva n = 1686	Enox n = 1678	Riva n = 961	Enox n = 962	Riva n = 908	Enox n = 925	Riva n = 1122	Enox n = 1112
Major VTE*	4 (0.2%)	33 (2.0%)	6 (0.6%)	49 (5.1%)	9 (1.0%)	24 (2.6%)	13 (1.2%)	22 (2.0%)
<i>"Total VTE" components</i>								
DVT, Proximal	1 ($< 0.1\%$)	31 (1.9%)	5 (0.5%)	44 (4.6%)	9 (1.0%)	20 (2.2%)	8 (0.7%)	14 (1.3%)
Nonfatal PE	4 (0.2%)	1 (0.1%)	1 (0.1%)	4 (0.4%)	0	4 (0.4%)	5 (0.5%)	8 (0.7%)
VTE Death	0	1 ($< 0.1\%$)	0	1 (0.1%)	0	0	1 (0.1%)	0

*p-values for comparison of rates < 0.05 (Mantel-Haenszel-weighted difference) in RECORD 1, 2 and 3; in RECORD 4 p-value = 0.12

Multiple other secondary endpoints were analyzed within the individual RECORD studies. The numbers of patients with symptomatic VTE events was relatively small within each study, with numerically lower rates reported for patients in the rivaroxaban groups, but nominal statistical significance evident only in the RECORD 2 and 3 studies. During the follow-up (post-therapy) period, the occurrence of symptomatic VTE events remained uncommon in each RECORD study. In general, the rates during this period were similar between the rivaroxaban and enoxaparin groups in each study.

e. Integrated Analyses across the RECORD Studies:

Of particular note were the prespecified integrated analyses for the RECORD studies. The primary endpoint in these analyses was a comparison of the rates of symptomatic VTE (DVT and/or PE) or death from all causes (which ever comes first) during the treatment period of the studies. This endpoint was analyzed as a time to event comparison using a Cox regression model with study (RECORD 1, 2, 3 and 4) and treatment group as covariates to determine the hazard ratios for the primary endpoint and the corresponding 95% CI. The analytical population consisted of all patients who received at least one dose of study drug (the "safety population").

Shown in Table 8 is a summary of the rates of symptomatic VTE or death during the treatment phase of each of the RECORD studies.

Table 8. "Symptomatic VTE or Death" in RECORD Studies (safety population)

Out- come	RECORD 1 (hip)		RECORD 2 (hip)		RECORD 3 (knee)		RECORD 4 (knee)	
	Riva n = 2209	Enox n = 2224	Riva n = 1228	Enox n = 1229	Riva n = 1220	Enox n = 1239	Riva n = 1526	Enox n = 1508
Any event	10 (0.5%)	15 (0.7%)	5 (0.4%)	20 (1.6%)	8 (0.7%)	26 (2.1%)	12 (0.8%)	21 (1.4%)
<i>Components of "Symptomatic VTE or Death" Endpoint*</i>								
DVT	3 (0.1%)	9 (0.4%)	2 (0.2%)	10 (0.8%)	8 (0.7%)	20 (1.6%)	6 (0.4%)	10 (0.7%)
PE	4 (0.2%)	2 (0.1%)	1 (0.1%)	5 (0.4%)	0	4 (0.3%)	5 (0.3%)	8 (0.5%)
Death	4 (0.2%)	5 (0.2%)	2 (0.2%)	6 (0.5%)	0	2 (0.2%)	2 (0.1%)	3 (0.2%)

*some patients could have both a PE and DVT

The integrated summary is shown in Table 9.

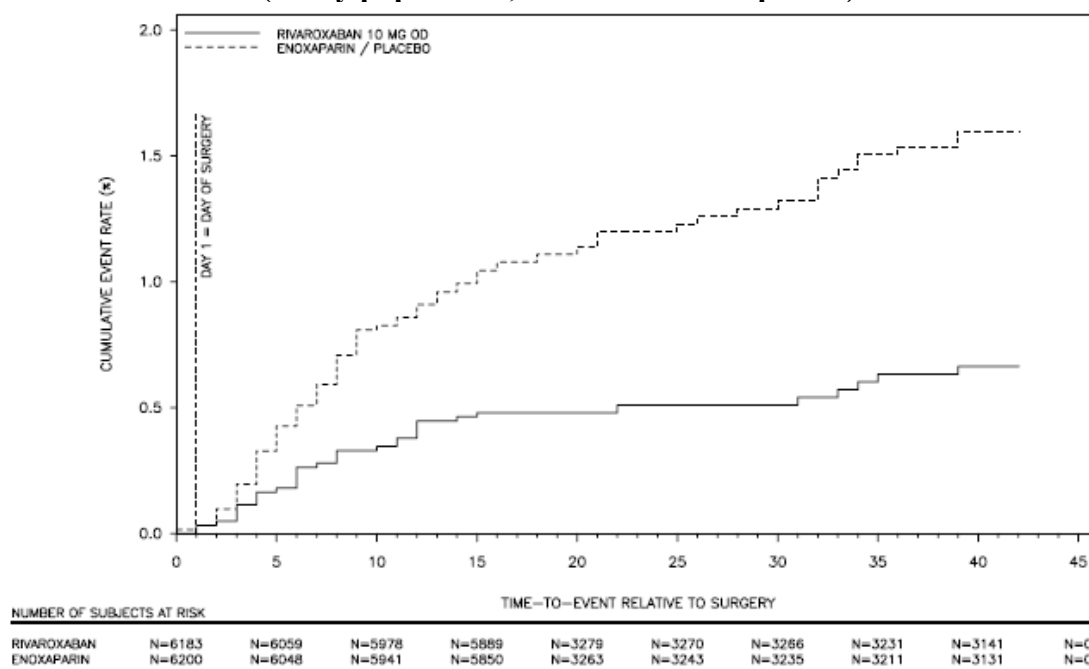
Table 9. Integrated Summary of "Symptomatic VTE or Death" in RECORD Studies (safety population; active treatment period)

Outcome	Rivaroxaban n = 6183	Enoxaparin n = 6200	Hazard Ratio, point estimate and 95% CI	p-value
VTE/Death	35 (0.6%)	82 (1.3%)	0.42 (0.29 - 0.63)	< 0.05
VTE (DVT &/or PE)	28 (0.5%)	68 (1.1%)	0.41 (0.26 - 0.64)	< 0.05
PE	10 (0.2%)	19 (0.3%)	0.53 (0.24 - 1.13)	0.10
Death	8 (0.1%)	16 (0.3%)	0.50 (0.21 - 1.17)	0.11

Overall, twice as many deaths were reported in the enoxparin group than in the rivaroxaban group, although the numbers of death were too small to show a nominal statistically significant difference between the two groups. Determining the cause of death is vulnerable to considerable error. Nevertheless, the investigators assessed pulmonary emboli as the cause for death in three patients in the rivaroxaban group and the cause of death in two enoxaparin group patients.

Figure 2 shows the Kaplan-Meier curves corresponding to the data in Table 9 (time to onset of symptomatic VTE or death, whichever comes first).

Figure 2. Kaplan-Meier Curves of Symptomatic VTE/Death in RECORD Studies (safety population; active treatment period)



Analyses that compared the symptomatic VTE events or death throughout the studies (active treatment period plus the 30 day follow-up period) showed results that did not importantly differ from those observed during the active treatment period. Table 10 summarizes the rates of symptomatic VTE and/or death that occurred during the follow-up period.

Table 10. Rates of Symptomatic VTE and/or Death that Occurred during the RECORD Studies Follow-up Period (Integrated Summary)

Event	Rivaroxaban n = 6183	Enoxaparin n = 6200
VTE (DVT and/or PE)	10 (0.2%)	12 (0.2%)
PE	7 (0.1%)	6 (0.1%)
Death	5 (0.1%)	9 (0.2%)

6. Safety

Overall, the safety database consists of detailed data contained within the original NDA (10,600 subjects exposed to rivaroxaban) plus interim safety data updates from nine ongoing clinical studies (20,875 subjects receiving rivaroxaban or a comparator drug). Most of the interim safety data from ongoing clinical studies (~60%) remains blinded to treatment assignment. Additionally, data clarification and verification has not been completed for the ongoing clinical studies. Hence, the bulk of clinical safety data derive from the information contained within the original NDA.

In the original NDA submission, most of the safety data were derived from the RECORD studies (rivaroxaban exposure in 6,183 subjects) and this summary will focus upon these studies.

Overall, the major safety concerns from the RECORD studies pertain to:

- hemorrhage
- cardiovascular events following treatment discontinuation
- liver test abnormalities and potential liver injury

The major safety concerns will be summarized following a brief overview of the adverse events reported in the RECORD studies.

In addition to the major safety concerns, a small imbalance in certain renal test abnormalities were detected in the RECORD studies. Specifically, within the integrated pool of RECORD studies, treatment-emergent creatinine abnormalities were observed in 10% of the rivaroxaban group patients versus 8% of the enoxaparin group patients. Treatment-emergent blood urea abnormalities were observed in 9% and 8% of the same groups, respectively. These abnormalities were predominantly for 1X to 2X elevations in the tests.

a. Summary of Adverse Events:

As shown in Table 12, aggregate analyses of top-line adverse events showed incidence rates for rivaroxaban that were either lower or similar to those for enoxaparin.

Table 12. Summary of Adverse Events in RECORD Studies

Incidence of subjects with:	Rivaroxaban n = 6183	Enoxaparin n = 6200
Any treatment-emergent adverse event*	4179 (68%)	4306 (69%)
Any adverse event during full study period	4365 (71%)	4497 (73%)
Any treatment-emergent serious adverse event	406 (7%)	528 (9%)
Any serious adverse event during full study period	511 (8%)	622 (10%)
Any adverse event resulting in permanent study drug discontinuation	230 (4%)	288 (5%)
Death	13 (<1%)	25 (< 1%)

*treatment emergent, i.e., within 2 days following last dose of study drug

In general, adverse events (by preferred term) occurred at similar rates between the two study groups in the pooled RECORD study summary, with no notable differences between analyses that examined treatment-emergent events and events that occurred during the full study periods. Among the group of preferred term, treatment-emergent

adverse events that occurred at a rate of $\geq 1\%$ in either group and also at a rate higher in the rivaroxaban group, three events were detected: pruritis (4% vs 3%), blister (2% vs 1%) and hematuria (1% vs < 1%).

Overall, the rate of treatment-emergent serious adverse events was similar between the two treatment groups in the RECORD studies (Table 13).

Table 13. Incidence Rates of the Most Frequently Reported Serious Treatment-emergent Adverse Events, by Preferred Term in RECORD Studies

Term	Rivaroxaban n = 6183	Enoxaparin n = 6200
Any serious event	406 (6.57%)	528 (8.52%)
Deep vein thrombosis	41 (0.66%)	110 (1.77%)
Dislocation of 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 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 14 summarizes the 10 serious adverse events that occurred most frequently in the rivaroxaban group and at a higher rate than in the enoxaparin group.

Table 14. Most Frequently Reported Serious Treatment-emergent Adverse Events for Rivaroxaban, by Preferred Term in RECORD Studies where the Rivaroxaban Group Rate exceeded the Enoxaparin Group Rate

Term	Rivaroxaban n = 6183	Enoxaparin n = 6200
Alanine aminotransferase increased	17 (0.27%)	11 (0.18%)
Wound infection	14 (0.23%)	9 (0.15%)
Femur fracture	13 (0.21%)	6 (0.10%)
Operative hemorrhage	11 (0.18%)	7 (0.11%)
Wound secretion	10 (0.16%)	7 (0.11%)
Anemia	9 (0.15%)	5 (0.08%)
Post-operative wound infection	8 (0.13%)	7 (0.11%)
Acute renal failure	6 (0.10%)	5 (0.08%)
Hemorrhage	6 (0.10%)	1 (0.02%)
Device-related infection	6 (0.10%)	2 (0.03%)

As shown in Table 15, the overall rate of permanent study drug discontinuation due to an adverse event was numerically higher for the enoxaparin group in the RECORD studies.

Table 15. Incidence Rates of the Most Frequently Reported Adverse Event Preferred Terms Resulting in Permanent Study Drug Discontinuation in the RECORD Studies

Term	Rivaroxaban n = 6183	Enoxaparin n = 6200
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%)

b. Bleeding Events:

Bleeding events were adjudicated for the RECORD studies by a committee blinded to treatment assignment. A prespecified charter described the types of information reviewed and the activities of the three-member committee. Specifically, any bleeding event was classified into two major categories:

- Major bleeding event
- Non-major bleeding event

Major bleeding events were defined as (any one of the following):

- fatal bleeding
- bleeding into a critical organ (e.g., retroperitoneal, intracranial, intraocular or intraspinal)
- bleeding requiring re-operation
- clinically overt extrasurgical site bleeding associated with a decrease in hemoglobin of 2 g/dL or more
- clinically overt extrasurgical site bleeding leading to infusion of 2 or more units of blood

Non-major bleeding events were further classified as to whether the events were clinically relevant or not, using specific criteria. It is important to note that surgical site bleeding was not a component of the definition of "major bleeding." However, surgical site bleeding was recorded and analyzed. Table 16 provides a general overview of bleeding events in the RECORD studies.

**Table 16. Incidence Rates of Treatment-emergent Bleeding Events
in the RECORD Studies**

Endpoint	Riva n = 6183	Enox n = 6200	Absolute risk difference (95% CI)	Hazard ratio* (95% CI)	Nominal p-value
Major bleeding	24 (0.39%)	13 (0.21%)	0.18% (-0.01%, 0.37%)	1.8 (0.9, 3.6)	0.08
Major bleeding combined with surgical site bleeding	111 (1.80%)	85 (1.37%)	0.42% (-0.01%, 0.86%)	1.3 (1.0, 1.7)	0.06
Major or non- major clinically relevant bleeding	197 (3.19%)	158 (2.55%)	0.64% (0.05%, 1.23%)	1.3 (1.0, 1.5)	0.04
Any bleeding event	434 (7.02%)	401 (6.47%)	0.53% (-0.35%, 1.42%)	1.08 (1.0, 1.2)	0.3

*based on a Cox-regression analysis with study treatment as a covariate

Overall, the incidence of major bleeding was low (< 1%). However, the rate for rivaroxaban was numerically approximately twice that for enoxaparin and this increase was statistically significant at the 10% nominal level. This is a particularly important concern since the clinical care and oversight in the use of concomitant medications in the RECORD studies likely exceeded that one would expect in the general marketplace. Hence, the market usage of rivaroxaban may be associated with considerably more bleeding, particularly if the drug is used with concomitant medications that also increase the risk for bleeding.

Table 17 summarizes the bleeding endpoints by type of study (hip versus knee) and Table 18 summarizes the components of the Major bleeding endpoint. In general, bleeding rates were higher for patients undergoing knee surgery. However the signal for increased bleeding in association with rivaroxaban was evident in both the hip and knee surgery studies.

**Table 17. Incidence Rates of Treatment-emergent Bleeding Events
Within RECORD "Hip" or "Knee" Studies**

Endpoint	Hip Studies RECORD 1 and 2		Knee Studies RECORD 3 and 4	
	Rivaroxaban n = 3437	Enoxaparin n = 3453	Rivaroxaban n = 2746	Enoxaparin n = 2747
Major bleeding	7 (0.20%)	3 (0.09%)	17 (0.62%)	10 (0.36%)
Major bleeding combined with surgical site bleeding	63 (1.83%)	52 (1.51%)	48 (1.75%)	33 (1.20%)
Any bleeding	214 (6.23%)	199 (5.76%)	220 (8.01%)	202 (7.35%)

**Table 18. Components of the Treatment-emergent Bleeding Event Endpoint
in the RECORD Studies**

Endpoint	Rivaroxaban n = 6183	Enoxaparin n = 6200
Any major bleeding event	24 (0.39%)	13 (0.21%)
Fatal bleeding	2*	0
Critical organ bleeding	3 (0.05%)	5 (0.08%)
Bleeding that required re-operation	12 (0.19%)	7 (0.11%)
Clinically overt extrasurgical bleeding	8 (0.13%)	1 (0.02%)

*one subject received enoxaparin/placebo instead of rivaroxaban

All of the clinically overt extrasurgical bleeding events related to gastrointestinal hemorrhage. The two fatal bleeding events are summarized below:

In RECORD 1, a 74 year old female was randomized to rivaroxaban but received an injection of placebo pre-operatively. She subsequently experienced fatal bleeding (surgical site and urogenital bleeding) during and shortly following the hip replacement surgery. The patient did not receive rivaroxaban at any point during the study.

In RECORD 4, a 53 year old male developed a gastric hemorrhage and died five days after initiation of rivaroxaban. The patient had a history of obesity, smoking, congestive heart failure, hypertension and osteoarthritis. His baseline medications included oxapozin (Daypro), amitriptyline (Elavil), methocarbamol (Robaxin), furosemide (Lasix), carvedilol (Coreg) along with potassium chloride and lisinopril. He underwent right knee surgery on May 23, 2007 and was discharged from the hospital on May 25, 2007. Following discharge from the hospital, his medications included oxaprozin (Daypro), naproxen (Aleve) and Goddy's powder along with various analgesics and his usual medications. On [REDACTED] he presented to an emergency room with upper

gastrointestinal hemorrhage. He received five units of blood and underwent a gastroscopy that was assessed as suboptimal due to extensive blood in the stomach. Later in the day [REDACTED] he died. Autopsy showed multiple benign gastric ulcers with no evidence of gastric perforation, 40% stenosis of the circumflex coronary artery, mild aortic atherosclerosis and hepatomegaly. Reports indicate that the patient received only two days of rivaroxaban therapy prior to the gastric hemorrhage and death.

The occurrence of the fatal bleeding event in a patient who was receiving rivaroxaban and concomitant non-steroidal anti-inflammatory agents (NSAID) underscores the importance of minimizing the use of NSAIDs during rivaroxaban therapy.

c. Cardiovascular events following treatment discontinuation

A Cardiovascular Events Adjudication Committee adjudicated all deaths in the RECORD studies (with each death designated as either "cardiovascular" or "noncardiovascular"). The Committee also adjudicated investigator-identified cases of myocardial infarction or stroke.

Overall, the occurrence of cardiovascular events (myocardial infarction, ischemic stroke, cardiovascular death or unexplained death) was uncommon (< 1%) within each RECORD study as well as the integrated pool of the studies. As shown in Table 19, the incidences of cardiovascular events in the integrated data pool did not importantly differ between the two study groups, when analyzed for the combination of active treatment period and the follow-up period, as well as each individual period.

Within the table, the numeric imbalance in the occurrence of ischemic stroke is highlighted in the follow-up period. While the rates are low, the imbalance in the occurrence of ischemic stroke in the follow-up period, combined with a general pattern in which most of the rivaroxaban cardiovascular events occurring early in the follow-up period (within 10 days following study drug discontinuation) somewhat suggests that rivaroxaban may be associated with an increased tendency for thrombotic events in the early post-treatment period. However, the numbers of patients with these events were very small and the data appear inconclusive.

Table 19. Incidence Rates of Cardiovascular (CV) Events in RECORD Studies, Safety Population

Endpoint	Rivaroxaban n = 6097	Enoxaparin n = 6196
Any CV event in treatment or follow-up period	30 (0.49%)	39 (0.63%)
Any CV event in treatment period	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
Any CV event in follow-up period	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%)

d. Liver Test Abnormalities and Potential Liver Injury:

As shown previously, a small imbalance between the two study groups was evident in the incidence of serious adverse events reported as due to increased alanine aminotransferase levels in the RECORD studies. In general, this imbalance was not evident in the comparison of the rates of other serious adverse events reported for liver test abnormalities, as shown in Table 20.

Table 20. Incidence Rates of Serious Adverse Events reported for Liver Test Abnormalities in the RECORD Studies

Event	Rivaroxaban n = 6183	Enoxaparin n = 6200
"Treatment-emergent" (during active treatment period and up to 2 days after last study drug dose)		
Alanine aminotransferase increased	17 (0.27%)	11 (0.18%)
Aspartate aminotransferase increased	5 (0.08%)	6 (0.10%)
Bilirubin increased	5 (0.08%)	4 (0.06%)
Alkaline phosphatase increased	0	1 (0.02%)
"Post-baseline" (at any time point during each study)		
Alanine aminotransferase increased	18 (0.29%)	14 (0.23%)
Aspartate aminotransferase increased	6 (0.10%)	8 (0.13%)
Bilirubin increased	5 (0.08%)	4 (0.06%)
Alkaline phosphatase increased	0	1 (0.02%)

Overall, the incidences of liver test abnormalities in the RECORD studies appeared similar between the study groups, as shown in Table 21.

Table 21. Incidence Rates of Post-baseline Liver Test Abnormalities in the RECORD Studies*

Event	Rivaroxaban n = 6131	Enoxaparin n = 6131
ALT > 3X ULN concurrent with total bilirubin > 2X ULN	9 (0.15%)	7 (0.11%)
ALT > 3X ULN	152 (2.48%)	227 (3.70%)
ALT > 5X ULN	56 (0.91%)	78 (1.27%)
ALT > 8X ULN	18 (0.29%)	20 (0.33%)
ALT > 10X ULN	10 (0.16%)	9 (0.15%)
ALT > 20X ULN	2 (0.03%)	1 (0.02%)

*central laboratory results

ULN = upper limit of normal

The occurrence of blood ALT > 3X ULN concurrent with total bilirubin > 2X ULN has been proposed as potentially important indicator of drug-induced liver injury. Overall, within the pool of completed and ongoing studies (with available data) this outcome occurred in four rivaroxaban-treated patients who subsequently died with liver test abnormalities. The outcome (liver test abnormalities and death) occurred in two comparator group subjects. The patients who died all had comorbid conditions, as summarized below, for the four patients who received rivaroxaban (additional details are provided in the medical officer's draft review document):

Subject (b) (4) year old female with a history of hypertension, cardiac and renal insufficiency, cholecystolithiasis and Parkinson's disease who was enrolled in a phase 2 VTE prophylaxis study. The subject underwent a total hip replacement (day 1) and received eight days of rivaroxaban therapy (10 mg twice daily). She received one unit of blood in the peri-operative period. On day 47, the subject was rehospitalized with jaundice (ALT 190 U/L and total bilirubin 18.3 mg/dL). An ultrasound showed cholecystolithiasis. On day 50, an endoscopic retrograde cholangiopancreatography (ERCP) was performed with papillotomy. On day 60, a liver biopsy showed mild to moderate fatty degeneration without evidence of inflammation. Liver test abnormalities had also increased (total bilirubin within the range of 30 to 40 mg/dL). On day 117, an abdominal ultrasound showed "phlegmonic cholecystitis." The subject died on day 127 and autopsy reported the death as due to "septic-cholemic cardiovascular failure with accompanying bronchopneumonia and acute necrotizing pancreatitis." Additional details are provided in the medical officer's review.

(b) (4) year old female with a history of abdominal hysterectomy for a uterine sarcoma (with metastatic disease) who was undergoing chemotherapy at the time of randomization into a phase 2 VTE treatment study. The subject had a history of multiple blood transfusions and on day 1 (prior to rivaroxaban initiation) tested HBsAg positive. On day 7, ALT and bilirubin levels were normal but by day 20, the ALT was 80X ULN and the bilirubin was 1X ULN. Rivaroxaban (40 mg once daily) was stopped on day 22, and the subject was diagnosed as having active hepatitis B (based upon a threefold increase in anti-HBc IgM). The subject subsequently experienced fulminant

liver failure and died on day 47. A limited autopsy report showed liver histopathology as "subacute necrosis. Toxic origin of the changes is probable."

Subject (b) (4) year old female with a history of hypertension, asthma and emphysema who was enrolled in a phase 3 (ongoing) VTE treatment study (EINSTEIN DVT/PE). Baseline liver tests were normal and the subject began rivaroxaban (15 mg twice daily). She was hospitalized for dyspnea approximately two weeks after study drug initiation; she was treated with antibiotics, bronchodilators and oxygen. Two days later her liver tests were reported as elevated (ALT of 5,371 U/L and AST of 10,506 U/L) and the study drug was discontinued. She was transferred to another hospital for consideration of liver transplant and subsequently experienced a cardiac arrest and died due to multiple organ failure (approximately four weeks after study drug initiation). Autopsy showed "massive dilation of the right ventricle and left ventricular hypertrophy" with "hemorrhagic necrosis of the liver, especially in the centrilobular areas with minimal inflammation."

Subject (b) (4) year old male with a history of pancreatic cancer and surgery for gastric cancer who was enrolled in a phase 3 (ongoing) VTE treatment study (EINSTEIN DVT/PE). The subject initially received rivaroxaban at a dose of 30 mg daily, followed by a dose of 20 mg daily (total duration of approximately one month). On study day 27, the subject was first determined to have elevated liver tests (ALT 513 U/L, AST 537 U/L, total bilirubin 5.4 mg/dL). An ultrasound showed metastatic liver abnormalities with enlarged biliary tree and the subject was subsequently diagnosed with gastric cancer. The subject died approximately two months after study enrollment. No autopsy was performed.

7. Clinical Pharmacology Considerations

The submitted data provide evidence of an exposure-response (ER) relationship for the safety and effectiveness of rivaroxaban compared to enoxaparin, using total daily dose as the predictor (Figure). FDA regards the proposed daily dose of 10 mg as appropriate, given the shallow ER relationship for effectiveness and steep increase in the risk of major bleeding with increasing total daily dose.

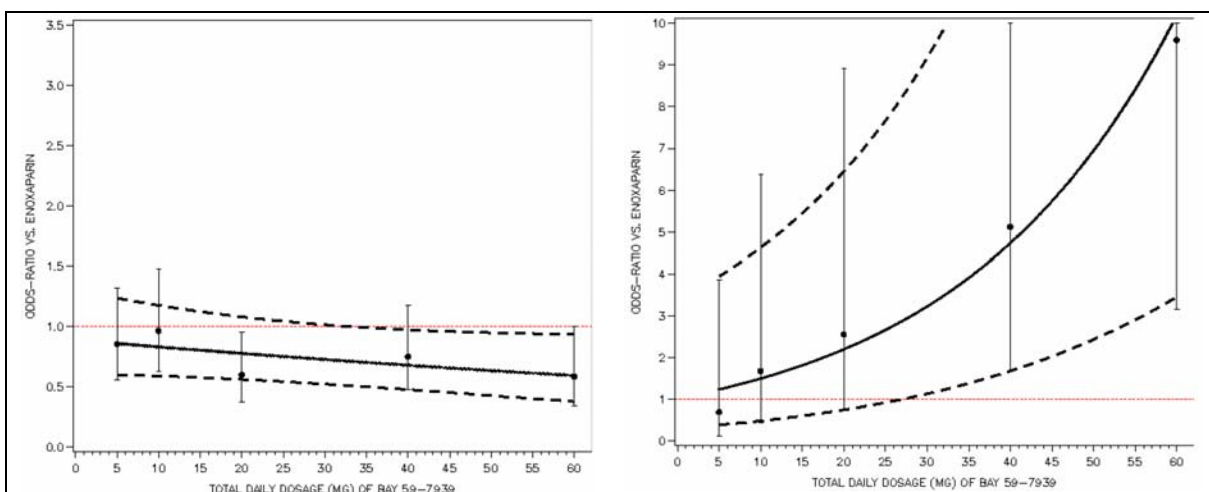


Figure 3: (Left) Total venous thrombotic events odds ratio curve of rivaroxaban vs enoxaparin and (Right) post-operative major bleeding odds ratio curve of rivaroxaban vs enoxaparin with total daily dose for studies 10942, 10944, and 10945-safety population.

Source: Applicant's Figure 4.3 and 5.1 in clinical overview on pages 41 and 64.

Rivaroxaban produces a maximum blood concentration 2 to 4 hours following oral ingestion of the dose. The drug is highly bound to blood albumin in humans (92% to 95%) and approximately two-thirds of the drug undergoes metabolic degradation, with half eliminated renally and the other half eliminated by the fecal route (liver metabolism and/or gastrointestinal transit). The remaining one-third of the administered dose undergoes direct renal excretion as unchanged active substance. Elimination of rivaroxaban from plasma occurs with a terminal half-life of 5 to 9 hours in young individuals and with a terminal half-life of 11 to 13 hours in the elderly. Rivaroxaban prolongs the blood prothrombin time (PT) and activated partial thromboplastin time (aPTT) although monitoring of these laboratory tests are not proposed for use during rivaroxaban therapy.

The clinical pharmacology of rivaroxaban is particularly notable for its dual pathway of elimination. Within the liver, the drug undergoes oxidative degradation by the cytochrome P450 enzyme system (specifically CYP3A4/5 and CYP2J2). Alteration of one or both these pathways by patient-specific factors (such as liver or renal disease) and/or the concomitant use of certain medications may importantly increase blood rivaroxaban concentrations. This increased rivaroxaban exposure, in turn, may increase the risk for bleeding.

With respect to active renal excretion, *in vitro* studies have shown rivaroxaban is a substrate of the transporter protein, P-gp, and breast cancer resistance protein (Bcrp). The consequence of reliance on this active renal secretion process is that co-administration of rivaroxaban with drugs that are moderate to strong inhibitor drugs of certain cytochrome P450 enzymes and/or the P-gp transporter (such as ketoconazole and ritonavir) will block both elimination pathways for rivaroxaban and may result in

clinically relevant increases in plasma rivaroxaban levels and may increase the risk for bleeding. A similar concern exists when these drugs are used in patients with preexisting renal and hepatic disease since both elimination pathways are affected and a greater than additive increase in exposure is possible.

This complexity is further complicated by the increased potential for bleeding associated with co-administration of rivaroxaban and drugs that also affect coagulation. Of special note, limited data have signaled a prolongation of the bleeding time during concomitant rivaroxaban and clopidogrel therapy, even though clopidogrel did not alter rivaroxaban pharmacokinetics.

The risks for bleeding may relate, in large part, to the use of concomitant medications. These concerns are especially notable for the use of rivaroxaban in the hip replacement indication, where patients are expected to take the drug for 35 days. This population of patients may include substantial numbers of patients with comorbidities (such as arthritis or cardiovascular disease) and who are maintained on anti-inflammatory agents (e.g., non-steroidals), immune modulators (e.g., cyclosporine) anti-arrhythmics (e.g., verapamil, amiodarone, quinidine) and anti-platelet drugs (e.g., clopidogrel or ticlopidine). Additionally, hip replacement is occasionally necessary in patients receiving HIV-protease inhibitor drugs. These various drugs, combined with rivaroxaban, may importantly increase the risk for hemorrhage. As previously noted, 85% of the patients in the RECORD studies were enrolled at non-USA sites, raising some concern that the concomitant medication usage in the RECORD studies may not fully reflect the usage one might expect in the USA.

Table 22. Concomitant Medication Use and Clinically Relevant Bleeding (major or nonmajor) in RECORD Studies

Concomitant Medication	Bleeding with Rivaroxaban	Bleeding with Enoxaparin	% patient time exposure
CYP3A4 or Pgp inhibitors*	12/173 (7%)	2/128 (2%)	5% riva 5% enox
Statin	39/173 (23%)	24/130 (18%)	15% riva 14% enox
NSAIDs	92/173 (53%)	64/130 (49%)	36% for riva 36% for enox
Opioids	130/173 (75%)	93/130 (72%)	39% for riva 40% for enox
Platelet inhibitors (including aspirin)	8/173 (5%)	5/130 (4%)	5% riva 4% enox
Nitrates	8/173 (5%)	7/130 (5%)	3% riva 3% enox

*Amiodarone, Aprepitant, Cimetidine, Clarithromycin, Diltiazem, Erythromycin, Fluconazole, Fluoxetine, Fluvoxamine, Itraconazole, Ketoconazole, Telithromycin, Udamil, Verapamil, Cyclosporine, and Quinidine

Additional details of clinical pharmacology concerns are described within the draft clinical pharmacology review document. During this review cycle, the FDA requested the sponsor to develop a lower dose (e.g., 5 mg) tablet or scored 10 mg tablet to permit downward dose titration in the special populations at risk for clinically relevant higher rivaroxaban drug exposure at the proposed dose (e.g., certain patients with renal or hepatic impairment as well as for use among patients receiving concomitant therapy with moderate or strong CYP3A4 or P-gp inhibitor drugs). To date, the sponsor has regarded this modification as unnecessary.

8. On-going Clinical Studies

The sponsor currently has nine on-going clinical studies and has provided summary information from 20,875 patients enrolled in these studies. Of note, approximately 67% of these patients are enrolled in blinded clinical studies and the summary data are not denoted by the assigned treatment regimen (instead, an aggregate summary is provided). Additionally, these data have generally not undergone thorough data quality verification. Hence, the data are useful primarily for the detection of major outcomes of special concern (such as major bleeding events, liver toxicity or death). Table 23 summarizes the major design features for these studies. Notably, most of the studies use rivaroxaban doses that exceed those proposed for use in the prophylaxis of VTE among patients undergoing hip or knee replacement surgery.

Table 23. Overview of Ongoing Clinical Studies

Study Name	Phase	Population	Comparator	Riva daily dose	Safety population n	Data presentation
ATLAS ACS TIMI 46	2	ACS	placebo	2 to 20 mg	(b) (4)	unblinded
EINSTEIN DVT/PE	3	acute DVT/PE	enoxaparin VKA	30 mg for 3 wks then 20 mg	(b) (4)	unblinded
ROCKET-AF	3	atrial fibrillation	warfarin	20 mg/15 mg	(b) (4)	blinded
J-ROCKET-AF	3	atrial fibrillation (Japan)	warfarin	15 mg/10 mg	(b) (4)	blinded
EINSTEIN Extension	3	DVT/PE after 6 mths of std therapy	placebo	20 mg	(b) (4)	blinded
MAGELLaN	3	hospitalized medically ill (VTE prevention)	enoxaparin/ placebo	10 mg	(b) (4)	blinded
ATLAS ACS TIMI 51	3	ACS	placebo	5 and 10 mg	(b) (4)	blinded
CHF	1	CHF	enoxaparin/ placebo	10 mg	(b) (4)	blinded

As of the cut-off date of the six month safety update (December 5, 2008 for all studies except J-ROCKET-AF which had a data cut-off of October, 31, 2008), rivaroxaban has been administered to several thousands of patients for six months or more (Table 24).

Table 24. Rivaroxaban Exposure in Ongoing Clinical Studies

Rivaroxaban exposure	Numbers of patients
≥ 1 month	9859
≥ 6 months	5865
≥ 12 months	1557

Overall, the supplied summary data do not appear to raise safety concerns that importantly differ from those evidenced in the RECORD studies. The most important data derive from the unblinded clinical studies, ATLAS ACS TIMI 46 and EINSTEIN DVT/PE because only these two studies have comparative safety data.

a. ATLAS ACS TIMI 46:

This was a phase 2, randomized, double-blind, placebo controlled study in which patients with acute coronary syndromes were randomized to placebo or various rivaroxaban doses (with aspirin alone or with aspirin and a thienopyridine), administered daily for six months. The primary efficacy endpoint was the composite of death, myocardial infarction, stroke or severe recurrent ischemia requiring revascularization. The primary safety endpoint was the incidence of clinically significant bleeding (TIMI major bleeding, TIMI minor bleeding or bleeding requiring medical attention). Notably, the definitions of bleeding (TIMI classification) in this study differed from those used in the RECORD studies.

TIMI major bleeding = any intracranial bleeding or clinically overt bleeding associated with a decrease in hemoglobin of ≥ 5 g/dL or an absolute drop in hematocrit of $\geq 15\%$.

TIMI minor bleeding = any clinically overt bleeding associated with a decrease in hemoglobin ≥ 3 g/dL but is < 5 g/dL from the baseline hemoglobin value.

The summary data (study report is under development) are particularly notable for suggesting a dose-related increased risk for bleeding, as shown in Table 25.

Table 25. Incidence Rates of Treatment-emergent Bleeding-related Adverse Events, Centrally Adjudicated in the ATLAS ACS TIMI 46 Study

Bleeding Event	Riva 5 mg n = 307	Riva 10 mg n = 1046	Riva 15 mg n = 353	Riva 20 mg n = 603	Placebo n = 1153
Clinically significant	17 (5.5%)	109 (10.4%)	43 (12.2%)	89 (14.8%)	36 (3.1%)
TIMI major	1 (0.3%)	16 (1.5%)	6 (1.7%)	9 (1.5%)	1 (0.1%)
TIMI minor	1 (0.3%)	6 (0.6%)	3 (0.8%)	5 (0.8%)	2 (0.2%)
Requiring medical attention	17 (5.5%)	88 (8.4%)	35 (9.9%)	76 (12.6%)	33 (2.9%)

ATLAS ACS TIMI 46 is also important for assessing liver test outcomes since the comparator is a placebo. Table 26 summarizes the major liver test results, with pooling of the rivaroxaban cohorts.

Table 28. Incidence Rates of Treatment-emergent Abnormal Liver Test Results in the EINSTEIN DVT/PE Study

(b) (4)



Overall, hepatic disorder serious adverse events occurred in 5 patients in the rivaroxaban group and 10 patients in the enoxaparin/VKA group. One of these serious hepatic disorder events resulted in death (a rivaroxaban patient). As previously described, this 63 year old female with a history of pulmonary emphysema was hospitalized for worsening dyspnea and experienced progressive liver test abnormalities. Review of her clinical course by an adjudication committee assessed her death as due to "ischemic injury leading to hepatocellular necrosis in the setting of multi-organ failure."

9. Major Aspects of the Nonclinical Pharmacology and Toxicology

Nonclinical safety was evaluated predominantly in rats and dogs. Repeat-dose toxicity studies were performed to support long term administration to humans. Overall, rivaroxaban was administered as daily treatment for up to six months in rats and up to 12 months in dogs.

Dog studies showed that rivaroxaban produced anticoagulation, with the major toxicity related to hemorrhage. In rats, overt bleeding was not observed up to the highest tested dose. Important, organ-specific toxicity was not evident in either species.

DRAFT Statistical review and assessment of incidence of Bleeding for NDA 022204

This section addresses the concerns of bleeding events for patients undergoing THR or TKR surgery receiving treatment of Rivaroxaban in comparison with Enoxaparin. The statistical reviewer analyzed the bleeding event data submitted by sponsor in their NDA 022406

The overall conclusion from the statistical reviewer's analysis results is that there is a trend toward increased incidence of bleeding events in the Rivaroxaban group compared to Enoxaparin group. Especially, the incidence of major or non-major clinically relevant bleeding events for the patients following THR and TKR surgery were statistically significantly increased in the Rivaroxaban group compared to the Enoxaparin group.

To capture the full picture of bleeding events for four pivotal Phases 3 randomized, double-blind, enoxaparin controlled trials (RECORD1 [Study 11354], RECORD2 [Study 11357], RECORD3 [Study 11356], RECODE4 [Study 11355]), the protocol-specified assessment included 2 categories: major bleeding event and non-major bleeding event by Bleeding Event Adjudication Committee (AC/BE)

Major bleeding events were defined as:

- 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
- Clinically overt extrasurgical site bleeding requiring transfusion of ≥ 2 g/dL units of whole blood or packed cells

All bleeding events not adjudicated as major bleeding were considered non-major bleeding events. Non-major bleeding events were further classified by the AC/BE into those that were clinically relevant or non-clinically relevant. Non-major clinically relevant bleeding events were defined in the protocol as:

- Multiple source bleeding
- Spontaneous hematoma $> 25\text{cm}^2$
- Excessive wound hematoma
- Spontaneous nose bleeding lasting for ≥ 5 minutes
- Gingival bleeding > 5 minutes
- Macroscopic hematuria
- Spontaneous rectal bleeding
- Coughing blood (hemoptysis)
- Hematemesis
- Prolonged bleeding after venipuncture > 5 minutes

Assessment of Bleeding Event (Pooled Record 1-4 Studies)

The figures and tables presented below show the observed proportion of subjects with bleeding event using pooled RECORD 1-4 data analyzed over 3 different time periods. Four categories of bleeding that include 1) major bleeding event, 2) major bleeding combined with surgical site bleeding events, 3) major or non-major clinically relevant bleeding event and 4) any bleeding event are presented. Tables include hazard ratio and the corresponding 95% confidence interval for time to first event. The p-value using Cox-regression model for time to first event and p-value with time to multiple events using Andersen-Gill (AG) proportional hazards model can also be found in the tables.

Bleeding Event for Total Duration

A statistically significant increase was observed in the proportion of subjects with bleeding event over the total duration for major bleeding event (24 (0.39%) vs 13 (0.21%)), major bleeding combined with surgical site bleeding events (111 (1.8%) vs 85 (1.37%)), and major or non-major clinically relevant bleeding event (197 (3.19%) vs 158 (2.55%)) in Rivaroxaban group compared to active control (Enoxaparin) group. The hazard ratios are all > 1 by using Cox proportional hazard model in Rivaroxaban compared with Enoxaparin, and p-values for major bleeding, for major bleeding combined with surgical site and for major or non-major clinically relevant bleeding event are all statistically significant at 10% level of significance in favor of Enoxaparin and against Rivaroxaban.

Figure 1 % of Bleeding Event Total duration in Pooled Study

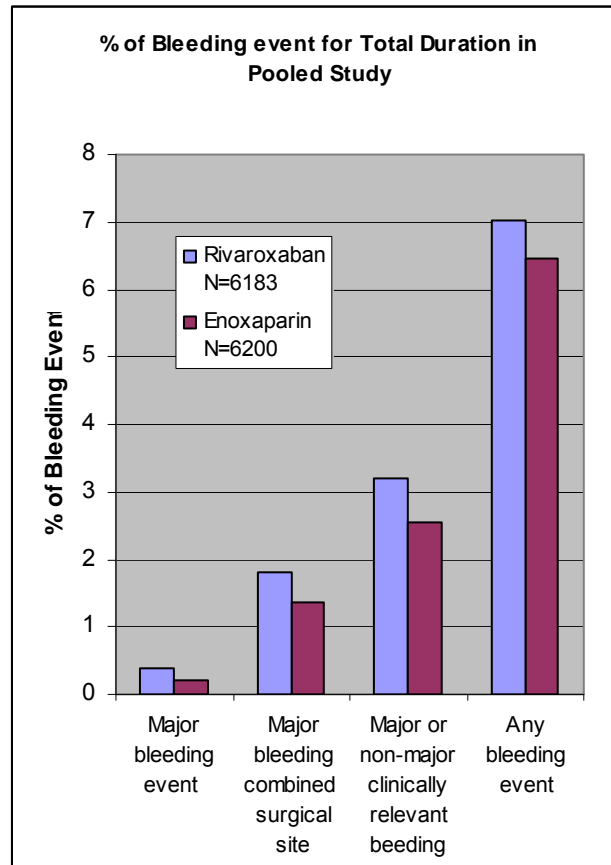


Table 1 % of Bleeding Event Total duration in Pooled Study

Endpoint	Rivaroxaban N=6183	Enoxaparin N=6200	Hazard Ratio for time to first event (95% CI)	P-value (time to first event)	P-value (time to multiple event)
Major bleeding	24 (0.39%)	13 (0.21%)	1.8 (0.9, 3.6)	0.076	0.05
Major bleeding combined with surgical site	111 (1.80%)	85 (1.37%)	1.3 (1.0, 1.7)	0.06	0.05
Major or non- major clinically relevant bleeding	197 (3.19%)	158 (2.55%)	1.3 (1, 1.5)	0.039	0.02
Any bleeding	434 (7.02%)	401 (6.47)	1.1 (0.9, 1.2)	0.3	0.3

Bleeding Event until Day 12±2

Analysis of the data until day 12±2 again showed that significant increase was observed in the proportion of subjects with bleeding event for major bleeding event (21 (0.34%) vs 13 (0.21%)), major bleeding combined with surgical site bleeding events (111 (1.8%) vs 84 (1.35%)), major or non-major clinically relevant bleeding event (176 (2.85%) vs 152 (2.45%)) and any bleeding event (409 (6.61%) vs 384 (6.19%)) in Rivaroxaban group compared to Enoxaparin control group. The hazard ratios are all > 1 by using Cox

proportional hazard model, and p-values for major bleeding combined with surgical site bleeding event are 0.08 and 0.06 (statistically significant at 10% level) for time to first event and time to multiple events, respectively.

Figure 2 % of Bleeding Event until Day 12 ± 2 in Pooled Study

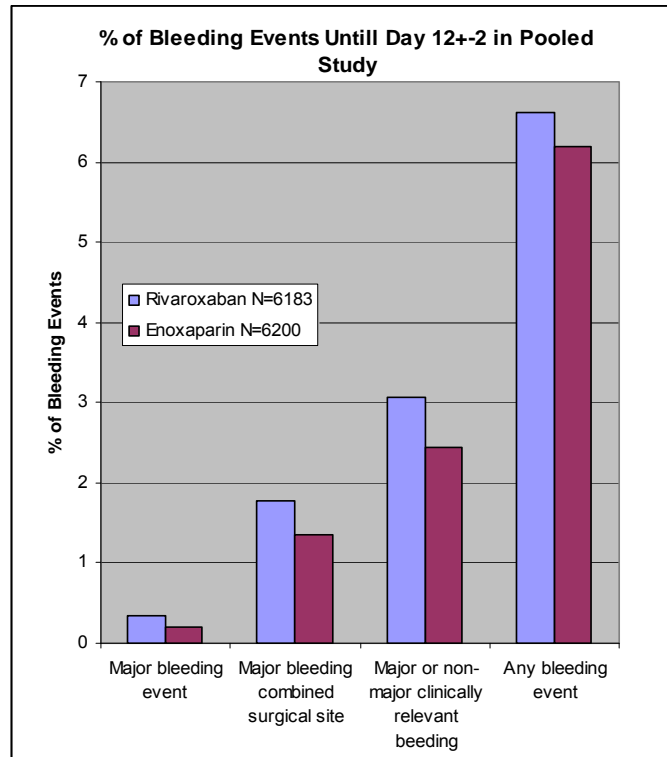


Table 2 % of Bleeding Event until Day 12 ± 2 in Pooled Study

Endpoint	Rivaroxaban N=6183	Enoxaparin N=6200	Hazard Ratio for time to first event (95% CI)	P-value (time to first event)	P-value (time to multiple event)
Major bleeding	21 (0.34%)	13 (0.21%)	1.61 (0.8, 3.2)	0.175	0.09
Major bleeding combined with surgical site	108 (1.75%)	84 (1.35%)	1.3 (1.0, 1.7)	0.082	0.06
Major or non- major clinically relevant bleeding	176 (2.85%)	152 (2.45%)	1.2 (0.9, 0.4)	0.186	0.17
Any bleeding	409 (6.61%)	384 (6.19)	1.1 (0.9, 1.2)	0.38	0.3

Bleeding Event for Active Control Phase

When data were analyzed over active control phase, again a statistically significant increase was observed in the proportion of subjects with bleeding event for major

bleeding event (23 (0.37%) vs 13 (0.21%)), major bleeding combined with surgical site bleeding events (110 (1.78%) vs 84 (1.35%)), and major or non-major clinically relevant bleeding event (190 (3.07%) vs 156 (2.52%) in Rivaroxaban group compared to active control (Enoxaparin)group. The hazard ratios are all > 1 by using Cox proportional hazard model, and p-values for major bleeding, major bleeding combined with surgical site and for major or non-major clinically relevant bleeding event are all statistically significant at 10% level of significance in favor of enoxaparin and against Rivaroxaban for both time to first event and time to multiple events,.

Figure 3 % of Bleeding Event for Active Control Phase in Pooled Study

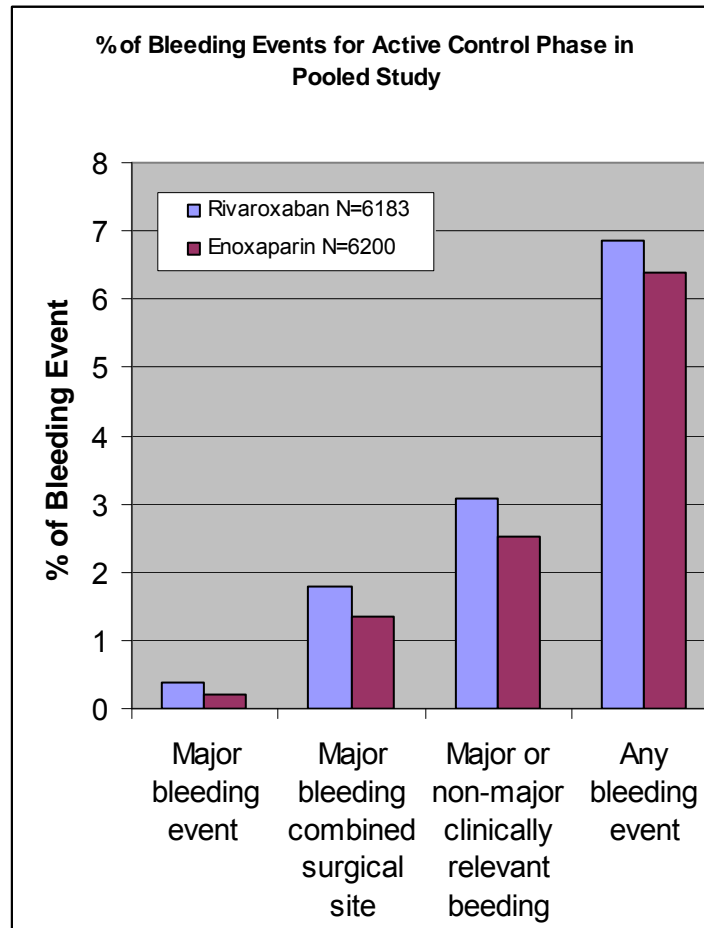


Table 3 % of Bleeding Event for Active Control Phase in Pooled Study

Endpoint	Rivaroxaban N=6183	Enoxaparin N=6200	Hazard Ratio for time to first event (95% CI)	P-value (time to first event)	P-value (time to multiple event)
Major bleeding	23 (0.37%)	13 (0.21%)	1.8 (0.9, 3.5)	0.1	0.08
Major bleeding combined with surgical site	110 (1.78%)	84 (1.35%)	1.3 (1.0, 1.7)	0.06	0.049
Major or non- major clinically relevant bleeding	190 (3.07%)	156 (2.52%)	1.3 (1, 1.5)	0.068	0.055
Any bleeding	424 (6.86%)	397(6.40%)	1.1 (0.9, 1.2)	0.3	0.19

Conclusion

The data provided in this NDA demonstrate that for patients following THR and TKR surgery, administration of Rivaroxaban for prophylaxis of DVT and PE increases the incidence of bleeding in comparison with the active control Enoxaparin, based on the results from categories of major bleeding alone or combined with surgical site or non-major clinically relevant bleeding as assessed by Bleeding Event Adjudication Committee (AC/BE). It is known (from the label) that the most common side effect associated with using Enoxaparin is the risk of bleeding. The evidence that administration of Rivaroxaban could lead to bleeding events in significantly more patients relative to Enoxaparin amplifies this safety concern for Rivaroxaban in comparison to placebo in the setting of prophylaxis of DVT and PE following THR or TKR surgery.

DRAFT CLINICAL REVIEW

Application Type	NDA
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Reviewer Name	Min Lu, M.D., M.P.H.
Review Completion Date	03-Feb-2009
Established Name	Rivaroxaban
(Proposed) Trade Name	XARELTO TM
Therapeutic Class	Anticoagulation
Applicant	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Priority Designation	S
Formulation	Oral tablet
Dosing Regimen	10 mg once daily
Indication	Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE)
Intended Population	Patients undergoing hip or knee replacement surgeries.

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List of Abbreviations

AC/BE	Adjudication Committee/Bleeding Event
AC/CV	Adjudication Committee/Cardiovascular Event
AC/VTE	Adjudication Committee/Venous Thromboembolic Event
AE	adverse event
ALT	alanine aminotransferase
AP (ALKO PHOS)	alkaline phosphatase
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
bid	<i>bis in die</i> , twice daily
BMI	body mass index
BPM	beats per minute
BUN	blood urea nitrogen
CI	confidence interval
CK MB	creatinine kinase muscle-brain
CYP	cytochrome P450 isoforms
CT	computed tomography
CV	cardiovascular
DSMB	Data Safety and Monitoring Board
DVT	deep vein thrombosis
ECG	electrocardiogram
EMD	electromechanical dissociation
FiO ₂	fraction of inspired oxygen
FU	follow-up
FXa	Factor Xa
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GI	gastrointestinal
Hb	hemoglobin
Hct	hemotocrit
HIV	human immunodeficiency virus
ICAC	Independent Central Adjudication Committee
ICU	intensive care unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent to treat
IU	international unit
IV	intravenous(ly)
kg	kilogram
L	liter
LAP	Liver Advisory Panel
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
min	minute
MITT	Modified Intent to Treat (population)

mmHg	millimeter <i>hydrargyrum</i> (millimeter of mercury)
mmol	millimol
mL	milliliter
MRSA	methicillin-resistant staphylococcus aureus
ms	millisecond
N/A	not applicable
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
od	once daily
PE	pulmonary embolism
P-gp	P-glycoprotein
PO	<i>per os</i> (by mouth, orally)
PP	per protocol
prn	<i>pro re nata</i> (when daily doses for medication is variable)
PT	prothrombin time (in seconds)
RBC	red blood cell (count)
RECORD	RE gulation of Co agulation in OR thopedic Surgery to prevent
SC	subcutaneously
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TB	total bilirubin
TEAE	treatment-emergent adverse event
THR	total hip replacement
TKR	total knee replacement
UH	unfractionated heparin
ULN	upper limit of normal
VKA	vitamin K antagonist
VTE	venous thromboembolic events
WBC	white blood cell (count)

1 Executive Summary

Xarelto (rivaroxaban) is a selective Factor Xa (FXa) inhibitor with oral bioavailability and is under development as an oral anticoagulant for the treatment of multiple thrombosis-mediated conditions. The currently proposed indication is for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgeries. The proposed dose of rivaroxaban is 10 mg once daily administered orally. The proposed treatment duration for rivaroxaban is 35 days for patients undergoing hip replacement surgery and 14 days for patients undergoing knee replacement surgery.

Efficacy Findings

Four multi-center, randomized controlled trials (RECORD 1-4) were conducted to support the currently proposed indication for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgeries. RECORD 1 and 2 studies were conducted in patients undergoing hip replacement surgery (THR) and RECORD 3 and 4 studies were in patients undergoing knee replacement surgery (TKR). In all 4 RECORD trials, rivaroxaban 10 mg once daily administered orally at least 6 to 8 hours after surgery was compared with enoxaparin administered subcutaneously. The enoxaparin dosing regimen was 40 mg once daily starting 12 hours preoperatively in RECORD 1-3 studies and was 30 mg twice daily starting 12 to 24 hours postoperatively in RECORD 4 study. The durations of active treatment for rivaroxaban and enoxaparin were similar in the RECORD studies with the exception of RECORD 2, in which treatment duration of Rivaroxaban was much longer than enoxaparin control (rivaroxaban 35 days versus enoxaparin 12 days). The dose regimen of enoxaparin (40 mg once daily) control in RECORD 3 study is not a recommended dose regimen of enoxaparin for the prophylaxis of DVT in patients undergoing TKR in the United States.

Altogether a total of 12,729 patients (6356 in the rivaroxaban group and 6373 in the enoxaparin group) were randomized in 4 RECORD studies and 8,512 (67%) (4248 in the rivaroxaban group and 4264 in the enoxaparin group) were included in the Modified Intent to Treat (MITT) population for the primary efficacy analysis. About 30-39% of randomized patients in RECORD studies were excluded from MITT population mainly due to no adequate assessment of DVT. The primary efficacy endpoint was a composite endpoint of total VTE consisting of any DVT (proximal and/or distal), non-fatal PE, or death from all causes at the end of treatment in all 4 RECORD studies.

For patients undergoing THR surgery, the total VTE rate was 1.1% in the rivaroxaban group as compared to 3.7% in the enoxaparin group in RECORD 1 trial with similar treatment duration (35 days). In RECORD 2 study, the total VTE rate was 2.0% with rivaroxaban for 35 days as compared to 9.3% with enoxaparin for 12 days. The RECORD 1 study was designed as a non-inferiority trial and the result showed rivaroxaban to be non-inferior to enoxaparin (95% CI - 3.55%, -1.51%) and superiority was further tested. There was a statistically significant difference in the total VTE rate between the two treatment groups in both studies ($p < 0.001$).

For patients undergoing TKR surgery, the total VTE rate was 9.6% with rivaroxaban and 18.9% with enoxaparin 40 mg once daily, an unapproved regimen, in the RECORD 3 trial. In the RECORD 4 study, the total VTE was 6.9% with rivaroxaban and 10.1% with enoxaparin 30 mg twice daily. The RECORD 4 was designed as a non-inferiority trial and the result showed rivaroxaban to be non-inferior to enoxaparin (95% CI -5.25%, -0.17%) and superiority was further tested. There was a statistically significant difference in the total VTE rate between the two treatment groups in both studies ($p < 0.05$).

For the secondary efficacy endpoints, the major VTE (consisted of VTE-related death, non-fatal PE, or proximal DVT) was statistically significantly different ($p < 0.05$) between two treatment groups in RECORD 1 (0.2% and 2.0%, rivaroxaban and enoxaparin, respectively), RECORD 2 (0.6% and 5.1%, rivaroxaban 35 days and enoxaparin 12 day, respectively), and RECORD 3 (1.0% and 2.6%, rivaroxaban and enoxaparin 40mg, respectively) based on MITT population. In RECORD 4 study, the major VTE rate was not statistically significantly different between rivaroxaban and enoxaparin 30 mg bid regimen based on MITT population (1.2% and 2.0%, respectively).

Symptomatic VTE as one of the secondary efficacy endpoints was analyzed based on the safety population that included 12,383 (97%) subjects of randomized population. The symptomatic VTE rate was 0.27% in the rivaroxaban group as compared to 0.49% in the enoxaparin group in RECORD 1 study. In RECORD 2 study, the symptomatic VTE rate was 0.08% with rivaroxaban and 0.33% with enoxaparin during the enoxaparin control period, and 0.16% with rivaroxaban and 0.90% with placebo during the placebo control period. In TKR trial, the symptomatic VTE was 0.66% with rivaroxaban and 1.94% with enoxaparin 40 mg once daily in RECORD 3, and 0.72% with rivaroxaban and 1.19% with enoxaparin 30 mg twice daily in RECORD 4 study. There was statistically significant difference in symptomatic VTE between the two treatment groups in RECORD 3 and in the placebo control period in RECORD 2 study only ($p < 0.05$).

Overall, rivaroxaban demonstrates efficacy in prophylaxis of total VTE in patients undergoing elective hip or knee replacement surgeries. The absolute risk reduction of rivaroxaban for total VTE was 2.6% for total hip replacement surgery (RECORD 1 study), and 3.2% for total knee replacement surgery (RECORD 4 study) compared to currently available product (enoxaparin) with the similar treatment duration. The difference between the two treatments was mostly due to asymptomatic DVT. These results were based on 67% of all randomized population. There was no significant difference for the symptomatic VTE between the two treatments in these two studies based on 97% of randomized population.

Safety Findings

A total of 10,600 patients were exposed to rivaroxaban treatment in completed clinical studies including 6183 from phase 3 RECORD studies, 2232 from phase 2 VTE prophylaxis trials, 883 from phase 2 VTE treatment trials, 185 from phase 2 atrial fibrillation trials, and 1117 from phase 1 trials. Among all exposed patients, 6095 (57.5%) were exposed to rivaroxaban for ≤ 12 days, 3622 (34.2%) for 28-35 days, 203 (2%) between 36 and 12 weeks, and 635 (6%) for at least 12 weeks.

In RECORD phase 3 studies, there were 13 (0.2%) and 25 (0.4%) deaths reported in the safety populations of rivaroxaban and enoxaparin, respectively, during the treatment and follow-up period. The serious treatment-emergent adverse event rate was 6.6% in the rivaroxaban group and 8.5% in the enoxaparin group. The serious adverse events that were reported more frequently with rivaroxaban compared to enoxaparin were ALT increased, wound infection, femur fracture, operative hemorrhage, wound secretion, anemia, post-operative wound infection, acute renal failure, device related infection, hemorrhage, and nausea. The overall percentage of adverse events that led to discontinuation was 3.7% in the rivaroxaban group and 4.7% in the enoxaparin group. The adverse events leading to permanent discontinuation that were higher with rivaroxaban compared to enoxaparin were hematuria, angina pectoris, upper abdominal pain, tachycardia, anesthetic complication, vomiting, peripheral edema, and acute myocardial infarction. Overall, 68% of rivaroxaban subjects and 69% of enoxaparin subjects reported at least one treatment-emergent adverse event. The common adverse event were reported more frequently on rivaroxaban compared to enoxaparin were peripheral edema, dizziness, pruritus, pain in extremity, urinary retention, muscle spasms, and wound secretion.

The following are main safety concerns for rivaroxaban based on the integrated review of safety data from the submission.

Bleeding events

The incidence of major bleeding was higher with rivaroxaban treatment (24, 0.39%) than with enoxaparin (13, 0.21%) in RECORD studies ($p=0.07$). There were two fatal bleeding events in the rivaroxaban group as compared to none in the enoxaparin group. Of the two subjects who experienced fatal bleeding events, one did not receive active treatment and another received rivaroxaban for 6 days and died of GI bleeding. Major bleeding events requiring re-operation was in 12 (0.19%) subjects in rivaroxaban group as compared to 7 (0.11%) subjects in the enoxaparin group. More patients experienced clinically overt extrasurgical site bleeding associated with a >2 g/dL decrease in hemoglobin or requiring blood transfusion >2 units in the rivaroxaban group (8, 0.13%) than in the enoxaparin group (1, 0.02%).

The incidence of major bleeding was relatively higher in the TKR patients (0.62% with rivaroxaban and 0.36% with enoxaparin) compared to the THR patients (0.20% with rivaroxaban and 0.09% with enoxaparin). The incidence of major bleeding was higher with rivaroxaban comparing with enoxaparin in all RECORD studies except RECORD 2 study (0.27% and 0.09% in RECORD 1, 0.08% and 0.08% in RECORD 2, 0.57% and 0.48% in RECORD 3, and 0.39% and 0.21% in RECORD 4 for rivaroxaban and enoxaparin, respectively).

In the RECORD studies, the incidence of clinically relevant non-major bleeding was also higher in the rivaroxaban group (177, 2.86%) than the enoxaparin group (145, 2.34%). The bleeding events reported more frequently in the rivaroxaban group than in the enoxaparin group were macroscopic hematuria (0.45% vs. 0.13%), rectal bleeding (0.32% vs. 0.1%), nose bleeding (>5 minutes) (0.13% vs. 0.06%), and vaginal bleeding (0.13% vs. 0.03%). Overall, the incidence of any bleeding was 7.0% in the rivaroxaban group as compared to 6.5% in the enoxaparin group.

In subgroup analyses, in Asian subjects, subjects with body weight ≤ 50 kg or > 110 kg, or subjects with BMI < 18.5 or ≥ 40 , the risk of major or non-major clinically relevant bleeding events appear to be higher with rivaroxaban as compared to other groups.

Exploration of the data for potential drug-drug interactions suggested that patients on rivaroxaban with concomitant use of opioids and statins had 2.5 and 1.5-fold higher risk of major or clinical relevant non-major bleeding, respectively, as compared to those without use of these medications. The relative rate with use of opioids versus no use for major or non-major clinically relevant bleeding was nearly 2 fold on rivaroxaban (2.52) compared to enoxaparin (1.31). The relative rate with use of statin versus no use major or non-major clinically relevant bleeding was also higher on rivaroxaban (1.52) compared to enoxaparin (1.26). These potential drug-drug-interactions require further investigation.

Cardiovascular events

In RECORD 1 and 2 studies, retrospective adjudication was conducted for all deaths after the studies were unblinded. After retrospective adjudication, 5 more cardiovascular deaths and 1 more unexplained death were added in the enoxaparin control group and none was added in the rivaroxaban group. In 4 RECORD studies, the total adjudicated cardiovascular events were in 31 (0.5%) subjects in the rivaroxaban group as compared to 39 (0.63%) subjects in the enoxaparin group during study drug treatment and the 30-day post-study drug follow-up period. There were more adjudicated ischemic stroke events in the rivaroxaban group (12, 0.19%) as compared to the enoxaparin group (7, 0.11%).

During the off-treatment period, 17 (0.28%) subjects experienced cardiovascular events in the rivaroxaban group as compared to 14 (0.23%) in the enoxaparin group. Among those patients, 11 (66%) events (4 MI, 3 stroke and 4 cardiovascular death) in the rivaroxaban group and 2 (14%) events (1 cardiovascular death and 1 unexplained death) in the enoxaparin group occurred within 10 days after the last dose of treatment; 7 (41%) events (2 MI, 2 stroke, and 3 CV deaths) in the rivaroxaban group and 1 (7%) events (CV death) in the enoxaparin group occurred within 5 days after the last dose of treatment.

There were more subjects who had ischemic stroke in the rivaroxaban group (6, 0.10%) than in the enoxaparin group (1, 0.02%) during the off treatment period. The 6 stroke events occurred in 4, 5, 8, 13, 34, and 39 days after the last dose of treatment in 6 subjects, respectively. One stroke event in the enoxaparin group occurred 26 days after the last dose of treatment.

The early occurrence of cardiovascular events and a higher incidence of ischemic stroke during off-treatment period in the rivaroxaban group as compared to the enoxaparin group raise concerns for possible rebound effect of rivaroxaban after the treatment withdrawal.

Hepatic events

In the Phase 3 RECORD studies, laboratory evaluation showed that the elevation of ALT $> 3 \times$ ULN was observed in 152 (2.5%) subjects in the rivaroxaban group as compared to 227 (3.7%) subjects in the enoxaparin group. There were 9 (0.15%) patients who had ALT $> 3 \times$ ULN

concurrent with TB >2xULN in the rivaroxaban group as compared to 7 (0.11%) patients in the enoxaparin group. The events of ALT >3xULN concurrent with TB >2xULN in 7 (0.11%) subjects in the rivaroxaban group as compared to 3 (0.05%) subjects in the enoxaparin group were considered to be possible related to the study drug by at least one member of the sponsor's liver advisory panel.

In the RECORD studies, 290 subjects (4.7%) in the rivaroxaban group and 400 subjects (6.5%) in the enoxaparin group reported a post-baseline hepatic disorder adverse event. The vast majority of these adverse events reported by investigators in both treatment groups were adverse events due to abnormal liver-related laboratory tests. Of these, the most frequently reported events included the following: increased ALT (144 [2.3%] with rivaroxaban and 200 [3.2%] with enoxaparin); increased AST (116 [1.9%] with rivaroxaban and 152 [2.5%] with enoxaparin); and increased GGT (126 [2.0%] with rivaroxaban and 183 [3.0%] with enoxaparin). Overall, 33 subjects (0.53%) administered rivaroxaban and 27 subjects (0.44%) administered enoxaparin had hepatic disorder serious adverse events. The vast majority of these subjects (28 subjects [0.5%] receiving rivaroxaban and 26 subjects [0.4%] receiving enoxaparin) had adverse events that were increases in liver-related laboratory parameters. The most common hepatic disorder serious adverse event was increased ALT levels, seen in 17 subjects (0.3%) in the rivaroxaban group and 14 subjects (0.2%) in the enoxaparin group.

In Phase 2 VTE prophylaxis trials (8 days), 4 subjects in the rivaroxaban group and 2 subjects in the enoxaparin group had ALT >3xULN concurrent with TB >2xULN. The events in all 4 subjects in the rivaroxaban group were considered by the investigator to be related to the study treatment and the events in 2 subjects in the enoxaparin group were considered by the investigator to be not related to the study drug. One subject in the rivaroxaban group was hospitalized with clinical symptoms, increased liver enzymes, bilirubin, alkaline phosphatase, and GGT 39 days after the last dose of rivaroxaban and subsequently died of "septic, cholemic heart and circulatory failure with bronchial pneumonia, acute cholecystitis and acute pancreatitis" per autopsy. Autopsy performed 3 days after the death showed "hepatocytes already altered due to autolysis, portal fields not greatly enlarged, no glycogen nuclei, no signs of intrahepatic cholestasis". The investigator considered the liver impairment and pancreatitis as related to the study drug. The liver advisory panel concluded that this may be a drug-induced cholestasis but it was unlikely to be related to rivaroxaban although temporal association cannot exclude rivaroxaban.

In Phase 2 VTE treatment trials (12 week), one subject in the rivaroxaban group had ALT >3xULN concurrent with TB >2xULN as compared to none in the heparin/VKA control group. This subject died of liver failure after 48 days of treatment with rivaroxaban 40 mg once daily. This subject was diagnosed with acute hepatitis B infection by positive HBcAb IgM. The patient had HBsAg positive at baseline identified by retention blood sample. The autopsy showed liver tissue with subacute necrosis without acute inflammatory changes and suggested the presence of acute exacerbation of chronic hepatitis B and of probably toxic origin. The pathologist in the liver advisory panel concluded that the submassive necrosis of liver can be explained by severe hepatitis B viral infection taking into account the serological profile of hepatitis B but such lesion might also be consistent with drug-induced or toxic damage to the liver.

In a Phase 2 Japanese atrial fibrillation trial (28 days) in 102 subjects, the ALT >1x ULN was reported in 13% in the rivaroxaban group (75 subjects) as compared to 4% in the warfarin group (27 subjects) although the sample size was relatively small.

In 5 ongoing studies (2 open-label and 3 blinded), a total of 27 subjects were reported as having ALT >3xULN concurrent with TB >2xULN. In two open-labeled studies, these included 3 subjects in phase 2 ATLAS ACS TIMI 46 study (all 3 in placebo group), 3 subjects in EINSTEIN DVT/PE study (all 3 in rivaroxaban group) who had ALT >3xULN concurrent with TB >2xULN. One subject in placebo group in ATLAS ACS TIMI 46 study and all 3 subjects in the rivaroxaban group in EINSTEIN DVT/PE subsequently died. One subject in the rivaroxaban group died with liver failure and the liver advisory panel member raised concerns of likely drug-induced toxic injury based on autopsy findings. In the 3 blinded ongoing studies, there were 16 cases in ROCKET-AF study, 3 in J-ROCKET-AF study, and 2 in MAGELLAN study. Three cases in ROCKET-AF were unblinded and all had received warfarin. One case in J-ROCKET-AF study was unblinded and had received rivaroxaban. A total of 17 cases are still blinded.

Overall, in completed studies, there were 14 (0.15%) subjects who had ALT >3xULN concurrent with TB >2xULN in the rivaroxaban group as compared to 9 (0.13%) in the control group. In RECORD phase 3 trials, 7 (0.11%) in the rivaroxaban group and 3 (0.05%) in the enoxaparin group were considered to be possibly related to rivaroxaban by at least one member of the sponsor's liver advisory panel. Two of 14 subjects in the rivaroxaban group subsequently died with liver failure as compared to none in the enoxaparin group. One death was considered to be drug-induced cholestasis by the liver advisory panel. Another death was considered to be hepatitis B infection but the autopsy findings of liver tissues raised concerns for possible toxic origin of lesions. In both cases, the role of rivaroxaban could not be excluded. An additional 27 cases of ALT >3xULN concurrent with the TB >2xULN were reported in 5 ongoing studies. These included 4 in the rivaroxaban group, 3 in the placebo group, and 3 in the warfarin group, and 17 still blinded cases. One subject in the rivaroxaban group in ongoing studies died with liver failure and the autopsy findings again raised concerns of likely drug-induced toxic injury to a liver advisory panel member.

In the RECORD studies, serious treatment-emergent ALT increased was reported more often in subjects in the rivaroxaban group (17, 0.27%) as compared to enoxaparin group (11, 0.18%) although the rate of ALT >3x ULN was lower with rivaroxaban (152, 2.48%) than with enoxaparin (227, 3.70%). Because enoxaparin control has been known to cause benign liver enzyme elevation and such elevations are fully reversible (NDA 20-164, Lovenox labeling), the comparison of liver enzyme elevation between the two treatments would not eliminate the concerns of possible serious liver toxicity for rivaroxaban.

Previous experience with EXANTA (ximelagatran) that causes drug-induced liver injury suggested even short term tolerance does not necessarily predict long term safety (NDA 21-686, Medical Review, Dr. Ruyi He, M.D., 9/27/04; Cardiovascular and Renal Drug Advisory Committee Transcript, 9/10/04). In the current application, 92% of study patients were exposed to <35 days of rivaroxaban treatment and only 6% (635 patients) were exposed to rivaroxaban for 3 months based on completed studies. Therefore, the long-term safety data from ongoing

studies, using a control that has not been shown to increase liver enzymes, such as warfarin, will be needed to fully evaluate the hepatotoxicity for rivaroxaban.

Furthermore, because rivaroxaban is an oral anticoagulant that doesn't require routine monitoring during treatment, off-label, long-term use could be widespread in clinical practice to replace current available oral product (coumadin) due to convenience, especially in atrial fibrillation population for stroke prevention and in patients who require long-term VTE prophylaxis and treatment. The prevalence of atrial fibrillation in the United States has been projected to increase from 2 to 5 million in 2000 to 6 to 12 million in 2050 (Special Report, Prevention of Atrial Fibrillation, Report from a National Heart, Lung, and Blood Institute Workshop, *Circulation* 2009; 119:606-618). Therefore, thorough evaluation for hepatotoxicity and long-term safety in the long-term clinical trial is extremely important.

Creatinine and urea abnormalities

In RECORD studies, the incidence of treatment-emergent creatinine and urea abnormalities $>1\times$ ULN was higher in the rivaroxaban group as compared to enoxaparin group in THR trials (10.3% and 8.0% for creatinine, and 9.2% and 7.5% for urea, in rivaroxaban and enoxaparin respectively) as well as TKR trials (12.9% and 11.6% for creatinine, and 9.6% and 7.8% for urea, in rivaroxaban and enoxaparin respectively). There were slightly more reported serious treatment-emergent renal and urinary disorders [13 (0.21%) and 10 (0.16%)] and any treatment-emergent renal and urinary disorders [(5.39%) and 309 (4.98%)] in the rivaroxaban group than in the enoxaparin group. More urinary retention, hematuria, serious acute renal failure, and renal impairment events were reported in the rivaroxaban group than in the enoxaparin group. These raise concerns of possible renal toxicity for rivaroxaban and will require further investigation.

In summary, rivaroxaban increased absolute risk of major bleeding by 0.2% as compared to currently available product (enoxaparin) in patients undergoing THR or TKR surgeries. Rivaroxaban has been associated with fatal bleeding, required more re-operation and blood transfusions in phase 3 trials. In addition, rivaroxaban increased absolute risk of clinical relevant non-major bleeding by 0.5% comparing to current available therapy. It was associated with more macroscopic hematuria, rectal bleeding, nose bleeding >5 minutes, and vaginal bleeding.

There were more ischemic stroke and earlier occurrence of cardiovascular events during the off-treatment period with rivaroxaban than with enoxaparin. This raises concerns of possible rebound effect of rivaroxaban after the treatment withdrawal.

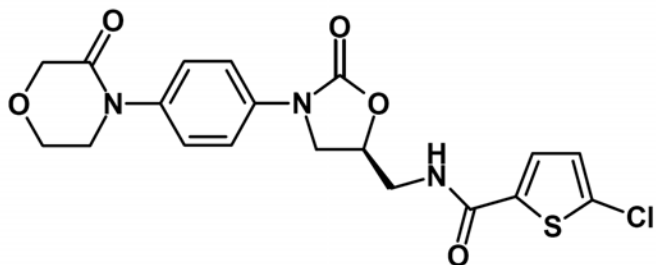
There were more possible related ALT $>3\times$ ULN concurrent with total bilirubin $>2\times$ ULN, more reported serious ALT increased with rivaroxaban than with enoxaparin in phase 3 trials. In addition, 2 subjects with ALT $>3\times$ ULN concurrent with total bilirubin $>2\times$ ULN subsequently died with liver failure in the rivaroxaban group as compared no liver-related deaths in the enoxaparin group in the completed studies, and additional one death with liver failure in ongoing study raise concerns of possible liver toxicity for rivaroxaban. Long-term safety data will be needed to fully evaluate the hepatotoxicity for rivaroxaban. Several long-term studies are ongoing and they should provide sufficient data for evaluation.

There was a higher incidence of creatinine and urea elevations with rivaroxaban than with enoxaparin in phase 3 trials. This raises concerns of possible renal toxicity and will require further investigation.

2 Introduction and Regulatory Background

2.1 Product Information

Rivaroxaban is a selective Factor Xa inhibitor with oral bioavailability. The chemical name of rivaroxaban is: 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide. The structural formula is:



The molecular formula of rivaroxaban is $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.89. Rivaroxaban is a pure (*S*)-enantiomer. It is an odorless, non-hygroscopic, white to yellowish powder.

Drug established name: Rivaroxaban (BAY 59-7939) (JNJ-39039039)

Proposed trade name: Xarelto

Pharmaceutical class: Anti-Factor Xa products

Proposed indication: The proposed indication is for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing:

- hip replacement surgery
- knee replacement surgery.

Proposed Dosage Form, Route of Administration, and Dosing Regimen:

The drug product proposed for marketing is a rivaroxaban 10 mg film coated oral tablet. The tablets are round, light red biconvex film-coated marked with a triangle pointing down above a “10” on one side, and an “Xa” on the other side.

The proposed dose of rivaroxaban is 10 mg taken orally once daily.

The proposed treatment duration is 35 days for patients undergoing hip replacement surgery and 14 days for patients undergoing knee replacement surgery.

2.2 Tables of Currently Available Treatments for Proposed Indications

The currently approved available products for the proposed indications, including populations, main safety concerns, dosage and administrations are shown in the table below.

Currently approved anticoagulants for prophylaxis of DVT or PE in patients undergoing hip or knee surgeries in US

Indications	Approved Products	Populations	Safety	Dosage And administration
Prophylaxis of DVT in patients undergoing hip replacement surgery	Lovenox (enoxaparin sodium)	Adults	Boxed WARNING for Spinal/epidural hematoma	30 mg q12 hrs beginning post-operatively; continue for 7-10 days, up to 14 days; 40 mg q.d. beginning pre-operatively for 7-10 days; may continue for 3 weeks; SC
	Fragmin (dalteparin sodium)	Adults		5000 IU q.d.; may beginning pre-operatively; continue for 5-10 days, up to 14 days; SC
	Arixtra (Fondaparinux sodium)	Adults		2.5 mg administered by subcutaneous injection once daily beginning 6 to 8 hours post-operatively; continuing for 5-9 days
Prophylaxis of DVT in patients undergoing knee replacement surgery	Lovenox (enoxaparin sodium)	Adults		30 mg q12 hrs beginning post-operatively; continuing for 7-10 days, up to 14 days; SC
	Arixtra (Fondaparinux sodium)	Adults		2.5 mg administered by subcutaneous injection once daily beginning 6 to 8 hours post-operatively; continuing for 5-9 days
Prophylaxis of DVT (Non-specific patient population)	Heparin Sodium (unfractionated heparin)	Adults and Pediatrics	WARNINGS for Hemorrhage, Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia Thrombosis (HITT)	5000 U t.i.d or b.i.d beginning pre-operatively; continuing for 7 days; SC
	Argatroban	Adults and Pediatrics with heparin-induced thrombocytopenia.	WARNINGS for Hemorrhage	Initial dose of 2 mcg/kg/min, administered as a continuous infusion
	Coumadin (warfarin Sodium)	Adults	WARNINGS for bleeding risk	Individualized to INR of 2.0-3.0; Oral

Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

This product has not been approved in the U.S. No product containing rivaroxaban is approved in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

Anticoagulants have been associated with risk of hemorrhage. Low molecular weight heparins (Lovenox and Fragmin) and Arixtra have a black boxed warning for spinal or epidural hematomas when neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed. Heparin and low molecular weight heparins have warnings for heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia thrombosis (HITT).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Initial IND (64,892) for Rivaroxaban (BAY 59-7939) for prophylaxis of VTE was submitted on May 29, 2002 by Bayer HealthCare Pharmaceuticals. Two End of Phase 2 meetings were held on July 5, 2005 and November 18, 2005 to discuss the phase 3 clinical programs. All clinical studies including phase 3 studies were conducted under the INDs. Four phase 3 efficacy and safety studies were submitted in December 2005 for special protocol review and subsequently the four protocols were revised as requested by the Division. The Division agreed that the revised study design and planned analysis of studies adequately address the objectives necessary to support a regulatory submission. A Pre-NDA meeting was held between the sponsor and the Agency on (July 20, 2007) to discuss the adequacy of the completed clinical, pre-clinical and chemistry, manufacturing and controls data for submitting a NDA and NDA format.

2.6 Other Relevant Background Information

N/A

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission of this NDA is in eCTD format. There were 17 amendments to the original submission.

The following material in the NDA submission was reviewed:

- NDA 22-406 No. 0000, eCTD format, submitted July 28, 2008
- Amendment No. 0001, General correspondence, submitted on August 11, 2008
- Amendment No. 0003, General correspondence (response to questions), submitted on November 4, 2008
- Amendment No. 0007, 4-month safety update for ongoing clinical studies, submitted on November 25, 2008
- Amendment No. 0009, Response to information request, submitted on December 18, 2008

- Amendment No. 0011, Response to information request, submitted on December 24, 2008
- Amendment No. 0012, Response to information request, submitted on January 6, 2009
- Amendment No. 0013, Response to information request, submitted on January 13, 2009
- Amendment No. 0015, Response to information request, submitted on January 23, 2009
- Amendment No. 0016, Response to information request, submitted on January 23, 2009
- Amendment No. 0020, 6-month Safety Update, submitted on February 2, 2009

Two sites (14029 and 32006) under two different investigators in RECORD 4 study were identified having significant issues in conducting clinical trials. One site (14029) was excluded and another site (32006) was included in the data analysis by the sponsor.

Inspection by the FDA field investigators was requested for eight study sites that showed strong efficacy (two in each of the 4 pivotal studies). The inspection results are currently pending.

3.2 Compliance with Good Clinical Practices

Informed consent was required from patients in all clinical trials. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

3.3 Financial Disclosures

The sponsor certified that there was no financial arrangement with clinical investigators who conducted the clinical studies (Form FDA 3454).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Pending.

4.2 Clinical Microbiology

Pending.

4.3 Preclinical Pharmacology/Toxicology

In a 13-week repeat-dose toxicity studies in mice at oral gavage doses of 50, 100 and 200 mg/kg/day (PEG-6000 co-precipitate), higher incidences of fibrosis of the heart, mononuclear cell infiltration in kidneys, hyperplastic spindle cells in adrenal, increased cellularity of marginal zones of the spleen in males, and high incidences of Kupffer cell foci in the liver of high dose group indicated the liver and kidneys being the target organs of toxicity in both sexes, and additional targets of toxicity in males were adrenal and spleen. A 100 mg/kg/day dose was a

MTD in the study. The plasma exposure was 20 and 29.5 times the exposure produced by the clinical dose in man.

In another 13-week toxicity study, CD-1 mice were fed 1250, 2500 and 5000 ppm of compound in dietary admixture (10% PEG-6000 coprecipitate) and mean drug administered was 237, 476 and 1007 mg/kg/day. A dose dependent increase in coagulation time and, increased liver enzymes activities and incidences of focal renal tubular hypertrophy in males in the highest dose group, and focal necrosis of liver in females in the middle and the highest dose groups was noted. The kidney and liver were the target organs of toxicity in males and females and 5000 ppm in diet appears to be the MTD. The exposure levels (AUC_{0-24h}) at study MTD (high doses) were 31.3 and 43.0 mg.h/L in males and females, i.e., about 7 and 10 times the human exposures at the clinical dose of 60 mg/day (30 mg b.i.d).

In a 4-week oral gavage toxicity study in rats conducted at doses of 0, 12.5, 50 and 200 mg/kg/day, 12% decrease in body weight of high dose males and, treatment related increase in several liver enzyme activities in treated animals. High incidences of bilateral retinal atrophy, focal inflammation of the pancreas and unilateral diffuse tubular dilatation of the testes were suggestive of eyes, pancreas and testes as the target organs of toxicity. A dose between 50 and 200 mg/kg/day was highest tolerable dose and it provides 68 to 162 multiples of human plasma concentration.

In a 13-week oral gavage toxicity study in rats, oral doses of 12.5, 50 and 200 mg/kg/day produced treatment related increase in ALT in high dose treatment group.

The another 13-week oral gavage toxicity study in rats, at oral doses of 12.5, 50 and 200 mg/kg/day and an increased ALT levels (23%) were seen in high dose group animals and these were not completely reversed in recovery group. The incidences of pigment deposition in the pancreas, mesenteric lymph node hemorrhage and focal retinal atrophy in the eye were seen in males and the increased incidences of epicarditis, congestion of lungs, thymic and mesenteric lymph node hemorrhage were seen in females. The high dose (200 mg/kg/day) appeared to be the MTD in this study.

In the 26-week study in rats using administration by gavage, an increase of ALT was seen at the interim clinical-pathological investigation. In all studies, the effect was transient and vanished despite continuation of treatment.

In the 26-week study in rats, birefringent crystals were seen in the urine at 50 mg/kg and above which were shown to consist of rivaroxaban in a separate mechanistic study. It is assumed that rivaroxaban concentrations in the highly concentrated rat urine exceed the maximum rivaroxaban solubility resulting in precipitation of unchanged drug. Morphological investigation of the kidneys and the lower urinary tract, did not reveal any irritative effects deriving thereof.

Pharmacology/Toxicology review is pending.

4.4 Clinical Pharmacology

4.2.1 Mechanism of Action

Rivaroxaban inhibits Factor Xa in the coagulation cascade that would therefore be hypothesized to inhibit coagulation and thrombus formation.

4.2.2 Pharmacodynamics

Dose-dependent inhibition of FXa activity was observed in humans and the prothrombin time, activated partial thromboplastin time and HepTest® are prolonged dose-dependently. The relationship between prothrombin time and rivaroxaban plasma concentration is linear and closely correlated. In accordance with the pharmacokinetics, prolongation of the prothrombin time using the Neoplastin® assay reached half of the maximum effect within 0.5-1 hours and maximum effect within 2-4 hours after administration of a tablet. The offset of pharmacodynamic effect also closely parallels the pharmacokinetic half-life.

Clinical pharmacology review is pending.

4.2.3 Pharmacokinetics

Rivaroxaban was readily absorbed after oral administration of the immediate-release tablet, with peak plasma concentrations approximately 2 to 4 hours after dosing. Rivaroxaban is highly bound to plasma proteins at approximately 92% to 95%, with serum albumin being the main binding component. Due to its high plasma protein binding rivaroxaban is not expected to be dialyzable.

Excretion of rivaroxaban and metabolites occurred via both renal and fecal routes. Of the administered rivaroxaban dose, approximately two thirds underwent metabolic degradation, with half eliminated renally and the other half eliminated by the fecal route. The final one third of the administered dose underwent direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Major metabolic pathways include oxidative degradation (hydroxylation followed by ring cleavage) and hydrolysis (with subsequent conjugation). In addition to unchanged rivaroxaban, one main metabolite, which does not possess any anticoagulant activity, was identified in excreta. Unchanged rivaroxaban was the most important compound in human plasma with no major or active circulating metabolites being present. Cytochrome P-450 (CYP) 3A4/3A5 accounts for approximately 18% and CYP2J2 for approximately 14% of total rivaroxaban elimination, respectively. The terminal half-life of rivaroxaban is approximately 5 – 9 hours in young male healthy subjects, and 11-13 hours in the healthy elderly.

Seventeen drug-drug interaction studies were conducted. The results of those studies showed that strong inhibitors of both metabolism (i.e., CYP3A4) and active secretion (i.e., P-glycoprotein [P-gp] and breast cancer resistance protein [Bcrp]) may result in a clinically relevant increased systemic exposure of rivaroxaban.

In healthy elderly subjects (65-80 years of age) higher mean AUC values by 52% in males and by 39% in females were observed when compared to young subjects of the same sex. This was accompanied by an increase in C_{max} by 35% in both sexes and by terminal half-lives between 11 and 13 h. The study in subjects older than 75 years confirmed these results, showing approximately 41% higher AUC values in comparison to young subjects, which was mainly due to reduced (apparent) total body clearance and renal clearance. No relevant age effects could be observed for C_{max} (8% increase in elderly) or time to reach the maximum plasma concentration (t_{max}).

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 (C_{max} and AUC) were increased and 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). In addition, the increased overall plasma concentrations were associated with an increased sensitivity of prothrombin time prolongation. No clinical data are available for patients with kidney failure (creatinine clearance <15 mL/min).

Cirrhotic subjects with mild liver impairment (Child-Pugh Grade A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase for AUC on average) and pharmacodynamics, which were comparable to their matched healthy control group. In cirrhotic subjects with moderate hepatic impairment (Child-Pugh Grade B- all with baseline prothrombin time prolongations), 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. Cirrhotic subjects with severe hepatic impairment (Child Pugh Grade C) were not studied.

Clinical pharmacology review is pending.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The following tables list the completed and ongoing studies in the rivaroxaban development program. All completed studies were short-term studies. Among those studies over 10,000 patients were exposed to rivaroxaban treatment. These included 4 RECORD phase 3 studies in patients undergoing hip or knee replacement surgeries, 9 phase 2 studies, and about 50 phase 1 studies.

Among the ongoing studies, 4 are long-term phase 3 studies including 2 in patients with atrial fibrillation for prevention of stroke and 2 in patients with symptomatic VTE for prevention of recurrent VTE. These 4 studies planned to enroll about 22,000 patients.

Completed Clinical 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 3: VTE Prevention				
RECORD 1 (11354)	10 mg od	Enox 40 od	4433/2209	35,36±4 days ^l
RECORD 2 (11357)	10 mg od	Enox 40 od	2457/1228	35±4, 13±24 days ^b
RECORD 3 (11356)	10 mg od	Enox 40 od	2459/1220	12, 13±2 days ^l
RECORD 4 (11355)	10 mg od	Enox 30 bid	3034/1526	12±2 days
Total			12,383/6,183	
Phase 2: VTE Prevention				
10942	2.5, 5, 10, 20, and 30 mg bid; 30 mg od	Enox 40 od	625/463	8, 9±2 days ^b
10944	2.5, 5, 10, 20, and 30 mg bid	Enox 40 od	704/572 ^c	8, 9±2 days ^b
10945	2.5, 5, 10, 20, and 30 mg bid	Enox 30 bid	613/509	8±2 days
11527	5, 10, 20, 30, and 40 mg od	Enox 40 od	845/688 ^d	8, 9±2 days ^b
Total			2787/2232	
Phase 2: VTE Treatment				
11223	10, 20 and 30 mg bid; 40 mg od	Enox/VKA	604/478	12 weeks
11528	20, 30, and 40 mg od	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 od	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				
51 Studies	Variable ^e	Variable ^e	1298/1117	≤10 days ^e
Grand Total			17,852/10,600	

^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 (Figure 11-1, Study 11527 [MRR-00174])

^e The majority of Phase 1 clinical pharmacology studies were uncontrolled or of a crossover design. Fifteen of 51 studies used a concurrent placebo group. More than 80% of subjects exposed to rivaroxaban received study drug for 1 day only.

Key: RIVA = rivaroxaban; od = once daily; bid = twice a day; Enox = Enoxaparin ; 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

Table 1: Overview of Ongoing Clinical Studies in Patients

Study Details Phase / Study Number	Rivaroxaban Total Daily Dose(s)	Comparator	All Subjects in Safety Population (N/total planned enrollment)	Scheduled Treatment duration
Phase 3: EINSTEIN DVT/PE ^a (11702)	30 mg for 3 weeks; then 20 mg	Enoxaparin/ VKA	3358/6200+	3, 6 or 12 months
EINSTEIN Extension (11899)	20 mg	Placebo	840/1300+	6 or 12 months
ROCKET-AF (11630)	20 mg 15 mg ^b	Warfarin	11018/14000+	Chronic (up to 4 years)
J-ROCKET-AF (12620) Japan	15 mg 10 mg ^c	Warfarin	1184/1200*	Chronic (up to 2.5 years)
MAGELLAN (12839)	10 mg	Enoxaparin/ Placebo	987/~8000+	35 days
ATLAS ACS 2 TIMI 51 (13194)	5 and 10 mg	Placebo	5/13500+	Chronic (up to 2.5 years)
Phase 2 ATLAS ACS TIMI 46 (11898)	5, 10, 15 and 20 mg	Placebo	3462/3500+	6 months
Phase 1 CHF (12980)	10 mg	Placebo or Enoxaparin	21/36+	6 days
Grand Total			20,875/47,736	

Key: CHF = congestive heart failure.

^a For the purpose of this ISS, the 2 studies (EINSTEIN-DVT and EINSTEIN-PE) are presented together.

^b In ROCKET-AF, subjects with moderate renal impairment on entry to the study received 15 mg rivaroxaban.

^c In J-ROCKET-AF, subjects with moderate renal impairment on entry to the study received 10 mg rivaroxaban.

Note: Safety data from these 9 ongoing studies are presented as of last subject visit cutoff date of either 31 October 2008 or 5 December 2008.

Source: Study 11898, Table 1.1; Study 11702, Table 1; Study 11899, Table 1;

Study 11630, Table 1.1.1; Study 12620, Table 1.1.1; Study 12839, Table 1, and Study 12980, Table 1.

+ As of cutoff date of 5 December 2008. For ATLAS ACS TIMI 46, the database was locked 18 October 2008.

* As of cutoff date of 31 October 2008.

5.2 Review Strategy

Four RECORD phase 3 studies were reviewed for efficacy for the proposed indications. These four trials were reviewed separately in the same depth. These four trials and other completed and ongoing trials were reviewed for safety.

5.3 Discussion of Individual Studies

RECORD Studies

Four RECORD studies (RECORD 1, 2, 3 and 4) were conducted to support the proposed indication for Rivaroxaban. All 4 trials were randomized, double-blind, double-dummy, active-controlled studies that evaluated the efficacy and safety of oral rivaroxaban. RECORD 1 and 2

studies were in patients undergoing hip replacement surgery (THR) and RECORD 3 and studies were in patients undergoing knee replacement surgery (TKR).

In all 4 RECORD trials, Rivaroxaban was administered at a dose of 10 mg once daily at least 6 to 8 hours after surgery (wound closure) for the prevention of DVT and PE after elective THR or TKR surgery.

Subcutaneous enoxaparin was chosen as the active comparator in all 4 RECORD studies. The enoxaparin dosing regimen in RECORD 1 (11354), RECORD 2 (11357) and RECORD 3 (11356) was 40 mg once daily starting 12 hours preoperatively. The enoxaparin regimen in RECORD 4 (11355) was 30 mg twice daily starting 12 to 24 hours postoperatively. It should be noted that the enoxaparin dose regimen (40 mg once daily) in RECORD 3 study is not an approved dose regimen of enoxaparin for the prophylaxis of DVT in patients undergoing TKR surgery in United States.

The durations of active treatment for rivaroxaban and enoxaparin were similar in each of the RECORD studies with the exception of RECORD 2, in which treatment duration of Rivaroxaban was much longer than enoxaparin control (35 days rivaroxaban versus 13 days enoxaparin).

The following table shows the study design, treatment and duration, number of patients in each of the RECORD trials.

Study design, dose regimen and treatment duration in RECORD studies

Study Identifier, Location of Study Reports, Study Dates (FPV-LPV)*	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Total and Per Dose (Safety Population)	Population	Scheduled Duration of Active Treatment	Top 3 Enrolling Countries
RECORD 1 11354 (MRR-00233) February 2006 to March 2007	Randomized, double-blind, double-dummy, active control	Rivaroxaban oral: 10 mg od Enoxaparin SC: 40 mg od	4433 treated 2209 2224	Total hip replacement	Rivaroxaban 10 mg od: 35 ± 4 days Enoxaparin 40 mg od: 36 ± 4 days	Poland Germany Austria
RECORD 2 11357 (MRR-00234) February 2006 to June 2007	Randomized, double-blind, double-dummy, active control	Rivaroxaban oral: 10 mg od Enoxaparin SC: 40 mg od	2457 treated 1228 1229	Total hip replacement	Rivaroxaban 10 mg od: 35 ± 4 days Enoxaparin 40 mg od: 13 ± 2 days	China Sweden United Kingdom
RECORD 3 11356 (MRR-00218) February 2006 to January 2007	Randomized, double-blind, double-dummy, active control	Rivaroxaban oral: 10 mg od Enoxaparin SC: 40 mg od	2459 treated 1220 1239	Total knee replacement	Rivaroxaban 10 mg od: 12 ± 2 days Enoxaparin 40 mg od: 13 ± 2 days	Spain Poland Germany
RECORD 4 11355 (MRR-A41857) June 2006 to January 2008	Randomized, double-blind, double-dummy, active control	Rivaroxaban oral: 10 mg od Enoxaparin SC: 30 mg bid	3034 treated 1526 1508	Total knee replacement	Rivaroxaban 10 mg od: 12 ± 2 days Enoxaparin 30 mg bid: 12 ± 2 days	United States India Canada

*FPV = First patient visit; LPV = Last patient visit.

Active treatment = pharmacologically active study drug (not dummy placebo)

Key: bid = twice daily; od = once daily; SC = subcutaneous

Sponsor's table

Four RECORD studies used the same inclusion and exclusion criteria except few indicated below.

Inclusion criteria

- Men and women aged ≥ 18 years.
- Subjects scheduled for elective total hip replacement (RECORD 1 and 2) or total knee replacement surgery (RECORD 3-4).
- Subjects giving written informed consent for participation after receiving detailed written and oral information prior to any study specific procedures.

Exclusion criteria

- Planned, staged total bilateral hip replacement (RECORD 1 and 2 only).
- Active bleeding or high risk of bleeding contraindicating treatment with low molecular-weight heparin.

- Significant liver disease (eg acute clinical hepatitis, chronic active hepatitis, cirrhosis) (*modified in Amendment 1*).
- Contraindication listed in the labeling or conditions precluding subject treatment with enoxaparin requiring dose adjustment (e.g. severe renal impairment; refer to the local label of enoxaparin of the respective country) (*modified in Amendment 1*).
- Conditions prohibiting bilateral venography (amputation of 1 leg, allergy to contrast media).
- Pregnant and breast-feeding women. Women with child-bearing potential not using adequate birth control method. (Note: as adequate method of birth control oral contraception was recommended. If oral contraception was not feasible both partners were to use adequate barrier birth control).
- Drug or alcohol abuse.
- Concomitant use of HIV-protease inhibitors or fibrinolytics.
- Therapy with another investigational product within 30 days prior start of study.
- Planned intermittent pneumatic compression during active treatment period.
- Concomitant participation in another trial or study.
- Ongoing oral anticoagulant therapy that could not be stopped in the opinion of the investigator.
- Treatment with strong inhibitors of cytochrome P450 3A4, such as ketoconazole or protease inhibitors, within 4 days before randomization, or planned treatment during the time period of the study (modified text per Amendment 1) (RECORD 4 only)

All four studies used the same primary and secondary efficacy endpoints as specified below.

The primary efficacy endpoint was a composite endpoint of

- Any deep vein thrombosis (DVT) (proximal and/or distal)
- Non-fatal pulmonary embolism (PE)
- Death from all causes.

The pre-specified secondary efficacy endpoints were:

- Major VTE (proximal DVT, non-fatal PE, VTE-related death) as main secondary endpoint.
- Incidence of DVT (total, proximal, distal).
- Incidence of symptomatic VTE (DVT, PE).
- Incidence of symptomatic VTE during follow-up (i.e., after the end of the time window for primary efficacy assessment).
- “Net clinical benefit” assessed by the composite endpoint comprising major VTE and treatment-emergent major bleeding.
- Incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death (composite of any DVT and non-fatal PE and VTE-related death).
- Incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death (composite of proximal DVT and non-fatal PE and death from all causes).

Asymptomatic DVT was assessed by bilateral venography at the end of study treatment. In case of a suspected symptomatic DVT, an ultrasound was to be performed first. If a DVT was confirmed by ultrasound, a venography has to be performed. If symptoms of PE occur, pulmonary angiography or a perfusion/Ventilation lung scintigraphy combined with chest radiography or spiral CT were performed. The analysis of the primary efficacy endpoint and all secondary efficacy endpoints related to VTE was based solely on the assessments made by the Independent Central Adjudication Committee (ICAC) and VTE Adjudication Committees (AC/VTE).

The efficacy of rivaroxaban was to be assessed in 2 steps. First, a non-inferiority test as described below was to be performed based on the per protocol population. If non-inferiority was shown, a superiority test was performed subsequently based on the modified intent to treat (MITT) population.

RECORD 2 and 3 were designed as superiority trials and a superiority test was performed based on the MITT population.

MITT population included study patients who received at least one dose of study medication, underwent the appropriate surgery, and had an adequate assessment of VTE.

The safety assessment was the same in all 4 RECORD studies.

The primary safety endpoint in each study was the incidence of treatment-emergent major bleeding observed not later than 2 days after the last administration of study drug. Major bleeding events were defined as:

- Fatal bleeding
- Bleeding into critical organ (e.g., retroperitoneal, intracranial, intraocular or intraspinal bleeding/hemorrhagic puncture)
- Bleeding requiring reoperation
- Clinically overt extra-surgical site bleeding associated with ≥ 2 g/dL fall in hemoglobin
- Clinically overt extra-surgical site bleeding leading to infusion of equal or more than 2 units of whole blood or packed cells

Any bleeding and non-major clinical relevant bleedings were also assessed in each study. Non-major clinically relevant bleeding events were defined in the protocol as:

- Multiple source bleeding
- Spontaneous hematoma >25 cm²
- 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

Other interested adverse events included cardiovascular events and hepatic events.

Liver function tests (LFTs) were monitored at Days 1, 6, 13, 36 (RECORD 1 and 2 only), 42 (RECORD 3 and 4 only), and 65 (RECORD 1 and 2 only).

Safety analysis was based on safety population that included study patients who received at least one dose of study medication.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing:

- hip replacement surgery
- knee replacement surgery.

6.2.1 Methods

Four randomized controlled pivotal trials were reviewed for efficacy for the proposed indications. These included two studies (RECORD 1 and 2) in patients undergoing total hip replacement surgery (THR) and two studies (RECORD 3 and 4) in patients undergoing total knee replacement surgery (TKR). All four clinical studies were randomized, double-blind, double-dummy, active-controlled studies. Enoxaparin was used as active control treatment for all studies. Two trials (RECORD 2 and 3) were designed as superiority trials and two trials (RECORD 1 and 4) were designed as non-inferiority trials.

In all 4 RECORD trials, Rivaroxaban was administered at a dose of 10 mg once daily at least 6 to 8 hours after surgery (wound closure) after elective THR or TKR surgery. The treatment duration of Rivaroxaban was 35 days for patients undergoing THR and 12 days for patients undergoing TKR.

The enoxaparin dosing regimen in RECORD 1 (11354), RECORD 2 (11357) and RECORD 3 (11356) was 40 mg once daily starting 12 hours preoperatively. The enoxaparin regimen in RECORD 4 (11355) was 30 mg twice daily starting 12 to 24 hours postoperatively. It should be noted that enoxaparin dose regimen (40 mg once daily) in RECORD 3 study is not an approved dose regimen of enoxaparin for the prophylaxis of DVT in patients undergoing TKR surgery in United States.

It should be noted that the treatment duration was much longer in the rivaroxaban group (35 days) as compared to enoxaparin control (12 days) in RECORD 2 study.

The following table shows the number of randomized patients in each trial.

Number of randomized patients and treatment duration in RECORD studies

Studies	Rivaroxaban 10 mg OD	Enoxaparin 40 mg OD/30 mg BID
THR (Study treatment for 35 days)		
RECORD 1	2266	2275
RECORD 2	1252	1257 (Enoxaparin for 12 days followed by placebo for 23 days)
TKR (Study treatment for 12 days)		
RECORD 3	1254	1277 (40mg QD-unapproved dose regimen)
RECORD 4	1584	1564
Total	6356	6373

Reviewer's table

6.2.2 Demographics and baseline characteristics

The following table shows the demographic characteristics of study patients in RECORD studies. There were more females (60%) than males (40%). The mean age was 64 years with about one half of study patients over 65 years. The majority of study patients were Caucasians with 10% of Asians and 10% of other races.

	THR RECORD 1-2 (N=6890)	TKR RECORD 3-4 (N=5493)	Total (N=12383)
Gender			
Male	3110 (45%)	1841 (34%)	4951 (40%)
Female	3780 (55%)	3652 (66%)	7432 (60%)
Age (years)	62.6 ±12.2	65.9 ±9.5	64.1 ±11.2
Age			
<65 yrs	3532 (51%)	2288 (42%)	5820 (47%)
65-75 yrs	2460 (36%)	2275 (41%)	4735 (38%)
>75 yrs	898 (14%)	930 (17%)	1828 (15%)
Race			

White	5687 (83%)	4037 (73%)	9724 (79%)
Black	103 (1%)	181 (3%)	284 (2%)
Asian	498 (7%)	736 (13%)	1234 (10%)
Hispanic	329 (5%)	353 (6%)	682 (6%)
Other or missing	273 (4%)	186 (4%)	459 (4%)

6.2.3 Patient Disposition

The following table shows the patient disposition in RECORD 1 and 2 studies in patients undergoing total hip replacement surgery. More than 87% of patients completed the study and 11-13% of patients had premature termination. The main reasons for premature termination were consent withdrawal (4-5%) and adverse events (4%). The distribution of patient disposition was similar between the rivaroxaban and enoxaparin treatment groups.

Patient Disposition in THR Trials

	RECORD 1		RECORD 2	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Randomized	2266	2275	1252	1257
Completed	2010 (88.7%)	2011 (88.4%)	1117 (89.2%)	1092 (86.9%)
Premature termination	256 (11.3%)	264 (11.6%)	135 (10.8%)	165 (13.1%)
-AE	82 (3.6%)	92 (4.0%)	44 (3.5%)	54 (4.3%)
-Consent withdrawn	121 (5.3%)	115 (5.1%)	51 (4.1%)	51 (4.1%)

The following table shows the patient disposition in RECORD 3 and 4 studies in patients undergoing total knee replacement surgery. More than 88% of patients completed the study and 10-12% of patients had premature termination. The main reasons for premature termination were consent withdrawal (3-5%) and adverse events (3-4%). The distribution of patient disposition was similar between the rivaroxaban and enoxaparin treatment groups.

Patient Disposition in TKR Trials

	RECORD 3		RECORD 4	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Randomized	1254	1277	1584	1564

Completed	1127 (89.9%)	1122 (87.9%)	1425 (90.0%)	1413 (90.4%)
Premature termination	127 (10.1%)	155 (12.1%)	159 (10.0%)	151 (9.6%)
-AE	36 (2.9%)	42 (3.3%)	62 (3.9%)	56 (3.6%)
-Consent withdrawn	68 (5.4%)	60 (4.7%)	49 (3.1%)	47 (3.0%)

The following table shows the study patients who were included in the MITT population for the primary efficacy analysis. Overall, about one third of randomized patients were excluded from the MITT population in RECORD studies with the highest in RECORD 4 study (39%).

Patients were included in the MITT Population

Studies	Rivaroxaban 10 mg OD	Enoxaparin 40 mg OD/30 mg BID
THR		
RECORD 1	1595 (70%)	1558 (69%)
RECORD 2	864 (69%)	869 (69%)
TKR		
RECORD 3	824 (66%)	878 (69%)
RECORD 4	965 (61%)	959 (61%)
Total	4248 (67%)	4264 (67%)

The reasons for exclusion from the MITT population in RECORD 1 and 2 in patients undergoing THR are shown below. The majority of excluded patients had no adequate assessment of DVT due to venography not done (50%), unilateral venography (17%), and venography too early or late (3-7%). These were similar between the two treatment groups.

Reasons for Excluded from MITT population in THR Trials

	RECORD 1		RECORD 2	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Excluded from MITT pop.	671 (30%)	711 (32%)	388 (31%)	388 (31%)
No surgery	17 (1%)	21 (1%)	16 (1%)	22 (2%)
No treatment	57 (3%)	51 (2%)	24 (2%)	28 (2%)
No adequate assessment	588 (26%)	635 (28%)	348 (28%)	338 (27%)

-Venography not done	319 (54%)	322 (51%)	155 (45%)	159 (47%)
-Unilateral venography	105 (18%)	105 (17%)	57 (16%)	57 (17%)
-Unevaluable venography	121 (21%)	164 (26%)	127 (37%)	111 (33%)
-Venography too early/late	43 (7%)	44 (7%)	9 (3%)	11 (3%)

The reasons for exclusion from the MITT population in RECORD 3 and 4 in patients undergoing TKR are shown below. The reasons were similar to RECORD 1 and 2 studies with more patients who had no adequate assessment of DVT in RECORD 4 study (35%) mostly due to unevaluable venography.

Reasons for Excluded from MITT population in TKR Trials

	RECORD 3		RECORD 4	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Excluded from MITT pop.	430 (34%)	399 (31%)	619 (39%)	605 (39%)
No surgery	20 (2%)	22 (2%)	2 (<1%)	3 (<1%)
No treatment	34 (3%)	38 (3%)	58 (4%)	56 (4%)
No adequate assessment	376 (30%)	339 (27%)	559 (35%)	546 (35%)
-Venography not done	156 (41.5%)	166 (49.0%)	189 (34%)	184 (34%)
-Unilateral venography	82 (21.8%)	69 (20.4%)	116 (21%)	105 (19%)
-Unevaluable venography	131 (34.8%)	96 (28.3%)	244 (44%)	253 (46%)
-Venography too early/late	7 (1.9%)	8 (2.3%)	10 (2%)	4 (<1%)

The main reasons for venography not done were failed venipuncture, subject refused venography and premature termination in each study (see Tables below). The reasons were similar between the two treatment groups.

Reasons for Venography Not Done in THR Trials

	RECORD 1		RECORD 2	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Venography not done	319 (54%)	322 (51%)	155 (45%)	159 (47%)
-Failed venipuncture	60 (10.2%)	65 (10.2%)	37 (10.6%)	28 (8.3)
-Subject refused venography	73 (12.4%)	64 (10.1%)	13 (3.7%)	8 (2.4%)

-Premature termination	147 (25.0%)	165 (26.0%)	85 (24.4%)	93 (27.5%)
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Reasons for Venography Not Done in TKR Trials

	RECORD 3		RECORD 4	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Venography not done	156 (41.5%)	166 (49.0%)	189 (34%)	184 (34%)
-Failed venipuncture	38 (10.1%)	43 (12.7%)	68 (12.2%)	65 (11.9%)
-Subject refused venography	32 (8.5%)	30 (8.8%)	34 (6.1%)	34 (6.2%)
-Premature termination	59 (15.7%)	67 (19.8%)	70 (12.5%)	60 (11.0%)

The following tables show the demographics in MITT population in each RECORD study by study treatment. There were similar demographical distributions between the two treatment groups in each study.

Demographics in MITT population in RECORD 1 study

Demographic variable	Rivaroxaban 10 mg od (n=1595) n (%)	Enoxaparin 40 mg od (n=1558) n (%)	Total (n=3153) n (%)
Sex, n (%)			
Male	745 (46.7)	710 (45.6)	1455 (46.1)
Female	850 (53.3)	848 (54.4)	1698 (53.9)
Race, n (%)			
Missing	74 (4.6)	73 (4.7)	147 (4.7)
White	1491 (93.5)	1452 (93.2)	2943 (93.3)
Black	11 (0.7)	13 (0.8)	24 (0.8)
Asian	2 (0.1)	2 (0.1)	4 (0.1)
American Indian	1 (<0.1)	0 (0.0)	1 (<0.1)
Hispanic	12 (0.8)	11 (0.7)	23 (0.7)
Uncodable	4 (0.3)	7 (0.4)	11 (0.3)
Age (years)			
Missing	0	0	0
Mean \pm SD	62.4 \pm 11.4	63.1 \pm 11.1	62.7 \pm 11.2
Range	18.0 – 91.0	20.0 – 89.0	18.0 – 91.0
Age (categorized)			
18 to 40 years	72 (4.5)	54 (3.5)	126 (4.0)
>40 to <65 years	776 (48.7)	743 (47.7)	1519 (48.2)
65 to 75 years	579 (36.3)	569 (36.5)	1148 (36.4)
>75 years	168 (10.5)	192 (12.3)	360 (11.4)
Weight (kg)			
Missing	1	2	3
Mean \pm SD	78.2 \pm 15.8	78.1 \pm 15.6	78.2 \pm 15.7
Range	37.0 – 158.8	40.0 – 130.0	37.0 – 158.8
Weight (categorized), n (%)			
Missing	1 (<0.1)	2 (0.1)	3 (<0.1)
≤ 50 kg	36 (2.3)	39 (2.5)	75 (2.4)
>50 to 70 kg	506 (31.7)	482 (30.9)	988 (31.3)
>70 to 90 kg	726 (45.5)	716 (46.0)	1442 (45.7)
>90 to 110 kg	280 (17.6)	278 (17.8)	558 (17.7)
>110 kg	46 (2.9)	41 (2.6)	87 (2.8)
BMI (kg/m ²)			
Missing	4	3	7
Mean \pm SD	27.8 \pm 4.6	27.7 \pm 4.6	27.7 \pm 4.6
Range	16.2 – 53.4	15.2 – 50.2	15.2 – 53.4
BMI (categorized), n (%)			
Missing	4 (0.3)	3 (0.2)	7 (0.2)
<18.5 kg/m ²	13 (0.8)	19 (1.2)	32 (1.0)
18.5 to <25 kg/m ²	427 (26.8)	430 (27.6)	857 (27.2)
25 to <30 kg/m ²	694 (43.5)	676 (43.4)	1370 (43.5)
30 to <40 kg/m ²	431 (27.0)	417 (26.8)	848 (26.9)
≥ 40 kg/m ²	26 (1.6)	13 (0.8)	39 (1.2)
Current alcohol consumption, n (%)			
Missing	7 (0.4)	4 (0.3)	11 (0.3)
Abstinent	630 (39.5)	683 (43.8)	1313 (41.6)
Light alcohol consumption	836 (52.4)	730 (46.9)	1566 (49.7)
Moderate alcohol consumption	122 (7.7)	138 (8.9)	260 (8.3)
Heavy alcohol consumption	0 (0.0)	3 (0.2)	3 (0.1)

Abbreviations: BMI=body mass index; MITT=modified intent-to-treat; od=once daily; SD=standard deviation

Demographics in MITT population in RECORD 2 study

Demographic variable	Rivaroxaban 10 mg od (N=864) n (%)	Enoxaparin 40 mg od (N=869) n (%)	Total (N=1733) n (%)
Sex, n (%)			
Male	409 (47)	415 (48)	824 (48)
Female	455 (53)	454 (52)	909 (52)
Race, n (%)			
White	564 (65)	543 (62)	1107 (64)
Black	18 (2)	16 (2)	34 (2)
Asian	177 (20)	182 (21)	359 (21)
American Indian	1 (<1)	1 (<1)	2 (<1)
Hispanic	96 (11)	116 (13)	212 (12)
Uncodable	8 (1)	11 (1)	19 (1)
Age (years)			
Missing	0	0	0
Mean \pm SD	61.2 \pm 12.9	61.0 \pm 13.7	61.1 \pm 13.3
Range	19.0 – 91.0	20.0 – 93.0	19.0 – 93.0
Age (categorized)			
18 to 40 years	63 (7.3)	79 (9.1)	142 (8.2)
>40 to <65 years	407 (47.1)	401 (46.1)	808 (46.6)
65 to 75 years	302 (35.0)	285 (32.8)	587 (33.9)
>75 years	92 (10.7)	104 (12.0)	196 (11.3)
Weight (kg)			
Missing	0	0	0
Mean \pm SD	74.3 \pm 15.3	74.3 \pm 16.9	74.3 \pm 16.1
Range	41.0 – 140.0	33.2 – 151.0	33.2 – 151.0
Weight (categorized), n (%)			
\leq 50 kg	40 (4.6)	55 (6.3)	95 (5.5)
>50 to 70 kg	361 (41.8)	346 (39.8)	707 (40.8)
>70 to 90 kg	333 (38.5)	336 (38.7)	669 (38.6)
>90 to 110 kg	121 (14.0)	107 (12.3)	228 (13.2)
>110 kg	9 (1.0)	25 (2.9)	34 (2.0)
BMI (kg/m ²)			
Missing	0	1	1
Mean \pm SD	26.6 \pm 4.5	26.7 \pm 4.9	26.7 \pm 4.7
Range	15.6 – 50.9	15.5 – 59.0	15.5 – 59.0
BMI (categorized), n (%)			
Missing	0 (0.0)	1 (0.1)	1 (0.1)
<18.5 kg/m ²	11 (1.3)	23 (2.7)	34 (2.0)
18.5 to <25 kg/m ²	322 (37.3)	320 (36.8)	642 (37.1)
25 to <30 kg/m ²	362 (41.9)	329 (37.9)	691 (39.9)
30 to <40 kg/m ²	160 (18.5)	185 (21.3)	345 (19.9)
\geq 40 kg/m ²	9 (1.0)	11 (1.3)	20 (1.2)
Current alcohol consumption, n (%)			
Missing	0 (0.0)	1 (0.1)	1 (0.1)
Abstinent	393 (45.5)	399 (45.9)	792 (45.7)
Light alcohol consumption	393 (45.5)	372 (42.8)	765 (44.1)
Moderate alcohol consumption	77 (8.9)	96 (11.1)	173 (10.0)
Heavy alcohol consumption	1 (0.1)	1 (0.1)	2 (0.1)

Abbreviations: BMI=body mass index; MITT=modified intent-to-treat; od=once daily; SD=standard deviation

Demographics in MITT population in RECORD 3 study

Demographic variable	Rivaroxaban 10 mg od (N=824)	Enoxaparin 40 mg od (N=878)	Total (N=1702)
Sex, n (%)			
Male	259 (31.4)	314 (35.8)	573 (33.7)
Female	565 (68.6)	564 (64.2)	1129 (66.3)
Race, n (%)			
Missing	41 (5.0)	50 (5.7)	91 (5.4)
White	675 (81.9)	668 (78.4)	1363 (80.1)
Black	8 (1.0)	8 (0.9)	16 (0.9)
Asian	64 (7.8)	68 (7.7)	132 (7.8)
Hispanic	33 (4.0)	48 (5.5)	81 (4.8)
Uncodable	3 (0.4)	16 (1.8)	19 (1.1)
Age (yr)			
Mean \pm SD	67.4 \pm 9.0	67.2 \pm 8.6	67.6 \pm 9.0
Range	28 – 87	30 – 87	28 – 87
Age (categorized)			
18 to 40 yr	4 (0.5)	1 (0.1)	5 (0.3)
> 40 to < 65 yr	282 (34.2)	318 (36.2)	600 (35.3)
65 to 75 yr	365 (44.3)	402 (45.8)	767 (45.1)
> 75 yr	173 (21.0)	157 (17.9)	330 (19.4)
Weight (kg)			
N	823	877	1700
Missing	1	1	2
Mean \pm SD	80.0 \pm 14.8	81.0 \pm 15.0	80.5 \pm 14.9
Range	46 – 150	48 – 150	46 – 150
Weight (categorized), n (%)			
Missing	1 (0.1)	1 (0.1)	2 (0.1)
\leq 50 kg	11 (1.3)	6 (0.7)	17 (1.0)
> 50 to 70 kg	237 (28.8)	220 (25.1)	457 (26.9)
> 70 to 90 kg	388 (47.1)	437 (49.8)	825 (48.5)
> 90 to 110 kg	163 (19.8)	180 (20.5)	343 (20.2)
> 110 kg	24 (2.9)	34 (3.9)	58 (3.4)
BMI (kg/m ²)			
N	823	877	1700
Missing	1	1	2
Mean \pm SD	29.3 \pm 4.8	29.7 \pm 4.8	29.5 \pm 4.8
Range	16.9 – 48.4	17.7 – 53.3	16.9 – 53.3
BMI (categorized), n (%)			
Missing	1 (0.1)	1 (0.1)	2 (0.1)
< 18.5 kg/m ²	4 (0.5)	1 (0.1)	5 (0.3)
18.5 to < 25 kg/m ²	133 (16.1)	121 (13.8)	254 (14.9)
25 to < 30 kg/m ²	359 (43.6)	400 (45.6)	759 (44.6)
30 to < 40 kg/m ²	307 (37.3)	325 (37.0)	632 (37.1)
\geq 40 kg/m ²	20 (2.4)	30 (3.4)	50 (2.9)

Abbreviations: BMI=body mass index; MITT=modified intent to treat; od=once daily; SD=standard deviation; and yr=year

Demographics in MITT population in RECORD 4 study

Demographic variable	Rivaroxaban 10 mg od (N=965)	Enoxaparin 30 mg bld (N=959)	Total (N=1924)
Sex, n (%)			
Male	343 (35.5)	353 (36.8)	696 (36.2)
Female	622 (64.5)	606 (63.2)	1228 (63.8)
Race, n (%)			
Missing	1 (0.1)	0	1 (<0.1)
White	671 (69.5)	683 (71.2)	1354 (70.4)
Black	48 (5.0)	42 (4.4)	90 (4.7)
Asian	156 (16.2)	149 (15.5)	305 (15.8)
American Indian	0	4 (0.4)	4 (0.2)
Hispanic	88 (9.1)	80 (8.3)	168 (8.7)
Uncodable	1 (0.1)	1 (0.1)	2 (0.1)
Age (yr)			
Mean \pm SD	64.4 \pm 9.9	64.6 \pm 9.7	64.5 \pm 9.8
Range	21 – 87	24 – 89	21 – 89
Age (categorized)			
18 to 40 yr	12 (1.2)	10 (1.0)	22 (1.1)
> 40 to < 65 yr	465 (48.2)	435 (45.4)	900 (46.8)
65 to 75 yr	338 (35.0)	390 (40.7)	728 (37.8)
> 75 yr	150 (15.5)	124 (12.9)	274 (14.2)
Weight (kg)			
N	965	959	1924
Missing	0	0	0
Mean \pm SD	84.5 \pm 19.8	85.0 \pm 20.5	84.7 \pm 20.1
Range	41 – 163.3	35 – 171.5	35 – 171.5
Weight (categorized), n (%)			
Missing	0	0	0
\leq 50 kg	13 (1.4)	19 (2.0)	32 (1.7)
> 50 to 70 kg	235 (24.4)	218 (22.7)	453 (23.5)
> 70 to 90 kg	386 (40.0)	385 (40.2)	771 (40.1)
> 90 to 110 kg	221 (22.9)	225 (23.5)	446 (23.2)
> 110 kg	110 (11.4)	112 (11.7)	222 (11.5)
BMI (kg/m ²)			
N	965	959	1924
Missing	0	0	0
Mean \pm SD	30.7 \pm 5.9	30.7 \pm 5.9	30.7 \pm 5.9
Range	17.9 – 56.0	13.7 – 53.6	13.7 – 56.0
BMI (categorized), n (%)			
Missing	0	0	0
< 18.5 kg/m ²	1 (0.1)	4 (0.4)	5 (0.3)
18.5 to < 25 kg/m ²	142 (14.7)	138 (14.4)	280 (14.6)
25 to < 30 kg/m ²	341 (35.3)	341 (35.6)	682 (35.4)
30 to < 40 kg/m ²	405 (42.0)	396 (41.3)	801 (41.6)
\geq 40 kg/m ²	76 (7.9)	80 (8.3)	156 (8.1)

Abbreviations: BMI=body mass index; enoxaparin 30 mg bld=enoxaparin 30 mg q 12h \pm 2h;
MITT=modified intent to treat; od=once daily; SD=standard deviation; and yr=year

6.2.4 Analysis of Primary Endpoint

In patients undergoing total hip replacement surgery

The following table shows the efficacy results for the primary efficacy endpoint of total VTE and its components from RECORD 1 and 2 trials based on MITT population.

RECORD 1 study was designed as a non-inferiority trial with a stepwise approach. The efficacy of rivaroxaban was assessed by a non-inferiority test based on the per protocol population (PP) first and if non-inferiority was shown, a superiority test was performed subsequently based on the MITT population. In the PP population analysis, total VTE occurred in 13 (0.9%) and 50 (3.4%) subjects randomized to rivaroxaban or enoxaparin, respectively; which showed non-inferiority (95% CI: -3.55%, -1.51%) of rivaroxaban 10 mg once daily as compared to enoxaparin 40 mg once daily.

In RECORD 1 study based on MITT population, the total VTE was 1.1% in the rivaroxaban group as compared to 3.7% in the enoxaparin control group. The difference in the total VTE rate between the two treatment groups was statistically significant ($p < 0.001$). The difference between the two treatment groups was mainly due to proximal and distal DVT. It should be noted that there were 4 (0.5%) non-fatal PE in the Rivaroxaban group as compared to 1 (0.1%) in the enoxaparin group.

In RECORD 2 study, the treatment duration was more than twice as long in the Rivaroxaban group (35 days) as in the enoxaparin control group (13 days). The total VTE was lower in the Rivaroxaban group (2.0%) as compared to the enoxaparin group (9.3%). The difference in the total VTE rate between the two treatment groups was statistically significant ($p < 0.001$). The difference between the 2 treatment groups was mainly due to proximal and distal DVT. There were also fewer deaths and nonfatal PE in the Rivaroxaban group than in the enoxaparin control group. The difference in the total VTE rate between the two treatment groups may largely be due to the different treatment durations (rivaroxaban 35 days vs. enoxaparin 12 days) between the two treatment groups.

Efficacy Results in THR Trials: Primary Efficacy Endpoint in MITT population

	RECORD 1		RECORD 2	
Endpoint	Rivaroxaban 10mg qd N=1595	Enoxaparin 40mg qd N=1558	Rivaroxaban 10mg qd N=864	Enoxaparin 40 mg qd + Placebo N=869
Total VTE	18 (1.1%) ^a	58 (3.7%)	17 (2.0%) ^a	81 (9.3%)
All cause death	4 (0.3%)	4 (0.3%)	2 (0.2%)	6 (0.7%)
Nonfatal PE	4 (0.3%)	1 (<0.1%)	1 (0.1%)	4 (0.5%)

Proximal DVT	1 (<0.1%)	31 (2.0%)	5 (0.6%)	44 (5.1%)
Distal DVT	12 (0.8%)	27 (1.7%)	11 (1.3%)	49 (5.6%)

a: $p < 0.001$

In patients undergoing total knee replacement surgery

The following table shows the efficacy results for the primary efficacy endpoint of total VTE and its components from RECORD 3 and 4 trials based on MITT population.

The RECORD 4 study was designed as a non-inferiority trial with a stepwise approach. The efficacy of rivaroxaban was assessed by a non-inferiority test based on the PP population first and if non-inferiority was shown, a superiority test was performed subsequently based on the MITT population. In the PP population analysis, total VTE occurred in 58 (6.7%) and 82 (9.3%) of subjects randomized to rivaroxaban or enoxaparin, respectively; which showed non-inferiority (95% CI: -5.25%, -0.17%) of rivaroxaban 10 mg once daily as compared to enoxaparin 30 mg twice daily.

In the RECORD 3 study the enoxaparin dosing regimen used (40 mg once daily) is not an approved dosing regimen for the prophylaxis of DVT in patients undergoing total knee replacement surgery in United States. Based on MITT population, the total VTE was 9.6% in the rivaroxaban group as compared to 18.9% in the enoxaparin group. The difference in the total VTE rate between the two treatment groups was statistically significant ($p < 0.001$). The difference between the two treatment groups was mainly due to distal DVT. There were also fewer deaths, nonfatal PE and proximal DVT in the Rivaroxaban group than in the enoxaparin group.

In the RECORD 4 study based on MITT population, the total VTE was lower in the Rivaroxaban group (6.9%) as compared to the enoxaparin group (10.1%). The difference in the total VTE rate between the two treatment groups was statistically significant ($p < 0.05$). Similar to RECORD 2, the difference between the 2 treatment groups was mainly due to the distal DVT. There were also fewer deaths and nonfatal PE in the Rivaroxaban group than in the enoxaparin control group.

Efficacy Results in TKR Trials: Primary Efficacy Endpoint in MITT population

	RECORD 3		RECORD 4	
Endpoint	Rivaroxaban 10mg qd N=824	Enoxaparin 40mg qd N=878	Rivaroxaban 10mg qd N=965	Enoxaparin 30mg bid N=959
Total VTE	79 (9.6%) ^a	166 (18.9%)	67 (6.9%) ^b	97 (10.1%)
All cause death	0	2 (0.2%)	2 (0.2%)	3 (0.3%)

Nonfatal PE	0	4 (0.5%)	5 (0.5%)	8 (0.8 %)
Proximal DVT	9 (1.1 %)	20 (2.3%)	8 (0.8%)	14 (1.5%)
Distal DVT	74 (9.0 %)	156 (17.8%)	57 (5.9%)	82 (8.6%)

a: $p < 0.001$; b: $p = 0.012$

Sensitivity analysis

The following table shows the sensitivity analysis for the primary efficacy endpoint in the RECORD studies. It used different scenarios for handling missing responses in the subjects invalidated due to no adequate assessment of DVT in all randomized population.

All analyses showed statistical superiority of the rivaroxaban as compared to the enoxaparin with the exception of the pessimistic scenario in RECORD 3 and 4 studies.

Sensitivity Analysis in RECORD 1-4 Studies

RECORD 1

Primary efficacy endpoint				
Observed cases ^b				
Rivaroxaban 10 mg od	20/2266	(0.9%)	-1.90%	[-2.67%, -1.12%]
Enoxaparin 40 mg od	63/2275	(2.8%)		
Realistic scenario ^c				
Rivaroxaban 10 mg od	24/2266	(1.1%)	-2.46%	[-3.32%, -1.60%]
Enoxaparin 40 mg od	80/2275	(3.5%)		
Optimistic scenario ^d				
Rivaroxaban 10 mg od	18/2266	(0.8%)	-1.80%	[-2.55%, -1.06%]
Enoxaparin 40 mg od	59/2275	(2.6%)		
Pessimistic scenario ^e				
Rivaroxaban 10 mg od	689/2266	(30.4%)	-3.49%	[-6.14%, -0.84%]
Enoxaparin 40 mg od	775/2275	(34.1%)		
Adjudicated and non-assessable findings ^f				
Rivaroxaban 10 mg od	21/2266	(0.9%)	-1.76%	[-2.53%, -0.99%]
Enoxaparin 40 mg od	61/2275	(2.7%)		

RECORD 2

Primary efficacy endpoint				
Observed cases ^b				
Rivaroxaban 10 mg od	21/1252	(1.68%)	-5.01%	[-6.55%, -3.47%]
Enoxaparin 40 mg od	84/1257	(6.68%)		
Realistic scenario ^c				
Rivaroxaban 10 mg od	24/1252	(1.92%)	-6.68%	[-8.39%, -4.98%]
Enoxaparin 40 mg od	108/1257	(8.59%)		
Optimistic scenario ^d				
Rivaroxaban 10 mg od	18/1252	(1.44%)	-5.01%	[-6.51%, -3.51%]
Enoxaparin 40 mg od	81/1257	(6.44%)		
Pessimistic scenario ^e				
Rivaroxaban 10 mg od	405/1252	(32.25%)	-5.01%	[-8.65%, -1.37%]
Enoxaparin 40 mg od	469/1257	(37.31%)		
Adjudicated and non-assessable findings ^f				
Rivaroxaban 10 mg od	23/1252	(1.84%)	-5.01%	[-6.58%, -3.44%]
Enoxaparin 40 mg od	86/1257	(6.84%)		

RECORD 3

Primary efficacy endpoint				
Observed cases ^b				
Rivaroxaban 10 mg od	85/1254	(6.8%)	-6.62%	[-8.94%, -4.31%]
Enoxaparin 40 mg od	171/1277	(13.4%)		
Realistic scenario ^c				
Rivaroxaban 10 mg od	122/1254	(9.7%)	-8.43%	[-11.07%, -5.79%]
Enoxaparin 40 mg od	232/1277	(18.2%)		
Optimistic scenario ^d				
Rivaroxaban 10 mg od	79/1254	(6.3%)	-6.71%	[-8.98%, -4.45%]
Enoxaparin 40 mg od	166/1277	(13.0%)		
Pessimistic scenario ^e				
Rivaroxaban 10 mg od	509/1254	(40.6%)	-3.56%	[-7.33%, 0.20%]
Enoxaparin 40 mg od	565/1277	(44.2%)		
Adjudicated and nonassessable findings ^f				
Rivaroxaban 10 mg od	82/1254	(6.5%)	-6.71%	[-9.01%, -4.42%]
Enoxaparin 40 mg od	169/1277	(13.2%)		

RECORD 4

Primary efficacy endpoint				
Observed cases ^b				
Rivaroxaban 10 mg od	75/1584	(4.7%)	-1.79%	[-3.40%, -0.18%]
Enoxaparin 30 mg bid	102/1564	(6.5%)		
Realistic scenario ^c				
Rivaroxaban 10 mg od	104/1584	(6.6%)	-2.39%	[-4.25%, -0.53%]
Enoxaparin 30 mg bid	140/1564	(9.0%)		
Optimistic scenario ^d				
Rivaroxaban 10 mg od	67/1584	(4.2%)	-1.98%	[-3.52%, -0.43%]
Enoxaparin 30 mg bid	97/1564	(6.2%)		
Pessimistic scenario ^e				
Rivaroxaban 10 mg od	686/1584	(43.3%)	-1.57%	[-5.03%, 1.89%]
Enoxaparin 30 mg bid	702/1564	(44.9%)		
Adjudicated and nonassessable findings ^f				
Rivaroxaban 10 mg od	68/1584	(4.3%)	-2.10%	[-3.67%, -0.54%]
Enoxaparin 30 mg bid	100/1564	(6.4%)		

- b Subjects without adequate assessment due to either too early or too late assessments were included
- c Within a geographic region, subjects without adequate assessment of thromboembolism were assumed to have the same risk for asymptomatic DVT as the subjects with adequate assessment belonging to the same treatment group
- d None of the subjects without adequate assessment of thromboembolism were assumed to be a treatment failure (i.e., have an event)
- e Subjects without adequate assessment of thromboembolism were assumed to be a treatment failure (i.e., have an event)
- f In addition to adjudicated findings, symptomatic findings reported by the investigator that were deemed non-assessable by the VTE adjudication committee were included, if finding occurred within the time window

6.2.5 Analysis of Secondary Endpoints

Main Secondary Efficacy Endpoint

Major VTE was a pre-specified main secondary efficacy endpoint in the RECORD studies. The following table shows the major VTE endpoint and its components in RECORD 1 and 2 trials in MITT population in patients undergoing THR surgery. The major VTE rate was lower in the Rivaroxaban group as compared to control in both studies.

Major VTE in MITT population in THR Trials

	RECORD 1		RECORD 2	
Endpoint	Rivaroxaban 10mg qd N=1686	Enoxaparin 40mg qd N=1678	Rivaroxaban 10mg qd N=961	Enoxaparin 40 mg qd + Placebo N=962
Major VTE	4 (0.2%) ^a	33 (2.0%)	6 (0.6%) ^a	49 (5.1%)
VTE-related death	0	1 (<0.1%)	0	1 (0.1%)
Nonfatal PE	4 (0.2%)	1 (<0.1%)	1 (0.1%)	4 (0.4%)
Proximal DVT	1 (<0.1%)	31 (1.9%)	5 (0.5%)	44 (4.6%)

a: p<0.001

The following table shows the major VTE and its components in RECORD 3 and 4 trials in MITT population in patients undergoing TKR surgery. The major VTE rate was lower in the Rivaroxaban group as compared to control in RECORD 3 study. The difference in the major VTE rate between the two treatment groups was not statistically significant in the RECORD 4 trial (p>0.05).

Major VTE in MITT population in TKR Trials

	RECORD 3		RECORD 4	
Endpoint	Rivaroxaban 10mg qd N=908	Enoxaparin 40mg qd N=925	Rivaroxaban 10mg qd N=1122	Enoxaparin 30mg bid N=1112
Major VTE	9 (1.0%) ^a	24 (2.6%)	13 (1.2%) ^b	22 (2.0%)
VTE-related death	0	0	1 (0.1%)	0
Nonfatal PE	0	4 (0.4%)	5 (0.5%)	8 (0.7 %)
Proximal DVT	9 (1.0 %)	20 (2.2%)	8 (0.7%)	14 (1.3%)

a: p=0.010; b: p=0.124

Symptomatic VTE

Symptomatic VTE was analyzed based on the safety population in RECORD studies. The following table shows the rate of symptomatic VTE in RECORD 1 and 2 in patients undergoing THR surgery. There was a statistically significant difference in the symptomatic VTE rate between the two treatment groups in RECORD 2 trial only (p<0.01 using Fisher's exact test).

In the RECORD 2 trial, study patients in the enoxaparin control group received enoxaparin 40 mg once daily for 12 days followed by placebo for 23 days. When the symptomatic VTE rate was analyzed by enoxaparin control period and placebo control period separately, the symptomatic VTE rate was similar between the Rivaroxaban treatment and enoxaparin treatment during the enoxaparin control period (p=0.19 using Fisher's exact test) and lower with Rivaroxaban treatment than with placebo during the placebo control period (p=0.02 using Fisher's exact test). The difference in the symptomatic VTE rate between the two treatment groups was mainly due to more symptomatic proximal and distal DVT reported with placebo treatment.

Symptomatic VTE in Safety Population in THR Trials

	RECORD 1		RECORD 2	
Endpoint	Rivaroxaban 10mg qd N=2209	Enoxaparin 40mg qd N=2224	Rivaroxaban 10mg qd N=1228	Enoxaparin 40 mg qd + Placebo N=1229
Symptomatic VTE	6 (0.27%)	11 (0.49%)	3 (0.24%) E ^a : 1 (0.08%) P ^b : 2 (0.16%)	15 (1.22%) E: 4 (0.33%) P: 11 (0.90%)

Nonfatal PE	4 (0.18%)	1 (0.04%)	1 (0.08%) E: 0 P: 1 (0.08%)	4 (0.33%) E: 1 (0.08%) P: 3 (0.24%)
Fatal PE	0	1 (0.04%)	0 E: 0 P: 0	1 (0.08%) E: 1 (0.08%) P: 0
Proximal DVT	0	5 (0.22%)	1 (0.08%) E: 1 (0.1%) P: 0	9 (0.73%) E: 2 (0.16%) P: 7 (0.57%)
Distal DVT	3 (0.14%)	6 (0.27%)	1 (0.08%) E: 1 (0.08%) P: 0	7 (0.57%) E: 2 (0.16%) P: 5 (0.41%)

a: E-enoxaparin control period

b: P-placebo control period

The following table shows the symptomatic VTE in RECORD 3 and 4 studies in patients undergoing TKR surgery. The symptomatic VTE rate was numerically lower with Rivaroxaban treatment as compared to enoxaparin treatment but the difference between the two treatment groups was statistically significant in RECORD 3 only ($p < 0.05$ using Fisher's exact test). It was noted that more symptomatic proximal DVT events occurred in the Rivaroxaban group than in the enoxaparin control group in both RECORD 3 and 4 studies.

Symptomatic VTE in Safety Population in TKR Trials

	RECORD 3		RECORD 4	
Endpoint	Rivaroxaban 10mg qd N=1220	Enoxaparin 40mg qd N=1239	Rivaroxaban 10mg qd N=1526	Enoxaparin 30mg bid N=1508
Symptomatic VTE	8 (0.66%)	24 (1.94%)	11 (0.72%)	18 (1.19%)
Nonfatal PE	0	4 (0.32%)	5 (0.33%)	8 (0.53%)
Fatal PE	0	0	1 (0.06%)	0
Proximal DVT	3 (0.25%)	1 (0.08%)	5 (0.33%)	1 (0.07%)
Distal DVT	6 (0.50%)	20 (1.61%)	3 (0.20%)	9 (0.60%)

The following table shows the symptomatic VTE events reported during the follow-up period from RECORD studies. The rate was similar between the two treatment groups (0.16% vs. 0.19%). It was noted that there were more VTE events in the rivaroxaban group (5, 0.41%) than

in the enoxaparin group (3, 0.24%) in RECORD 3 trial (11356). Overall, there were 7 PE and 2 proximal DVT and 1 distal DVT in the rivaroxaban group comparing 6 PE, 5 proximal DVT and 5 distal DVT in enoxaparin group.

Symptomatic VTE during the follow-up period in RECORD studies

	Rivaroxaban	Enoxaparin
SYMPTOMATIC VENOUS THROMBOEMBOLISM (FOLLOW-UP)		
ANY EVENT		
11354	1/ 2209 (0.05%)	4/ 2224 (0.18%)
11355	3/ 1526 (0.20%)	3/ 1508 (0.20%)
11356	5/ 1220 (0.41%)	3/ 1239 (0.24%)
11357	1/ 1228 (0.08%)	2/ 1229 (0.16%)
POOLED	10/ 6183 (0.16%)	12/ 6200 (0.19%)
PULMONARY EMBOLISM (FOLLOW-UP)		
11354	0/ 2209 (0.00%)	0/ 2224 (0.00%)
11355	3/ 1526 (0.20%)	2/ 1508 (0.13%)
11356	3/ 1220 (0.25%)	2/ 1239 (0.16%)
11357	1/ 1228 (0.08%)	2/ 1229 (0.16%)
POOLED	7/ 6183 (0.11%)	6/ 6200 (0.10%)
DEEP VEIN THROMBOSIS, PROXIMAL (FOLLOW-UP)		
11354	1/ 2209 (0.05%)	3/ 2224 (0.13%)
11355	0/ 1526 (0.00%)	1/ 1508 (0.07%)
11356	1/ 1220 (0.08%)	0/ 1239 (0.00%)
11357	0/ 1228 (0.00%)	1/ 1229 (0.08%)
POOLED	2/ 6183 (0.03%)	5/ 6200 (0.08%)
DEEP VEIN THROMBOSIS, DISTAL (FOLLOW-UP)		
11354	0/ 2209 (0.00%)	4/ 2224 (0.18%)
11355	0/ 1526 (0.00%)	0/ 1508 (0.00%)
11356	1/ 1220 (0.08%)	1/ 1239 (0.08%)
11357	0/ 1228 (0.00%)	0/ 1229 (0.00%)
POOLED	1/ 6183 (0.02%)	5/ 6200 (0.08%)

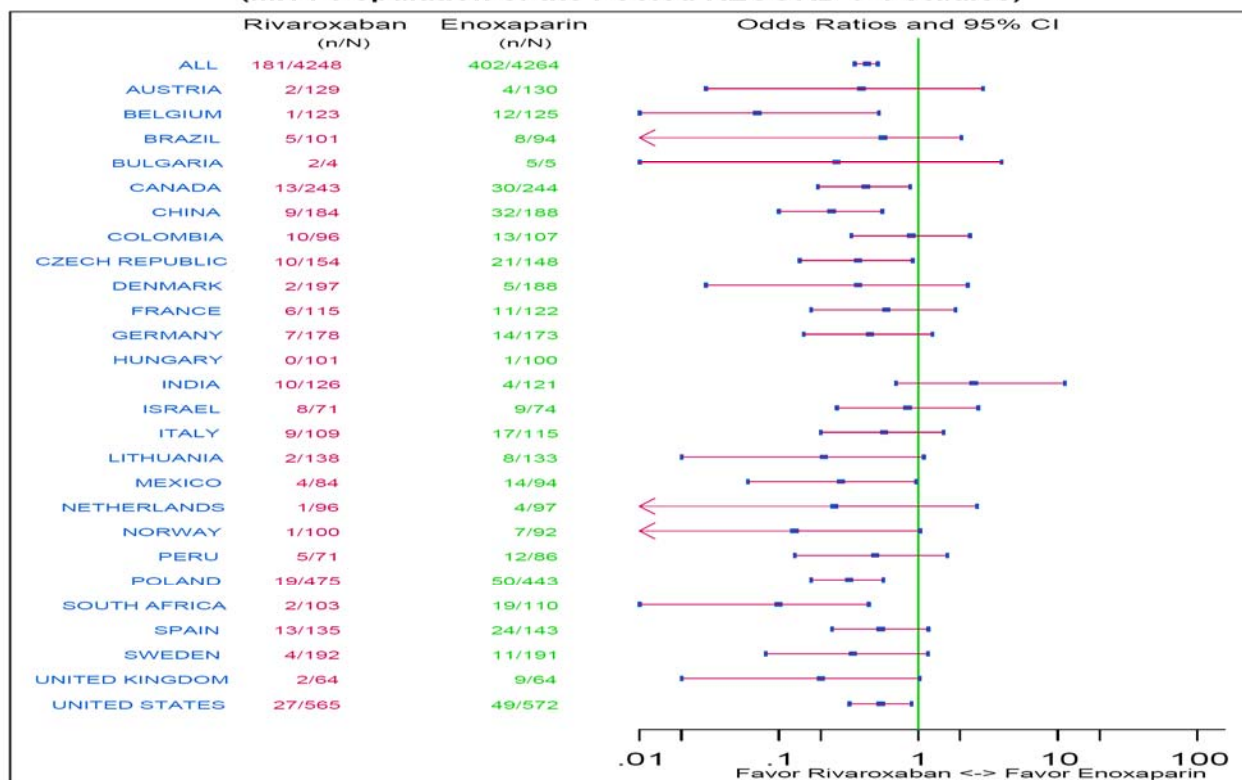
6.2.6 Other Endpoints

The sponsor performed additional efficacy analysis for composite endpoint of symptomatic VTE or death in RECORD studies. This composite endpoint is not a pre-specified endpoint for the efficacy analysis in the study protocol in RECORD studies.

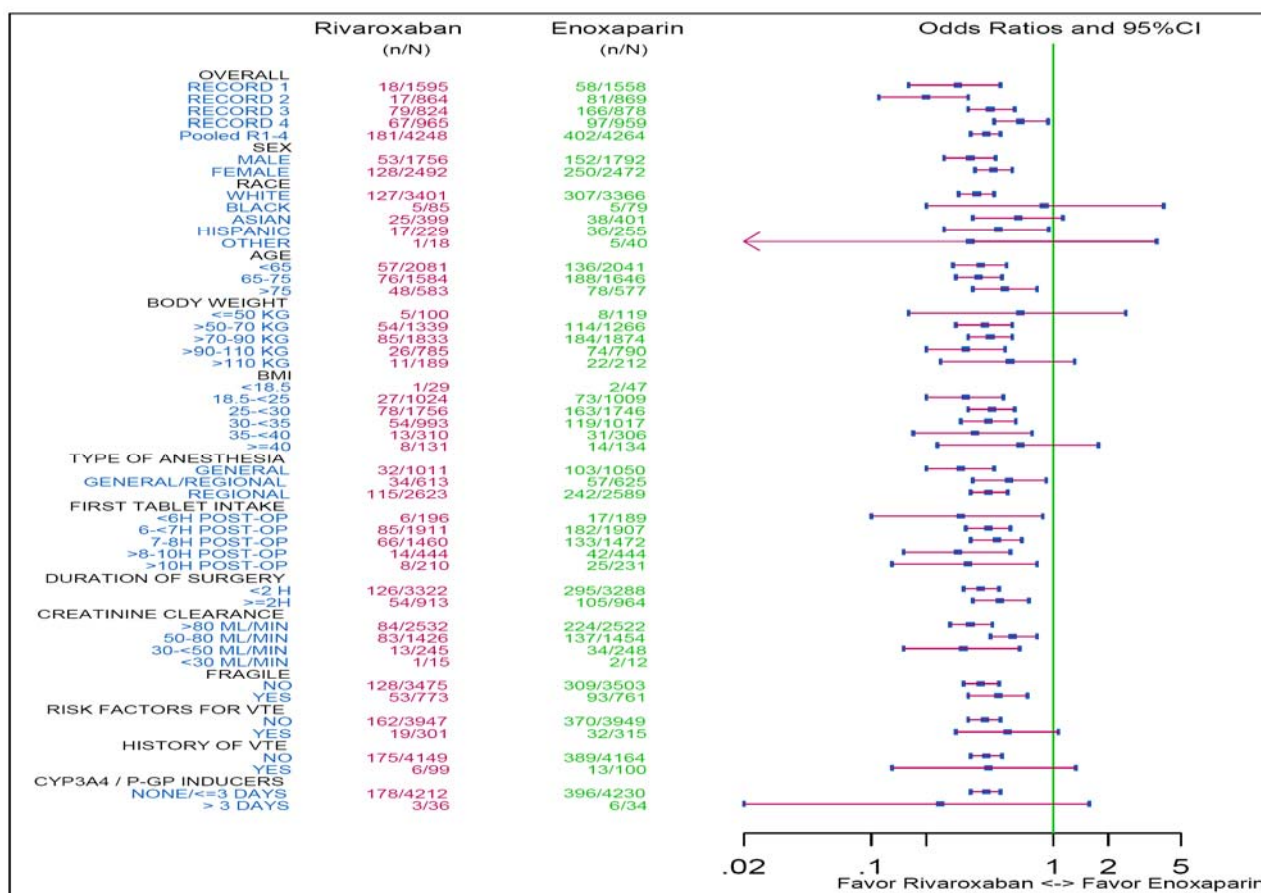
6.2.7 Subpopulations

The following Figure shows the total VTE and its odds ratio by country in pooled RECORD studies. The efficacy results were consistent with the primary efficacy analysis result in most countries except in India where enoxaparin showed better efficacy than Rivaroxaban treatment.

**Figure 3-7: Total VTE and Corresponding Odds Ratio (95% CI) by Country
(MITT Population of the Pooled RECORD 1-4 Studies)**



The following figure shows the total VTE by treatment in subgroup analysis in pooled RECORD studies. The efficacy results were consistent with the primary efficacy analysis results in most subgroups except in black patients with no difference between the two treatment groups.



6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dose of Rivaroxaban (10 mg) was evaluated in phase 3 trials. The selection of Rivaroxaban 10 mg once daily dosing regimen in phase 3 trials was based on the efficacy and safety results from 4 phase 2 dose ranging studies.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No studies have been conducted to evaluate the persistence of efficacy and/or tolerance effects of Rivaroxaban treatment.

6.2.10 Additional Efficacy Issues/Analyses

The sponsor presented a analysis of a composite endpoint of symptomatic VTE or death as one efficacy endpoint for RECORD studies in the submission. This composite endpoint was not a pre-specified efficacy endpoint in the RECORD study protocols. This analysis is considered as a post-hoc analysis for efficacy.

7 Review of Safety

Safety Summary

7.1 Methods

7.2.1 Clinical Studies Used to Evaluate Safety

All completed clinical studies and safety update from ongoing studies listed under Section 5.1 Table of Clinical Studies were used to evaluate the safety of Rivaroxaban. Some safety data from the ongoing studies are still blinded.

7.2.2 Adequacy of Data

The current safety database based on completed clinical studies is insufficient to evaluate hepatotoxicity of rivaroxaban. In completed clinical studies, 92% of study patients were exposed to <35 days of Rivaroxaban treatment and only 6% (635 patients) were exposed to Rivaroxaban for 3 months. Previous experience with product, EXANTA (ximelagatran), that causes drug-induced liver injury suggested short term tolerance does not necessarily predict long term safety (NDA 21-686, Medical Review, Dr. Ruyi He, M.D., 9/27/04; Cardiovascular and Renal Drug Advisory Committee Transcript, 9/10/04). In addition, enoxaparin, which is known to cause benign liver enzyme elevations and such elevations are fully reversible (NDA 20-164, Lovenox labeling), was used as control in all completed short-term Phase 3 clinical trials and that may confound the evaluation of hepatic signal in these trials. Therefore, long-term safety data with a different control that has not been shown to increase liver enzymes, such as coumadin, will be needed to fully evaluate the hepatotoxicity of rivaroxaban.

Furthermore, because rivaroxaban is an oral anticoagulant that doesn't require routine monitoring during treatment, off-label, long-term use could be widespread in clinical practice to replace current available oral product (coumadin) due to convenience, especially in atrial fibrillation population for stroke prevention and in patients who require long-term VTE prophylaxis and treatment. The prevalence of atrial fibrillation in the United States has been projected to increase from 2 to 5 million in 2000 to 6 to 12 million in 2050 (Special Report, Prevention of Atrial Fibrillation, Report from a National Heart, Lung, and Blood Institute Workshop, *Circulation* 2009; 119:606-618). Therefore, thorough evaluation for hepatotoxicity and long-term safety in the long-term clinical trial is extremely important.

7.2.3 Pooling Data across Studies to Estimate and Compare Incidence

Pooling data across studies to estimate and compare mortality, incidence of all SAEs, bleeding events, cardiovascular events, and hepatic events.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The following table summarizes the Rivaroxaban exposure in completed clinical studies. Among 10,600 patients who were exposed to Rivaroxaban in completed studies, 6183 were from phase 3 trials, 3300 were from phase 2 trials, and 1117 were from phase 1 trials. Among all exposed patients, 6095 (57.5%) were exposed to Rivaroxaban for ≤ 12 days, 3622 (34.2%) for 28-35 days, 203 (2%) between 36 and 12 weeks and 635 (6%) received rivaroxaban for at least 12 weeks.

Rivaroxaban Exposure in Completed Studies

Indication/Population	Rivaroxaban Dose	Duration (Mean \pm SD)	Number of patients
Phase 3 VTE prophylaxis			
RECORD 1-2 (THR)	10 mg once daily	33 \pm 7 days	3437
RECORD 3-4 (TKR)	10 mg once daily	12 \pm 3 days	2746
Phase 2 VTE prophylaxis	5, 10, 20, 30, 40 and 60mg total daily dose	8 days	2232
Phase 2 VTE treatment	20, 30, 40 and 60 mg total daily dose	78 (≥ 12 week)	883 (635)
Phase 2 Atrial Fibrillation (Japan)	5, 10, 15, 20, 30, 40, and 60 mg total daily dose	28 days	185
Phase 1	variable	≤ 10 days	1117
Total		≤ 35 days (92%) ≥ 12 week (6%)	10,600

Drug exposure in RECORD studies

In the 4 RECORD studies, 6,183 subjects who were randomized to rivaroxaban and 6,200 who were randomized to enoxaparin comparator received at least 1 dose of blinded study medication (see table below). Eighty-six randomized subjects in the rivaroxaban group and 5 in the enoxaparin group never received active study medication due to the unbalanced start times of the treatments.

Number of subjects in the safety population of each RECORD study

Study	Rivaroxaban	Enoxaparin	Total
RECORD 1	2209	2224	4433
RECORD 2	1228	1229	2457
Total # hip subjects	3437	3453	6890
RECORD 3	1220	1239	2459
RECORD 4	1526	1508	3034
Total # knee subjects	2746	2747	5493
Grand Total	6183	6200	12,383

The following table shows the duration of treatment with active study drug in each of the RECORD studies. In the RECORD 2 study, after Day 12, active enoxaparin was discontinued and placebo was continued until Day 35.

**Table 1-3: Duration of Treatment of Active Study Medication by Study (Mean Days \pm SD)
(Subjects Valid for Safety Analysis in RECORD Studies)**

Study	Rivaroxaban	Enoxaparin
RECORD 1	33.4 \pm 6.9	33.7 \pm 8.2
RECORD 2	33.5 \pm 6.9	12.4 \pm 3.0
RECORD 3	11.9 \pm 2.3	12.5 \pm 3.0
RECORD 4	11.7 \pm 2.5	11.0 \pm 2.4

Demographics and Baseline Characteristics in RECORD Studies

The following table shows the demographic and baseline characteristics of the safety population in the combined 4 Phase 3 RECORD studies. Among the 12,383 subjects (6183 received Rivaroxaban, 6200 received enoxaparin) undergoing elective THR or TKR surgery, 4951 were men (40%) and 7432 (60%) were women, and 79% were White. Mean age of subjects was 64 years with 53% of subjects over 65 years and 15% of the subjects over 75 years. The mean BMI was 28.8 kg/m² with 36% of the subjects having a BMI >30 kg/m². Seven percent of the subjects had a calculated creatinine clearance <50 mL/min (moderate renal impairment) and 0.5% (35 in the rivaroxaban group and 22 in the enoxaparin group) had a calculated creatinine clearance <30 mL/min (severe renal impairment). Medical history findings showed that 52% of subjects had hypertensive disorders, and 7% of subjects had upper or lower limb fractures/dislocations. Hepatic disease was reported in the medical history of 3% of subjects. This was mostly a history of gallbladder disease (1.7%) and hepatocellular damage/hepatitis (1.0%).

Compared with the combined 2 THR studies (RECORD 1 and 2), there were slightly more women, fewer Whites with greater mean age and weight in the combined 2 TKR studies (RECORD 3 and 4). There was a similar percentage of subjects with at least moderate or severe renal impairment, and hepatic disorder (2.7%-3.4%). There was a similar percentage of fragile subjects who were defined as those with age >75 years and/or body weight <50 kg and/or a calculated creatinine clearance <50 mL/min at baseline. There was a lower percentage of subjects in the THR studies with a history of hypertensive disorders (45%) than in the TKR studies (61%).

For the pooled RECORD 1-4 studies and for the separately pooled THR and TKR studies, demographic and baseline characteristics of subjects were well balanced in each of the 2 treatment groups, showing very similar characteristics to those of the respective total populations of each study pool. The medical history findings for the THR and TKR studies were similar for both treatment groups.

Demographics and Baseline Characteristics in Safety Population in 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 (%)			
Missing	230 (3%)	153 (3%)	383 (3%)
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%)
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%)
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/m²) 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, CL_{CR} = creatinine clearance

Note: Percentages are calculated including missing values.

^a Fragile definition: Age >75 years and/or calculated creatinine clearance (CL_{CR}) <50 ml/min and/or weight ≤50 kg

Phase 2 studies

Demographic and baseline characteristics for subjects included in the 4 Phase 2 orthopedic VTE studies were similar and well balanced between the rivaroxaban and enoxaparin

treatment groups. Approximately 98% of subjects in both treatment groups were white, and more than 58% were female. Approximately 15% of subjects in both treatment groups were more than 75 years of age, and mean BMI was approximately 28 kg/m² in both treatment groups.

**Demographics and Baseline Characteristics in safety population in VTE prophylaxis trials
(Studies 10942, 10944, 10945, and 11527)**

Characteristics	RIVA Total (N=2232)		ENOX Total (N=555)	
Sex, n (%)				
Male	896	(40.1%)	231	(41.6%)
Female	1336	(59.9%)	324	(58.4%)
Race, n (%)				
White	2184	(97.8%)	546	(98.4%)
Black	21	(0.9%)	3	(0.5%)
Asian	12	(0.5%)	2	(0.4%)
American Indian	3	(0.1%)	0	(0%)
Hispanic	8	(0.4%)	3	(0.5%)
Uncoded	4	(0.2%)	1	(0.2%)
Age (years)				
Mean	65.3		65.2	
Median	66.0		66.0	
Range	26.0 – 93.0		27.0 – 92.0	
Age (categorized), n (%)				
< 65 years	1000	(44.8%)	231	(41.6%)
65 – 75 years	878	(39.3%)	238	(42.9%)
> 75 years	354	(15.9%)	86	(15.5%)
Weight (kg)				
Mean	79.9		79.4	
Median	79.0		79.2	
Range	45.0 – 173.0		45.5 – 145.0	
Body mass index (kg/m²)				
Mean	28.6		28.5	
Median	27.8		28.1	
Range	17.2 – 61.3		15.9 – 51.6	
BMI (categorized), n (%)				
<18.5 (kg/m ²)	16	(0.7%)	8	(1.4%)
18.5 - <25 (kg/m ²)	540	(24.2%)	131	(23.6%)
25 - <30 (kg/m ²)	937	(42.0%)	226	(40.7%)
30 - <40 (kg/m ²)	665	(29.8%)	176	(31.7%)
≥40 (kg/m ²)	74	(3.3%)	14	(2.5%)

Key: BMI = body mass index; ENOX = enoxaparin; RIVA = rivaroxaban

Source: Table 11-2 in MRR-00300 5.3.5.3.3-17

Demographic and baseline characteristics for subjects included in the 2 Phase 2 DVT treatment studies were similar and well balanced between the 2 treatment groups. Approximately 92% of subjects in both groups were white, and more than 55% of subjects in each group were male. In Study 11223, a prior history of DVT was the most common thromboembolism risk factor, occurring in 108 (18%) of all subjects in the safety population.

**Demographics and Baseline Characteristics in safety population in DVT treatment trials
(Studies 11223 and 11528)**

Characteristics	Rivaroxaban Total (N=883)		Heparin/VKA Total (N=263)	
Sex, n (%)				
Male	495	(56.1%)	150	(57.0%)
Female	388	(43.9%)	113	(43.0%)
Race				
White	818	(92.6%)	243	(92.4%)
Black	28	(3.2%)	12	(4.6%)
Asian	4	(0.5%)	1	(0.4%)
American Indian	1	(0.1%)	0	(0%)
Hispanic	28	(3.2%)	7	(2.7%)
Uncoded	4	(0.5%)	0	(0%)
Age (years)				
Mean	58.8		57.7	
Median	61.0		59.0	
Range	18.0 – 94.0		21.0 – 92.0	
Age (categorized), n (%)				
< 65 years	520	(58.9%)	151	(57.4%)
65 – 75 years	208	(23.6%)	60	(22.8%)
> 75 years	155	(17.6%)	52	(19.8%)
Weight (kg)				
Mean	80.2		81.1	
Median	79.0		80.0	
Range	37.0 - 209.0		41.0 – 138.0	
BMI (kg/m²)				
Mean	27.5		27.7	
Median	26.9		26.8	
Range	13.8 – 56.7		18.2 – 44.4	
BMI (categorized), n (%)				
<18.5 (kg/m ²)	40	(4.5%)	6	(2.3%)
18.5 - <25 (kg/m ²)	273	(30.9%)	84	(31.9%)
25 - <30 (kg/m ²)	343	(38.8%)	97	(36.9%)
30 - <40 (kg/m ²)	204	(23.1%)	72	(27.4%)
≥40 (kg/m ²)	23	(2.6%)	4	(1.5%)

Key: BMI = body mass index; LMW = low molecular weight; VKA = vitamin K antagonist

Three phase 2 atrial fibrillation studies were conducted in Japan. Study 11390 was an open-label, uncontrolled, sequential dose panel study, while Studies 11866 and 12024 were randomized, open-label, warfarin-controlled, parallel-group, dose-range studies (5 to 20 mg daily doses for 28 days). The age ranges of rivaroxaban subjects in Studies 11390, 11866, and 12024 were 34-81 years, 45-85 years, and 30-92 years, respectively. Approximately 94%, 80%, and 76%, respectively of all rivaroxaban subjects were male. Demographic and baseline characteristics for subjects included in warfarin-controlled studies were similar and well balanced between the treatments groups except more males in the warfarin group in Study 12024.

7.2.2 Explorations for Dose Response

Four phase 2 trials were conducted to explore the dose response relationship and all 4 studies showed an increased risk of bleeding events with increasing rivaroxaban dose. Total daily doses

from 5 to 20 mg were considered to be similar to the comparator, enoxaparin, while doses over 20 mg had increased rates of bleeding events. Only one dose of rivaroxaban (10 mg daily) was studied in all phase 3 trials.

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

Liver function tests, routine hematology and clinical chemistry including renal function (creatinine and urea) were measured during the clinical trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Phase 1 clinical pharmacokinetic studies were conducted to study the metabolism and clearance of rivaroxaban. Seventeen drug-drug interaction studies were conducted and showed that strong inhibitors of both metabolism (i.e., CYP3A4) and active secretion (i.e., P-glycoprotein [P-gp] and breast cancer resistance protein [Bcrp]) may result in a clinically relevant increased systemic exposure of rivaroxaban. (See Clinical Pharmacology review)

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Bleeding events were evaluated in phase 3 trials and the results are included under Section 7.3.4.1 Bleeding events.

7.3 Major Safety Results

7.2.1 Deaths

RECORD Studies

There were 13 (0.2%) and 25 (0.4%) deaths reported in the safety populations of rivaroxaban and enoxaparin, respectively, during the treatment (8 rivaroxaban and 15 enoxaparin) and follow-up (5 rivaroxaban and 10 enoxaparin) period in 4 RECORD studies.

One subject (RECORD 2 Subject 11357-120037004) was randomized to rivaroxaban but did not receive any study medication and was not counted as an event in the safety population.

One subject in the rivaroxaban group (11354-160084031) and one subject in the enoxaparin group (11355-90002-25006, not included in the table below) did not receive active study treatment but received placebo treatment and was included in the safety population.

Two subjects randomized to rivaroxaban died of fatal bleeding. One did receive study drug (placebo enoxaparin) prior to surgery but did not receive active rivaroxaban treatment after

surgery. 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. However, the causes of death from case report forms mentioned pulmonary embolism in 3 deaths with rivaroxaban and in 6 deaths with enoxaparin.

There were 7 and 12 deaths adjudicated as cardiovascular deaths on rivaroxaban and enoxaparin, respectively.

There were no hepatic disorder deaths observed in the RECORD studies.

The following Table lists the investigator-reported causes of death for each subject who died.

Deaths in RECORD Studies

Study Medication Study-Subject Number	Age	Race	Sex	Date of Last ASM	Day of Death Relative to ASM Start	Cause of Death (from case report form)
Rivaroxaban 10 mg od						
11354-160084031	74	NA	F	Subject did not receive active study medication		Hemorrhage which led to collapse; disseminated intravascular coagulation syndrome
11354-300014007	85	White	F	35	(b)	Septic shock with multiorgan failure
11354-180214015	70	White	F	8	(4)	Adenocarcinoma of the stomach
11354-520014023	81	White	M	2		Suspected pulmonary embolism
11354-240204007	77	White	M	10		Suspected massive pulmonary thromboembolism
11357-500087008	57	White	F	34		Acute respiratory failure
11357-500107008	91	White	F	1		Respiratory insufficiency; shock; hypovolemic post-hip arthroplasty
11357-120037004*	70	White	M	Subject did not receive any study medication		Multiple injuries
11355-260195005	83	White	F	2	(b)	Acute interstitial pneumonia
11355-600095029	71	Asian	M	10	(4)	Natural death
11355-140105153	53	White	M	6		Upper gastrointestinal bleed
11355-140165070	79	White	F	4		Sepsis
11355-140235019	80	White	F	2		Cardiopulmonary arrest, cardiac arrest x 2, pulmonary embolism
11355-140495008	69	White	F	3		Aspiration pneumonia; pulmonary edema; respiratory failure
Enoxaparin 40 mg od						
11354--280074017	78	White	F	1	(b)	Postanemic coma after cardiac arrest and cardiopulmonary reanimation
11354-180104005	46	White	M	4	(4)	Pulmonary embolism
11354-370124003	73	NA	F	4		Multiorgan failure
11354-470034006	46	White	F	16		Sepsis
11354-470034009	87	White	F	18		Cardiac arrest
11357-500027004	84	White	F	3		Unexpected bleeding; blood polytransfusion; SIRS/SARA; septic shock; death
11357-500027009	76	White	F	13		Massive pulmonary embolism after prosthetic right hip dislocation
11357-540067004	75	Asian	F	1		Fat embolus syndrome
11357-480027027	81	Hispanic	F	11		Septic shock
11357-320057006	86	White	F	11		Respiratory failure

11357-320057017	83	White	F	4	(b)	Bronchoaspiration
11357-320057018	74	White	M	7)	Acute abdominal distention; elevated transaminases; renal failure; intestinal palsy
11357-370087001	69	White	F	10	(4	Pulmonary embolism
11356-280166007	75	White	M	14)	Suspected pulmonary embolism
11356-540156016	76	Asian	M	5)	Acute myocardial infarction
11356-100116011	79	White	M	14)	Pneumonia
11356-640036002	75	Hispanic	M	13)	Respiratory failure Type I-II
11356-370056011	77	White	F	11)	Unknown; likely an acute myocardial infarction or acute pulmonary embolism
11356-370106019	67	White	M	15	(b)	Pulmonary embolism
Enoxaparin 30 mg bid						
11355-600075027	79	Asian	M	6	(b)	Cardiac arrest
11355-600105007	67	Asian	F	6	(4	Myocardial infarction
11355-600105031	78	Asian	M	6)	Septicemia
11355-320075009	86	Hispanic	F	4)	Pneumonia and septic shock
11355-140045010	72	White	M	10)	Metastatic cancer

* Subject received no study medication and was not included in the safety population.

Key: ASM = active study medication; F = female; M = male; NA = not available; SIRS = systemic inflammatory response syndrome; SARA = sexually acquired reactive arthritis

Source: Table 14.3.2/1 in Study RECORD 1 (MRR-00233), Study RECORD 2 (MRR-00234); Study RECORD 3 (MRR-00218); and Study RECORD 4 (MRR-A41857).

Phase 2 and Phase 1 Studies

In the orthopedic VTE prophylaxis studies a total of 8 (0.4%) deaths were observed in the pooled rivaroxaban arm compared with 0 (0%) deaths in the pooled enoxaparin arm. There were 4-fold more subjects exposed to rivaroxaban compared with enoxaparin. The causes of death for 7 deaths in Rivaroxaban are listed in the table below. Three of them died of PE. One death in the rivaroxaban group, not included in the table below, occurred approximately 4 months after the last dose of study medication. The subject (10944-84008) received rivaroxaban 10 mg twice daily for 8 days and developed liver failure 39 days after the end of treatment and subsequently died. This case will be discussed further in hepatic event section.

**Deaths in VTE prophylaxis Phase 2 trials
(Subjects in Studies 10942, 10944, 10945, and 11527)**

Treatment Subject	Sex	Race	Age	Cause of Death	Day of Death ^a
RIVA 2.5 mg bid					
10942-63-034	F	White	76	Sudden death, cardiac arrest, pulmonary embolism	1 day
10945-009-009006	M	White	79	Shortness of breath Pulmonary edema Respiratory failure	21 days
10945-129-129010	F	White	71	Acute respiratory distress Pulmonary embolism	5 days
RIVA 5 mg bid					
10944-31-014	F	White	81	Sepsis, pneumonia	41 days
RIVA 10 mg bid					
10944-79-005	M	White	93	Bronchopneumonia	24 days
10945-010-010040	F	White	75	Pulmonary embolism	31 days
RIVA 30 mg od					
10942-46-024	M	White	80	Cardiorespiratory arrest	0 days

^a Day of death relative to the day of last dose of study treatment (source of relative dates for death and dosing information is the narrative summary for each subject).

Key: bid = twice daily; od = once daily; RIVA = rivaroxaban

Source: Subject narratives in Study 10942 (MRR-00086); Study 10944 (MRR-00135); Study 10945 (MRR-00161); and Study 11527 (MRR-00174).

In the DVT treatment studies, a total of 30 (3.4%, n=883) rivaroxaban subjects and 6 (2.3%, n=263) comparator subjects, died either during or after study treatment. The causes of deaths assessed by the investigators are listed in the Table below. Among 30 deaths in the Rivaroxaban subjects, the cause of death was considered to be cancer in 12 subjects, infection in 4 subjects, sudden death in 2 subjects, PE in 1 subject, bleeding in 1 subject, and liver failure in 1 subject. The subject (11223-506006) who died of liver failure will be further discussed in hepatic event section. Among 6 deaths in enoxaparin subjects, 2 each died of cancer and bleeding, and 1 each died of PE and infection.

**Deaths in DVT treatment Trials
(Subjects in Studies 11223 and 11528)**

Treatment Subject	Sex	Race	Age	Cause of Death^a	Day of Death^b
RIVA 10 mg bid					
11223-505007	F	White	82	Unknown	13
11223-378002	F	Hispanic	62	Lung adenocarcinoma	9
				Pulmonary embolism (acute)	
				Respiratory failure	
11223-356001	M	White	71	Graft infection	54
11223-759001	M	White	77	Septic shock	58
				Acute respiratory distress syndrome	
				Renal failure	
11223-702001	M	White	71	Acute multiple organ failure due to disseminated intravascular coagulation	1
RIVA 20 mg od					
11528-552003	F	White	63	Unknown	0
11528-553009	M	White	78	Gastric cancer	35
11528-503004	F	White	76	Myocardial infarction	41
11528-253003	M	White	74	Cardiorespiratory arrest	0
RIVA 30 mg od					
11528-551003	F	White	76	Lower GI bleeding	107
11528-554001	M	Black	67	Pulmonary embolism	61
11528-351010	F	White	75	Pancreatic cancer	69
11528-301003	M	White	52	Unknown	49
11528-51002	M	White	59	Lung metastases	3
11528-52009	F	Asian	56	Complications of pancreatic cancer	4
11528-57004	M	White	41	Injury (car accident)	1
11528-204003	M	White	56	Colon cancer	1
11528-103003	F	White	79	Sudden death	1
RIVA 20 mg bid					
11223-304004	F	White	68	Multiorgan failure; metastatic carcinoma	18
11223-306002	F	White	34	Metastatic adenocarcinoma of cervix	85
11223-651001	M	White	77	Pneumonia	81
11223-402004	M	White	68	Lung carcinoma	64
RIVA 40 mg od					
11223-506006	F	White	72	Hepatitis B; liver failure	25
11223-252007	M	White	79	Sudden cardiac death	0
11528-306008	M	White	74	Pulmonary edema	40
11528-308001	F	White	52	Metastatic cancer of cervix	16
11528-51011	F	White	47	Renal cell adenocarcinoma	19
11528-151003	F	Black	51	Renal failure	18
RIVA 30 mg bid					
11223-278001	M	Hispanic	50	Cancer	14
11223-603005	M	White	69	Dyspnea; metastatic adenocarcinoma	46
Comparator					
11223-378001	M	Hispanic	77	Sepsis	0
11528-552008	M	White	78	Hemorrhagic stroke	4
11528-312002	M	White	86	Pulmonary embolism; metastatic pancreatic tumor; liver metastases	1
11528-51003	M	White	61	Prostate carcinoma	1
11528-51007	F	White	62	Recurrent rectal hemorrhage	1
11528-59001	M	White	75	Advanced bladder cancer	0

^a Cause of death reflects that reported by the investigator on the CRF. If no reason for death was listed on the CRF, adverse events with outcomes of death are listed.

^b Day of death is relative to the day of last dose of study treatment.

Key: bid = twice daily; od = once daily; RIVA = rivaroxaban

Source: Table 14.3.2/1 in Study 11223 (MRR-00150) and Study 11528 (MRR-00223)

No deaths were reported in the phase 2 atrial fibrillation studies (Japan), or in the Phase 1 studies.

7.2.2 Nonfatal Serious Adverse Events

RECORD Studies

The overall percentage of serious treatment-emergent adverse events was 6.6% in the rivaroxaban group and 8.5% in the enoxaparin group. The following table presents the incidence of serious treatment-emergent adverse events that occurred at $\geq 0.1\%$ in descending order of frequency, based on events on rivaroxaban.

The adverse events that were higher with rivaroxaban compared to enoxaparin were ALT increased, wound infection, femur fracture, operative hemorrhage, wound secretion, anemia, post-operative wound infection, acute renal failure, device related infection, hemorrhage, and nausea.

**Incidence of the Serious Treatment-emergent Adverse Event
that Occurred at $\geq 0.10\%$ in the Rivaroxaban-treated Patients
in Pooled RECORD 1-4 Studies**

Preferred Term	Rivaroxaban (N=6183)	Enoxaparin (N=6200)
ANY EVENT	406 (6.57%)	528 (8.52%)
Deep vein thrombosis	41 (0.66%)	110 (1.77%)
Alanine aminotransferase (ALT) increased	17 (0.27%)	11 (0.18%)
Dislocation joint prosthesis	14 (0.23%)	28 (0.45%)
Wound infection	14 (0.23%)	9 (0.15%)
Femur fracture	13 (0.21%)	6 (0.10%)
Pulmonary embolism	12 (0.19%)	22 (0.35%)
Joint dislocation	11 (0.18%)	24 (0.39%)
Operative hemorrhage	11 (0.18%)	7 (0.11%)
Hematoma	10 (0.16%)	10 (0.16%)
Wound secretion	10 (0.16%)	7 (0.11%)
Atrial fibrillation	9 (0.15%)	11 (0.18%)
Anemia	9 (0.15%)	5 (0.08%)
Hemoglobin decreased	8 (0.13%)	11 (0.18%)
Post operative wound infection	8 (0.13%)	7 (0.11%)
Myocardial infarction	6 (0.10%)	11 (0.18%)
Hepatic enzyme increased	6 (0.10%)	7 (0.11%)
Acute renal failure	6 (0.10%)	5 (0.08%)
Device related infection	6 (0.10%)	2 (0.03%)
Hemorrhage	6 (0.10%)	1 (0.02%)
Nausea	6 (0.10%)	1 (0.02%)

Phase 2 and Phase 1 Studies

In the orthopedic VTE prophylaxis studies, a total of 237 (11%) of subjects in the total rivaroxaban and 58 (10%) subjects in the total enoxaparin treatment groups reported serious adverse events. The incidence of treatment-emergent serious adverse events was higher at higher total daily doses of rivaroxaban due to the bleeding events of operative hemorrhage and hematoma. The most commonly-reported adverse events occurring at an incidence of $>5\%$ in the

total rivaroxaban group were constipation (10% vs. 9%), nausea (16% vs. 19%), vomiting (11% vs. 12%), pyrexia (9% vs. 8%), anemia (7.2% vs. 6.8%), wound secretion (6% vs. 4.1%), decreased hemoglobin (5.4% vs. 4.9%), dizziness (5.3% vs. 5.6%), insomnia (6.6% vs. 7.9%), DVT (7.6% vs. 11.9%), and hematoma (5.8% vs. 4%) in rivaroxaban and enoxaparin subjects, respectively.

In the Phase 2 DVT treatment studies, a total of 117 (13.3%) rivaroxaban subjects and 38 (14.4%) comparator subjects reported serious treatment-emergent adverse events. Among rivaroxaban subjects, the incidence of serious adverse events among dose groups did not suggest a dose-relationship.

In the Atrial Fibrillation Studies, in Study 11866, 1 rivaroxaban subject, and in Study 12024, 2 rivaroxaban subjects and 1 warfarin experienced treatment-emergent serious adverse events. In the Phase 1 studies, serious adverse events were reported by 8 subjects in 7 studies.

7.2.3 Dropouts and/or Discontinuations

The overall percentage of adverse events that led to discontinuation was 3.7% in the rivaroxaban group and 4.7% in the enoxaparin group. The following table presents the incidence of frequently-occurring adverse event that resulted in permanent discontinuation in descending order of frequency. The adverse events leading to permanent discontinuation were higher with rivaroxaban compared to enoxaparin were hematuria, angina pectoris, upper abdominal pain, tachycardia, anesthetic complication, vomiting, peripheral edema, and acute myocardial infarction.

**AEs Leading to Permanent Discontinuation of Study Drug
in RECORD 1-4 Studies**

Preferred Term	Rivaroxaban (N=6183)	Enoxaparin (N=6200)
ANY EVENT	230 (3.72%)	288 (4.65%)
DVT	20 (0.32%)	39 (0.63%)
PE	11 (0.18%)	23 (0.37%)
Nausea	7 (0.11%)	13 (0.21%)
ALT increased	7 (0.11%)	7 (0.11%)
Vomiting	6 (0.10%)	5 (0.08%)
Atrial fibrillation	5 (0.08%)	12 (0.19%)
Operative hemorrhage	5 (0.08%)	9 (0.15%)
Myocardial infarction	5 (0.08%)	6 (0.10%)
Peripheral edema	5 (0.08%)	4 (0.06%)
Hematuria	5 (0.08%)	0 (0.00%)
Acute myocardial infarction	4 (0.06%)	3 (0.05%)
Angina pectoris	4 (0.06%)	1 (0.02%)
Tachycardia	4 (0.06%)	2 (0.03%)
Upper abdominal pain	4 (0.06%)	1 (0.02%)
Anesthetic complication	4 (0.06%)	2 (0.03%)

7.2.4 Significant Adverse Events

7.3.4.1 Bleeding Events

Major Bleeding

The following table shows the treatment-emergent major bleeding and its components in the pooled RECORD studies. The treatment-emergent bleeding events were those that occurred after double-blind administration of first study drug and no later than 2 days after the last intake of study drug. There were a total of 24 (0.4%) and 13 (0.2%) adjudicated treatment-emergent major bleeding events in the rivaroxaban and enoxaparin groups, respectively, with a study-stratified hazard ratio of 1.8 (95% CI: 0.9 to 3.6, p=0.076).

The incidence of major bleeding rate was relatively higher in the TKR patients (0.62% with rivaroxaban and 0.36% with enoxaparin) compared to the THR patients (0.20% with rivaroxaban and 0.09% with enoxaparin). The incidence of major bleeding was higher with rivaroxaban

compared to enoxaparin in all RECORD studies except RECORD 2 study (0.27% and 0.09% in RECORD 1, 0.08% and 0.08% in RECORD 2, 0.57% and 0.48% in RECORD 3, and 0.39% and 0.21% in RECORD 4 for rivaroxaban and enoxaparin, respectively).

Major Bleeding Events in RECORD 1-4

	THR: RECORD 1-2		TKR: RECORD 3-4		Overall	
Bleeding Events	Rivaroxaban N=3437	Enoxaparin N=3453	Rivaroxaban N=2746	Enoxaparin N=2747	Rivaroxaban N=6183	Enoxaparin N=6200
Major Bleeding	7 (0.20%)	3 (0.09%)	17 (0.62%)	10 (0.36%)	24 (0.39%)*	13 (0.21%)
-Fatal bleeding	1 (0.03%)	0	1 (0.04%)	0	2 (0.03%)	0
-Bleeding into a critical organ	1 (0.03%)	1 (0.03%)	2 (0.07%)	4 (0.15 %)	3 (0.05%)	5 (0.08 %)
-Bleeding that required re-operation	2 (0.06%)	1 (0.03%)	10 (0.36%)	6 (0.22%)	12 (0.19%)	7 (0.11%)
-Clinically overt extrasurgical site bleeding associated with a >2 g/dL decrease in Hb	3 (0.09%)	1 (0.03%)	5 (0.18%)	0	8 (0.13%)	1 (0.02%)
-Clinically overt extrasurgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.09%)	1 (0.03%)	5 (0.18%)	0	8 (0.13%)	1 (0.02%)

*p=0.076

There were 2 fatal bleeding events reported in the rivaroxaban group as compared to none in the enoxaparin group.

One of the fatal bleeding events occurred in a subject (11354-160084031) who was randomized to study drug in RECORD 1 study but experienced a fatal bleed prior to receiving active rivaroxaban. The subject entered the study on 02 Oct 2006 and received placebo injection prior surgery at 22:00 on 02 Oct 2006. On 03 Oct 2006, at 18:30, the subject underwent total hip replacement. He experienced hemorrhage at surgical site and urogenital hemorrhage. About 1 hour after surgery, his condition worsened and he was intubated. The subject received 9 transfusions with packed cells (1 x autologous, 8 x donor blood), a total of 3577 mL, within 7½ hours on the day of surgery. Despite new transfusions, the subject experienced hemolysis and “cardiovascular collapse”, secondary to massive transfusion required due to severe hemorrhage.

Disseminated intravascular coagulation (DIC) syndrome was suspected. Despite treatment with transfusion and adrenalin, ephedrine and dopamine for cardiovascular collapse (shock), and cardiac massage for resuscitation, the subject died on 03 Oct 2006 at 23:55 from hemorrhage at surgical site, urogenital hemorrhage and finally from cardiovascular shock.

The second fatal bleed occurred in a subject (11355-14010-5153) undergoing TKR surgery in RECORD 4 study. This 53 year old American male was randomized to receive rivaroxaban. On (b) (4) the subject underwent primary right knee arthroplasty under general anesthesia. He started Rivaroxaban on (b) (4). Intra-operative blood loss was 50 mL and an autotransfusion system was not used. A wound drain was present, and the subject had 140 mL and 30 mL of bloody drainage on (b) (4) and (b) (4) respectively. The subject was discharged from the hospital on (b) (4). The subject received Daypro® (oxaprozin) 1200 mg (b) (4), Aleve® (naproxen) dose unspecified (b) (4) 27 May 2007, and Goody's Powder® (aspirin, caffeine, acetaminophen) 3 packets (b) (4) to (b) (4) for osteoporosis knee pain. On (b) (4), the subject experienced tachycardia (The time was unspecified in the CRF). This adverse event was assessed as non-serious and unrelated to study drug. It remained unchanged with no action taken. On (b) (4) the subject presented to the emergency room with acute onset of hematemesis and melena associated with upper abdominal discomfort. Upper gastrointestinal endoscopy revealed massive upper gastrointestinal hemorrhage (felt to be likely secondary to nonsteroidal, anti-inflammatory drug), ulcer, and suboptimal visualization of the gastric lumen due to a large amount of retained blood and clots. He was transfused with of 250 mL x5 of donor packed cells. His oxygen saturation reportedly dropped into the mid 80's; he was intubated, became unresponsive, and a code was called unsuccessfully. Autopsy on (b) (4) revealed multiple benign gastric ulcers with no evidence of gastric perforation, 40 % stenosis of the circumflex coronary artery, mild aortic atherosclerosis, and hepatomegaly (2450 grams due to passive congestion). The investigator considered the event as related to the study drug. The Bleeding Adjudication Committee assessed the upper gastrointestinal bleed as constituting major bleeding.

Critical organ bleeding events occurred in 3 rivaroxaban subjects (retinal hemorrhage, adrenal hemorrhage, and post-procedural hematoma). The "post-procedural hematoma" was a subject experiencing a spinal hematoma before the start of active rivaroxaban. Critical organ bleeding events occurred in 5 enoxaparin subjects (catheter-site hemorrhage, subdural hemorrhage, extradural hematoma, catheter-related complication, and spinal epidural hemorrhage). The subject with a "catheter-site hemorrhage" had fluid in the epidural catheter that was blood-tinged. The subject with a "catheter-site complication" had a traumatic puncture during an epidural catheter insertion.

Most of the bleeding events in both groups were those that required re-operation (12 [0.19%] in the rivaroxaban group and 7 [0.11%] in the enoxaparin group).

More patients experienced clinically-overt extrasurgical site bleeding events that were associated with a decrease in hemoglobin or required a blood transfusion in the rivaroxaban group as compared to the enoxaparin group. 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. All of these events were gastrointestinal tract bleeding events.

The following table presents centrally adjudicated major bleeding events for individual subjects in the 4 RECORD studies. The bleeding events include major treatment-emergent bleeding events and those that occurred more than 2 days after the last intake of study medication. Four subjects in the rivaroxaban group (2 hematomas [4 and 24 days after the last dose, respectively], 1 hemarthrosis [25 days after the last dose], and a catheter site hemorrhage [prior to treatment]) and 4 subjects in the enoxaparin group (2 GI bleeding [6 days after the last dose in both] hematoma [18 days after the last dose], hemarthrosis [4 days after the last dose]) had major bleeding events more than 2 days after last intake of study medication, and these subjects are noted in the table with asterisks. One subject in the Rivaroxaban group experienced adrenal hemorrhage on Day 8 and later developed left frontal lobe infarct 8 days after the last dose of Rivaroxaban which transformed into hemorrhagic stroke in 2 weeks.

Major Bleeding Events (Central Adjudication) in RECORD 1-4 studies

Study Medication Study-Subject Number	Age	Sex	Adverse Event (MedDRA Preferred Term)	Date of Last ASM	Day of Bleeding Relative to ASM Start	Outcome
Rivaroxaban 10 mg od						
11354-100104016	67	M	Hematoma evacuation		(b) (4)	Resolved
11354-160084031	74	F	Hemorrhage	Subject did not receive active study drug		Death
11354-180154011	78	F	Gastrointestinal hemorrhage; hematemesis		(b) (4)	Resolved
11354-220014003	51	M	Retinal hemorrhage			Improved
11354-240054006	66	M	Gastrointestinal hemorrhage			Resolved
11354-350024032	64	M	Wound hemorrhage			Resolved
11357-120037006	54	F	Hematemesis; hemorrhagic diarrhea			Improved
11356-160016021	65	M	Operative hemorrhage			Resolved
11356-240036002	65	M	Post-procedural hemorrhage			Resolved
11356-240036020	78	F	Post-procedural hematoma	Subject did not receive active study drug		Resolved
11356-300026006*	49	M	Hematoma		(b) (4)	Resolved
11356-300026031	67	M	Hematoma			Resolved
11356-370056009	67	M	Rectal hemorrhage			Resolved
11356-370106010	54	M	Hemorrhage			Resolved
11356-370106022	60	M	Hemarthrosis			Resolved
11355-140045071*	80	F	Adrenal hemorrhage			Resolved
			Hemorrhagic stroke			Resolved
11355-140105018*	56	F	Subcutaneous hematoma			Resolved
11355-140105153	53	M	Upper GI hemorrhage			Death
11355-140115004	78	F	Hemarthrosis			Resolved
11355-140115016	69	F	Hematemesis			Resolved
11355-140205041*	69	F	Hemarthrosis			Resolved
11355-140225061	68	M	Incision site hemorrhage			Resolved
11355-140455077	59	M	Post-procedural hematoma			Resolved
11355-140705004	47	M	Hematoma			Resolved
11355-260135015	76	M	Gastrointestinal hemorrhage			Resolved
11355-350065008	63	F	Hemarthrosis			Resolved
11355-600015092*	60	M	Catheter site hemorrhage			Resolved
11355-900015002	71	F	Gastroduodenal hemorrhage			Resolved
Enoxaparin 40 mg od						
11354-100024030	69	M	Arterial hemorrhage		(b) (4)	Resolved
11354-180214023*	78	F	Feces discolored			Resolved
11354-260054017	76	M	Gastrointestinal hemorrhage			Resolved
11357-340017005	78	F	Spinal epidural hemorrhage			Resolved
11356-100056012*	65	M	Subcutaneous hematoma			Resolved
11356-100106003	74	F	Extradural hematoma			Resolved
11356-180036023	74	F	Post-procedural hemorrhage			Resolved
11356-180106016	77	F	Catheter-related complication			Resolved
11356-300026018	81	M	Hematoma			Resolved
11356-350016024	81	M	Post-procedural hemorrhage			Resolved
11356-370106015	71	F	Wound hemorrhage			Resolved
11356-440046019*	74	M	Hemarthrosis			Resolved
Enoxaparin 30 mg bid						
11355-140105112	47	F	Subcutaneous hematoma			Resolved
11355-320075009*	86	F	Gastrointestinal hemorrhage			Resolved
11355-600015098	66	F	Catheter site hemorrhage			Resolved
11355-600105031	78	M	Subdural hemorrhage			Improved

Key: ASM = active study medication; F = female; GI = gastrointestinal; M = male; MedDRA = Medical Dictionary of Regulatory Activities

Source: Table 14.3.2/5 in Study RECORD 1 (MRR-00233), Study RECORD 2 (MRR-00234); Study RECORD 3 (MRR-00218); and Study RECORD 4 (MRR-A41857).

* Bleeding events for these subjects were not treatment emergent.

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.

Other Bleeding Events

The following table summarizes the other bleeding events in the RECORD studies. There were more clinical relevant non-major bleeding events and any bleeding events with rivaroxaban than with enoxaparin in both patients undergoing hip and knee replacement surgeries.

Other Bleeding Events in RECORD 1-4

Bleeding Events	THR: RECORD 1-2		TKR: RECORD 3-4		Overall	
	Rivaroxaban N=3437	Enoxaparin N=3453	Rivaroxaban N=2746	Enoxaparin N=2747	Rivaroxaban N=6183	Enoxaparin N=6200
Any Bleeding	214(6.2%)	199(5.7%)	220 (8.0%)	202 (7.4%)	434 (7.0%)	401 (6.5%)
Clinically relevant non-major bleeding	105(3.1%)	87(2.5%)	72 (2.6%)	58 (2.1%)	177 (2.9%)	145 (2.3%)
Other non-major bleeding event	114(3.3%)	113(3.3%)	146(5.3%)	143(5.2%)	260 (4.2%)	256 (4.1%)

Non-major clinically relevant bleeding event categories are shown in table below. The most frequently reported non-major bleeding events for the both treatment groups were excessive wound hematomas and surgical site bleedings. More patients experienced macroscopic hematuria, rectal bleeding, nose bleeding, and vaginal bleeding in the rivaroxaban group as compared to enoxaparin group.

**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)**

Endpoint	Rivaroxaban (N = 6183)		Enoxaparin (N = 6200)	
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 hematuria ^a	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 cm ²)	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: Only bleeding event categories that were observed in at least 1 subject are shown

Note: Results based on total duration pool.

Additional analysis for adjudicated bleeding events in different pools.

The sponsor performed additional analysis using combined adjudicated bleeding events and different pooling method for bleeding events.

The following table summarizes the pooled incidence of treatment-emergent adjudicated bleeding events from the 4 RECORD studies and presents data for the total duration pool, the Day 12 ± 2 day pool, and the active control pool. The “total duration pool” considered all events occurring during the administration of double-blind study medication, including events occurring during the placebo period of RECORD 2. The “Day 12 ± 2 pool” considered events occurring during the double-blind period until Day 12 ± 2. The “active control pool” considered events occurring during the active control period from each of the RECORD studies (events occurring during the placebo period of RECORD 2 were excluded).

The incidence of treatment-emergent adjudicated bleeding events was higher in the rivaroxaban group as compared to the enoxaparin group for the various bleeding categories in all three duration pool analyses.

The incidence of major bleeding combined with surgical-site bleeding events was also higher, with a total of 111 (1.8%) and 85 (1.4%) events in the rivaroxaban and enoxaparin groups respectively, with a study-stratified hazard ratio of 1.3 (95% CI: 1.0, 1.7, p=0.082). There were 197 (3.2%) and 158 (2.6%) treatment-emergent major or non-major clinically-relevant adjudicated bleeding events, with a study-stratified hazard ratio of 1.3 (95% CI: 1.0 to 1.5%, p=0.039). The incidence of any treatment-emergent bleeding event was higher in the rivaroxaban

group than in the enoxaparin group (434 [7.0%] and 401 [6.5%], respectively) hazard ratio of 1.1, 95% CI: 0.9, 1.2, p=0.255. Similar results were seen based on the Day 12 ± 2 and active control pool analyses.

**Incidence of Treatment-emergent 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 ^c (95% CI)	Hazard Ratio P Value
Major bleeding event (total duration) ^a	24 (0.39%)	13 (0.21%)	0.18% (-0.01%, 0.37%)	1.84 (0.94, 3.62)	0.076
Major bleeding event until Day 12 ± 2 ^a	21 (0.34%)	13 (0.21%)	0.13% (-0.05%, 0.31%)	1.61 (0.81, 3.22)	0.175
Major bleeding event – active control phase	23 (0.37%)	13 (0.21%)	0.16% (-0.03%, 0.35%)	1.77 (0.90, 3.49)	0.101
Major bleeding combined with surgical site bleeding events (total duration) ^b	111 (1.80%)	85 (1.37%)	0.42% (-0.01%, 0.86%)	1.31 (0.99, 1.73)	0.063
Major bleeding combined with surgical site bleeding events until Day 12 ± 2 ^b	108 (1.75%)	84 (1.35%)	0.39% (-0.04%, 0.83%)	1.29 (0.97, 1.71)	0.082
Major bleeding combined with surgical site bleeding events – active control phase	110 (1.78%)	84 (1.35%)	0.42% (-0.01%, 0.86%)	1.31 (0.99, 1.74)	0.061
Major or non-major clinically relevant bleeding event (total duration)	197 (3.19%)	158 (2.55%)	0.64% (0.05%, 1.23%)	1.25 (1.01, 1.54)	0.039
Major or non-major clinically relevant bleeding event until Day 12 ± 2	176 (2.85%)	152 (2.45%)	0.40% (-0.17%, 0.96%)	1.16 (0.93, 1.44)	0.186
Major or non-major clinically relevant bleeding event, active control phase	190 (3.07%)	156 (2.52%)	0.56% (-0.02%, 1.14%)	1.22 (0.99, 1.51)	0.068
Any bleeding event (total duration)	434 (7.02%)	401 (6.47%)	0.53% (-0.35%, 1.42%)	1.08 (0.94, 1.24)	0.255
Any bleeding event until Day 12 ± 2	409 (6.61%)	384 (6.19%)	0.40% (-0.46%, 1.26%)	1.06 (0.93, 1.22)	0.376
Any bleeding event – active control phase	424 (6.86%)	397 (6.40%)	0.44% (-0.44%, 1.31%)	1.07 (0.93, 1.22)	0.348

^a 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.

^b This definition of major bleeding includes events occurring at the surgical site associated with a decrease in hemoglobin of at least 2 g/dL or for bleedings requiring transfusion of 2 or more units of whole blood or packed cells. Surgical-site bleeding events associated with a decrease in hemoglobin were based on a determination by the investigator. Surgical-site bleeding events requiring transfusion were based on an algorithmic assessment of blood transfusions given within 48 hours of the bleeding event. In addition, both types of surgical-site bleeding events must have been based on bleeding events confirmed by the adjudication committee and reported as overt surgical-site bleeding events by the investigator.

^c This is a Cox-regression analysis with study treated as a covariate.

Note: Total duration refers to the total duration pool (see Section 1.2.4.2).

Key: CI = confidence interval

The incidence of adjudicated, treatment-emergent bleeding events for various bleeding categories in each of the RECORD studies individually based on the total duration pool is shown in the following table. For most of the categories, the incidence was higher on rivaroxaban compared to enoxaparin in all studies. It was noted that there was a higher incidence rate of other non-major (non-clinically relevant) bleeding and also any bleeding in the RECORD 4 study as compared to RECORD 1, 2, and 3 for both treatment groups.

**Incidence of Treatment-emergent Bleeding by Study
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety in pooled RECORD 1-4 studies)**

Endpoint Study	Rivaroxaban)		Enoxaparin	
Major bleeding event				
RECORD 1	6/2209	(0.27%)	2/2224	(0.09%)
RECORD 2	1/1228	(0.08%)	1/1229	(0.08%)
RECORD 3	7/1220	(0.57%)	6/1239	(0.48%)
RECORD 4	10/1526	(0.66%)	4/1508	(0.27%)
All studies pooled	24/6183	(0.39%)	13/6200	(0.21%)
Non-major clinically relevant bleeding event				
RECORD 1	65/2209	(2.94%)	54/2224	(2.43%)
RECORD 2	40/1228	(3.26%)	33/1229	(2.69%)
RECORD 3	33/1220	(2.70%)	28/1239	(2.26%)
RECORD 4	39/1526	(2.56%)	30/1508	(1.99%)
All studies pooled	177/6183	(2.86%)	145/6200	(2.34%)
Other (non-clinically relevant) non-major bleeding event				
RECORD 1	71/2209	(3.21%)	77/2224	(3.46%)
RECORD 2	43/1228	(3.50%)	36/1229	(2.93%)
RECORD 3	22/1220	(1.80%)	31/1239	(2.50%)
RECORD 4	124/1526	(8.13%)	112/1508	(7.43%)
All studies pooled	260/6183	(4.21%)	256/6200	(4.13%)
Major bleeding combined with surgical site bleeding event				
RECORD 1	40/2209	(1.81%)	33/2224	(1.48%)
RECORD 2	23/1228	(1.87%)	19/1229	(1.55%)
RECORD 3	21/1220	(1.72%)	17/1239	(1.37%)
RECORD 4	27/1526	(1.77%)	16/1508	(1.06%)
All studies pooled	111/6183	(1.80%)	85/6200	(1.37%)
Major or non-major clinically relevant bleeding event				
RECORD 1	70/2209	(3.17%)	56/2224	(2.52%)
RECORD 2	41/1228	(3.34%)	34/1229	(2.77%)
RECORD 3	40/1220	(3.28%)	34/1239	(2.74%)
RECORD 4	46/1526	(3.01%)	34/1508	(2.25%)
All studies pooled	197/6183	(3.19%)	158/6200	(2.55%)
Any bleeding event				
RECORD 1	133/2209	(6.02%)	131/2224	(5.89%)
RECORD 2	81/1228	(6.60%)	68/1229	(5.53%)
RECORD 3	60/1220	(4.92%)	60/1239	(4.84%)
RECORD 4	160/1526	(10.48%)	142/1508	(9.42%)
All studies pooled	434/6183	(7.02%)	401/6200	(6.47%)

Note: Only bleeding event categories that were observed in at least 1 subject are shown

Note: Results based on total duration pool.

Consistent with what was observed in the 4 RECORD studies pooled, in the THR pool, the incidence of events in the various bleeding categories was higher on rivaroxaban as compared to

enoxaparin. The incidence of major bleeding was 0.2% in the Rivaroxaban group as compared to 0.09% in the enoxaparin group in patients undergoing total hip replacement surgery. The incidence of non-major clinically relevant bleeding events was 3.05% in the rivaroxaban group as compared to 2.52% in the enoxaparin group.

**Incidence of Treatment-emergent Bleeding by Study
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety in pooled RECORD 1 and 2 studies)**

Endpoint Study	Rivaroxaban N=3437	Enoxaparin N=3453	Hazard Ratio* (95% CI)	Hazard Ratio p-value
Major bleeding event	7(0.20%)	3(0.09%)	2.34 (0.60,9.04)	p=0.219
Non-major clinically relevant bleeding event	105(3.05%)	87(2.52%)	Not done	Not done
Other (non-clinically relevant) non-major bleeding event	114(3.32%)	113(3.27%)	Not done	Not done
Major bleeding combined with surgical site bleeding event	63(1.83%)	52(1.51%)	1.21 (0.84,1.75)	p=0.302
Major or non-major clinically relevant bleeding event	111(3.23%)	90(2.61%)	1.23 (0.93,1.63)	p=0.141
Any bleeding event	214(6.23%)	199(5.76%)	1.08 (0.89,1.30)	p=0.459

* This is a Cox-regression analysis with study treated as a covariate.

N = numerator; D = denominator

Note: Only bleeding event categories that were observed in at least 1 subject are shown

Note: Results based on total duration pool.

In the TKR pool, the incidence of events in the various bleeding categories was higher on rivaroxaban as compared to enoxaparin (see table below). The incidence of major bleeding was 0.62% in the rivaroxaban group as compared to 0.36% in the enoxaparin group inpatients undergoing the total knee replacement surgery. The incidence of non-major clinically relevant bleeding event was 2.62% in the rivaroxaban group as compared to 2.11% in the enoxaparin group.

Incidence of Treatment-emergent Bleeding by Study
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety in pooled RECORD 3 and 4 studies)

Endpoint Study	Rivaroxaban N=2746	Enoxaparin N=2747	Hazard Ratio* (95% CI)	Hazard Ratio p-value
Major bleeding event	17(0.62%)	10(0.36%)	1.70 (0.78,3.70)	p=0.185
Non-major clinically relevant bleeding event	72(2.62%)	58(2.11%)	Not done	Not done
Other (non-clinically relevant) non-major bleeding event	146(5.32%)	143(5.21%)	Not done	Not done
Major bleeding combined with surgical site bleeding event	48(1.75%)	33(1.20%)	1.46 (0.94,2.27)	p=0.096
Major or non-major clinically relevant bleeding event	86(3.13%)	68(2.48%)	1.27 (0.92,1.74)	p=0.145
Any bleeding event	220(8.01%)	202(7.35%)	1.09 (0.90,1.32)	p=0.380

* This is a Cox-regression analysis with study treated as a covariate.

N = numerator; D = denominator

Note: Only bleeding event categories that were observed in at least 1 subject are shown

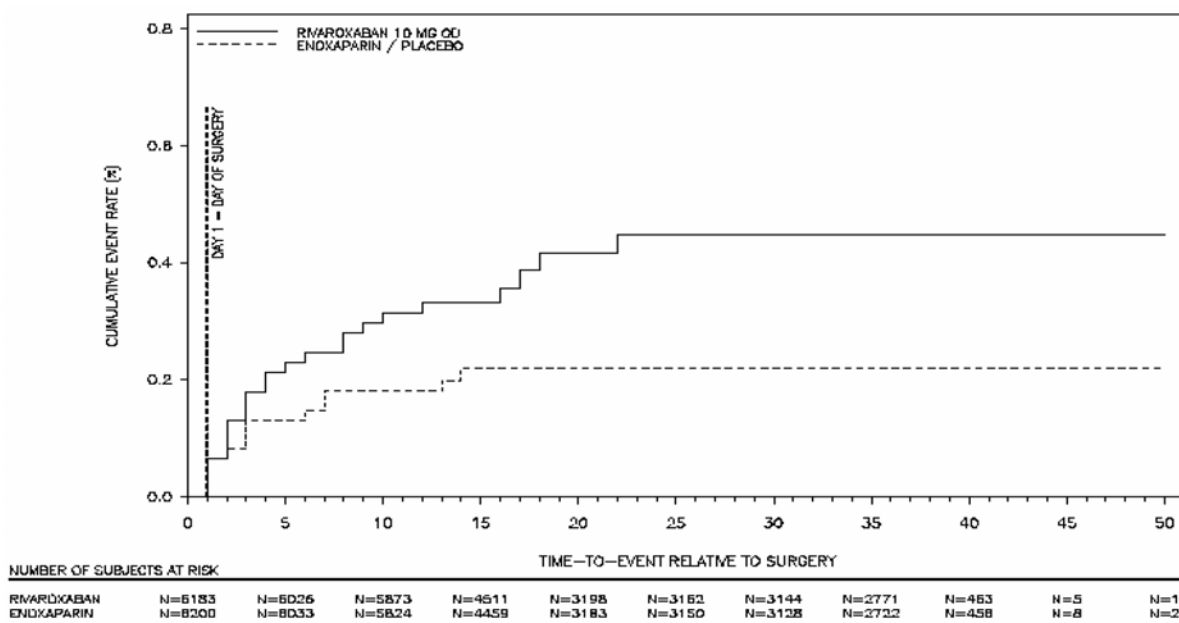
Note: All bleeding events that occurred more than 2 days after the last intake of study medication are not included.

Note: Results based on total duration pool.

Timing of Bleeding Events

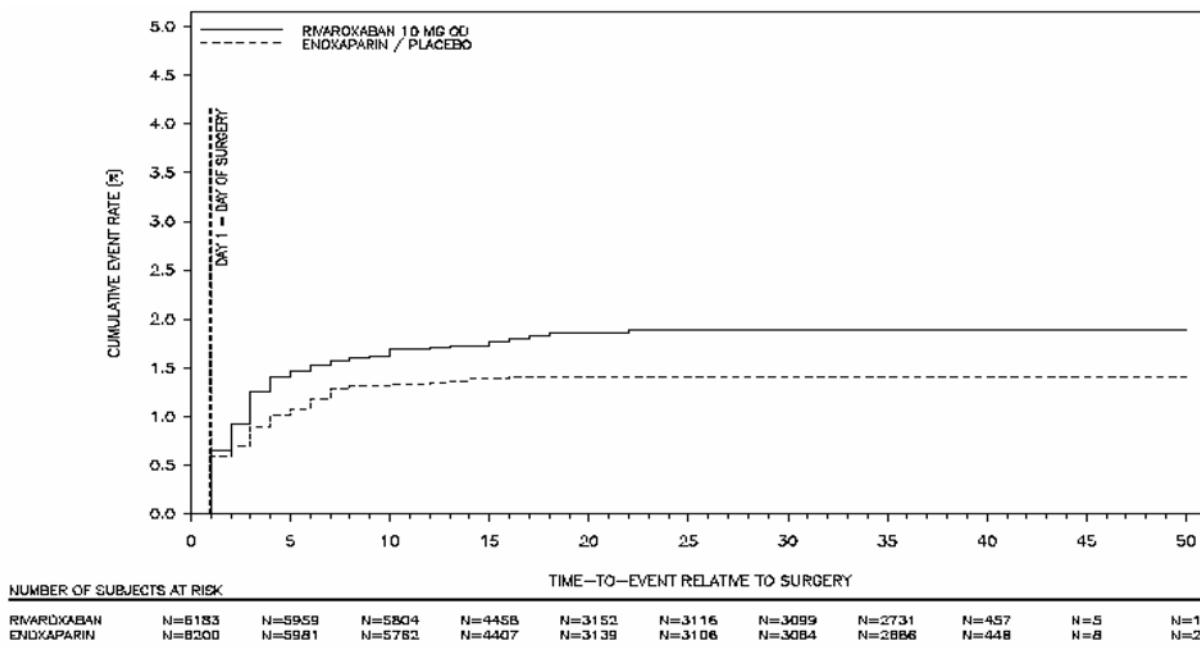
The following figure shows the Kaplan Meier plot of the time to any first major bleeding event. The two curves began to separate 2 days after surgery. The treatment-emergent major bleeding events occurred by Day 7 in 15 (63%) rivaroxaban subjects and 11 (85%) enoxaparin subjects.

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



The following figure shows the time to event for major bleeding combined with surgical bleeding events. Most major bleeding events combined with surgical site bleeding events, occurred within a few days of surgery. The 2 curves begin to separate by Day 2 with separation maintained thereafter.

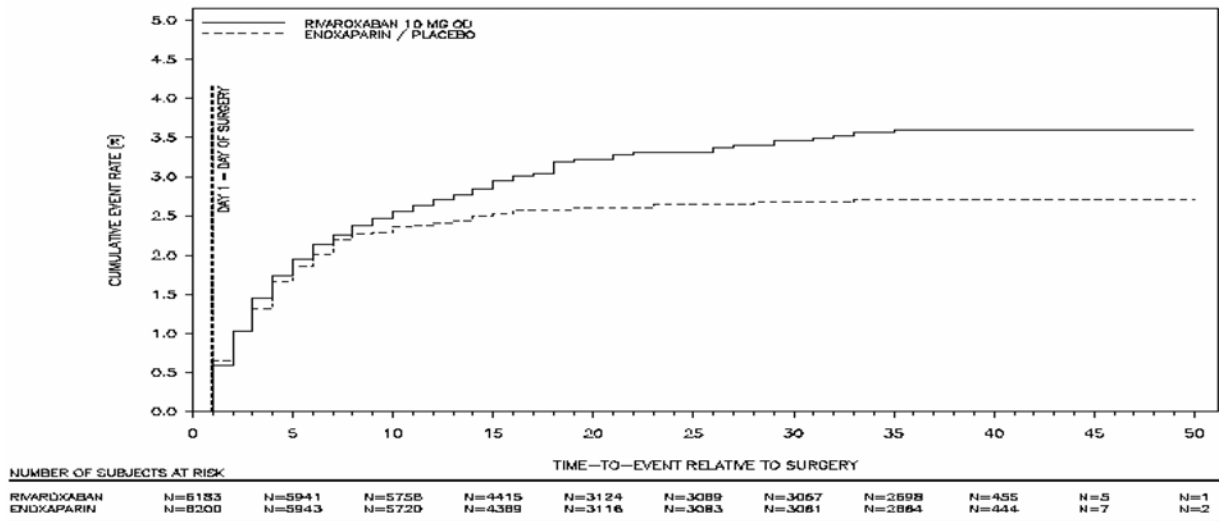
Figure 1-2: Cumulative Rate (Kaplan Meier) of Treatment-emergent Major Bleeding Events Including Surgical Site (Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)



Major or non-major clinically relevant bleeding events occurred by Day 7 in 137 [69.5%] rivaroxaban subjects and 134 [84.8%] enoxaparin subjects, respectively (see figure below). The

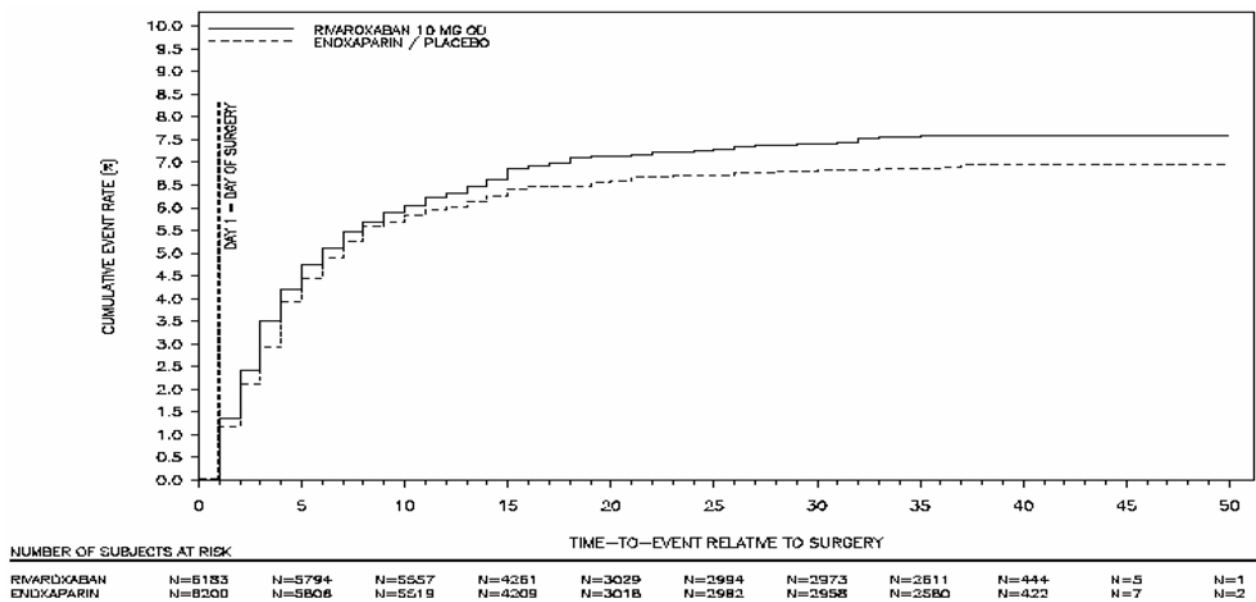
separation between the 2 curves occurred from Day 8 with separation becoming wider over the next 27 days and was maintained thereafter.

Figure 1-3: Cumulative Rate (Kaplan Meier) of Treatment-emergent Major or Non-major Clinically Relevant Bleeding Ever (Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)



The following figure shows the Kaplan Meier plot of the time to any first bleeding event. A majority of the bleeding events occurred by Day 7: 73.9% on rivaroxaban and 77.3% on enoxaparin.

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



The time to bleeding event results for each RECORD study were similar to the pooled RECORD 1-4 studies. Major bleeding events that began more than 2 days after last dose of study drug occurred in 4 (0.06%) subjects in both the rivaroxaban and enoxaparin groups. A total of 12 (0.19%) rivaroxaban subjects and 17 (0.27%) enoxaparin subjects had major or non-major clinically-relevant bleeding events during this period.

Surgical and Extrasurgical Site Bleeding

Slightly more than half of all reported bleeding events were surgical-site bleeding events. A total of 14 (0.2%) rivaroxaban and 7 (0.1%) enoxaparin subjects had treatment-emergent major surgical-site bleeding events (see table below). Of the 14 surgical-site bleeding events with rivaroxaban classified as major, 12 were bleeding events requiring reoperation, 1 was a fatal bleed in a subject who was randomized to rivaroxaban but never received active study medication, and 1 subject who was initially reported as a surgical-site bleed by the investigator, was subsequently adjudicated as an extrasurgical-site bleeding by the Adjudication Committee. Of the 7 enoxaparin major bleeding events, all were bleeding events that required re-operation. A majority (77 [69.4%] and 72 [68.6%]) of non-major, clinically relevant surgical-site bleeding events occurred by Day 4 in the rivaroxaban and enoxaparin treatment groups, respectively. The remainder of the events occurred after this time period.

**Incidence of Treatment-emergent Surgical Site Bleeding Events
(Subjects Valid for Safety in pooled RECORD 1-4 studies)**

Endpoint	Rivaroxaban (N=6183)		Enoxaparin (N=6200)	
Major bleeding event	14 ^a	(0.23%)	7	(0.11%)
Any major or non-major clinically relevant bleeding event	111	(1.80%)	105	(1.69%)
Any bleeding event	247	(3.99%)	224	(3.61%)

^a One subject who was initially reported with a surgical site bleed by the investigator, was later reported with an extrasurgical site bleeding by the Adjudication Committee.

Note: Results based on total duration pool.

Note: Subjects who experienced surgical site bleeding events and extrasurgical site bleeding events are counted separately in Tables 1-19 and 1-20.

The occurrence of major or non-major clinically relevant extrasurgical site bleeding events was relatively delayed compared with surgical site bleeding events. A total of 10 (0.2%) rivaroxaban and 6 (0.1%) enoxaparin subjects had treatment-emergent major surgical-site bleeding events. A total of 33 (36.2%) and 30 (54.5%) major or non-major, clinically relevant extrasurgical site bleeding events occurred by Day 4 in the rivaroxaban and enoxaparin arms, respectively (see Table below). The remainder of the 91 and 55 events in the rivaroxaban and enoxaparin arms, respectively, occurred after Day 4 with most occurring by Day 10.

**Incidence of Treatment-emergent Extrasurgical Site Bleeding Events
(Subjects Valid for Safety in pooled RECORD 1-4 studies)**

Endpoint	Rivaroxaban (N=6183)		Enoxaparin (N=6200)	
Major bleeding event	10	(0.16%)	6	(0.10%)
Any major or non-major clinically relevant bleeding event	91	(1.47%)	55	(0.89%)
Any bleeding event	206	(3.33%)	191	(3.08%)

Note: Results based on total duration pool.

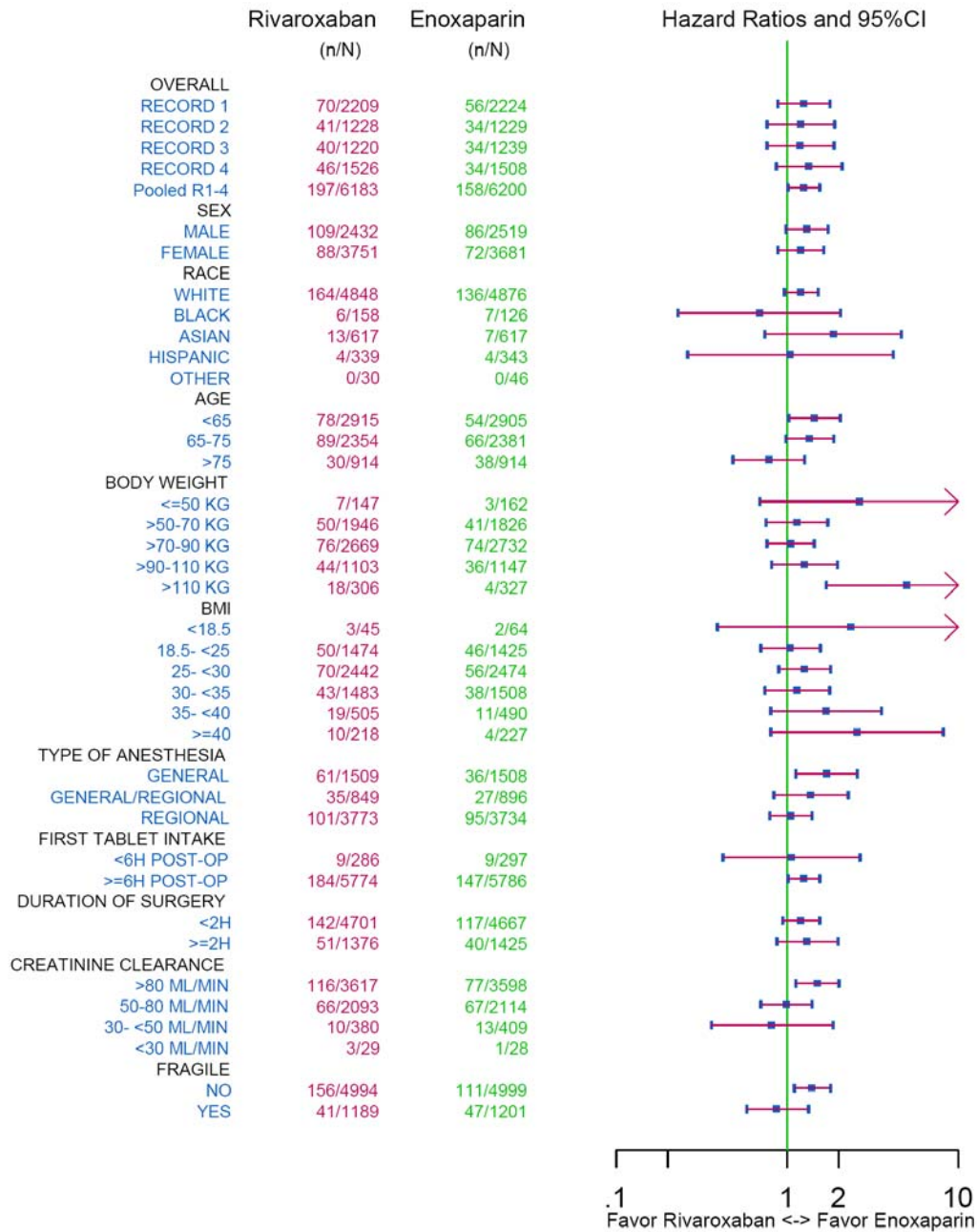
Bleeding Risk in Subgroups

The following figures show the hazard ratio of rivaroxaban relative to enoxaparin and its 95% CI for major or non-major clinically relevant bleeding events and any bleeding event using pooled RECORD 1-4 data in the subgroup analyses. The results in the majority of subgroups were consistent with the results seen in the overall population showing more bleeding events with Rivaroxaban treatment than with enoxaparin.

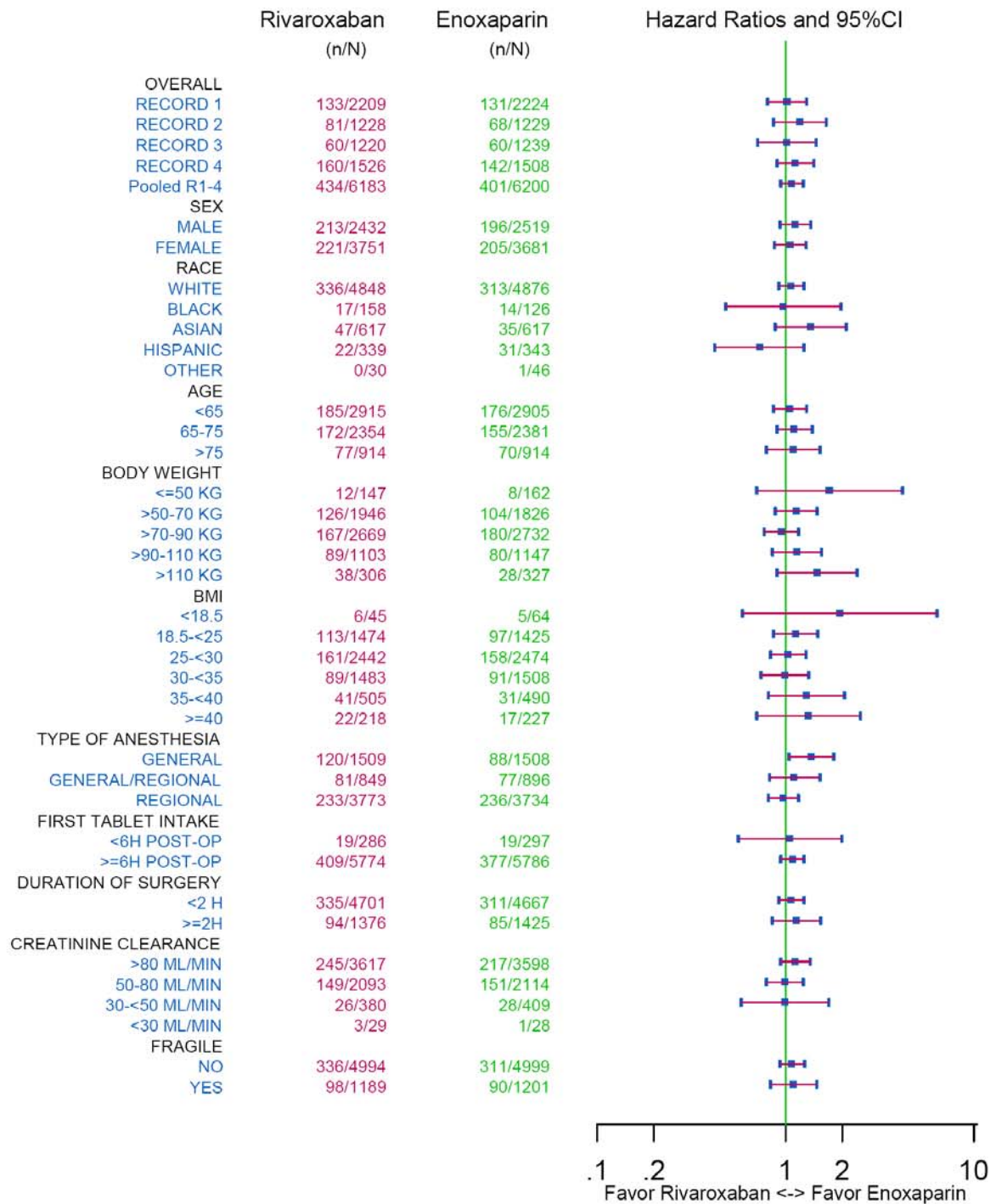
In certain subgroups, such as Asian subjects, subjects with body weight ≤ 50 kg or > 110 kg, BMI < 18.5 or ≥ 40 , the risk of major or non-major clinically relevant bleeding events appeared to be higher with rivaroxaban as compared to other groups.

The results of the subgroup analysis of any bleeding event are generally similar to the subgroup results observed with major or non-major clinically relevant bleeding events. In most subgroups, the results were consistent with results from the overall RECORD population. Asian subjects appear to have a higher risk of any bleeding event with rivaroxaban than other subjects.

Figure 1-5: Major and Non-major Clinically Relevant Bleeding Events and Corresponding Hazard Ratios (95% CI) by Subgroups
(Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)

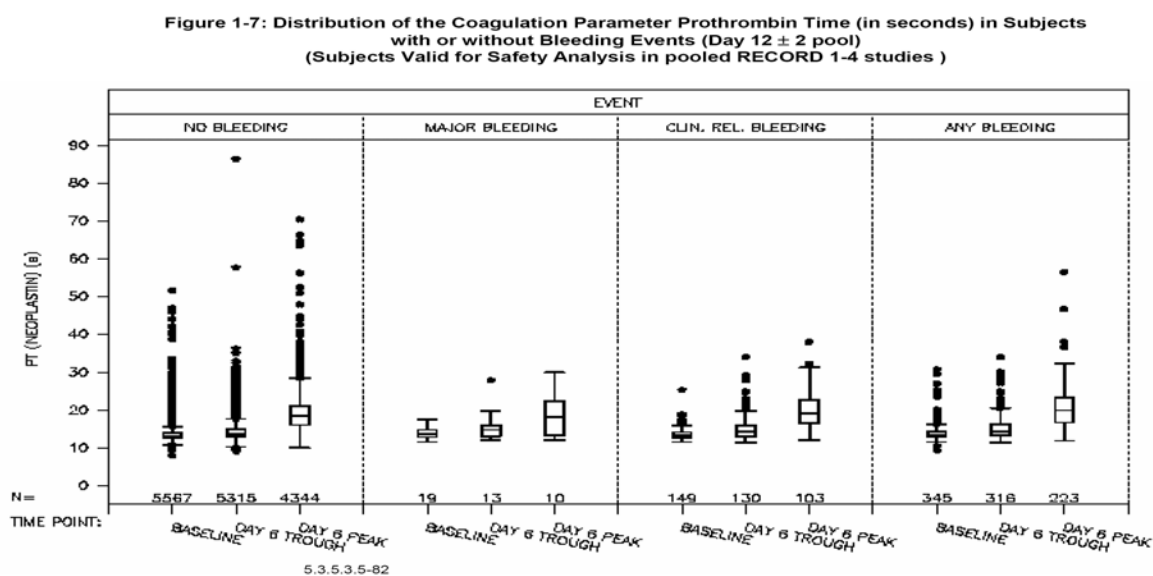


**Figure 1-6: Any Bleeding Events
and Corresponding Hazard Ratios (95% CI) by Subgroups
(Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)**



Bleeding Risk and Correlation to Prothrombin Time Prolongation

A total of 4,373 subjects in the rivaroxaban arm had baseline and Day 6 peak and trough prothrombin time (PT) measurements. The baseline, Day 6 trough, and Day 6 peak mean \pm standard deviation PT values were 13.5 ± 2.0 , 14.3 ± 2.7 , and 19.0 ± 4.5 seconds, respectively. About 90% of subjects had Day 6 peak PT between 13.3 and 26.4 seconds, 5% had Day 6 peak PT ≤ 13.3 seconds, and 5% had Day 6 peak PT ≥ 26.4 seconds. The following Figure shows the distribution of PT values observed at baseline, Day 6 trough, and Day 6 peak in subjects without any bleeding events, subjects with major bleeding events, subjects with clinically relevant non-major bleeding events, and subjects with any bleeding events. Bleeding events occurring until Day 12 \pm 2 are considered in the Figure. It appears that there is no significant difference in PT values in subjects experiencing bleeding events compared with subjects who were not experiencing bleeding events.



The Box-Whisker Plots in Figures 14.4/6, PH-35408 show the following: The upper and lower boundaries of the box indicate the upper quartile and lower quartile, respectively. The line inside the box indicates the median. The vertical lines below and above the box (whiskers), extend (at most) a distance of 1.5 times the length of the box. The whiskers end at the smallest or largest observed value within the 1.5 inter-quartile range. Values below or above the whiskers are denoted as "outliers" and plotted as stars.

Investigator-Assessed Bleeding Events

A total of 428 (6.9%) and 412 (6.7%) rivaroxaban and enoxaparin subjects, respectively, had investigator-assessed, treatment-emergent bleeding events. A total of 64 (1.0%) and 47 (0.8%) rivaroxaban and enoxaparin subjects, respectively had investigator-assessed serious treatment-emergent bleeding events. The most common bleeding events were hematoma, which occurred in 10 (0.2%) rivaroxaban and 10 (0.2%) enoxaparin subjects; operative hemorrhage, which occurred in 11 (0.2%) and 7 (0.1%) rivaroxaban and enoxaparin subjects, respectively; and wound hemorrhage, occurring in 3 (0.1%) and 6 (0.1%) rivaroxaban and enoxaparin subjects, respectively. A total of 50 (0.8%) and 36 (0.6%) rivaroxaban and enoxaparin subjects, respectively, experienced bleeding adverse events resulting in permanent study drug discontinuation. The most common adverse bleeding events leading to discontinuation were hematuria (5 [0.1%] and 0 [0%] of rivaroxaban and enoxaparin, respectively), operative hemorrhage (5 [0.1%] and 9 [0.2%] of rivaroxaban and enoxaparin subjects, respectively),

epistaxis (3 [$<0.1\%$] of rivaroxaban and enoxaparin subjects), and hematoma (3 [$<0.1\%$] of rivaroxaban and enoxaparin subjects).

Intraoperative Blood Loss and Blood Transfusion

The intraoperative blood loss in the THR studies (RECORD 1 and 2) was 479.7 ± 337.2 mL and 491.7 ± 357.6 mL on rivaroxaban and enoxaparin, respectively. The intraoperative blood loss in the TKR studies (RECORD 3 and 4) was 203.7 ± 240.4 mL and 196.1 ± 205.1 mL on rivaroxaban and enoxaparin, respectively. Similarly, the incidence of blood transfusion was higher in the hip studies compared with the knee studies. In the RECORD 1 and 2 hip studies, a total of 1695 (49.3%) and 1763 (51.1%) subjects, respectively received any blood transfusion. In the RECORD 3 and 4 knee studies, a total of 1247 (45.5%) and 1172 (42.7%) subjects, respectively, received any blood transfusion.

7.3.4.2 Cardiovascular Events

According to the operation manual, the Cardiovascular Events Adjudication Committee (AC/CV) adjudicated all investigator-identified cases of death (cardiovascular or non-cardiovascular), myocardial infarction or stroke. Originally, in RECORD 1 and 2, the AC/CV adjudicated only CV deaths identified by the sponsor medical monitor. Twenty-one CV events in 19 subjects were observed in the rivaroxaban group and 14 CV events in 14 subjects were observed in the enoxaparin group. Two subjects in the rivaroxaban group, both in RECORD 1, experienced 2 events; the first subject (180214015) had an MI on treatment (Day 8) and a CV death off treatment (Day 34), and the second subject (360044014) had an MI off treatment (Day 44) and an ischemic stroke off treatment (Day 69).

After the databases for RECORD 1 and 2 were unblinded, all deaths were sent to the AC/CV for the retrospective adjudication and these included 14 deaths (2 in the rivaroxaban group and 12 in the enoxaparin group) that had not originally been sent to the AC/CV for adjudication. In addition, one identified MI was also sent for the retrospective adjudication. The MI (RECORD 2 subject 260077025) was adjudicated as “no MI” by the AC/CV. The 14 deaths consisted of 5 subjects in RECORD 1 (1 in the rivaroxaban group and 4 in enoxaparin group) and 9 subjects in RECORD 2 (1 in the rivaroxaban group and 8 in the enoxaparin group). The AC/CV adjudicated these 14 cases in a fully blinded fashion, and did not re-adjudicate or reassess any of the originally adjudicated events. Of these 14 additional deaths that underwent adjudication by the AC/CV, 5 deaths were classified as “CV-death”, and 1 as “unexplained death”, all of these events occurred in the enoxaparin group, and no other CV events were identified in the rivaroxaban group. One subject with an “unexplained death” (RECORD 2 subject 370087001) had already had a prior adjudicated event of ischemic stroke entered into the database. After retrospective adjudication for RECORD 1 and 2 studies, a total of 20 CV events in 19 subjects were identified in the enoxaparin group and the data for the rivaroxaban group were unchanged as a total of 21 CV events in 19 subjects.

In RECORD 3 and 4, all deaths were sent for adjudication by the AC/CV.

The following table presents retrospectively adjudicated cardiovascular events that occurred in the safety population during study drug treatment and during the 30-day post-study drug follow-up in the 4 RECORD studies. There was one subject in the rivaroxaban group with an adjudicated event of ischemic stroke (occurring 8 days after last dose of study drug) who was not included in the clinical database because the adjudicated results were not available prior to database unblinding. This subject is included in the table below. The total number of cardiovascular events (centrally adjudicated myocardial infarction, stroke and death) during treatment and follow-up was 31 events (0.50%) in the rivaroxaban group and 39 events (0.63%) in the enoxaparin group.

A total of 12 (0.19%) adjudicated ischemic events were observed in the rivaroxaban group as compared to 7 (0.11%) ischemic stroke events in the enoxaparin group.

There was one rivaroxaban subject in whom an adverse event preferred term of “lacunar infarction” was reported; however, this potential event was not sent for adjudication because the investigator indicated that it was a pre-existing condition. This event occurred while the subject was on study drug.

In addition, 3 subjects in the enoxaparin group with a suspected myocardial infarction were considered not assessable by the AC/CV and are not included.

In the enoxaparin group, more than half (21 [54%]) of the events occurred through Day 6. In the rivaroxaban group, 12 (40%) of the total number of events occurred through Day 6.

**Incidence of Cardiovascular Events (Retrospective Central Adjudication)
(Subject Valid for Safety in pooled RECORD 1-4 studies)**

Preferred Term	Rivaroxaban (N=6183)	Enoxaparin (N=6200)
Any cardiovascular events	31 (0.50%)	39 (0.63%)
Myocardial infarction	13 (0.21%)	18 (0.29%)
Ischemic stroke	12 (0.19)	7 (0.11%)
Cardiovascular death	7 (0.11%)	12 (0.19%)
Unexplained death	1 (0.02%)	4 (0.06%)

The following table shows the cardiovascular events during on and off treatment period in RECORD studies. Cardiovascular events on active treatment are those that occur after 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 last intake of active study medication. The 1-day window for differentiating on-active treatment versus off-active treatment events was pre-specified.

The incidence of on-active treatment cardiovascular events was lower in subjects in the rivaroxaban group (13 [0.2%]) compared with enoxaparin (25 [0.4%]). The ischemic stroke

event rates were similar between the two treatment groups during the treatment period. Cardiovascular events occurring off active treatment were slightly more in subjects in the rivaroxaban group (17, 0.3%) than in the enoxaparin group (14, 0.2%).

Among the 17 subjects who experienced cardiovascular events in the rivaroxaban group and 14 in the enoxaparin group during the off-treatment period, 11 (66%) events (4 MI, 3 stroke and 4 CV deaths) in the rivaroxaban group and 2 (14%) events (1 CV death and 1 unexplained death) in the enoxaparin group occurred within 10 days after the last dose of treatment; 7 (41%) events (2 MI, 2 stroke, and 3 CV deaths) in the rivaroxaban group and 1 (7%) events (CV death) in the enoxaparin group occurred within 5 days after the last dose of treatment.

There were more ischemic stroke events in subjects in the rivaroxaban group (6, 0.10%) than in the enoxaparin group (1, 0.02%) during the off treatment period. The 6 stroke events occurred in 4, 5, 8, 13, 34, and 39 days after the last dose of treatment in 6 subjects. One stroke event in the enoxaparin group occurred 26 days after the last dose of treatment.

**Incidence of Cardiovascular Events (Retrospective Adjudication)
During On and Off Treatment Period in RECORD 1-4
(Subjects Valid for Safety with Active Study Drug in pooled RECORD 1-4 studies)**

	On Treatment		Off Treatment	
Preferred Term	Rivaroxaban (N=6183)	Enoxaparin (N=6200)	Rivaroxaban (N=6183)	Enoxaparin (N=6200)
Any cardiovascular events	13 (0.21)	25 (0.40)	17 (0.28)	14 (0.23)
Myocardial infarction	7 (0.11)	14 (0.23)	5 (0.08)	4 (0.06)
Ischemic stroke	5 (0.08)	6 (0.10)	6 (0.10)	1 (0.02)
Cardiovascular death	1 (0.02)	5 (0.08)	6 (0.10)	6 (0.10)
Unexplained death	0	0	1 (0.02)	4 (0.06)

7.3.4.3 Wound Complications

The incidence of any wound complication event was higher on rivaroxaban compared with enoxaparin. The incidence of infectious surgical wound complications was balanced between the 2 treatment groups. The incidence of non-infectious wound complications was higher on rivaroxaban compared with enoxaparin. The preferred term ‘wound secretion’ was the most

commonly reported noninfectious wound complication and was responsible for most of the increase. The majority of reported wound secretion adverse events were mild in severity. The incidence of any wound complication serious adverse event was comparable on rivaroxaban 46 (0.7%) and enoxaparin 47 (0.8%). The events of any wound complication adverse events resulting in permanent discontinuation of study drug occurred in 3 (0.1%) and 10 (0.2%) of subjects on rivaroxaban and enoxaparin, respectively.

Incidence of Treatment-emergent Wound Complications (Subjects Valid for Safety in pooled RECORD 1-4 studies)				
Endpoint Studies	Rivaroxaban (N =6183)		Enoxaparin (N =6200)	
Surgical Wound Complications				
Any event	332	(5.37%)	280	(4.52%)
Surgical wound complications, infectious				
Any event	78	(1.26%)	82	(1.32%)
Postoperative wound infection	27	(0.44%)	28	(0.45%)
Wound infection	38	(0.61%)	35	(0.56%)
Surgical wound complications, non-infectious				
Any event	269	(4.35%)	206	(3.32%)
Wound complication	39	(0.63%)	31	(0.50%)
Wound secretion	146	(2.36%)	106	(1.71%)
Key:	MedDRA = Medical Dictionary Regulatory Activities			
Note:	Only treatment-emergent adverse event that occurred up to 2 days after the last dose of study medication are included.			
Note:	Incidence rate = # of events / # at risk, where: # of events = # of subjects reporting the event after the start of treatment			
Note:	The table presents MedDRA terms of the primary path			

7.3.4.4 Hepatic Events

7.3.4.4.1 RECORD Studies

Abnormal Liver-related Laboratory Values

The liver-related laboratory parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, 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 placebo tablet) but after the first injection dose of the study drug (enoxaparin or matching dummy placebo injection) in RECORD 1-3.

The following table shows the incidence of liver-related laboratory abnormalities post-baseline in pooled RECORD studies. The elevation of ALT>3xULN was observed in 152 (2.5%) subjects in the rivaroxaban group as compared to 227 (3.7%) subjects in the enoxaparin group. For ALT

abnormality, there were fewer patients with ALT >3xULN, >5xULN, and >8xULN in the Rivaroxaban group as compared to the enoxaparin group. However, for ALT >10xULN and >20xULN, there was 1 more patient in the rivaroxaban group than in the enoxaparin group for each category. There were slightly more patients with total bilirubin (TB) >1.5xULN in the rivaroxaban group as compared to the enoxaparin group.

There were 9 (0.15%) patients who had ALT >3xULN concurrent with TB >2xULN in the rivaroxaban group as compared to 7 (0.11%) patients in the enoxaparin group. Concurrent refers to laboratory analyses drawn from the same sample. These subjects will be discussed later in this review.

There were 10 subjects in the rivaroxaban group and 9 subjects in the enoxaparin group with elevations in ALT levels to >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 subject in RECORD 4 (11355-600095028) 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. Additional follow-up on this subject after the RECORD 4 study results were unblinded revealed that ALT levels had normalized 2 weeks later. In addition, 1 subject in RECORD 2 (11357-120087009) received enoxaparin for 9 days and subsequently had an ALT level >10x ULN one day later (Day 10). This subject had incomplete laboratory follow-up.

There were 8 (0.13%) patients who had AST levels >3x ULN concurrent with TB >2x ULN in each treatment groups.

With respect to elevations of ALT levels >3x ULN concurrent with total bilirubin levels >2x ULN with the ratio of conjugated to total bilirubin ≥ 0.5 , there were 4 and 5 such cases observed in the rivaroxaban and enoxaparin arms, respectively.

There were fewer subjects with AST >3xULN and high categories, ALK PHOS > 3xULN and GGT >3xULN in rivaroxaban group than in the enoxaparin group.

Pooled Incidence Rates of Liver-related Post-baseline Laboratory Abnormalities
– After Day 0 Baseline
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

Laboratory Variable Limit	Rivaroxaban (N=6183)		Enoxaparin (N=6200)	
ALT >3x ULN concurrent with total bilirubin >2x ULN	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				
>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%)
AST >3x ULN concurrent with total bilirubin >2x ULN	8/6131	(0.13%)	8/6131	(0.13%)
AST >3x ULN concurrent with total bilirubin >2x ULN and conjugated bilirubin ≥0.5 total bilirubin	5/6131	(0.08%)	6/6130	(0.10%)
AST				
>3x ULN	160/6131	(2.61%)	209/6131	(3.41%)
>5x ULN	61/6131	(0.99%)	84/6131	(1.37%)
>8x ULN	28/6131	(0.46%)	29/6131	(0.47%)
>10x ULN	19/6131	(0.31%)	20/6131	(0.33%)
>20x ULN	4/6131	(0.07%)	4/6131	(0.07%)
Total bilirubin				
>1.5x ULN	169/6133	(2.76%)	158/6131	(2.58%)
>2x ULN	48/6133	(0.78%)	48/6131	(0.78%)
>3x ULN	10/6133	(0.16%)	11/6131	(0.18%)
>5x ULN	2/6133	(0.03%)	4/6131	(0.07%)
>8x ULN	1/6133	(0.02%)	1/6131	(0.02%)
Alkaline phosphatase				
>3x ULN	20/6133	(0.33%)	21/6132	(0.34%)
>5x ULN	0/6133	(0.00%)	1/6132	(0.02%)
>8x ULN	0/6133	(0.00%)	0/6132	(0.00%)
>10x ULN	0/6133	(0.00%)	0/6132	(0.00%)
>20x ULN	0/6133	(0.00%)	0/6132	(0.00%)
GGT				
>3x ULN	401/6133	(6.54%)	553/6132	(9.02%)
>5x ULN	139/6133	(2.27%)	211/6132	(3.44%)
>8x ULN	38/6133	(0.62%)	75/6132	(1.22%)
>10x ULN	15/6133	(0.24%)	33/6132	(0.54%)
>20x ULN	0/6133	(0.00%)	4/6132	(0.07%)

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

Note: The scheduled Day 0 visit is used as baseline.

Note: Incidence rate = # of events / # at risk, where:
of events = # of subjects reporting the abnormality after Day 0
at risk = # of subjects with values after Day 0

Note: All measurements after the start of double-blind study medication are included regardless of onset relative to the last dose.

Note: The subjects reported in higher threshold categories are also included in lower threshold categories.

An additional analysis was performed for liver-related laboratory abnormalities by race. In the RECORD studies, there were about 80% Caucasians, 10% Asians and 10% of subjects with

other races. The following table shows the liver-related abnormalities in two treatment groups in Asian and Caucasian. It was noted that there were significantly higher incidence of ALT>3xULN and TB>2xULN in the rivaroxaban group (4, 0.65%) than in the enoxaparin group (1, 0.16%) in Asians but it was not seen in Caucasians. The four Asian in the rivaroxaban group were from China, Indonesia, India and Sri Lanka, respectively. The one Asian in enoxaparin group was from India. There were also higher rate of ALT>10 xULN and >20xULN with rivaroxaban than with enoxaparin in Asian. The difference between the races was not seen for other abnormalities.

Incidence Rates of Liver-Related Abnormalities in RECORD 1-4 in Asian and Caucasian

	Asian		Caucasian	
LFTs and others	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
ALT >3x ULN and TB>2x ULN	4 / 614 (0.65%)	1/611 (0.16%)	4 / 4811 (0.08%)	5 / 4817 (0.10%)
ALT> 3x ULN	20 / 614 (3.26%)	34/611 (5.56%)	118 / 4811(2.45%)	166 / 4817 (3.45%)
>5x ULN	6 / 614 (0.98%)	13/611 (2.13%)	44 / 4811 (0.91%)	55 / 4817 (1.14%)
> 8x ULN	5 / 614 (0.81%)	5/611 (0.82%)	12 / 4811 (0.25%)	12 / 4817 (0.25%)
> 10x ULN	4 / 614 (0.65%)	2/611 (0.33%)	6 / 4811 (0.12%)	6 / 4817 (0.12%)
> 20x ULN	2 / 614 (0.33%)	1/611 (0.16%)	0 / 4811 (0.00%)	0 / 4817 (0.00%)
AST >3x ULN and TB>2x ULN	4 / 614 (0.65%)	1/611 (0.16%)	3 / 4811 (0.06%)	7 / 4817 (0.15%)
AST>3x ULN	17 / 614 (2.77%)	26/611 (4.26%)	128 / 4811 (2.66%)	166 / 4817 (3.45%)
>5x ULN	5 / 614 (0.81%)	8/611 (1.13%)	49 / 4811 (1.02%)	55 / 4817 (1.14%)
>8x ULN	4 / 614 (0.65%)	4/611 (0.65%)	21 / 4811 (0.44%)	12 / 4817 (0.25%)
>10x ULN	4 / 614 (0.65%)	3/611 (0.49%)	13 / 4811 (0.27%)	6 / 4817 (0.12%)
>20x ULN	1 / 614 (0.16%)	1/611 (0.16%)	3 / 4811 (0.06%)	0 / 4817 (0.00%)
TB >1.5x ULN	50 / 614 (8.14%)	50/611 (8.18%)	110 / 4813 (2.29%)	97 / 4817 (2.01%)
>2x ULN	14 / 614 (2.28%)	12/611 (1.96%)	32 / 4813 (0.66%)	31 / 4817 (0.64%)
ALP >3x ULN	3 / 614 (0.49%)	2/611 (0.33%)	14 / 4813 (0.29%)	17 / 4818 (0.35%)
GGT >3x ULN	25 / 614 (4.07%)	30/611 (4.91%)	313 / 4813 (6.50%)	429 / 4818 (8.90%)

ALT Elevations Over Time

There were mean increases in ALT levels in both the THR and TKR studies occurring on Days 6 and 13 in both treatment groups. There was more increase from baseline on Days 6 and 13 in the

enoxaparin group compared with rivaroxaban in both the THR and TKR studies (see Tables below).

**Mean (SD) Changes from Day 0 Baseline in ALT Levels in THR trials
(Subjects Valid for Safety in RECORD 1 and 2)**

	Rivaroxaban Mean (SD) U/L	Enoxaparin Mean (SD) U/L
Day 0 (baseline)	22.1 (13.0)	22.4 (14.2)
Change from baseline (Day 1)	-0.4 (22.6)	-1.1 (15.4)
Change from baseline (Day 6 ± 2)	12.0 (30.3)	18.8 (65.2)
Change from baseline (Day 13 ± 2)	7.2 (24.2)	14.5 (33.4)
Change from baseline (Day 36 ± 4)	-2.7 (26.8)	1.0 (18.9)
Change from baseline (Day 65 + 5)	-1.6 (12.5)	-1.7 (15.0)

Key: ALT = alanine aminotransferase; SD = standard deviation

Note: The scheduled Day 0 visit is used as baseline; when earlier visits are present, the last value up to and including Day 0 is used as baseline.

Note: If more than 1 measurement is available for a subject at the same visit, the mean value is used for analysis.

Note: Only subjects having a non-missing baseline assessment and at least 1 non-missing postbaseline assessment are included.

**Mean (SD) Changes from Day 0 Baseline in ALT Levels in TKR Trials
(Subjects Valid for Safety in RECORD 3 and 4)**

	Rivaroxaban Mean (SD) U/L	Enoxaparin Mean (SD) U/L
Day 0 (baseline)	22.2 (13.2)	21.8 (12.0)
Change from baseline (Day 1)	0.0 (20.0)	1.0 (23.5)
Change from baseline (Day 6 ± 2)	8.1 (31.1)	12.6 (29.4)
Change from baseline (Day 13 ± 2)	4.7 (21.2)	13.1 (31.3)
Change from baseline (Day 42 + 5)	-2.4 (26.8)	-2.5 (12.2)

Key: ALT = alanine aminotransferase; SD = standard deviation

Note: The scheduled Day 0 visit is used as baseline; when earlier visits are present, the last value up to and including Day 0 is used as baseline.

Note: If more than 1 measurement is available for a subject at the same visit, the mean value is used for analysis.

Note: Only subjects having a non-missing baseline assessment and at least 1 non-missing postbaseline assessment are included.

The time to first occurrence (after Day 0) of ALT levels >3x ULN is presented in the following tables for THR and TKR trials. In the THR studies, there were more subjects with first ALT levels >3x ULN events on Day 1 but fewer after Day 1 in the rivaroxaban group than in the enoxaparin group. In the TKR studies, there were more subjects with first ALT levels >3x ULN events on interim Days 1-6 and ≥Day 42 but fewer on other days on rivaroxaban compared with enoxaparin.

**Time to First Occurrence of ALT > 3x ULN After Day 0 in THR Trials
(Subjects Valid for Safety in THR - RECORD 1 and 2)**

Time Point	Rivaroxaban		Enoxaparin	
	Number of Events/Number of Subjects w/ Labs	Event Rate	Number of Events/Number of Subjects w/ Labs	Event Rate
Day 1	18/3307	(0.54%)	11/3314	(0.33%)
Interim Days 1 - 6	1/28	(3.57%)	1/26	(3.85%)
Day 6 (± 2 days)	40/2928	(1.37%)	67/2922	(2.29%)
Interim Days 6 – 13	1/15	(6.67%)	2/28	(7.14%)
Day 13 (± 2 days)	20/3135	(0.64%)	34/3100	(1.10%)
Interim Days 13 - 36	0/25	(0.00%)	0/32	(0.00%)
Day 36 (± 4 days)	3/3043	(0.10%)	10/2964	(0.34%)
Interim Days 36 - 65	0/16	(0.00%)	0/10	(0.00%)
≥Day 65 (± 5 days)	4/2897	(0.14%)	7/2848	(0.25%)
Total time period	87		132	

Key: ALT = alanine aminotransferase; Labs = laboratory results; ULN = upper limit of normal

Note: Measurements taken more than 2 days after the end of treatment are included.

Note: Subjects with abnormality at Day 0 or Day 0 value only are not included.

Note: An “interim” assessment is a laboratory assessment at a non-protocol scheduled timepoint.

**Time to First Occurrence of ALT > 3x ULN After Day 0
(Subjects Valid for Safety in TKR - RECORD 3 and 4)**

Time Point	Rivaroxaban		Enoxaparin	
	Number of Events/Number of Subjects w/ Labs	Event Rate	Number of Events/Number of Subjects w/ Labs	Event Rate
Day 1	20/2642	(0.76%)	30/2644	(1.13%)
Interim Days 1 - 6	2/17	(11.76%)	0/8	(0.00%)
Day 6 (± 2 days)	27/2563	(1.05%)	32/2546	(1.26%)
Interim Days 6 – 13	0/22	(0.00%)	1/19	(5.26%)
Day 13 (± 2 days)	10/2486	(0.40%)	27/2471	(1.09%)
Interim Days 13 – 42	0/15	(0.00%)	0/24	(0.00%)
≥Day 42 (± 5 days)	4/2372	(0.17%)	2/2332	(0.09%)
Total time period	63		92	

Key: ALT = alanine aminotransferase; Labs = laboratory results; ULN = upper limit of normal

Note: Measurements taken more than 2 days after the end of treatment are included.

Note: Subjects with abnormality at Day 0 or Day 0 value only are excluded.

Note: An “interim” assessment is a laboratory assessment at a non-protocol scheduled timepoint.

The prevalence of subjects with ALT levels >3x ULN over time for the pooled RECORD studies is shown in Table below. A total of 40 rivaroxaban subjects [0.7%] and 43 enoxaparin subjects [0.7%] showed increased ALT levels on Day 1 before administration of rivaroxaban, due to the effects of surgery. The majority of subjects who had increased ALT levels experienced them in the period after surgery until Day 13. The prevalence of ALT levels >3x ULN after Day 13 was 0.3% and 0.5% in subjects receiving rivaroxaban and enoxaparin, respectively.

**Prevalence of ALT >3x ULN by Time Windows in RECORD Studies
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies)**

Visit/Time Window	Rivaroxaban		Enoxaparin	
Day 0	5/6103	(0.08%)	7/6109	(0.11%)
Day 1	40/5954	(0.67%)	43/5965	(0.72%)
After Day 1	119/6032	(1.97%)	188/6009	(3.13%)
Day 6 (± 2)	72/5529	(1.30%)	103/5513	(1.87%)
Day 13 (± 2)	39/5726	(0.68%)	71/5712	(1.24%)
Until Day 13 (± 2)	108/5992	(1.80%)	169/5971	(2.83%)
After Day 13 (± 2)	19/5648	(0.34%)	30/5614	(0.53%)

Key: ALT = alanine aminotransferase

Note: Day 0 visit scheduled prior to surgery

Note: Day 1 visit scheduled after surgery and prior to first tablet intake (active or dummy).

Note: In case of multiple measurements per visit/time window, the highest value is used.

Note: Measurements taken more than 2 days after the end of treatment are included.

Note: Time windows of "Until" and "After" include measurements from interim visits

The following Figures show the time course of ALT changes in individual subjects in each RECORD study who met the criteria for ALT levels >5x ULN at any time during the study on rivaroxaban and enoxaparin, respectively.

In the Record 1 study (see Figures below), the majority of peak elevations occur between Day 0 and Day 15, with a slightly shift to right in the rivaroxaban subjects as compared to enoxaparin subjects, followed by a decline back to baseline or $<1\times$ ULN either while study drug is continued or after study drug has been discontinued. There were 6 rivaroxaban subjects and 10 enoxaparin subjects who had a last measured ALT level $>3\times$ ULN.

Figure 1-1: Individual Plot of Subjects Administered Rivaroxaban with ALT $>5\times$ ULN at Any Time During the Study (Subjects Valid for the Safety Analysis in RECORD 1)

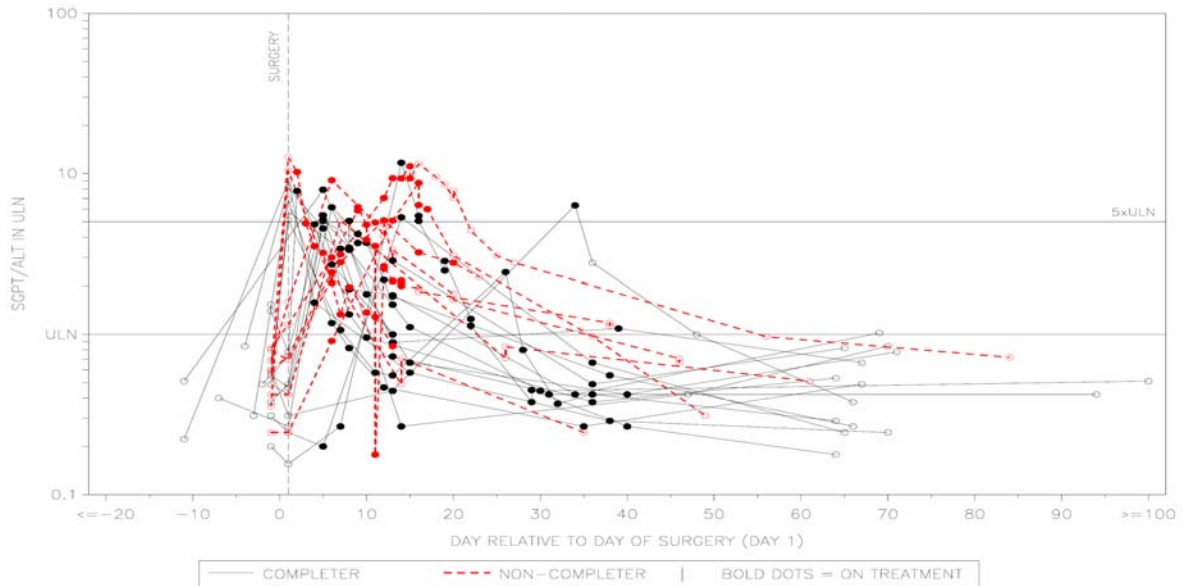
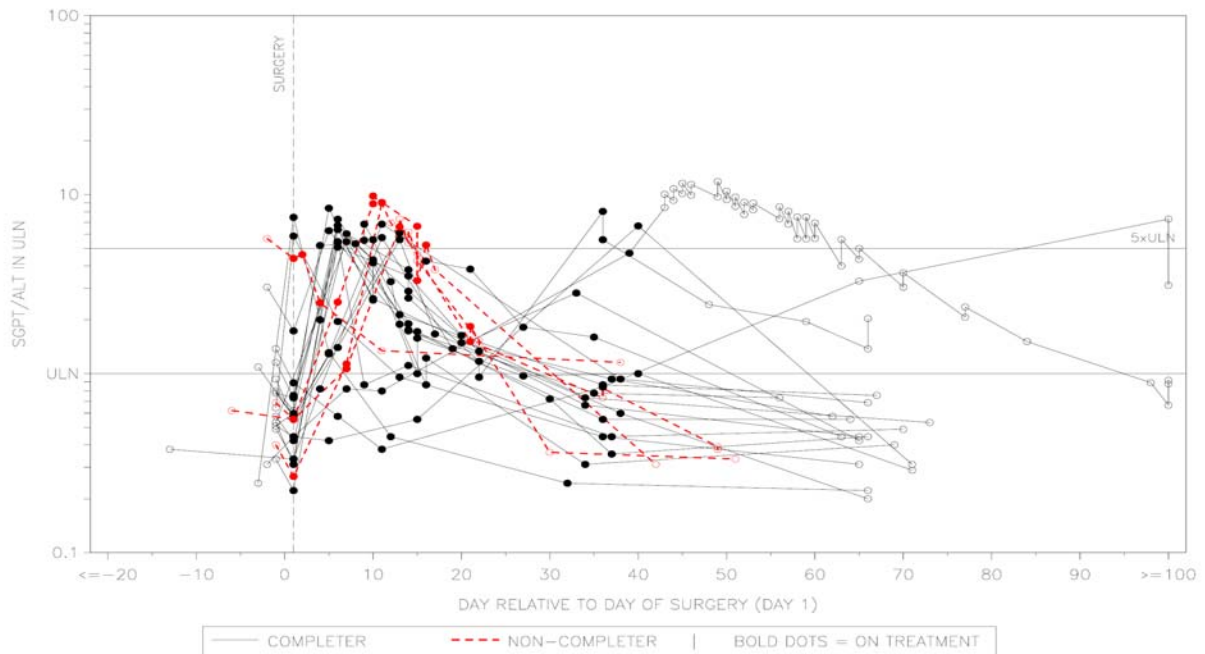
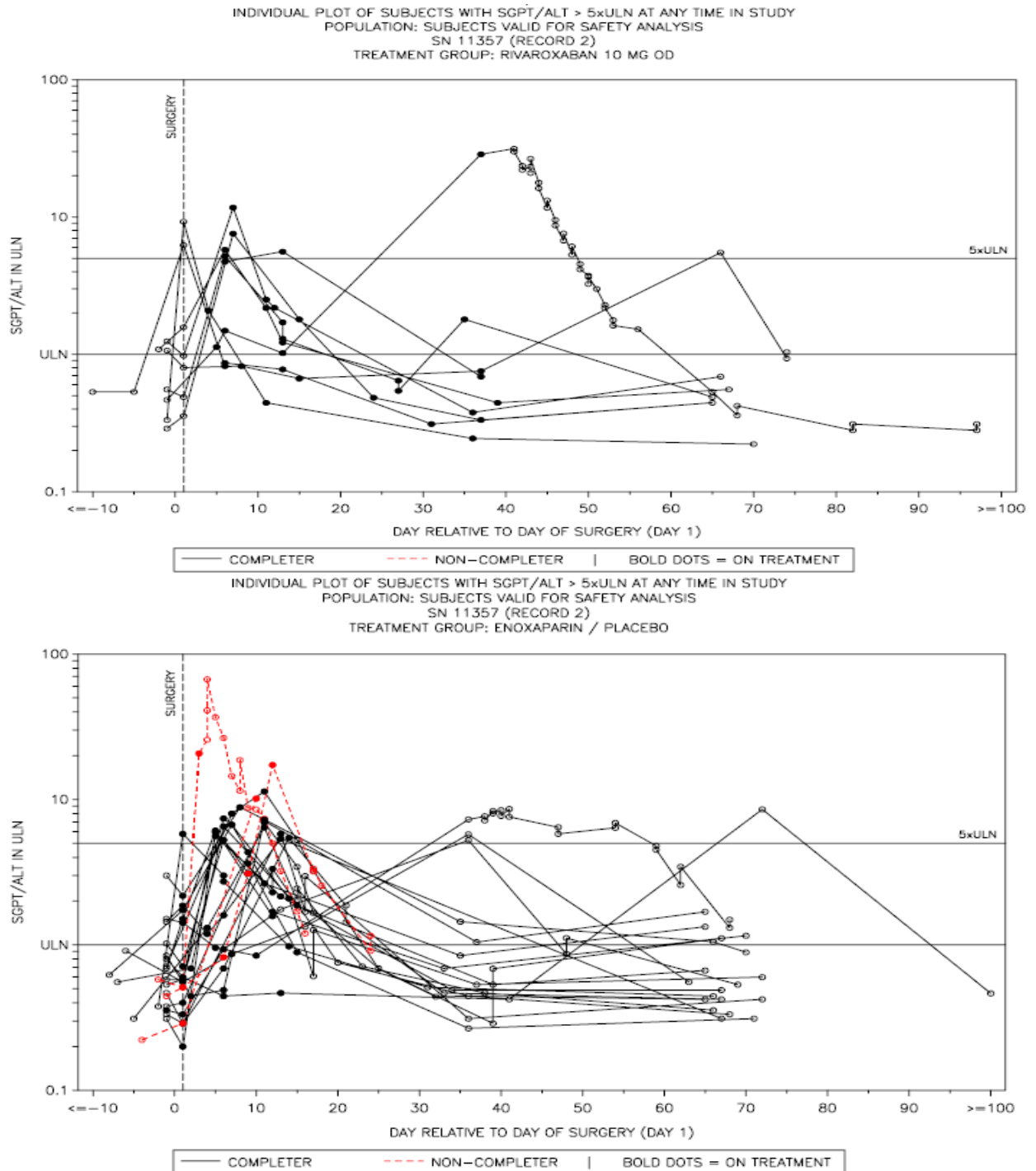


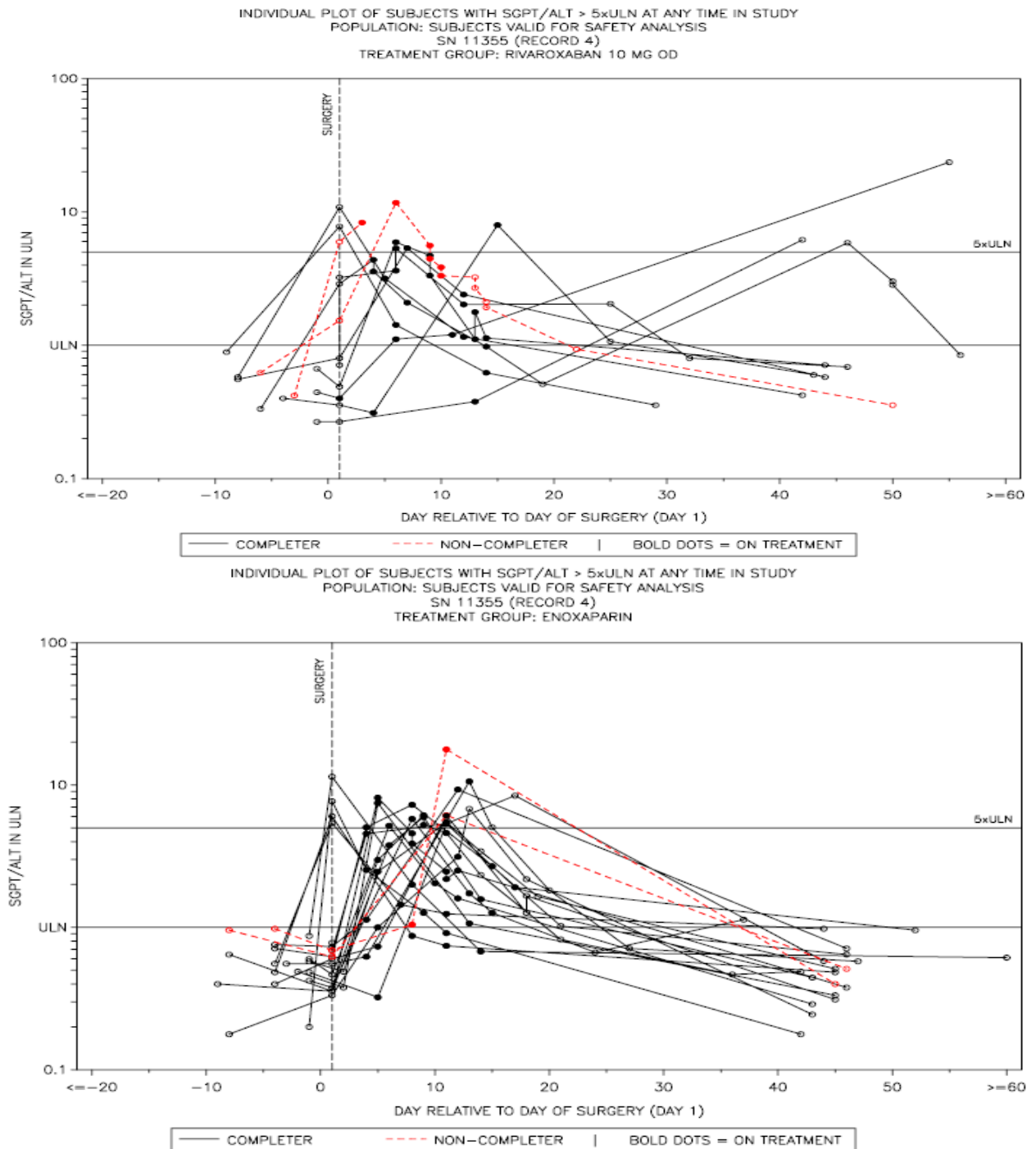
Figure 1-2: Individual Plot of Subjects Administered Enoxaparin with ALT $>5\times$ ULN at Any Time During the Study (Subjects Valid for the Safety Analysis in RECORD 1)



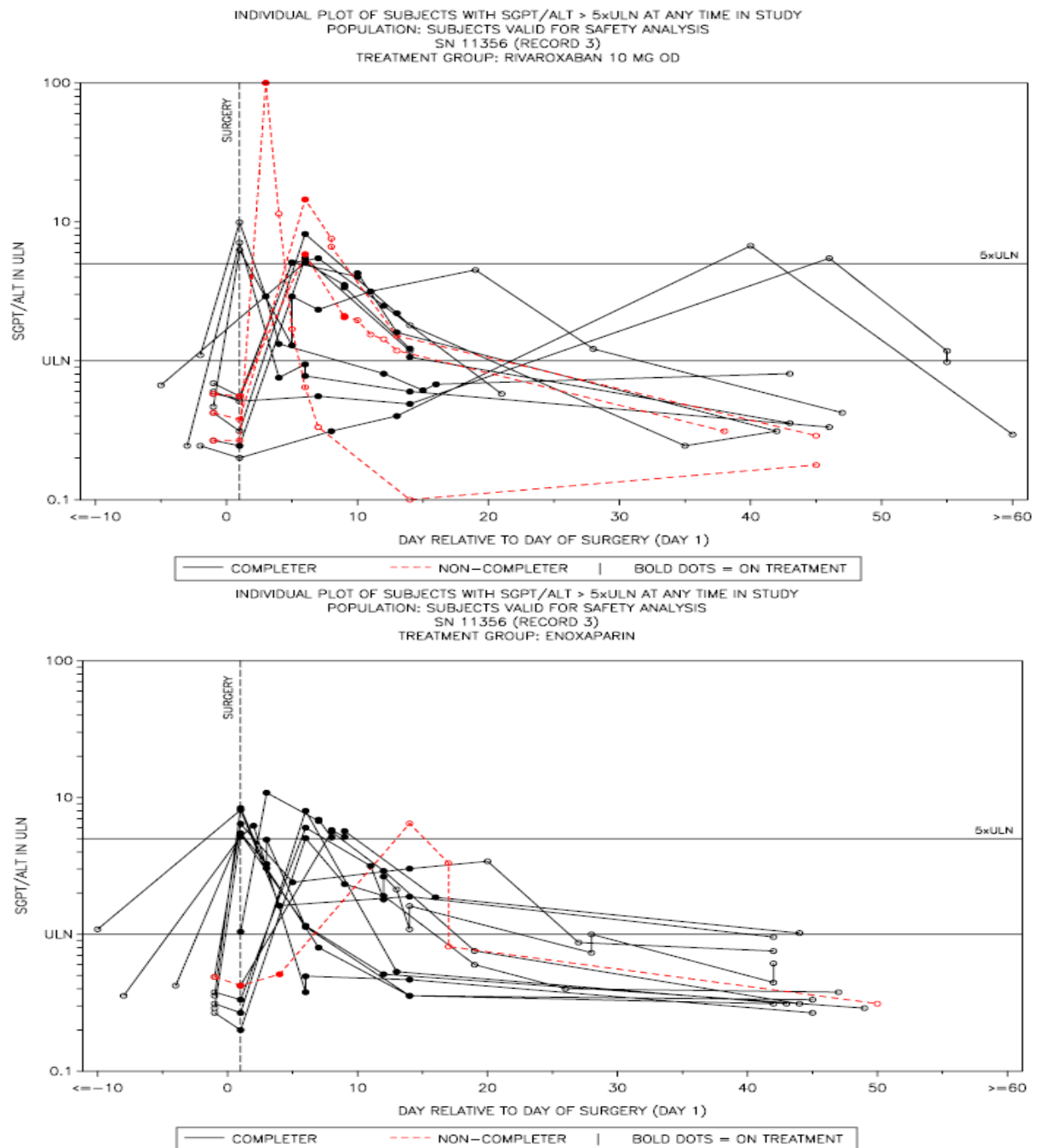
In RECORD 2 study (see Figure below), most subjects in both groups recovered quickly and few had late elevation of ALT and were back to normal in both groups.



In RECORD 3 study (see figures below), 3 subjects in the rivaroxaban group had a late elevation of ALT >5 x ULN about 40-50 days after surgery, approximately 1 month after the last dose of treatment. One subject had normalized ALT and 2 had no further value available.



In RECORD 4 study (see Figure below), a late elevation of ALT >5 xULN was also noted in 2 subjects in the rivaroxaban group at 40-45 days after surgery, approximately 1 month after the last dose of treatment. Both subjects had normalized ALT about 2 weeks later.



Subjects with elevated liver enzymes at baseline were not excluded from enrollment in the RECORD studies. Subjects that entered the RECORD studies with an ALT level >1.5x ULN at baseline (Day 0) did not show a worsening of ALT levels post baseline (while on study drug). Similar findings were seen in subjects with a baseline total bilirubin level >1.5x ULN.

ALT >3x ULN With a Concurrent Total Bilirubin >2x ULN

There were a total of 16 cases of ALT levels >3x ULN concurrent with a total bilirubin level >2x ULN in the RECORD studies. There were 9 subjects in the rivaroxaban group as compared to 7 in the enoxaparin group who met this criterion.

The following table lists the subjects with ALT levels >3x ULN concurrent with a total bilirubin level >2x ULN in the Rivaroxaban group in the RECORD studies along with the outcomes and Liver Advisory Panel (LAP) assessment for the subjects. Among those 16 subjects, 12 also had an elevated AST>3 xULN. Two rivaroxaban subjects experienced these elevations on the day of surgery (Day 1) before administration of rivaroxaban. The remaining 7 subjects had these elevations after Day 1.

Rivaroxaban: ALT >3x ULN Concurrent With TB>2x ULN Cases in RECORD 1-4 Studies

Age/ Sex/ Race/ ID	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment on role of study drug
83/M Unknown 11354- 16009-4016 France	35	1	ALT 231 TB 3.3	Resolved on study drug. Subject with elevations in ALT/AST/TB on Day 1 (ALT>5xULN, AST>8xULN, and TB>2xULN after surgery but prior to 1st dose of active Rivaroxaban). ALT/AST/TB resolved while study drug continued. There was a re-elevation in ALT/AST (ALT>2 xULN and AST>2xULN) on Day 26 that normalized on Day 36.	Excluded
49/F White 11354- 18003-4018 Poland	14	9	ALT 294 TB 2.5	Resolved after study drug discontinued. Subject with elevations in ALT/AST/TB on Day 6 and peaked on Day 9 (ALT>5xULN, AST>2xULN, and TB>2xULN). ALT/AST were resolving after study drug was stopped due to thrombocytopenia. ALT/AST were close to normal and TB>1.5xULN on Day 38. No further LFT values were available.	Possible related
32/M Asian 11357- 54001-7029 China	33	11	ALT 166 TB 2.7	ALT increased again at follow-up. Subject with elevations of ALT/AST on Day 6 and peaked on Day 11 (ALT>3xULN and AST>2xULN). Total bilirubin was increased on Day 1 (TB>5xULN) which resolved while study drug continued. ALT/AST resolved by Day 27 while study drug continued. ALT increased >1.5xULN again on Day 67 and no further LFT values were available.	Possible related
52/M Asian 11357- 55003-7007	36	37	ALT 1497 TB10.2	Hepatitis C was suspected. Subject with mild elevations of ALT/AST on Day 5-6 which was resolved on Day 13. Marked elevations of	Possible related by 1 member and unrelated by

Indonesia				<p>ALT/AST/TB on Day 37 (ALT>10xULN, AST>10xULN, and TB>3xULN) which gradually resolved over the next few weeks. Subject had nausea and darker urine 1 week before Day 36 visit, and was hospitalized on Day 42 with hepatomegaly and jaundice. The subject was treated by the remedial therapy including Vitamin B complex, pulverized curcuma roots (herb), and lecithin. ALT/AST/TB all normalized on Day 65. Investigator considered that these events were possible study drug related.</p> <p>The sponsor considered that these events were not study drug related and considered to be hepatitis C infection by serology and PCR tests.</p>	2 members
60/F White 11356-22001-6007 Italy	12	7	ALT 246 TB 2.7	<p>Resolved after study drug discontinued.</p> <p>Subject with elevations in ALT/AST/TB on Day 5 and peaked on Day 7 (ALT>5xULN, AST>3xULN and TB>2xULN). AST resolved by Day 12 and ALT/TB resolved by Day 21 after study drug was stopped.</p>	Possible related
55/F White 11356-26010-6008 Canada	14	1	ALT 319 TB 3.0	<p>Resolved on study drug.</p> <p>Subject with elevations in ALT/AST/TB on Day 1 (ALT>5xULN, AST>8xULN and TB>2xULN after surgery but before 1st dose of active rivaroxaban). These resolved in 2 days while study drug continued.</p>	Unrelated
79/M White 11356-28018-6004 Belgium	9	6	ALT 263 TB 3.0	<p>Resolved after study drug discontinued.</p> <p>Subject with elevations in ALT/AST/TB on Day 6 (ALT>5xULN, AST>3xULN, and TB>2xULN). Study drug was discontinued permanently due to this event. ALT/AST/TB all resolved on Day 38.</p>	Possible/ Probable related
72/M Asian 11355-60009-5028 India	10	55	ALT 1062 TB 3.3	<p>Insufficient follow-up.</p> <p>Mild elevation of ALT/AST on Day 6 and ALT on Day 11. Marked elevation of ALT/AST/TB on Day 55 (ALT>10xULN, AST>10xULN and TB>4xULN 45 days after last dose of study drug). No further LFT values were available. According to the sponsor that follow-up of lab values was obtained after the results of RECORD 4 were unblinded showed that there was resolution of ALT on Day 72.</p>	Possible related
57/M Asian 11355-90002-5011 Sri Lanka	19	6	ALT 528 TB 2.6	<p>Resolved after study drug discontinued.</p> <p>Elevated ALT/AST on Day 1 that peaked on Day 6 (ALT>10xULN, AST>10xULN and TB>3ULN). TB was elevated on Day 6. Study drug was discontinued permanently due to this event. ALT/AST/TB all resolved on Day 22.</p>	Possible related

The following table shows the subjects with ALT levels >3x ULN concurrent with a total bilirubin level >2x ULN in the Enoxaparin group in RECORD studies.

**Enoxaparin: ALT >3x ULN Concurrent With TB>2x ULN Cases
in RECORD 1-4 Studies**

Age/ sex	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment
74/M White 11354- 180194037 Poland	15	14	ALT 190 /TB 3.5	Resolved after study drug discontinued. Elevated ALT/AST/TB on Day 14 (ALT>3xULN, AST>8xULN, and TB>2xULN). Study drug was discontinued permanently. Elevation resolved by Day 21.	Possible/ Probable related
85/M White 11357- 120087009 United Kingdom	9	10	ALT 457 TB 3.8	Reported cholelithiasis and cholecystitis. Incomplete lab follow-up. ALT/AST/TB elevations on Day 10 (ALT>10xULN, AST>10xULN, and TB>3xULN). Study drug was discontinued permanently. Reported incomplete documentation of lab abnormality resolution. Increased liver enzyme elevations were attributed to cholecystitis.	Unrelated
64/F Other 11357- 480057034 Colombia	12	7	ALT 146 TB 3.0	Resolved after study drug discontinued. ALT/AST elevated on Day 7 (ALT>3xULN, AST>1.5xULN and TB>2xULN). Study drug discontinued permanently. ALT/AST resolved on Day 24. TB elevated on Day 1 (TB>3xULN) and resolved by Day 13.	Possible related
40/F Asian 11355- 600067001 India	2	3	ALT 3015 TB 6.6	Hypotension and acute renal failure were reported. Reported SAEs of hypotension and acute renal failure starting on Day 2 and study drug discontinued permanently. ALT/AST/TB first elevated on Day 3 (ALT 830, AST 1960, TB 3) with a peak on Day 4 (ALT 3015, AST 4500, TB 6.6) followed by gradual resolution over the next 2 weeks. Last follow-up labs on Day 16 where TB normalized and ALT/AST were nearly resolved.	Unlikely related
56/M White 11355- 140015020 United States	12	12	ALT 418 TB 8.6	Reported obstruction of the common bile duct. ALT/AST/TB elevation first noted on Day 4 and peaked on Day 12 (ALT>8xULN, AST>5xULN, and TB>8xULN). Cholelithiasis was reported as an SAE on Day 15. These liver enzymes were resolved by	Unlikely related

				Day 46.	
74/M White 11355- 140205027 United States	10	11	ALT 801/TB 5.7	Resolved after study drug discontinued. ALT/AST/TB elevation peaked on Day 11 (ALT>10x ULN, AST>10x ULN, and TB>3xULN). Study drug discontinued permanently. ALT/AST/TB were normalized on Day 45.	Possible related
65/M White 11355- 140205040 United States	2	2	ALT 191/TB 3.4	Absence of improvement after study drug discontinued. ALT/AST/TB elevation on Day 2 (ALT 3xULN, AST>2xULN, and TB>2xULN). Study drug discontinued permanently. ALT was mild elevation on Day 5 and 8 and normal on Day 10 and 12 and mild elevation on Day 16 and 19. AST normalized on Day 5. TB was elevated before surgery and remained elevated on Day 19. No further TB values were available.	Unlikely related

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 was managed by the Sponsor's Pharmacovigilance Department and 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 (2 clinicians on the Clinical Subteam and 2 pathologists on the Pathology Subteam) with strong backgrounds in hepatology. Additional external consultants could be requested at any time. Each clinician on the Clinical Subteam was to independently and blindly review single cases based on all available medical records and provide a written assessment. In select cases where a liver biopsy or autopsy was performed, if tissue specimens were available, they were to be sent to the Pathology Subteam. The Liver Advisory Panel assessed liver-related adverse events in the Phase 3 RECORD studies in a blinded manner. Cases with the following criteria were to be assessed by the panel:

- Clinical symptoms of liver disease plus elevated liver-related laboratory tests
- Elevated liver-related laboratory tests reported as serious adverse events
- Liver disease with a fatal outcome
- ALT levels >3x ULN concurrent with total bilirubin >2x ULN
- Discontinuation of study medication due to elevation of liver-related laboratory tests

The Liver Advisory Panel operating procedures were amended to allow for an assessment by a single expert on the Clinical subteam. In most cases, only serious events were reviewed by the Liver Advisory Panel, although non-serious hepatic disorder adverse event cases could be sent as deemed necessary by the Sponsor's Pharmacovigilance Department; the more severe cases were to be assessed by at least 2 experts. Causality classification was to be assigned as definite, probably, possible, unlikely, excluded, or non assessable, however, some reviewers attributed events that were "excluded" as "unrelated."

As shown in Table below, most of the assessments were done by 2 clinicians under Clinical subteam. One case in the table (11355-60095028) was assessed as possible by LAP (b) (4) after the NDA submission. Of the 16 cases in the table, one clinician (b) (4) reviewed all cases. Of the 9 rivaroxaban cases, his assessment was that the role of rivaroxaban was excluded in 3 cases and possible in 6 cases. Of the 7 enoxaparin cases reviewed, his assessment was that the role of enoxaparin was excluded/unlikely in 4 cases, possible/probable in 3 cases. Six of the 16 cases were also reviewed by the second clinician (b) (4) on the Clinical Subteam. There was agreement by the 2 members in 5 cases. In one case (Subject 11357-550037007), there was a disagreement between the 2 members. Additional clinician was involved. The following is the case with the disagreement involved.

This is a 52-year-old male without significant medical history and history of blood transfusion at past who was enrolled in RECORD 2 trial and received rivaroxaban for 35 days. The subject had marked elevation of liver enzymes on Day 37 on scheduled check-up, reported nausea and dark urine since Day 30. He was hospitalized on Day 42 for hepatomegaly, jaundice, nausea and vomiting, and was treated with vitamin B complex and herb medicine. The subject's condition improved on Day 56, discharged on Day 61, and liver enzyme normalized on Day 65. Hepatitis serology test showed non-reactive HCV-Ab at baseline and on Days 6, 13 and 37 but reactive on Days 47, 53 and 72. HCV-RNA PCR showed negative on Day 13, positive on Days 37, 47, 53, and negative again on Day 72. Blood sample from Day 86 showed quantitative and qualitative HCV-RNA-PCR (local lab) showed no virus. The subject refused any further blood drawing reporting that he felt very well. Retention samples at baseline also showed reactive IgG anti-HAV, HBsAg negative, positive HBs Ab, negative anti-HBc IgM and IgG. Blood sample on Day 72 also showed IgG anti-Toxoplasmosis, anti-Coxsackie (B2, B3, B4, B6). Investigator considered the event as study drug related. Hepatitis C was not listed in the case report form. The patient narrative and laboratory value are detailed in the narrative section following the table.

One LAP member () on the clinical subteam concluded that it is possible that the abnormalities seen were related to the study drug although hepatitis C must be considered as an alternative. There was a rather typical deceleration following drug removal and the peak laboratory values were noted in close proximity to the introduction of the drug. The patient did have elevated serum bilirubins in association with considerable elevations in aminotransferases suggesting the case enters the zone of concern. However there are certainly issues as to whether the patient had underlying chronic hepatitis C or developed a case of acute hepatitis C around the time of the event.

Another LAP member in the clinical subteam attributed these events to acute hepatitis C infection and the role of rivaroxaban was excluded.

An additional clinician considered these events to be unrelated to rivaroxaban treatment.

Liver Advisory Panel Assessments
(Cases of ALT >3x ULN Concurrent With Total Bilirubin >2x ULN)

Study Subject Number	Study Drug	(b) (4)		
RECORD 1				
11354- 160094016 ^a	RIVA	5.3.5.3.6-14 excluded		
11354- 180034018	RIVA	5.3.5.3.6-15 possible		
11354- 180194037	ENOX	5.3.5.3.6-24 probable	5.3.5.3.6-25 possible/probable	
RECORD 2				
11357- 120087009	ENOX	5.3.5.3.6-51 excluded	unrelated ^b 5.3.5.3.6-53	5.3.5.3.6-55 not related ^b
11357- 480057034	ENOX	5.3.5.3.6-63 Possible		
11357- 540017029	RIVA	5.3.5.3.6-67 possible		
11357- 550037007	RIVA	5.3.5.3.6-80 excluded	5.3.5.3.6-86 possible	5.3.5.3.6-82 unrelated ^b
11357- 600067001	ENOX	5.3.5.3.6-95 unlikely		
RECORD 3				
11356- 220016007	RIVA	5.3.5.3.6-104 possible	possible 5.3.5.3.6-105	
11356- 260106008	RIVA	5.3.5.3.6-106 excluded	5.3.5.3.6-107 unrelated ^b	
11356- 280186004	RIVA	5.3.5.3.6-112 possible	5.3.5.3.6-113 possible/probable	
RECORD 4				
11355- 140015020	ENOX	5.3.5.3.6-144 unlikely		
11355- 140205027	ENOX	5.3.5.3.6-151 possible		
11355- 140205040	ENOX	5.3.5.3.6-154 unlikely		
11355- 600095028 ^c	RIVA			
11355- 900025011	RIVA	5.3.5.3.6-161 possible		

^a Narrative for this subject is related to a bleeding event since liver related lab abnormalities were not reported as a serious adverse event

^b "Unrelated" or "not related" was the assessment provided by the Liver Advisory Panel expert; however, these terms are not included in the Causality Classification in the Liver Advisory Panel Manual of Operations.

^c Not assessed by the Liver Advisory Panel

Key: ENOX = enoxaparin; RIVA = rivaroxaban

The following are patient's brief narratives and LFT graphs over time for subjects with ALT levels >3x ULN concurrent with a total bilirubin level >2x ULN. The graphs marked the day of first dose and day of last dose of active study medication (ASM). The x-axis of the figure shows

the time in days and the y-axis represents liver laboratory values as a ratio of the actual value to the upper limit of normal.

Rivaroxaban Group

11354-16009-4016

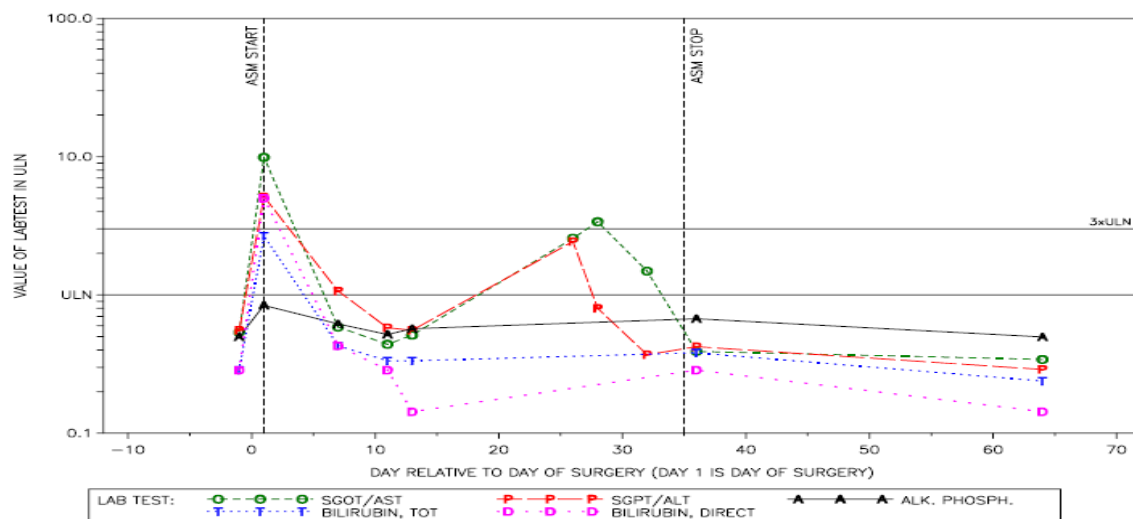
This 83 year old man had a medical history of polyp resection (1990), colectomy and colostomy (1996), prostate adenoma resection (1996), cholecystectomy (1996), vertigo ongoing, and deafness ongoing.

A primary hip arthroplasty (right side) due to osteoarthritis was performed on 08 Dec 2006. There were no known complications during surgery. The subject received rivaroxaban from (b) (4). Elevated transaminases were reported as non-serious events for the day of surgery prior to active rivaroxaban treatment (b) (4), with ALT>5xULN, AST>8xULN, TB>2xULN, and GGT >5 x ULN. ALT/AST/TB resolved while study drug continued. There was a re-elevation in ALT/AST (ALT>2 xULN and AST>2xULN) on (b) (4) that normalized on (b) (4) based on local lab. The subject completed rivaroxaban treatment and the treatment was stopped on (b) (4). All those hepatic enzyme elevations resolved by (b) (4).

The investigator considered these events on Day 1 as not related to study drug but the second period events on Day 26 as related to study drug.

No other adverse events were reported.

The Liver Advisory Panel Evaluation concluded that an alternative explanation of the LFT elevations was the surgery. Causality was excluded.



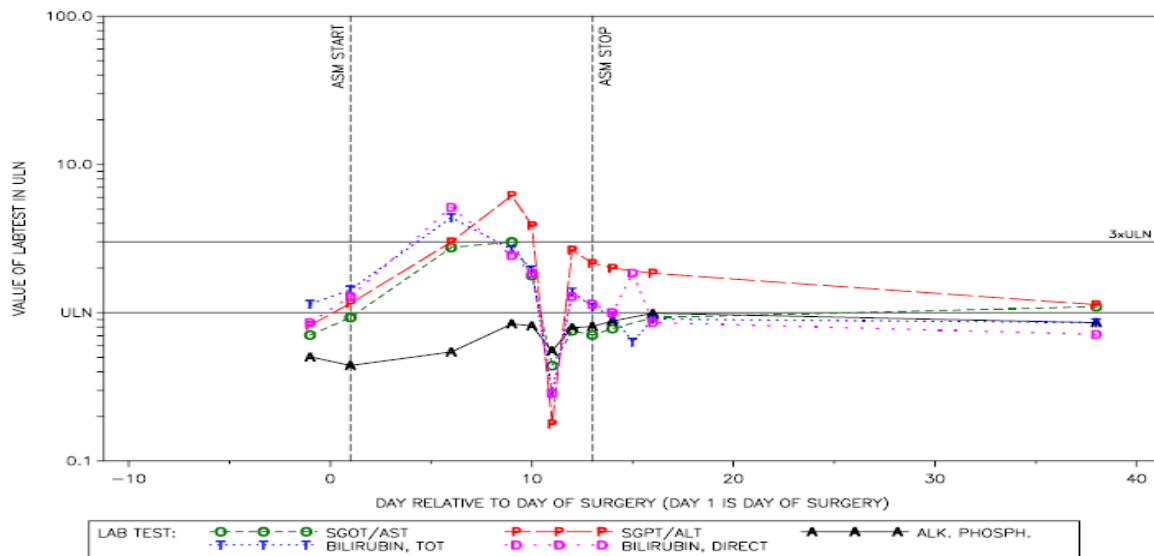
11354-18003-4018

This was a 49 year old white woman with a medical history of dislocation of left hip (1958), dysplastic arthritis of the left hip (2001-2006), appendectomy (2002), and electro-resection of cervix (2003).

A primary hip arthroplasty (left side) due to dysplastic arthritis was performed on (b) (4). The subject started rivaroxaban on (b) (4). Elevated levels of liver enzymes and bilirubin were found on (b) (4) and peaked on (b) (4) with ALT>5xULN, AST>2xULN, and TB>2xULN. The study drug treatment was discontinued due to thrombocytopenia on (b) (4). ALT/AST were resolving after study drug was stopped. ALT/AST were close to normal and TB>1.5xULN on (b) (4)8. No further LFT values were available. The investigator regarded these events as not related to the study drug.

No other reported adverse events except thrombocytopenia.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



11357-54001-7029

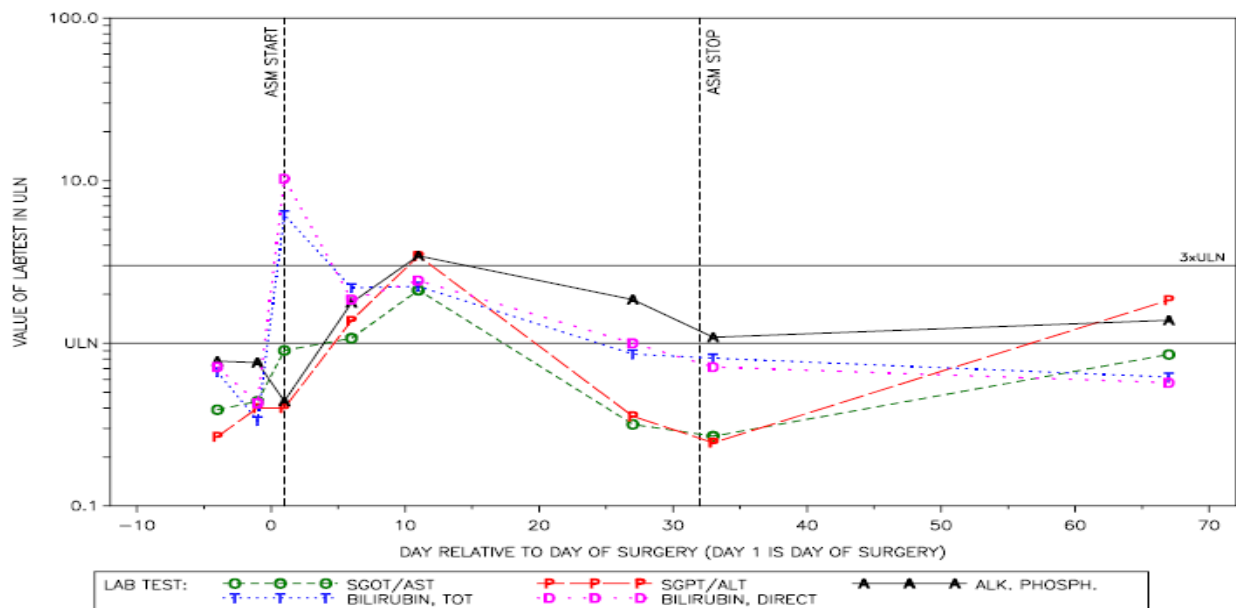
This 32 year old Asian male had a medical history of pulmonary tuberculosis (1996), and ankylosing and spondylitis (1996).

The subject was admitted for total hip replacement surgery under general anesthesia on (b) (4). On the same day he had started to receive BAY 59-7939 10 mg o.d. On (b) (4)1, the total bilirubin of the subject was reported as more than 6-fold upper limit of normal value. It decreased gradually while on study drug. Subject had elevations of ALT/AST on (b) (4) which peaked on (b) (4) (ALT>3xULN and AST>2xULN). Gluthion (1.200 mg, p.o. from (b) (4) [Day 11-12]) was administered to the subject for liver protection. ALT/AST resolved by (b) (4) while study drug continued. The subject completed Rivaroxaban treatment and the treatment was stopped on (b) (4). ALT increased >1.5xULN again on (b) (4)2006 (Day 67) and no further LFT values were available.

Investigator considered these events as not related to study drug.

Other reported adverse events included mild productive cough from (b) (4).

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug for LFT elevations.



11357-55003-7007

This was a 52 year old Asian male with no significant medical history.

On 08 Feb 2007, the subject had total hip replacement surgery under general anesthesia. On the same day he started rivaroxaban [REDACTED] p.o. The subject did not receive blood transfusion after surgery.

The subject had normal LFTs at baseline and mild elevations of ALT/AST/GGT on [REDACTED] (b) (4) and [REDACTED], AST was normal and ALT/GGT remained slightly elevated. The last dose of rivaroxaban was on [REDACTED]. Marked elevations of ALT/AST/TB were noted on [REDACTED] (Day 37) (ALT>10xULN, AST>10xULN, and TB>3xULN). The subject reported nausea, dark urine, and weakness for 1 week [REDACTED]. Subject was hospitalized on [REDACTED] (b) (4) [REDACTED] with hepatomegaly, jaundice, and vomiting. The subject was treated by the remedial therapy including Vitamin B complex, pulverized curcuma roots (herb), and lecithin. On [REDACTED] (b) (4), laboratory test for HbsAg was performed and the result was negative. On [REDACTED] (b) (4), ultrasonography showed no abnormality of liver, gall bladder and spleen. On [REDACTED] (b) (4) (Day 56), the condition of the subject was [REDACTED] the subject was discharged. Elevations of liver enzymes gradually resolved over the time and ALT/AST/TB all normalized on [REDACTED].

Hepatitis serology was performed on the retention samples of blood drawn at the time of each study visit. Blood samples from [REDACTED] showed HCV-Ab non-reactive and Blood samples from [REDACTED] showed HCV-Ab positive. Quantitative PCR showed HCV-RNA positive from blood samples collected on [REDACTED] (b) (4) [REDACTED]. HCV concentration was 17.3 kIU/ml on [REDACTED] (b) (4) Day 47 and 7.1 kIU/ml on 1 [REDACTED] (reference: <10kIU/ml low virus concentration; >500 kIU/mL high virus concentration). HCV-RNA was negative (<0.01 kIU/ml) on [REDACTED], positive (26800 kIU/ml) on [REDACTED] (b) (4) [REDACTED], and negative (<0.01kIU/ml) on [REDACTED].

Retention samples at baseline showed reactive IgG anti-HAV, HBsAg negative, positive HBs Ab, negative anti-HBc IgM and IgG, non-reactive anti-HCV.

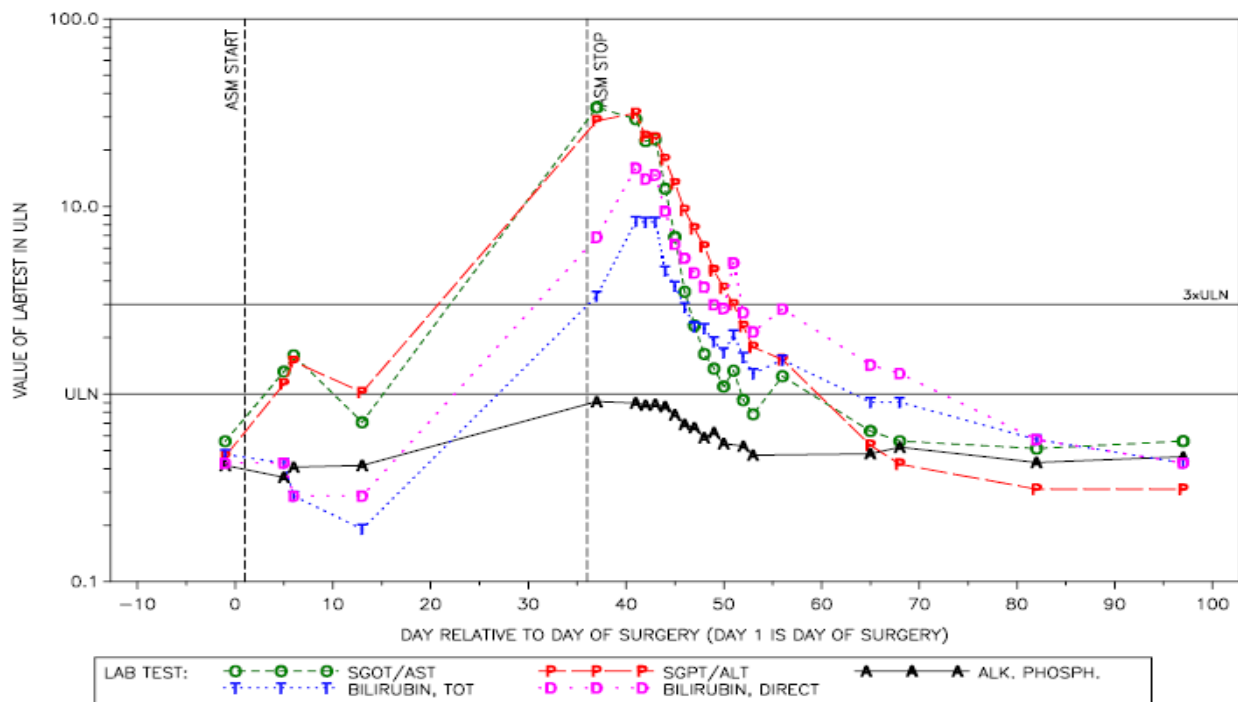
Blood sample on (b) (4) showed positive for anti-HCV (Elisa and RIBA), anti-HBs, IgG-anti-HSV1, IgG anti-Toxoplasmosis, anti-Coxsackie (B2, B3, B4, B6).

Blood sample from (b) (4) showed quantitative and qualitative HCV-RNA-PCR (local lab) showed no virus detected.

The subject refused any further blood drawing reporting that he felt very well.

Investigator considered all above events as study drug related. Hepatitis C was not listed in the case report form.

The sponsor considered that these events were not study drug related and attributed these to Hepatitis C infection based serology and PCR tests.



11356-22001-6007

This 60 year old White female had medical history significant for venous insufficiency (2001) and hypertension (1996).

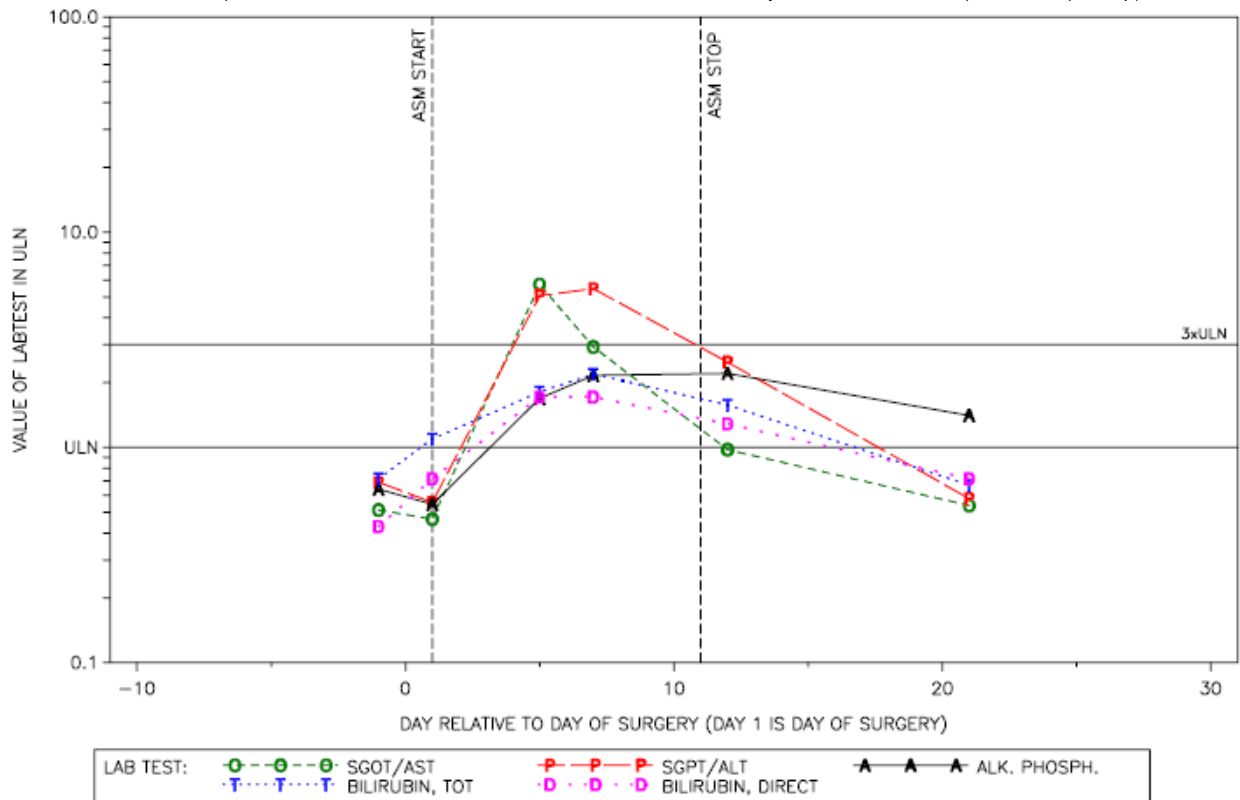
On (b) (4), the subject underwent a primary right knee arthroplasty under spinal anesthesia. On (b) (4) the subject was noted to have an elevated ALT, AST, bilirubin, GGT, LDH, and alkaline phosphatase. ALT/AST/TB peaked on (b) (4) (Day 7) with ALT>5xULN, AST>3xULN and TB>2xULN. No therapy was given, and the subject was discharged from the hospital on (b) (4). The subject completed Rivaroxaban treatment for 11 days and the treatment stopped on (b) (4).

(b) The elevated AST was reported to have resolved on [REDACTED]; the elevated ALT, bilirubin, GGT, LDH, and alkaline phosphatase were reported to have resolved on [REDACTED].

Investigator considered these events as related to study drug.

Other reported adverse events included symptomatic proximal and distal DVT in right leg on [REDACTED].

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



11356-26010-6008

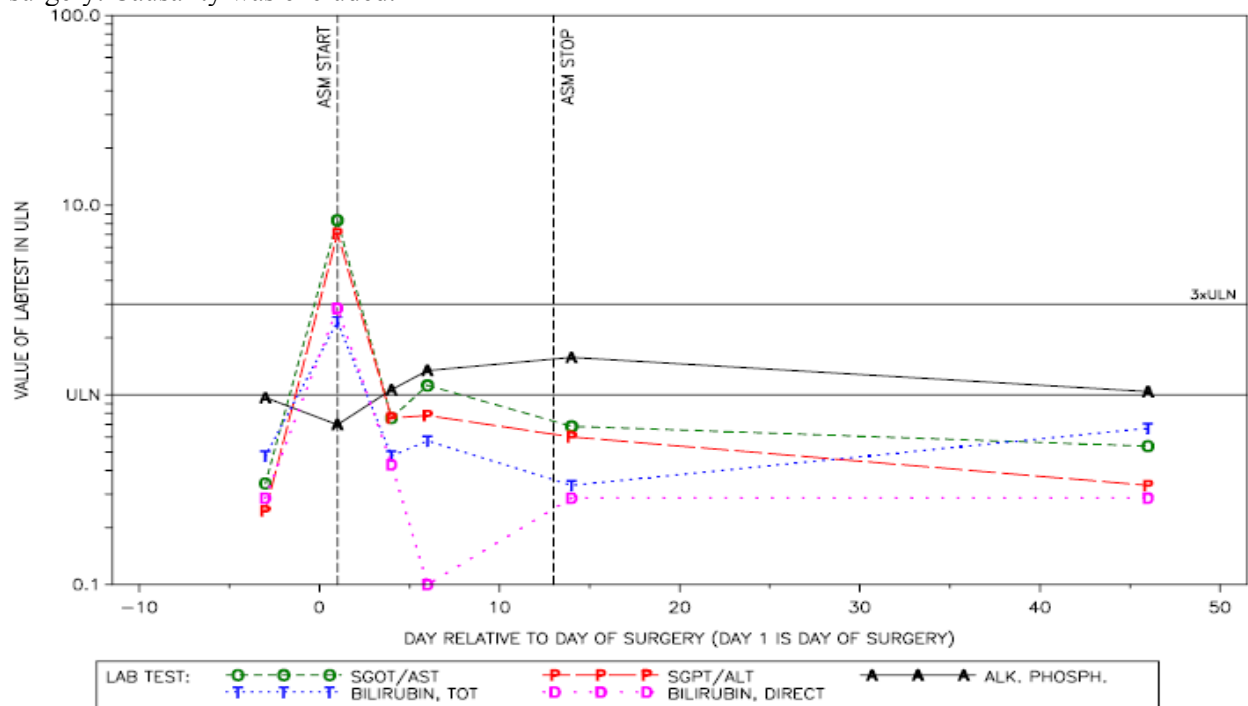
This 55 year old White woman had medical history significant for hyperlipidemia (2003), osteoarthritis of the left knee (2002), left leg muscle spasms (2002), jaundice (1963) and cholecystectomy (1990).

On [REDACTED], the subject underwent a primary left knee arthroplasty with general anesthesia. On [REDACTED] (Day1) after surgery but before 1st dose of active rivaroxaban, the subject was noted to have an elevated LFTs with ALT>5xULN, AST>8xULN and TB>2xULN. No action was taken, and these events were reported to have resolved on [REDACTED]. The subject completed rivaroxaban treatment and the treatment was stopped on [REDACTED]. The subject was discharged from the hospital on [REDACTED].

Investigator considered these events as not related to study drug.

No other adverse events were reported.

The Liver Advisory Panel Evaluation concluded that an alternative explanation of the elevations was the surgery. Causality was excluded.



11356-28018-6004

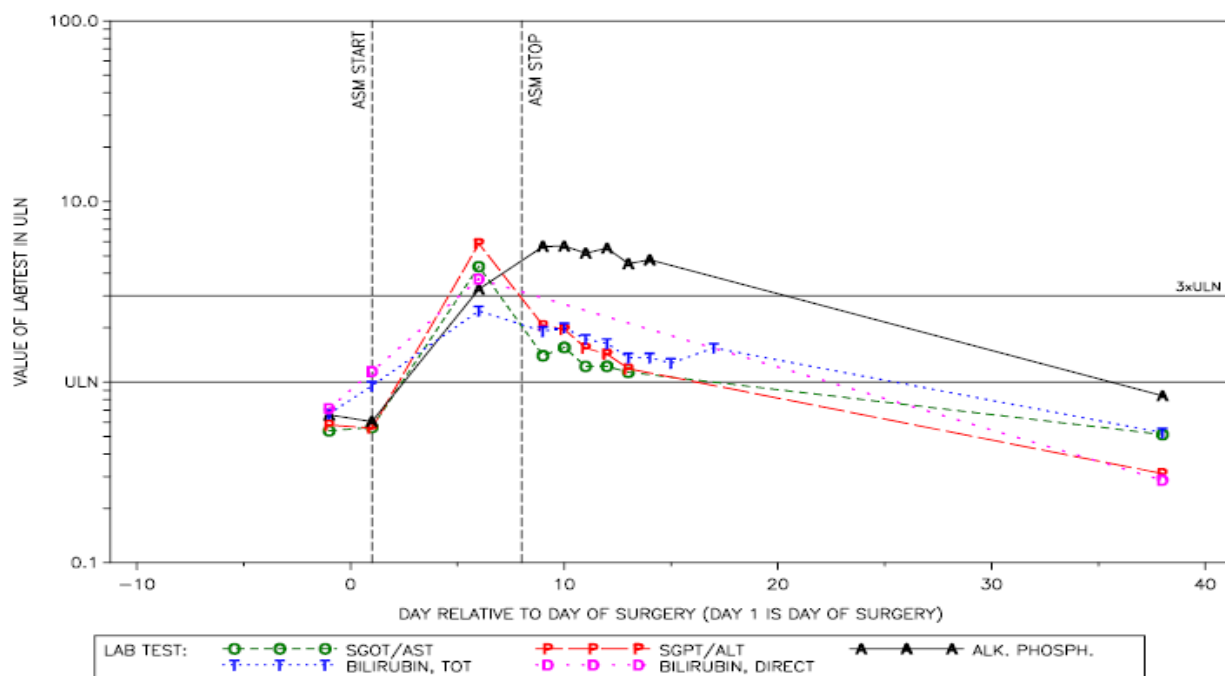
This 79 year old White male with medical history significant for prostatic hypertrophy (2006), bilateral inguinal hernia repair (1965), and osteoarthritis (ongoing, dates not reported).

On (b) (4), the subject underwent primary left knee arthroplasty with general anesthesia. On (b) (4) (b) (4) the subject was noted to have an elevated bilirubin, elevated AST, and elevated ALT. Each of these was reported as a serious adverse event. Study drug was permanently discontinued because of these events, with the last dose administered on (b) (4) (Day 8), and the events were reported to have resolved on (b) (4) (Day 38). The subject was discharged from the hospital on (b) (4).

Investigator considered these events as related to study drug.

No other adverse events were reported.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



11355-60009-5028

This 72 year old Asian male had medical history significant for hypertension (2000) and coronary artery disease (1999). Alcohol consumption was reported as “abstinent.”

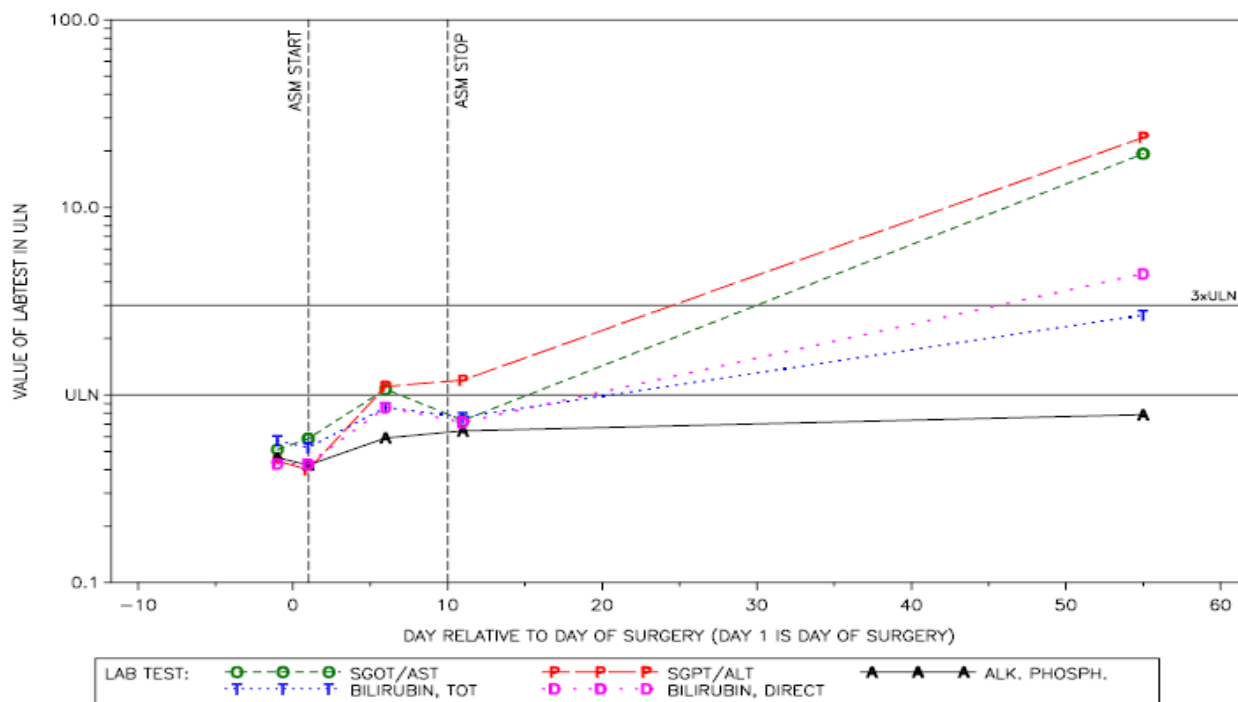
On [REDACTED] the subject underwent bilateral primary knee arthroplasties under spinal anesthesia. The subject was discharged on [REDACTED]. The subject had mild elevation of ALT/AST on [REDACTED] (b) (4) and ALT on [REDACTED]. Marked elevations of ALT/AST/TB were on [REDACTED] (b) (4) with ALT>10xULN, AST>10xULN and TB>4xULN. No further LFT values were available. No action was taken. The outcome of the event was not reported due to insufficient follow-up. No further laboratory results were available.

According to the sponsor that follow-up of lab values was obtained after the results of RECORD 4 were unblinded showed that there was resolution of ALT on Day 72.

Investigator considered these events as not related to study drug.

No other adverse events were reported.

This case was assessed by the Liver Advisory Panel as possible related.



11355-90002-5011

This was a 57 year old Asian male with no significant medical history. Alcohol consumption was reported as “light.”

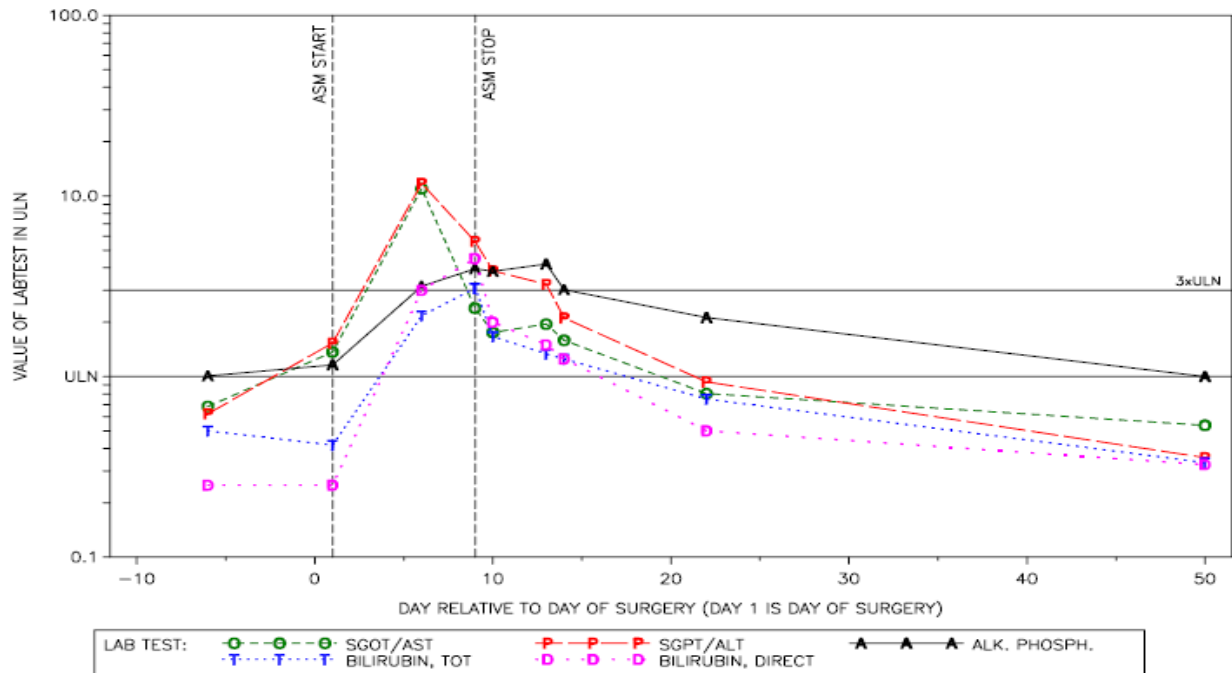
On 03 Oct 2007 the subject underwent a primary right knee arthroplasty for osteoarthritis with spinal anesthesia.

On [REDACTED] (Day 1), postoperatively but before the first dose of study drug, the subject was noted to have a mild elevation of liver function tests. On [REDACTED] ALT/AST were peaked with ALT>10xULN, AST>10xULN and TB>3ULN. TB was elevated on (b) (4). Study drug was discontinued permanently on [REDACTED]. Study drug was discontinued permanently due to these events. ALT/AST/TB were back to normal on [REDACTED]. The subject was discharged from the hospital on [REDACTED].

Investigator considered these events as related to study drug.

No other adverse events were reported.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



Enoxaparin Group

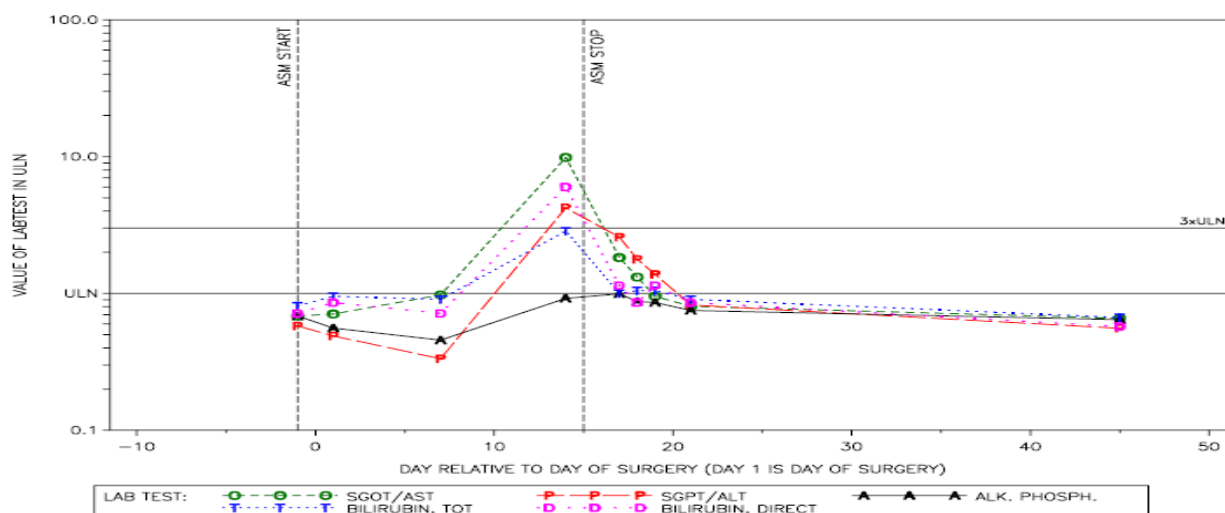
11354-18019-4037

This 74 year old White male had a medical history of right hand Dupuytren's contracture (1989-1994), brain circulatory insufficiency (1992), surgery for right hand Dupuytren's contracture (1994), coronary heart disease (1998), chronic gastritis (1998), esophageal hernia (1998), left hip osteoarthritis (1999-2006), and right hip osteoarthritis (2001).

A primary hip arthroplasty due to osteoarthritis was performed on (b) (4). There were no known complications during surgery. On (b) (4) a moderate increase of liver enzymes was reported. Study drug treatment was discontinued on the same day. Liver enzymes returned to normal levels by (b) (4).

The investigator considered this event as related to the study drug.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



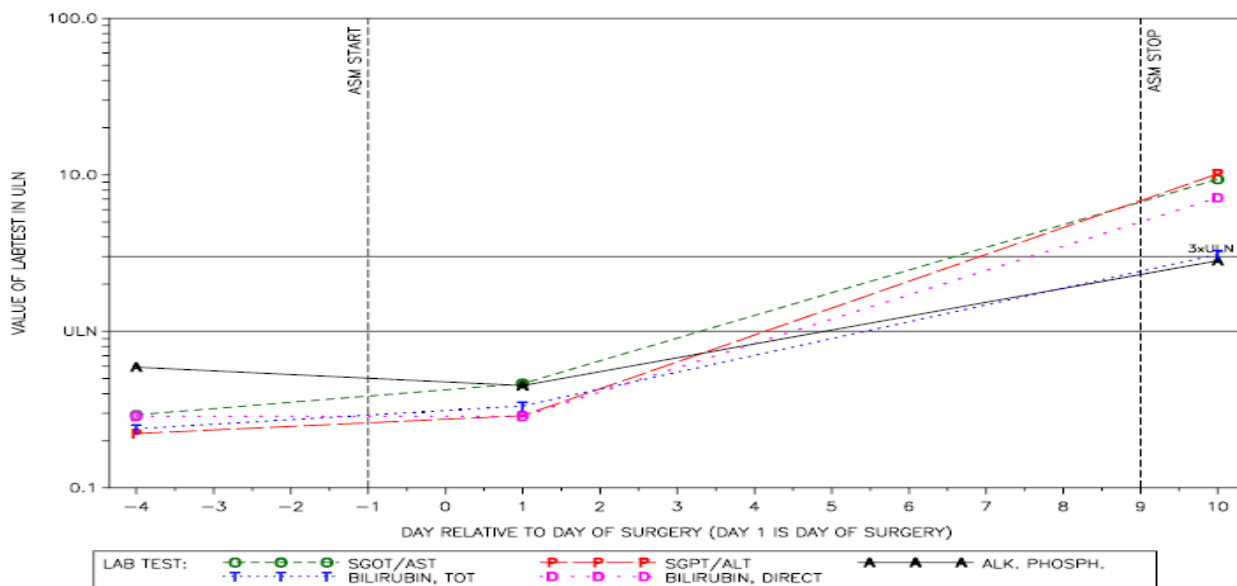
11357-12008-7009

This 85 year old White male had a medical history of right inguinal hernia repair, laser treatment of prostate gland, glaucoma right eye, hypertension and osteoarthritis.

The subject was admitted for total hip replacement surgery under spinal and epidural with indwelling catheter anesthesia on (b) (4). The day before, he had started to receive enoxaparin (b) (4). On (b) (4) the subject developed symptoms of feeling cold, raised pulse and diarrhea, and was hospitalized. The event was treated with cefuroxime and metronidazole. On (b) (4), subcutaneous study medication was withdrawn. On (b) (4), acute cholecystitis was diagnosed with elevations of bilirubin, AST, ALT, and GGT. An abdomen CT was reported as showing gallstones within a non distended, thin walled gall bladder. There was no gross dilatation of the common bile duct. On (b) (4), the subject was discharged from hospital. The outcome was resolved with comment "ERCP to be performed as outpatient". The subject declined to attend any further follow appointments.

The investigator attributed elevated liver enzymes to cholecystitis as not related to the study drug.

The Liver Advisory Panel Evaluation concluded that causality of study drug was excluded.



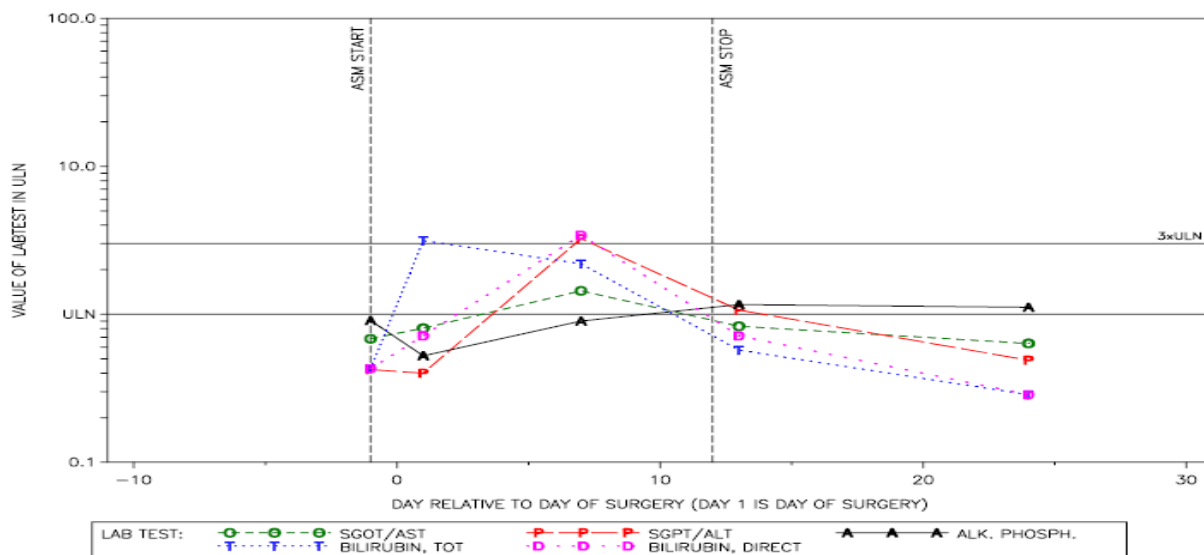
11357-48005-7034

This 64 year old female had medical history of rheumatoid arthritis, bladder surgery and hysterectomy.

The subject was admitted for total hip replacement surgery under spinal anesthesia on (b) (4). The day before she had started to receive (b) (4). On (b) (4), the Central lab showed a Total Bilirubin > 3 xULN with normal ALT. On (b) (4) ALT/TB both elevated with ALT > 3 xULN and TB > 2 xULN. On (b) (4) the study drug was discontinued. On (b) (4) the subject presented a complete normalization of ALT and Bilirubin values, after local and central retests.

The investigator considered this event as related to the study drug.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



11357-60006-7001

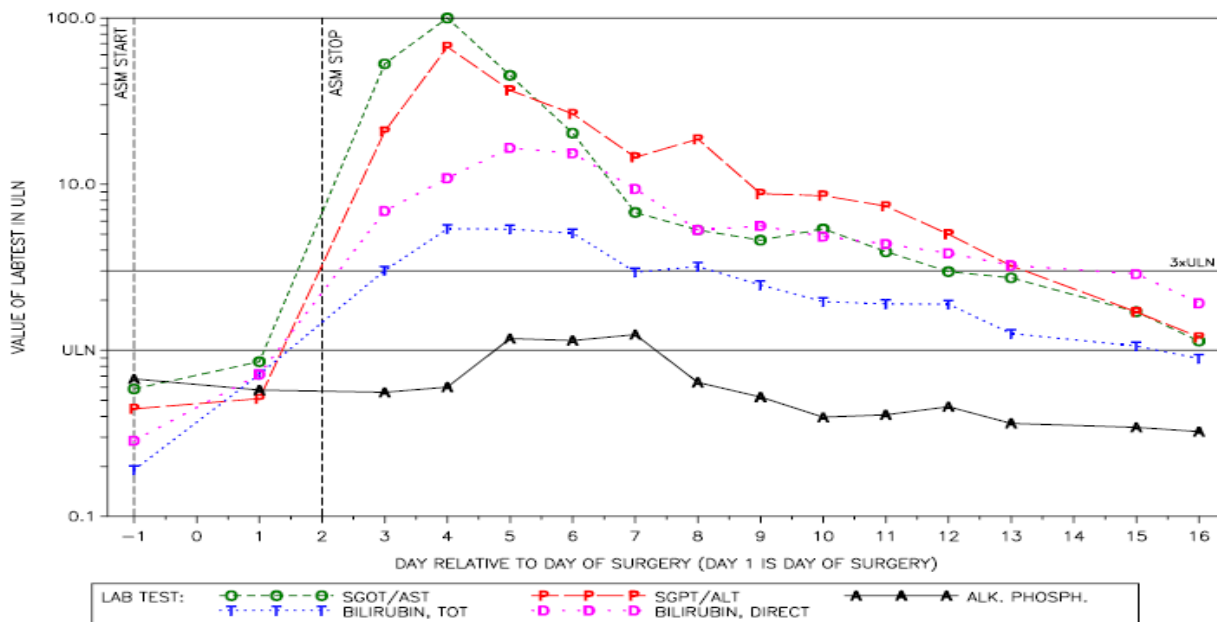
This 40 year old female had medical history of caesarean section surgery twice (1994 and 2001), tubal ligation (2001) and osteoarthritis of hips (since 2006).

The subject was admitted for total hip replacement surgery under general anesthesia on (b) (4). The day before, she had started to receive (b) (4).

On (b) (4) during surgery, intraoperative blood loss was 800 mL and 2 units of blood were transfused. On (b) (4), subject's blood pressure was low (90/60 mmHg) with decreased urine output and was treated with i.v. crystalloids (Ringer lactate and normal saline). Hypotension and acute renal failure were reported. On (b) (4) she was started on Dopamine to treat the hypotension. The study drug was permanently discontinued due to these events. On (b) (4), local laboratory showed elevation of ALT/AST/TB. On (b) (4), liver enzymes rose further with ALT- 1030 IU/L and AST - 5440 IU/L. On (b) (4) ALT was 1060 IU/L and AST -750 IU/L. LFTs were gradually resolved and close to normal on (b) (4).

The investigator considered elevated liver enzymes as not related to the study drug.

The Liver Advisory Panel Evaluation concluded that the causality of study drug was excluded.



11355-14001-5020

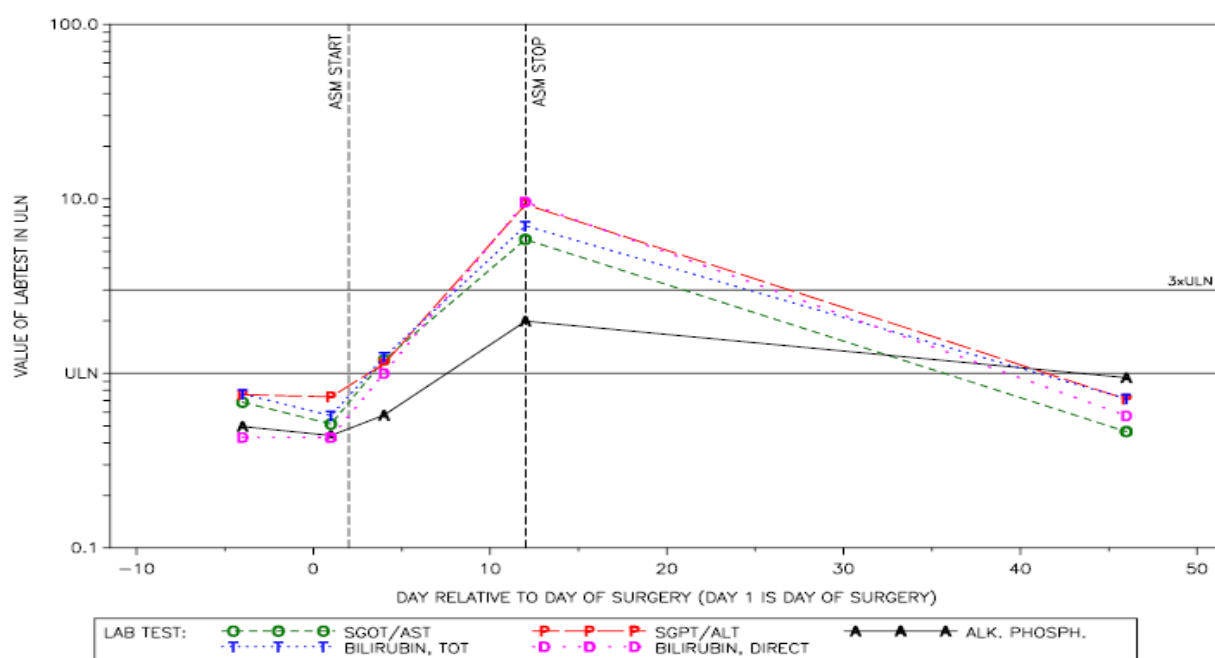
This 56 year old male had medical history significant for hypertension (2001), osteoarthritis of the left knee (2005), right knee arthroplasty (2005), gait instability (2005), moderate alcohol use, and hypercholesterolemia (2001).

On (b) (4), the subject underwent a primary left knee arthroplasty for osteoarthritis under general anesthesia. The day before, she had started to receive (b) (4).

On (b) (4) the subject was hospitalized for nausea, vomiting, diarrhea, and yellow skin, and a serious adverse event of elevated liver enzymes was reported. The elevated liver enzymes were repeated and monitored over the next several days. The subject was not able to complete an ERCP (endoscopic retrograde cholangiopancreatography) on (b) (4), so that an MCRP (magnetic resonance cholangiopancreatography) diagnostic procedure was performed on the same day. Results of the MCRP are not available. On (b) (4) a cholecystectomy was performed for cholelithiasis and total obstruction of the common bile duct. He was discharged from the hospital on (b) (4). LFT normalized on (b) (4).

The investigator considered that elevated liver enzymes as not related to the study drug.

The Liver Advisory Panel Evaluation concluded that causality of study drug was excluded.



11355-14020-5027

This 75 year old man had medical history significant for benign prostatic hypertrophy (2006); asthma (1999); myocardial infarction and cataract surgery (1992); cardiac catheterization (1992); hypertension, type II diabetes, hypercholesterolemia and coronary artery disease (1992); left hernia repair (1963); tonsillectomy and adenoidectomy (1943); and penicillin allergy (dates not reported). Alcohol consumption was reported as “abstinent.”

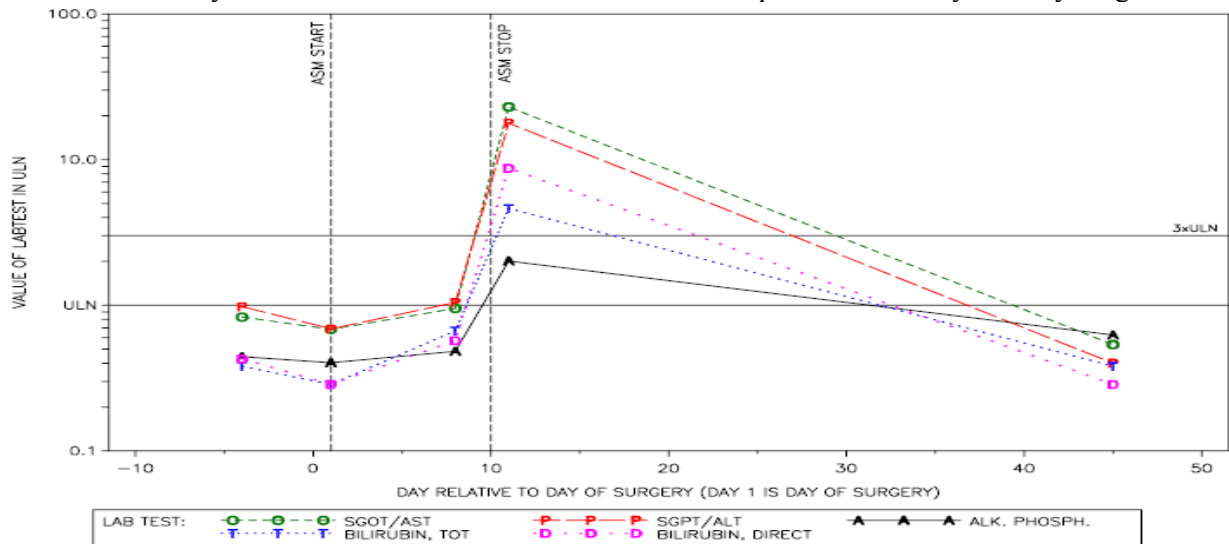
On (b) (4), the subject underwent a primary left knee arthroplasty under general anesthesia.

On (b) (4) the subject developed redness and swelling of the left (surgical) knee; he was diagnosed as having cellulitis of the left knee, and he was transferred from the rehabilitation center back to the hospital (b) (4). The subject was treated with antibiotics and the cellulitis was reported to have resolved on (b) (4).

On (b) (4), laboratory results revealed elevated liver enzymes. AST, ALT, and GGT values were > 8xULN and total bilirubin was > 4xULN. The subject was asymptomatic regarding liver failure. Study drug was discontinued permanently due to this event. The subject was discharged from the hospital on (b) (4) and the event was reported to have resolved on (b) (4) 1). Laboratory results showed normal LFTs on (b) (4).

The investigator considered this event as related to the study drug.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



11355-14020-5040

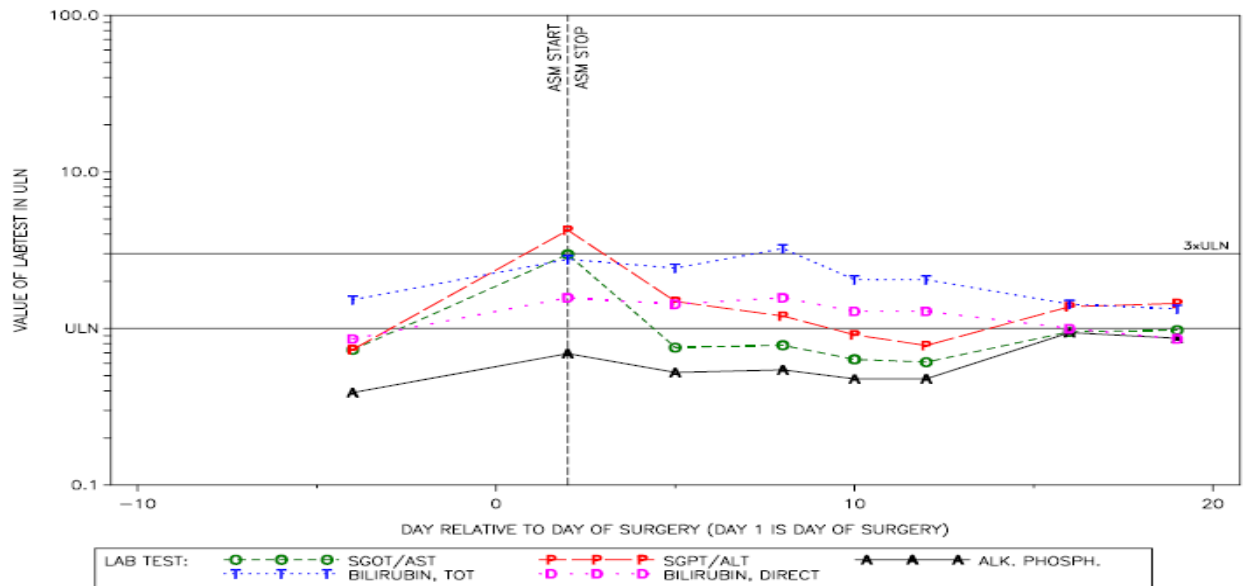
This 65 year old White male had medical history significant for hyperlipidemia, hypertension and osteoarthritis (2005), and right total knee replacement (2006). The following conditions were reported with unknown dates of onset and resolution: chronic leukopenia, arthrosclerosis of the carotid artery, tachycardia, colon polyps, status post endarterectomy, onychomycosis, carpal tunnel release, cholecystectomy, and hiatal hernia repair. Alcohol consumption was reported as “moderate.”

On (b) (4) the subject underwent primary left knee arthroplasty for osteoarthritis under spinal block anesthesia.

On (b) (4), central laboratory results showed normal liver function tests with the exception of total bilirubin and indirect bilirubin. On (b) (4) Day 2) elevated bilirubin and elevated ALT were reported. Study drug was discontinued permanently due to this event and the last dose was on (b) (4). The subject was discharged from the hospital on (b) (4). On (b) (4), elevated liver functions were again reported as an adverse event. ALT was mild elevation on (b) (4) and (b) (4) and normal on (b) (4) and mild elevation on (b) (4). AST normalized on (b) (4). No action was taken, and the event was reported to have resolved on (b) (4). TB was elevated before surgery and remained elevated on (b) (4). No further TB values were available.

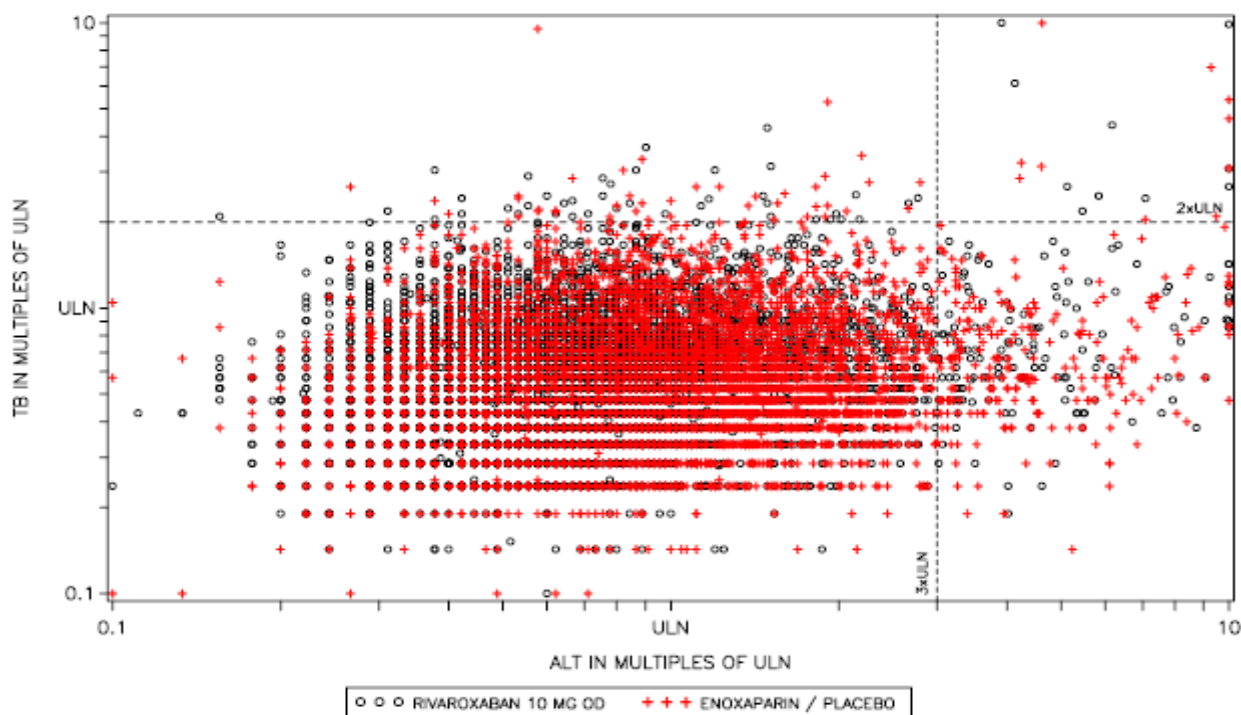
The investigator considered these events as not related to the study drug.

The Liver Advisory Panel Evaluation concluded that causality of study drug was excluded.



There was one additional enoxaparin subject (540017058) with non-concurrent ALT>3xULN (Day 11) with TB>2xULN (Day 2) based on central laboratory values. No rivaroxaban subject had non-concurrent ALT>3xULN with TB>2xULN based on central laboratory values. The following is plot of maximum of ALT with maximum TB in RECORD studies.

Figure 1-3: Scatter Plot of Maximum ALT Levels With Maximum Total Bilirubin Levels Occurring After Day 0
(Subjects Valid for the Safety Analysis in Pooled RECORD 1-4 Studies)



An additional one rivaroxaban subject and 2 enoxaparin subjects had non-concurrent ALT > 3xULN with TB > 2xULN based on local laboratory values. The 1 rivaroxaban subject and one enoxaparin subject had increased TB due to data entry error. Another enoxaparin subject with concurrent local laboratory elevations with a peak ALT of 309U/L (> 8X ULN) and TB of 2.09 mg/dL (> 2X ULN) on Day 3 with decreases thereafter.

AST > 3x ULN With a Concurrent Total Bilirubin > 2x ULN

Five additional subjects (2 rivaroxaban and 3 enoxaparin) had an AST level > 3x ULN concurrent with a total bilirubin level > 2x ULN (see table below) without an ALT level > 3x ULN. AST elevations occurred on Day 1 in both rivaroxaban subjects (i.e., prior to active rivaroxaban). In the enoxaparin group, 2 cases occurred on Day 1 and 1 case occurred on Day 8.

**Individual Subjects with AST >3x ULN and Total Bilirubin >2x ULN in Phase 3 Studies
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies)**

Study Drug Study/Subject ID Age/Sex	Day of Last Dose	Laboratory Values	Comments
Rivaroxaban			
11354-340054003 Figure 14.3.5/6.6.2A.2 79/female	34	AST = 188 U/L (Day 1) TB = 2.5 mg/dL (Day 1) DB = 1.0 mg/dL (Day 1)	Liver enzymes elevations began before first tablet administration; resolved while study drug continued
11357-540037018 Figure 14.3.5/6.6.2A.4 49/female	35	AST = 152 U/L (Day 1) TB = 3.9 mg/dL (Day 1) DB = 2.2 mg/dL (Day 1)	Liver enzymes elevations began before first tablet administration; resolving while study drug continued
Enoxaparin			
Figure 14.3.5/6.6.2A.1 78/female	32	AST = 177 U/L (Day 1) TB = 3.4 mg/dL (Day 1) DB = 1.9 mg/dL (Day 1)	Liver enzymes elevations resolved while study drug continued
11354-380034020 Figure 14.3.5/6.6.2A.3 69/male	31	AST = 291 U/L (Day 1) TB = 3.3 mg/dL (Day 1) DB = 1.1 mg/dL (Day 1)	Liver enzymes elevations resolving while study drug continued
11357-570017025 Figure 14.3.5/6.6.2A.5 75/female	11	AST = 125 U/L (Day 8) TB = 6.5 mg/dL (Day 8) DB = 3.8 mg/dL (Day 8)	Liver enzymes elevations resolved after discontinuation of study drug

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = direct bilirubin;
TB = total bilirubin; ULN = upper limit of normal

Note: Day 1 = day of surgery and day of first tablet intake (active or dummy)

Hepatic Disorder Adverse Events

Adverse Events

A following table summarizes the post-baseline hepatic adverse events in RECORD studies. Overall, 290 subjects (4.7%) administered rivaroxaban and 400 subjects (6.5%) administered enoxaparin reported a hepatic disorder adverse event. The vast majority of these adverse events reported by investigators in both treatment groups were adverse events due to abnormal liver-related laboratory tests. Of these, the most frequently reported events included the following: increased ALT, reported in 144 subjects (2.3%) given rivaroxaban and 200 subjects (3.2%) given enoxaparin; increased AST, reported in 116 subjects (1.9%) given rivaroxaban and 152 subjects (2.5%) given enoxaparin; and increased GGT, reported in 126 subjects (2.0%) given rivaroxaban and 183 subjects (3.0%) given enoxaparin. It was noted that more jaundice, ascites, and 1 hepatic failure were reported in the rivaroxaban group as compared to enoxaparin group.

Incidence of Postbaseline Hepatic Disorder Adverse Events^a
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

MSSO Search Category MedDRA Preferred Term	Rivaroxaban (N = 6183)		Enoxaparin (N = 6200)	
Any below mentioned search category				
Any event	290	(4.69%)	400	(6.45%)
MSSO: Cholestasis and jaundice of hepatic origin				
Any event	5	(0.08%)	5	(0.08%)
Hyperbilirubinemia ~	1	(0.02%)	4	(0.06%)
Jaundice	4	(0.06%)	1	(0.02%)
Ocular icterus	1	(0.02%)	0	(0.00%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions				
Any event	6	(0.10%)	5	(0.08%)
Ascites ~	2	(0.03%)	0	(0.00%)
Hepatic failure	1	(0.02%)	0	(0.00%)
Hepatic lesion	0	(0.00%)	2	(0.03%)
Hepatic steatosis	3	(0.05%)	2	(0.03%)
Hepatotoxicity	0	(0.00%)	1	(0.02%)
Varices esophageal	1	(0.02%)	0	(0.00%)
MSSO: Hepatitis, non-infectious				
Any event	1	(0.02%)	2	(0.03%)
Cytolytic hepatitis	1	(0.02%)	0	(0.00%)
Hepatitis	0	(0.00%)	2	(0.03%)

MSSO: Liver infections

Any event	1	(0.02%)	1	(0.02%)
Hepatitis B	1	(0.02%)	1	(0.02%)

MSSO: Liver neoplasms, benign

Any event	1	(0.02%)	0	(0.00%)
Hepatic cyst	1	(0.02%)	0	(0.00%)

MSSO: Liver-related investigations, signs, and symptoms

Any event	278	(4.50%)	395	(6.37%)
ALT abnormal	2	(0.03%)	1	(0.02%)
ALT increased	144	(2.33%)	200	(3.23%)
Ascites ~	2	(0.03%)	0	(0.00%)
AST abnormal	1	(0.02%)	1	(0.02%)
AST increased	116	(1.88%)	152	(2.45%)
Bilirubin conjugated increased	7	(0.11%)	6	(0.10%)
Blood Alk Phos abnormal	2	(0.03%)	0	(0.00%)
Blood Alk Phos increased	51	(0.82%)	81	(1.31%)
Blood bilirubin increased	23	(0.37%)	19	(0.31%)
Blood bilirubin unconjugated increased	8	(0.13%)	11	(0.18%)
GGT abnormal	1	(0.02%)	0	(0.00%)
GGT increased	126	(2.04%)	183	(2.95%)
Hepatic enzyme abnormal	2	(0.03%)	0	(0.00%)
Hepatic enzyme increased	20	(0.32%)	41	(0.66%)
Hepatic function abnormal	3	(0.05%)	5	(0.08%)
Hepatomegaly	1	(0.02%)	0	(0.00%)
Hyperbilirubinemia ~	1	(0.02%)	4	(0.06%)
Hypoalbuminemia	2	(0.03%)	8	(0.13%)
Liver function test abnormal	5	(0.08%)	12	(0.19%)
Liver palpable subcostal	0	(0.00%)	1	(0.02%)
Transaminases increased	2	(0.03%)	8	(0.13%)

MSSO: Possible liver-related coagulation and bleeding disturbances

Any event	2	(0.03%)	1	(0.02%)
Protein S decreased	0	(0.00%)	1	(0.02%)
Prothrombin level decreased	1	(0.02%)	0	(0.00%)
Prothrombin time ratio decreased	1	(0.02%)	0	(0.00%)

^a For MSSO search category Hepatic Disorders

Key: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary of Regulatory Activities; MSSO = Maintenance and Support Service Organization

Note: All events after start of study medication are included regardless of onset relative to last dose of study medication

Note: Incidence rate = # of events / # at risk, where:
of events = # of subjects reporting the event after the start of treatment

Note: Sorted alphabetically, first by search category then by MedDRA preferred term

Note: MedDRA preferred terms marked with ~ are allocated to multiple search categories

Deaths

In the 4 Phase 3 RECORD studies, no subjects died from hepatic disorder adverse events.

Serious Adverse Events

Overall, 33 subjects (0.53%) administered rivaroxaban and 27 subjects (0.44%) administered enoxaparin had hepatic disorder serious adverse events (see table below). The vast majority of these subjects (28 subjects [0.5%] receiving rivaroxaban and 26 subjects [0.4%] receiving enoxaparin) had adverse events that were increases in liver-related laboratory parameters. The most common hepatic disorder serious adverse event was increased ALT levels, seen in 17 subjects (0.3%) administered rivaroxaban and 14 subjects (0.2%) administered enoxaparin.

The subject with hepatic failure was a 72 year old White female who had a MI on Day 4 with hypotension. She developed acute renal and hepatic failure due to hypotension. AST/ALT levels were >10x ULN but TB was normal on Day 4. TB was slightly high on Day 6 and 7. All LFT abnormalities were resolved on Day 14. The investigator considered this event as not related. The LAP concluded that the causality of study drug was excluded.

The subject with ascites was an 81 year-old Asian male who was hospitalized on Day 40 for ascites and pleural effusions. LFTs were normal and albumin was 1.9 g/dL. This event was considered due to hypoproteinemia. The investigator considered this event as not related to the study drug.

Two subjects reported jaundice and both had bleeding events (wound of operation site and GI, respectively) and received transfusions. In both cases ALT levels were normal and TB was slightly higher with direct bilirubin >1.5 xULN. These two events were considered not related to the study drug by investigators. This event in both cases was resolved.

Incidence of Serious Post-baseline Hepatic Disorder Adverse Events^a
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

MSSO Search Category MedDRA Preferred Term	Rivaroxaban (N = 6183)		Enoxaparin (N = 6200)	
Any below mentioned search category				
Any event	33	(0.53%)	27	(0.44%)
MSSO: Cholestasis and jaundice of hepatic origin				
Any event	3	(0.05%)	0	(0.00%)
Jaundice	3	(0.05%)	0	(0.00%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions				
Any event	2	(0.03%)	0	(0.00%)
Ascites ~	1	(0.02%)	0	(0.00%)
Hepatic failure	1	(0.02%)	0	(0.00%)
MSSO: Hepatitis, non-infectious				
Any event	0	(0.00%)	2	(0.03%)
Hepatitis	0	(0.00%)	2	(0.03%)
MSSO: Liver-related investigations, signs, and symptoms				
Any event	28	(0.45%)	26	(0.42%)
Alanine aminotransferase abnormal	2	(0.03%)	0	(0.00%)
Alanine aminotransferase increased	17	(0.27%)	14	(0.23%)
Ascites ~	1	(0.02%)	0	(0.00%)
Aspartate aminotransferase increased	5	(0.08%)	7	(0.11%)
Bilirubin conjugated increased	1	(0.02%)	0	(0.00%)
Blood alkaline phosphatase increased	0	(0.00%)	1	(0.02%)
Blood bilirubin increased	5	(0.08%)	4	(0.06%)
Gamma-glutamyltransferase abnormal	1	(0.02%)	0	(0.00%)
Gamma-glutamyltransferase increased	2	(0.03%)	4	(0.06%)
MSSO: Liver-related investigations, signs, and symptoms (continued)				
Hepatic enzyme increased	6	(0.10%)	7	(0.11%)
Liver function test abnormal	3	(0.05%)	1	(0.02%)
Transaminases increased	0	(0.00%)	2	(0.03%)
MSSO: Possible liver-related coagulation and bleeding disturbances				
Any event	1	(0.02%)	0	(0.00%)
Prothrombin time ratio decreased	1	(0.02%)	0	(0.00%)

^a For MSSO search category Hepatic Disorders

Key: MedDRA = Medical Dictionary of Regulatory Activities; MSSO = Maintenance and Support Service Organization

Note: All events after start of study medication are included regardless of onset relative to last dose of study medication

Note: Incidence rate = # of events / # at risk, where:

of events = # of subjects reporting the event after the start of treatment

Note: Sorted alphabetically, first by search category then by MedDRA preferred term

Note: MedDRA preferred terms marked with ~ are allocated to multiple search categories

Adverse Events Leading to Discontinuation of Study Medication

Overall, 12 subjects (0.2%) receiving rivaroxaban and 17 subjects (0.3%) receiving enoxaparin in the RECORD studies experienced a hepatic disorder adverse event that led to permanent discontinuation of study medication (see Table below). 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.

**Incidence of Hepatic Disorder Adverse Events^a
Resulting in Permanent Discontinuation of Study Medication
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies)**

MSSO Search Category MedDRA Preferred Term	Rivaroxaban (N = 6183)		Enoxaparin (N = 6200)	
Any below mentioned search category				
Any event	12	(0.19%)	17	(0.27%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions				
Any event	1	(0.02%)	0	(0.00%)
Hepatic failure	1	(0.02%)	0	(0.00%)
MSSO: Hepatitis, non-infectious				
Any event	1	(0.02%)	1	(0.02%)
Cytolytic hepatitis	1	(0.02%)	0	(0.00%)
Hepatitis	0	(0.00%)	1	(0.02%)
MSSO: Liver infections				
Any event	0	(0.00%)	1	(0.02%)
Hepatitis B	0	(0.00%)	1	(0.02%)
MSSO: Liver-related investigations, signs, and symptoms				
Any event	10	(0.16%)	16	(0.26%)
Alanine aminotransferase increased	7	(0.11%)	7	(0.11%)
Aspartate aminotransferase increased	3	(0.05%)	2	(0.03%)
Bilirubin conjugated increased	1	(0.02%)	2	(0.03%)
Blood alkaline phosphatase abnormal	1	(0.02%)	0	(0.00%)
Blood alkaline phosphatase increased	0	(0.00%)	1	(0.02%)
Blood bilirubin increased	1	(0.02%)	6	(0.10%)
Blood bilirubin unconjugated increased	0	(0.00%)	1	(0.02%)
Gamma-glutamyltransferase abnormal	1	(0.02%)	0	(0.00%)
Gamma-glutamyltransferase increased	2	(0.03%)	3	(0.05%)
Hepatic enzyme increased	1	(0.02%)	3	(0.05%)
Liver function test abnormal	2	(0.03%)	2	(0.03%)
Transaminases increased	0	(0.00%)	2	(0.03%)

^a For MSSO search category Hepatic Disorders

Key: MedDRA = Medical Dictionary of Regulatory Activities; MSSO = Maintenance and Support Service Organization

Note: All events after start of study medication are included regardless of onset relative to last dose of study medication

Note: Incidence rate = # of events / # at risk, where:
of events = # of subjects reporting the event resulting in permanent disc. of study drug

Note: Sorted alphabetically, first by search category then by MedDRA preferred term

7.3.4.4.2 Phase 2 Clinical Studies

7.3.4.4.2.1 VTE Prophylaxis Studies (Studies 10942, 10944, 10945, and 11527)

Abnormal Liver-related Laboratory Values

The incidence of liver-related laboratory abnormalities (defined as any elevation > 3x ULN occurring after surgery with pre-surgery as the baseline value) is presented by dose of study drug in the following table. Over the 12-fold total daily dose range evaluated in these Phase 2 studies, there does not appear to be a consistent dose-dependent increase in the incidence of selected liver-related laboratory abnormalities.

Incidence of Selected Laboratory Abnormalities After Surgery Start with Presurgery Baseline by Dose of Study Drug in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)

Laboratory Abnormality >3x ULN	Rivaroxaban Total Daily Dose						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%)
ALK PHOS	2/425 (0.5%)	5/442 (1.1%)	2/435 (0.5%)	2/219 (0.9%)	1/434 (0.2%)	1/210 (0.5%)	13/2165 (0.6%)	2/538 (0.4%)
GGT	29/421 (6.9%)	40/430 (9.3%)	38/422 (9.0%)	21/217 (9.7%)	45/420 (10.7%)	17/197 (8.6%)	190/2107 (9.0%)	52/523 (9.9%)

^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: ALK PHOS = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; ULN = upper limit of normal

Note: Incidence rate = # of events / # at risk, where:

of events = # of subjects reporting the abnormality postbaseline.

at risk = # of subjects with readings pre and postbaseline who did not report abnormality at baseline.

Note: Highest value prior to start of surgery is used as baseline.

Note: Highest value after surgery is used as postbaseline.

Note: If available, even measurements taken more than 7 days after end of treatment are considered here.

The incidence of liver-related laboratory abnormalities at varying thresholds occurring after the start of surgery for all rivaroxaban doses pooled together is presented in the following table. The incidence of ALT levels >3x ULN was lower in subjects receiving rivaroxaban (4.9%) compared with enoxaparin (7.1%) but the incidence of ALT levels >8x ULN was slightly higher in subjects receiving rivaroxaban compared with enoxaparin. The incidence of AST levels >3x ULN was lower in subjects administered rivaroxaban (5.4%) compared with enoxaparin (6.4%). However, at higher thresholds the incidence was slightly higher in the rivaroxaban group as compared to the enoxaparin group. The incidence of abnormalities in total bilirubin >3 xULN and ALK PHOS>3xULN was slightly higher in the rivaroxaban group compared with enoxaparin. GGT were generally comparable at varying thresholds.

Four of 1700 subjects (0.2%) administered rivaroxaban and 2 of 379 subjects (0.5%) administered enoxaparin had ALT levels >3x ULN concurrent with bilirubin levels >2x ULN. One subject in the rivaroxaban group was not included in the table below. This subject had marked LFT elevation 39 days after the study treatment. These subjects are discussed in detail later.

Five of 1700 subjects (0.3%) administered rivaroxaban and 2 of 379 subjects (0.5%) administered enoxaparin had AST levels >3x ULN concurrent with bilirubin levels >2x ULN.

**Incidence of Selected Laboratory Abnormalities After Start of Surgery
(with Presurgery as Baseline) in Phase 2 Orthopedic Prophylaxis Studies
in Venous Thromboembolism
(Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)**

Laboratory Variable	Rivaroxaban N=2232		Enoxaparin N=555	
ALT >3x ULN and total bilirubin >2x ULN	3/1700	(0.2%)	2/379	(0.5%)
ALT, n (%)				
>3x ULN	107/2162	(4.9%)	38/533	(7.1%)
>5x ULN	42/2164	(1.9%)	14/534	(2.6%)
>8x ULN	17/2164	(0.8%)	3/534	(0.6%)
>10x ULN	9/2164	(0.4%)	2/534	(0.4%)
AST >3x ULN and total bilirubin >2x ULN	5/1700	(0.3%)	2/379	(0.5%)
AST, n (%)				
>3x ULN	117/2151	(5.4%)	34/532	(6.4%)
>5x ULN	50/2152	(2.3%)	11/532	(2.1%)
>8x ULN	24/2152	(1.1%)	5/532	(0.9%)
>10x ULN	21/2152	(1.0%)	3/532	(0.6%)
Total bilirubin, n (%)^a				
>2x ULN	30/1699	(1.8%)	8/378	(2.1%)
>3x ULN	6/1700	(0.4%)	0/379	(0.0%)
>5x ULN	0/1700	(0.0%)	0/379	(0.0%)
Alkaline phosphatase, n (%)				
>3x ULN	13/2165	(0.6%)	2/538	(0.4%)
>5x ULN	0/2166	(0.0%)	0/538	(0.0%)
GGT, n (%)				
>3x ULN	190/2107	(9.0%)	52/523	(9.9%)
>5x ULN	78/2144	(3.6%)	21/529	(4.0%)
>8x ULN	21/2156	(1.0%)	6/531	(1.1%)
>10x ULN	11/2156	(0.5%)	2/531	(0.4%)

^a Total bilirubin was not measured in Study 10942.

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; ULN = upper limit of normal

Note: Incidence calculated in the at-risk population of subjects with a pre-surgery laboratory measurement not showing the defined abnormality and at least one laboratory measurement after start of surgery.

Note: The subjects reported in higher threshold categories will not always be included in lower threshold categories because this analysis is based on a treatment emergent approach that excludes subjects with baseline abnormalities.

Note: If available, measurements taken more than 7 days after end of treatment are included.

Alanine Aminotransferase Elevations Over Time

Most subjects have peak ALT elevations that occur before Day 10 and subsequently return to baseline. In Studies 10942, 10944, and 10945, the protocol did not require assessments of laboratory tests at the 30-day follow-up visit. Consequently, some subjects discontinued from study drug with elevated ALT levels and incomplete laboratory follow-up.

ALT or AST >3x ULN With a Concurrent Total Bilirubin >2x ULN

Four subjects administered rivaroxaban and 2 subjects receiving enoxaparin reported ALT increases >3x ULN concurrent with total bilirubin levels >2x ULN. The following table summarizes the patient's information, outcomes and investigator's assessment.

One subject in the rivaroxaban group died subsequently and others had LFT normalized. All cases in the rivaroxaban group were considered to be related to study drug and all cases in the enoxaparin group were considered to be not related to the study drug by investigator. A Liver Advisory Panel (LAP) was not formally established to review hepatic disorder adverse events from Phase 2 VTE prophylaxis studies. However, the death case (10944-84008) was reviewed by LAP.

ALT >3x ULN Concurrent With TB>2x ULN Cases in Phase 2 VTE Prophylaxis Studies

Age/sex Race ID	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	Investigator/LAP Assessment
Rivaroxaban					
84/F White 10945-102- 102016	9	2	ALT 387/ TB 4.7	Resolving while study drug continued.	Related / -
78/F White 10945-111- 111011	6	2	ALT 206 / TB 2.4	Resolving while study drug continued.	Related / -
68/M White 11527-71005	4	1	ALT 518/ TB 2.9	Resolved after study drug stopped. The study drug was discontinued permanently.	Related / unlikely by one LAP member and possible by another LAP member
79/F White 10944-84008	8	47	ALT 190/ TB 18.3	Hospitalized for jaundice and nausea, loss appetite on Day 47 and died with liver failure on Day 127.	Related/Unlikely
Enoxaparin					
71/F White 10944-75006	9	1	ALT 119/ TB 2.3	Resolving while study drug continued.	Not related/ -

80/F White 10944-84001	7	1	ALT 579/ TB 2.6	Resolving on study drug continued. Cholecystolithiasis was found.	Not related/ -
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The following is the patient's narrative:

Rivaroxaban Group

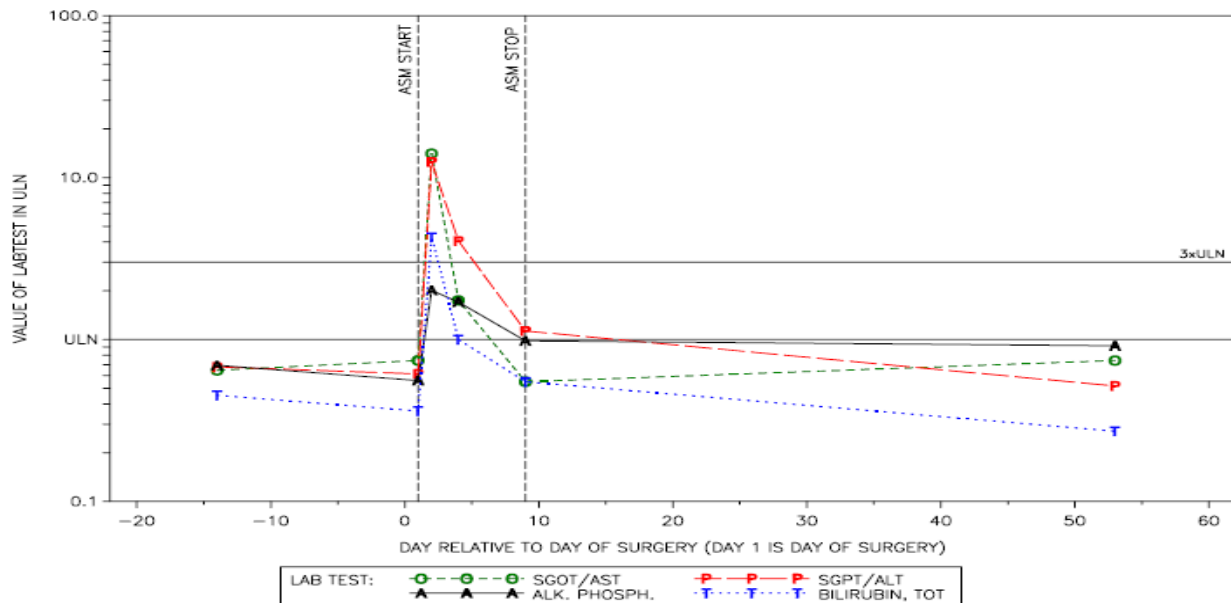
10945-102-102016

This 84-year-old White woman had a history of MI (1998) TIA (1998 & 2002), duodenal ulcer (1950), glaucoma (2003), diabetes mellitus (2003), right hip replacement (2003), titanium rods in neck (2000), cholecystectomy (1980), hypothyroidism (1994), hypercholesterolemia (1998), osteoarthritis, hypertension (1998) and CAD (1998).

The subject received rivaroxaban 20mg bid (b) (4) days.

On (b) (4), the total right knee replacement surgery was performed under spinal anesthesia. On (b) (4), the subject had elevated ALT, AST, GGT, alkaline phosphatase, bilirubin, amylase and lipase. No action was taken and the abnormal values returned to normal or near normal on (b) (4). On (b) (4), the subject was confused, agitated and appeared slightly jaundice. No action was taken. The jaundice resolved on the same day, the agitation on (b) (4) and the confusion on (b) (4). The dose of study drug was not changed during the course of hospital treatment.

The investigator considered all these events were as related to study drug.



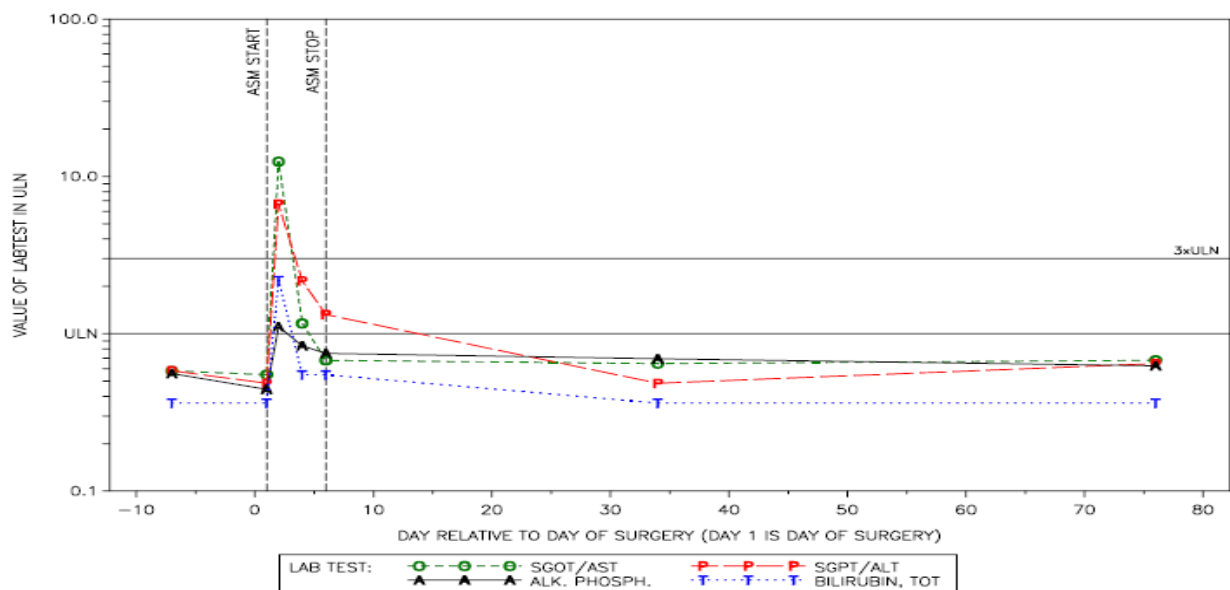
10945-111-111011

This 78-year-old White woman had a history of light alcohol consumption, smoking (1940 to 1990), osteoarthritis, chronic constipation, hypothyroidism, hypertension, GERD, hepatitis A (1959), right total hip replacement and nephrectomy on right kidney.

The subject received rivaroxaban 10mg bid from (b) (4) days.

Total knee replacement surgery was performed on (b) (4) (b) (4) ALT, AST, GGT, LDH, alkaline phosphatase and bilirubin were increased. All of the tests were moderate in severity and not serious except GGT which was considered as a serious event. The subject was retested at follow-up visit and GGT levels were slightly improved but still markedly elevated. All of the other liver function tests were transiently increased and were back to normal on (b) (4) the subject had vertigo and inability to concentrate, not requiring treatment. Both events resolved the next day. The dose of rivaroxaban was not changed, and the subject completed the study. On the follow-up visits of (b) (4) and (b) (4) the result of GGT test was still increased, but gradually resolved towards normal.

The investigator considered abnormality of liver function laboratory tests to be related to the study drug.



11527-71005

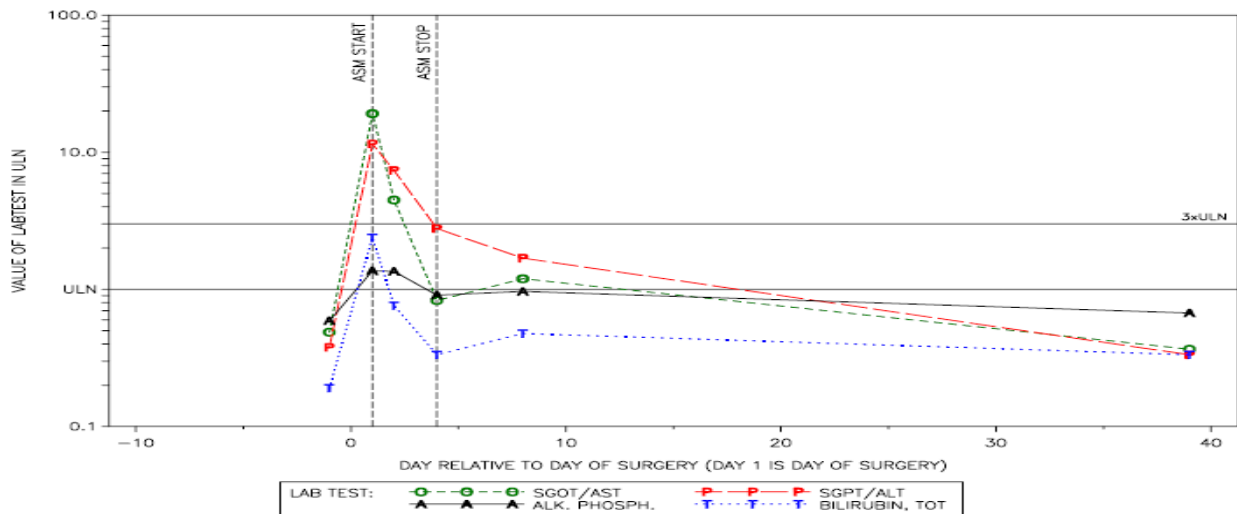
This 68 year old White male subject had medical history of appendectomy, cramps in legs, pleural plaque, hip pain, lactose intolerance, benign tumor in gallbladder, cholecystectomy and erectile dysfunction.

The subject received rivaroxaban (b) (4).

Elective hip replacement was performed on (b) (4). Elevated AST and ALT values were reported on (b) (4) with ALT > 10 x ULN, AST > 10 x ULN, and TB > 2 x ULN. GGT, ALK PHOS, and lipase also increased. The study drug was (b) (4) and the events resolved without any treatment on (b) (4).

The investigator considered elevated liver enzymes as related to the study drug.

The liver advisory panel considered as possible by one member and unlikely by another member.



10944-84008

This was a 79-year-old White female with a medical history of hypertension, cardiac insufficiency, compensated renal insufficiency, hyperuricemia, varicosis, coxarthrosis left side, cholecystolithiasis, hyperlipidemia and Parkinson's disease.

The subject received rivaroxaban from [REDACTED] (b) (4).

On [REDACTED] (b) (4), the patient underwent the elective hip replacement and received 1 unit heterologous packed cells in the evening. The patient suffered urinary tract infection on [REDACTED] (b) (4) which was treated with trimethoprim/sulfamethoxazole and resolved on [REDACTED] (b) (4). The subject was transferred to a rehabilitation facility from [REDACTED]. During rehabilitation tremor of right leg and right hand and mild distal edema of lower legs were reported and these improved after treatment.

On [REDACTED] the patient went to her family doctor due to loss of appetite, weight loss, brown urine, nausea and vomiting. The subject was hospitalized. On admission increased liver enzymes (ALT 190, AST 504, GGT 566 U/L) and bilirubin (18.3 mg/dL) were found. Icterus of the sclerae and integument was seen. Amylase and lipase were within the normal range. The abdomen was free of pain on pressure and there were no resistances palpable. Marked edema of lower legs and feet and tremor at rest were seen. No other pathological findings were reported.

On [REDACTED] ALT increased to 452 with AST of 178 U/L, GGT of 538 U/L, and AP of 566 U/L. In the hepatitis serology (ELISA) only positive CMV-IgG- and EBV-IgG-antibodies were found.

On [REDACTED] abdominal ultrasound and ERCP with papillotomy, due to the fact that papillitis stenosis could not be excluded, were performed and except cholecystolithiasis no other abnormalities were found. After ERCP increased lipase (928 U/L) and amylase (151 U/L) was measured.

On [REDACTED] APTT was prolonged to 40.2 sec. and on [REDACTED] (b) (4) to 180 sec., on [REDACTED] decreased to 29.8 sec. Prothrombin time was in normal range.

On (b) (4), the liver biopsy showed mild to moderate fatty degeneration and lipofuscin enrichment, but no signs of inflammation.

The patient got several blood transfusions: 2 units on (b) (4), 1 unit on 09 (b) (4) (D).

On (b) (4) the condition of the patient worsened, the patient became somnolent. A cerebral CT showed marked cerebral atrophy and arteriosclerosis. Ammonia was 59 µg/dL (normal range 19-87). The lipase improved on (b) (4) to 59 U/L.

During the hospital course liver-related parameters [ALT up to 639, AST to 550, GGT to 1987, AP to 2764 U/L on (b) (4) bilirubin [highest value 54.6 mg/dL on (b) (4) and inflammation parameter (CRP up to 12.4 mg/dL on (b) (4) – normal range < 0.5) increased further.

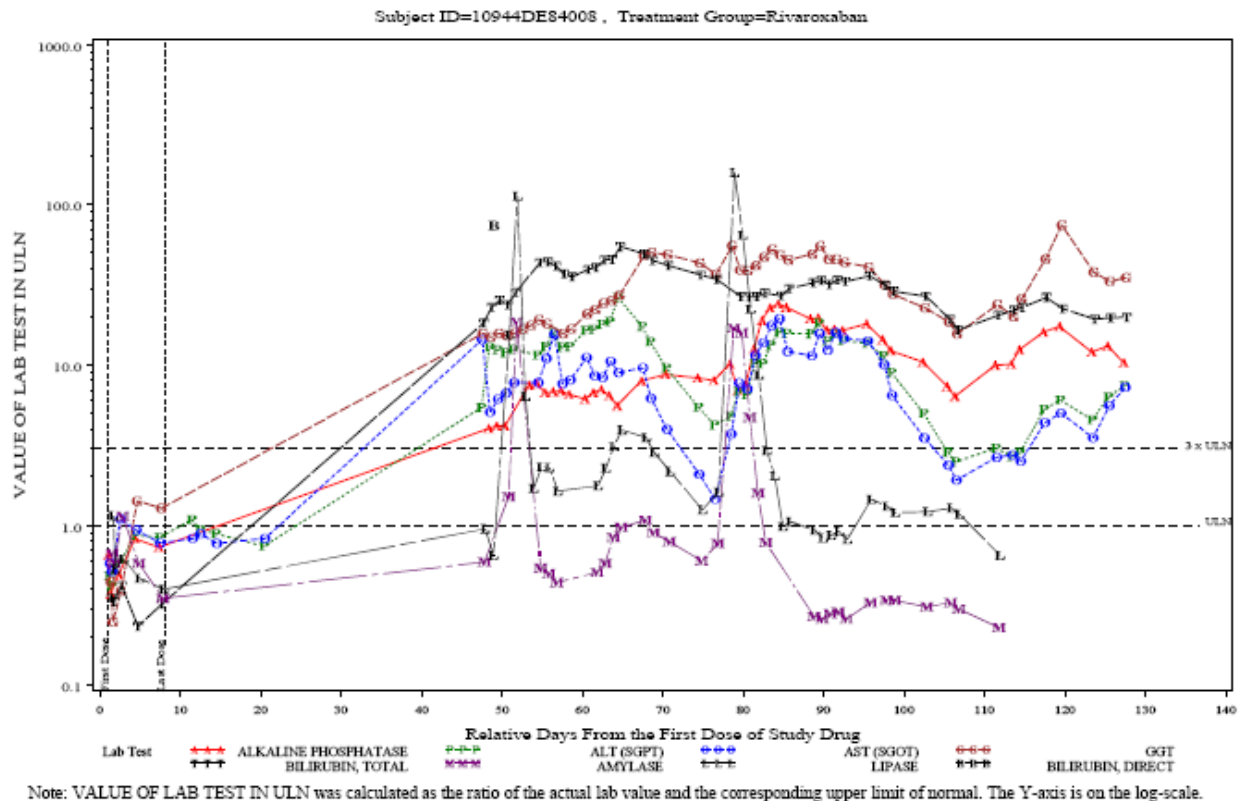
On (b) (4), phlegmonic cholecystitis with cholangitis was found in the sonography, which was resistant to antibiotic therapy. Additionally bronchopneumonia developed.

On (b) (4) the patient died.

The autopsy was performed on (b) (4). Post-mortem examination showed acute, necrotising pancreatitis with evidence of chronic or prior pancreatitis and acute cholecystitis due to cholecystolithiasis to be the cause of the jaundice. Findings also included bilateral bronchial pneumonia and bilateral pyelonephritis with septic spleen. Under the cause of death, it stated “Septic, cholemic heart and circulatory failure with bronchial pneumonia, acute cholecystitis and acute pancreatitis”. Under Liver section, it stated “Hepatocytes already altered due to autolysis, portal fields not greatly enlarged, no glycogen nuclei, no signs of intrahepatic cholestasis.”

The investigator considered the liver impairment and pancreatitis as related to the study drug.

The sponsor’s Liver Advisory Meeting (2/17/2008) including 3 LAP members for RECORD studies concluded “Although this patient’s cholestasis was unlikely related to rivaroxaban, this may be a drug-induced cholestasis. One potential candidate is Bactrim although temporal association cannot exclude rivaroxaban”. Committee stated this is not a “liver death”.



Enoxaparin group

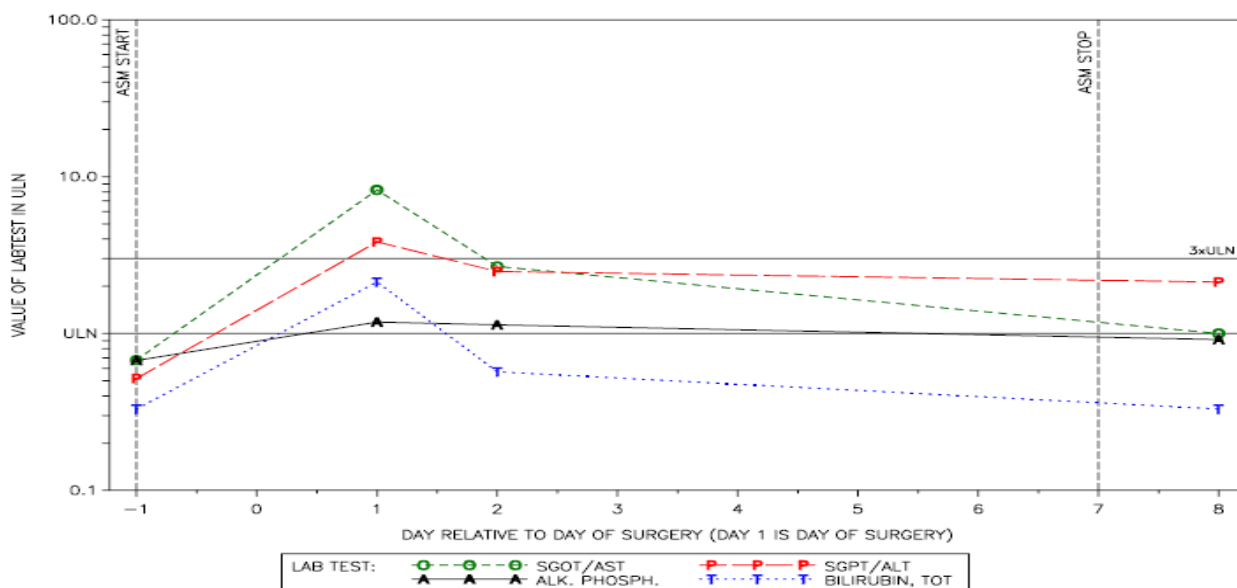
10944-75006

This 71-year old White female had a history of coxarthrosis left side (2001), phlegmona of hand (2002), cholecystectomy (1998) and fracture of right lower leg (1973).

The subject received [REDACTED] from [REDACTED] days.

Total hip replacement surgery took place on [REDACTED] until [REDACTED] (b) (4). [REDACTED] AST, ALT and total bilirubin increased. The next day the bilirubin value was in the normal range. At end of study drug therapy only GGT and ALT were slightly increased.

The investigator assessed the increase of AST and ALT as mild and not related to study drug.



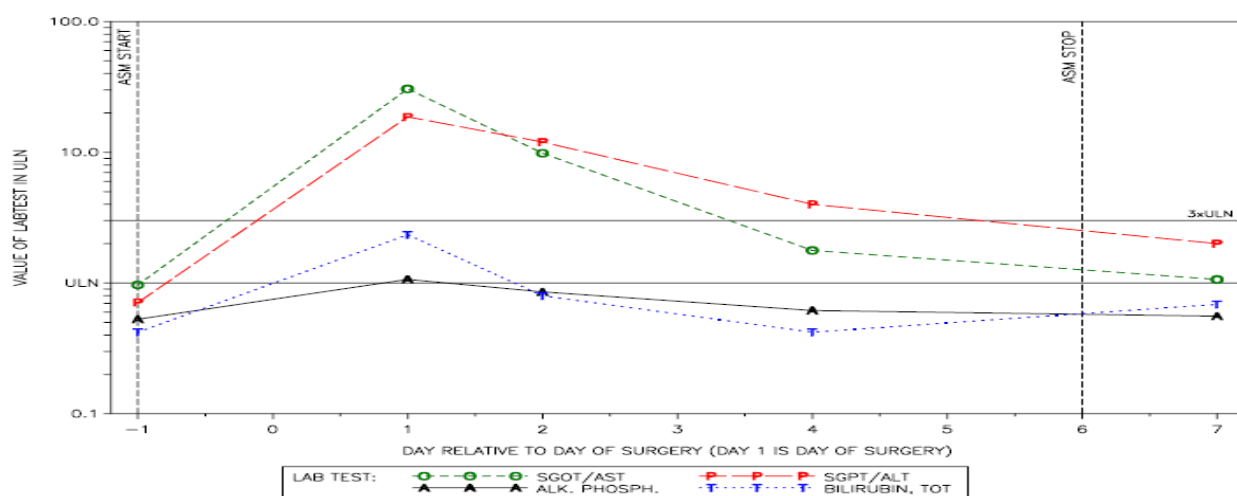
10944-84001

This 80 year old White female had medical history of coxarthrosis. Light alcohol consumption and non-smoking history were reported.

The subject received (b) (4) days.

Total elective hip replacement took place on (b) (4). On (b) (4) abnormal liver parameters were reported (AST 947 U/L, ALT 579 U/L, GGT 288 U/L, LDH 1547 U/L, AP 111 U/L, bilirubin 2.6 mg/dL, amylase 176 U/L and lipase 227 U/L). An abdominal CT showed cholecystolithiasis. No action was taken. The values started to decrease on (b) (4).

The investigator considered this event as related to study drug and attributed this to cholelithiasis and post-anesthetic setting.



AST>3xULN concurrent with TB>2xULN

Two additional rivaroxaban subjects (in Study 10945) had AST levels >3x ULN concurrent with total bilirubin levels >2x ULN without ALT levels >3x ULN (see Table below); these events occurred on Day 4 and Day 6, respectively. Due to the design of the study protocol, which did not require laboratory testing at the follow-up visit, there was incomplete laboratory follow-up for both subjects. Subject 10945-102010 had elevated liver-related laboratory tests at the time of study drug discontinuation, and AST values for Subject 10945-131013 remained elevated at the time of study drug discontinuation.

**Individual Subjects with AST >3x ULN and Total Bilirubin >2x ULN^a
in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism
(Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)**

Subject ID Age/Sex	Total Daily Dose	Day of Last Dose	Laboratory Values	Comments
Rivaroxaban				
10945/102010 Figure P/5.1.2.3 60/male	60 mg	Day 4	AST = 129 U/L (Day 6) TB = 4.1 mg/dL (Day 6)	Liver enzymes elevated after study drug discontinuation. Incomplete follow-up since labs not required by protocol.
10945/131013 Figure P/5.1.2.6 80/male	60 mg	Day 6	AST = 152 U/L (Day 2) TB = 3.8 mg/dL (Day 2)	AST elevations unresolved at the time of study drug discontinuation. Incomplete laboratory follow-up

^a Without a corresponding increase in ALT levels >3x ULN

Key: AST = aspartate aminotransferase; TB = bilirubin; ULN = upper limit of normal

Note: Day 1 = day of surgery

Hepatic Disorder Adverse Events

Adverse Events

A summary table of treatment-emergent hepatic disorder adverse events is presented in following table. Overall, 168 subjects (7.5%) administered rivaroxaban and 52 subjects (9.4%) administered enoxaparin reported a hepatic disorder adverse event. The vast majority of these adverse events reported by investigators in both treatment groups were adverse events due to abnormal liver-related laboratory tests. The most frequently reported events included increases in the laboratory parameters of ALT, AST, and GGT.

**Incidence of Treatment-Emergent Adverse Events
in the MSSO Search Category 'Hepatic Disorders'
in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism
(Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)**

MSSO Search Category/ MedDRA Preferred Term	Rivaroxaban Total (N=2232)	Enoxaparin (N=555)
Any event	168 (7.5%)	52 (9.4%)
MSSO: Cholestasis and jaundice of hepatic origin		
Any event	4 (0.2%)	0 (0.0%)
Hyperbilirubinemia ~	2 (<0.1%)	0 (0.0%)
Jaundice	2 (<0.1%)	0 (0.0%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions		
Any event	1 ^a (<0.1%)	1 (0.2%)
Asterixis	0 (0.0%)	1 (0.2%)
Liver disorder	1 ^a (<0.1%)	0 (0.0%)
MSSO: Liver-related investigations, signs and symptoms		
Any event	165 (7.4%)	51 (9.2%)
Alanine aminotransferase increased	67 (3.0%)	25 (4.5%)
Aspartate aminotransferase increased	72 (3.2%)	25 (4.5%)
Blood alkaline phosphatase increased	20 (0.9%)	5 (0.9%)
Blood bilirubin increased	19 (0.9%)	0 (0.0%)
Gamma-glutamyltransferase increased	87 (3.9%)	27 (4.9%)
Hepatic enzyme increased	12 (0.5%)	7 (1.3%)
Hyperbilirubinemia ~	2 (<0.1%)	0 (0.0%)
Hypoalbuminemia	5 (0.2%)	0 (0.0%)
Liver function test abnormal	0 (0.0%)	2 (0.4%)
Transaminases increased	7 (0.3%)	4 (0.7%)
MSSO: Possible liver-related coagulation and bleeding disturbances		
Any event	1 (<0.1%)	0 (0.0%)
Coagulation Factor VII level decreased	1 (<0.1%)	0 (0.0%)
Prothrombin time ratio decreased	1 (<0.1%)	0 (0.0%)

^a Subject 10944-84008 5.3.5.1.4-788

Key: MSSO = Maintenance and Support Services Organization

Note: All treatment-emergent events regardless of time after last study medication are included.

Note: Incidence = # of events / # at risk, where:

of events = # of subjects reporting the event after the start of treatment

at risk = # of subjects in reference population

Note: Sorted alphabetically first by search category and then by MedDRA preferred term

Note: MedDRA preferred terms marked with ~ are allocated to multiple search categories.

Deaths

One subject (b) (4) after the last dose of rivaroxaban. This subject also met the criteria for ALT level >3x ULN concurrent with total bilirubin level >2x ULN. The patient's narrative has been presented in the early section in the ALT level >3x ULN concurrent with total bilirubin level >2x ULN.

Serious Adverse Events

Fourteen subjects (0.6%) administered rivaroxaban and 4 subjects (0.7%) administered enoxaparin had hepatic disorder serious adverse events (see Table below); the vast majority of subjects (12 of 14 subjects receiving rivaroxaban and 4 of 4 subjects receiving enoxaparin) had adverse events that were increases in liver-related laboratory parameters. In most cases, the liver-related laboratory parameter (e.g., ALT and AST) increased on the day of surgery (Day 1) or the first few days after surgery and was resolving or had completely resolved while study drug administration continued. In subjects where complete resolution had not occurred at the time of study drug discontinuation, follow-up laboratory tests at the 30-day follow-up visit showed normalization of ALT and AST. In 2 subjects administered rivaroxaban ((b) (4)) and 1 subject receiving enoxaparin (b) (4) there was incomplete laboratory follow-up. As discussed earlier, laboratory assessments at the 30-day follow-up safety visit were not required and occurred at the discretion of the investigator.

In the table below, there was a serious adverse event with a preferred term of “liver disorder” that occurred in Subject (b) (4) this subject is discussed in Section 2.1.2.2.

Incidence of Treatment-Emergent Serious Adverse Events in the MSSO Search Category ‘Hepatic Disorders’ in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)

MSSO Search Category/ MedDRA Preferred Term	Rivaroxaban Total (N=2232)	Enoxaparin (N=555)
Any event	14 (0.6%)	4 (0.7%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions		
Any event	1 ^a (<0.1%)	0 (0.0%)
Liver disorder	1 ^a (<0.1%)	0 (0.0%)
MSSO: Liver-related investigations, signs and symptoms		
Any event	12 (0.5%)	4 (0.7%)
Alanine aminotransferase increased	5 (0.2%)	0 (0.0%)
Aspartate aminotransferase increased	7 (0.3%)	2 (0.4%)
Blood alkaline phosphatase increased	2 (<0.1%)	0 (0.0%)
Gamma-glutamyltransferase increased	3 (0.1%)	0 (0.0%)
Hepatic enzyme increased	1 (<0.1%)	0 (0.0%)
Liver function test abnormal	0 (0.0%)	1 (0.2%)
Transaminases increased	1 (<0.1%)	1 (0.2%)
MSSO: Possible liver-related coagulation and bleeding disturbances		
Any event	1 (<0.1%)	0 (0.0%)
Coagulation factor VII level decreased	1 (<0.1%)	0 (0.0%)
Prothrombin time ratio decreased	1 (<0.1%)	0 (0.0%)

^a Subject 10944-04000 5.3.5.1.4-788

Key: MedDRA = Medical Dictionary for Regulatory Activities; MSSO = Maintenance and Support Services Organization

Note: All treatment-emergent events regardless of time after last study medication are included.

Note: Incidence = # of events / # at risk, where:

of events = # of subjects reporting the event after the start of treatment

at risk = # of subjects in reference population

Note: Sorted alphabetically first by search category and then by MedDRA preferred term

Adverse Events Leading to Study Discontinuation

Overall, 5 subjects (0.2%) administered rivaroxaban and 0 subjects administered enoxaparin had hepatic disorder adverse events leading to study discontinuation (see Table below). The most common events included increased ALT, AST, and increased hepatic enzymes.

Incidence of Hepatic Disorder Adverse Events Leading to Study Discontinuation in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)

MSSO Search Category/ MedDRA Preferred Term	Total Rivaroxaban (N=2232)		Enoxaparin (N=555)	
Any event	5	(0.2%)	0	(0.0%)
MSSO: Liver-related investigations, signs, and symptoms				
Any event	4	(0.2%)	0	(0.0%)
Alanine aminotransferase increased	1	(<0.1%)	0	(0.0%)
Aspartate aminotransferase increased	1	(<0.1%)	0	(0.0%)
Hepatic enzymes increased	3	(0.1%)	0	(0.0%)
MSSO: Possible liver-related coagulation and bleeding disturbances				
Any event	1	(<0.1%)	0	(0.0%)
Coagulation factor VII level decreased	1	(<0.1%)	0	(0.0%)
Prothrombin time ratio decreased	1	(<0.1%)	0	(0.0%)
Key: MedDRA = Medical Dictionary for Regulatory Activities; MSSO = Maintenance and Support Services Organization				
Note: Incidence = # of events / # at risk, where:				
# of events = # of subjects reporting the event resulting in permanent disc. of study drug				
# at risk = # of subjects in reference population				
Note: Sorted alphabetically first by search category then by MedDRA preferred term				

7.3.4.4.2.2 VTE Treatment Studies (Studies 11223 and 11528)

The Phase 2 DVT treatment studies consisted of 2 randomized, active controlled, parallel-group studies in subjects with an acute symptomatic deep vein thrombosis that was objectively confirmed. The scheduled duration of treatment in the Phase 2 DVT treatment studies was 84 days. The control group in both studies received initial treatment (first 5 to 7 days) with heparin (enoxaparin in Study 11223 and unfractionated heparin, tinzaparin, or enoxaparin in Study 11528) followed by a vitamin K antagonist (VKA) for the remainder of the 84-day duration. Subjects with transaminases ≥ 2 x ULN were excluded from enrollment in these studies.

Summary of Liver-related Laboratory Values

A schedule of liver-related laboratory assessments in the 2 DVT treatment studies is provided in the following table. Day 1 laboratory measurements were obtained prior to study drug initiation in both studies.

**Schedule of Liver-related Laboratory Assessments
in Phase 2 Treatment Studies in Venous Thromboembolism**

Study	Day 1	Day 5-7	Day 21	Day 43	Day 56	Day 84	Follow-up
11223	X	X	X		X	X	No
11528	X			X		X	Yes

Note: Post treatment follow-up laboratory tests were not required

The incidence of treatment-emergent, liver-related laboratory abnormalities at varying thresholds is presented in the following table. At most thresholds of liver-related laboratory abnormalities, the incidence of elevated ALT, AST, and GGT levels was lower in subjects receiving rivaroxaban compared with subjects receiving comparator. There were more events of total bilirubin levels >2x ULN and ALK PHOS levels >3x ULN in subjects administered rivaroxaban. The lower incidence of ALT, AST, and GGT >3x ULN in subjects administered rivaroxaban compared with heparin/VKA in the pooled analysis was primarily driven by Study 11223. In Study 11528, there were few events of ALT, AST, or GGT levels >3x ULN and the incidence of these abnormalities was comparable between the treatment groups.

There were 1 case of ALT and AST levels >3x ULN concurrent with a total bilirubin level >2x ULN in the Rivaroxaban group and no case in the heparin/VKA group. The one case in the rivaroxaban group subsequently died of liver failure. The patient narrative and detailed information are provided in later section.

**Incidence of Treatment-emergent Liver-related Laboratory Abnormalities
(All Postbaseline Measurements) in Phase 2 Treatment Studies in Venous Thromboembolism
(Subjects Valid for Safety in Studies 11223 and 11528)**

Laboratory Variable	Rivaroxaban N=883		Heparin/VKA N=263	
ALT >3x ULN and bilirubin >2x ULN	1^a/824	(0.1%)	0/235	(0%)
ALT, n (%)				
>3x ULN	20/832	(2.4%)	26/238	(10.9%)
>5x ULN	5/834	(0.6%)	12/239	(5.0%)
>8x ULN	2/834	(0.2%)	4/239	(1.7%)
>10x ULN	1/834	(0.1%)	2/239	(0.8%)
AST >3x ULN and bilirubin >2x ULN	1^a/824	(0.1%)	0/235	(0%)
AST, n (%)				
>3x ULN	10/827	(1.2%)	16/237	(6.8%)
>5x ULN	4/831	(0.5%)	4/238	(1.7%)
>8x ULN	2/831	(0.2%)	1/238	(0.4%)
>10x ULN	1/831	(0.1%)	0/238	(0.0%)
Total bilirubin, n (%)				
>2x ULN	3/824	(0.4%)	0/235	(0.0%)
>3x ULN	2/824	(0.2%)	0/235	(0.0%)
>5x ULN	1/824	(0.1%)	0/235	(0.0%)
>8x ULN	1/824	(0.1%)	0/235	(0.0%)
>10x ULN	1/824	(0.1%)	0/235	(0.0%)

Alkaline phosphatase, n (%)

>3x ULN	4/829	(0.5%)	0/237	(0.0%)
>5x ULN	3/831	(0.4%)	1/238	(0.4%)
>8x ULN	0/833	(0.0%)	1/238	(0.4%)
>10x ULN	0/833	(0.0%)	1/238	(0.4%)

GGT, n (%)

>3x ULN	23/805	(2.9%)	13/228	(5.7%)
>5x ULN	11/825	(1.3%)	9/237	(3.8%)
>8x ULN	6/828	(0.7%)	2/238	(0.8%)
>10x ULN	5/831	(0.6%)	0/238	(0.0%)

^a Increased ALT and AST values seen in the same subject (11223-506006) 5.3.5.4.1-1211

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; ULN = upper limit of normal; VKA = vitamin K antagonist

Note: Incidence rate = # of events / # at risk, where:

of events = # of subjects reporting the abnormality postbaseline.

at risk = # of subjects with readings pre and postbaseline who did not report abnormality at baseline.

Note: Postbaseline measurements taken more than 2 days after last intake of study medication are included

Note: The subjects reported in higher threshold categories will not always be included in lower threshold categories because this analysis is based on a treatment emergent approach that excludes subjects with baseline abnormalities.

Alanine Aminotransferase Elevations Over Time

A pooled analysis of the frequency of ALT > 3x ULN by time window is shown in Table below. The incidence of ALT levels >3x ULN was lower on rivaroxaban compared with heparin/VKA before Weeks 2. However, the incidence of ALT levels >3x ULN was high on Rivaroxaban compared with heparin/VKA after Day 35 (1.4% vs. 0.9%).

**Frequency of ALT >3x ULN by Time Windows
(Subjects Valid for Safety in Studies 11223 and 11528)**

	Rivaroxaban		Heparin/VKA	
	# of Events/# Evaluable (%)		# of Events/# Evaluable (%)	
Baseline	3/856	(0.4%)	2/250	(0.8%)
Weeks 1-2 (Days 2-18)	7/467	(1.5%)	23/126	(18.3%)
Weeks 3-4 (Days 19-35)	3/442	(0.7%)	1/117	(0.9%)
Weeks 6-8 (Days 36-69)	8/797	(1.0%)	1/230	(0.4%)
Weeks 12 (Days 70-91)	3/750	(0.4%)	0/227	(0.0%)
After Day 35 ^a	11/805	(1.4%)	2/215	(0.9%)
After Day 91	2/413	(0.5%)	1/126	(0.8%)

^a Calculated as the number of subjects with a laboratory abnormality after Day 35 relative to all subjects with normal measurement(s) prior to Day 35 and at least 1 measurement after Day 35

Key: ALT = alanine aminotransferase; Labs = laboratory results; ULN = upper limit of normal; VKA = vitamin K antagonist

Note: Subjects with normal baseline and at least 1 postbaseline measurement are at risk.

Note: Postbaseline measurements taken more than 2 days after last intake of study medication are included.

Kaplan Meier plots of the time to first ALT level >3x ULN in Study 11223 and Study 11528 are presented in the following Figures.

Figure 2-3: Cumulative Risk (Kaplan Meier) of First Laboratory Abnormality Versus Time After Start of Study Medication
Abnormality: ALT >3x ULN
(Subjects Valid for Safety in Study 11223)

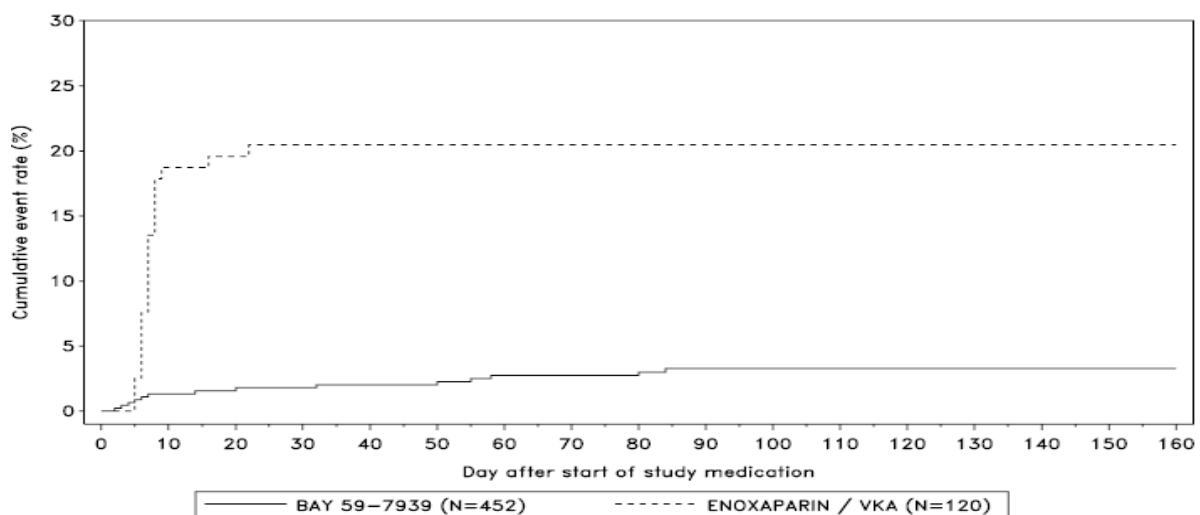
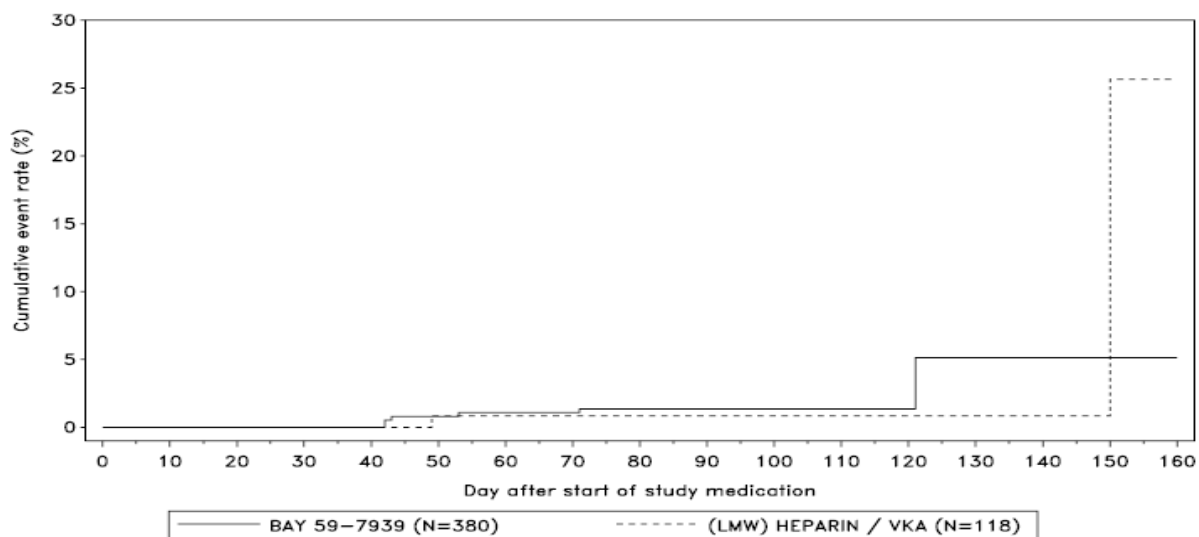


Figure 2-4: Cumulative Risk (Kaplan Meier) of First Laboratory Abnormality Versus Time After Start of Study Medication
Abnormality: ALT >3x ULN
(Subjects Valid for Safety in Study 11528)



The profile of the comparator arm (heparin/ VKA) is most notably different between the 2 studies and is considered due to the relatively intense laboratory sampling in Study 11223 occurring at a time when elevations in ALT are expected to occur on enoxaparin. In Study 11528, the relatively flat profile of the heparin/VKA arm through the first month reflects a lack of laboratory sampling at the time when elevations in ALT would be expected to occur. The profiles of time to first ALT level >3x ULN of the rivaroxaban arm in Studies 11223 and 11528 are comparable. In Study 11528, the time to first event comparison is considered primarily one of rivaroxaban versus a VKA because the VKA was used after the first 5 to 7 days of heparin/LWMH.

In Study 11528, 2 cases of late occurring elevations in liver enzymes after the last dose of study drug were observed, 1 in each study group. Laboratory assessment was not required in the follow-up period (after study drug discontinuation), but it was at the discretion of the investigator. Based on available data, 1 event in 35 subjects receiving rivaroxaban and 1 event in 4 subjects receiving enoxaparin.

ALT or AST >3x ULN With a Concurrent Total Bilirubin >2x ULN

In Phase 2 studies in VTE treatment, there was 1 case of ALT and AST levels >3x ULN concurrent with a total bilirubin level >2x ULN in the Rivaroxaban group and none in the heparin/VKA group.

The subject (11223-506006) randomized to receive rivaroxaban had ALT and/or AST levels >3x ULN in conjunction with total bilirubin levels >2x ULN and died of liver failure after 48 days of treatment with rivaroxaban 40 mg once daily.

The following is the patient narrative.

This is a 72 year old female subject with a medical history of hypertension, diabetes mellitus, DVT (2004), uterine malignancy (uterine sarcoma stabilized) with lung and mediastinal metastases (2004), and subsequent hysterectomy with bilateral adnectomy (2004) and 6 cycles palliative chemotherapy (2005). During the chemotherapy in (b) (4) the subject got (b) (4). On 14 Apr 2005 no liver metastases, but cyst or pseudocyst of pancreas up to 20 mm of size, were seen in ultrasound.

The patient started BAY 59-7939 40 mg once daily on 05 May 2005 due to femoropopliteal thrombosis.

On (b) (4) prior to start of rivaroxaban, liver related tests were normal except slight increased GGT level. On (b) (4) ALT, AST, GGT and bilirubin levels were within normal limits.

On (b) (4), marked elevations of ALT (2477 U/L), AST (1544 U/L), GGT (537 U/L), bilirubin (2 mg/dL) and AP (304 U/L) were noted. The subject was febrile and had slight icterus. In ultrasound no abnormalities were found.

On (b) (4) (Day 23), rivaroxaban was discontinued permanently due to these events. Serum protein electrophoresis showed: 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.

On (b) (4) (Day 26), hepatitis serology showed: 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. Ultrasound showed: liver no detectable lesions, gall bladder thickened wall, probable chronic cholecystitis, tumor can not be ruled out, intrahepatic bile ducts not enlarged, common bile duct slightly dilated, pancreas not enlarged, two round hypoechogenic structures of 10 and 21 mm size, similar structure at caudal of pancreas of 11 mm size (retroperitoneal lymph nodes or pseudocysts?), 11 mm hypoechogenic structure of 1mm diameter at pancreas caput (head).

Routine investigation of the blood donation samples revealed that they were negative for HBsAg and anti-HCV-AB; no PCR testing performed in transfusion samples; no retention samples are available for further investigations; no further information on blood donation samples is available.

On (b) (4), CT showed: 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: atherosclerotic changes. Spondylosis of thoracic and lumbar spine. Conclusion: no signs of cholelithiasis, suspected chronic cholecystitis, no signs of retroperitoneal lymphadenopathy.

On (b) (4) serology test showed: anti HBc IgM 3.2, anti HBe 65.34. The subject was transferred to the infection ward. Progression of icterus and development of liver failure 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 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.

On (b) (4) serum protein electrophoresis showed Albumin and alpha-2-globulin were slightly decreased and alpha-1-globulin and gamma-globulin increased.

On (b) (4) HBs Ag was 315.09, HBe Ag negative and anti-HBe 69.74 (normal <60). The diagnosis of acute hepatitis B was made based on serology tests– increase of HBs Ag titer, 3 fold 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 Ag at baseline prior to the start of rivaroxaban.

On (b) (4) liver enzymes decreased, considered by the investigator as sign of liver failure. Icterus progressed and the subject died on (b) (4) due to acute liver failure.

The following are liver-related test results:

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					

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									

The investigator attributed the event to acute hepatitis B infection as not related to the study drug.

The autopsy was performed on [REDACTED]. The autopsy report under the liver section stated:

“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). The autopsy report concluded “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?)”.

The sponsor requested independent analysis by several external liver experts, including 2 pathologists who examined the histopathology. The followings are the conclusions from the 2 pathologists.

In letter dated (b) (4) concluded:

“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. 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. Regenerative failure is uncommon in subjects with acute hepatitis, but when seen is generally in elderly subjects who often have chronic non-hepatic diseases (as was certainly true in this case).”

On (b) (4) (one of LAP members in Pathologic Subteam) concluded:

“The main histopathological lesions in this post-mortem material consisted of submassive necrosis of the liver with slight fibrosis and suggestion of mild hepatocellular regenerative activity. Such lesions are consistent with the clinical course of the patient. As frequently observed in such cases of submassive necrosis, etiology cannot be formally determined, only on the basis of histological grounds. Taking into account the serological profile of hepatitis B viral markers in the present case, the lesions can be explained by severe hepatitis B viral infection, although histological findings were not specific and immunohistochemical results not conclusive. In fulminant viral B hepatitis, immunohistochemical expression of hepatocellular HBs and HBe antigens is expected to be absent at the time the liver is destroyed by viral infection. In the present case, it must be stressed that post-mortem autolysis precluded any formal conclusion concerning immunohistochemistry. Such lesions might also be consistent with drug-induced or toxic damage to the liver. However, there was no predominance of eosinophils in the inflammatory infiltration, and epithelioid and giant cell granulomas were not noted; these two latter lesions are frequently seen in drug-induced damage, especially when this damage is explained by an immunoallergic mechanism. The etiology of iron overload cannot be determined on histological grounds. It could be multifactorial: transfusions and/or necroinflammatory lesions and/or genetic abnormality?”

The Liver Advisory Panel evaluated this case. One member’s assessment concluded that it was highly unlikely that the changes were drug related. He thought it was more likely that this was a case of hepatitis B exacerbated by immunosuppressive therapy in an elderly female with cancer. Another member’s assessment also excluded the role of study drug.

Hepatic Disorder Adverse Events

Treatment-emergent Adverse Events

The pooled incidence of treatment-emergent adverse events for hepatic disorders is presented in the following table. Overall, 86 subjects (9.7%) administered rivaroxaban had hepatic disorder events compared with 31 subjects (11.8%) administered heparin/VKA. The majority of hepatic disorder adverse events were laboratory abnormalities, which occurred in 69 subjects (7.8%) administered rivaroxaban and 31 subjects (11.8%) administered heparin/VKA. These laboratory adverse events most frequently included increases in ALT, AST, and GGT levels. It was noted that slightly more clinical events were reported in the rivaroxaban group as compared to heparin/VKA group in all categories except for liver-related investigations, signs and symptoms.

**Incidence of Treatment-emergent Adverse Events for “Hepatic Disorders”
in Phase 2 Treatment Studies in Venous Thromboembolism
(Subjects Valid for Safety in Studies 11223 and 11528)**

MSSO Search Category/ MedDRA Preferred Term	Total Rivaroxaban (N=883)		Heparin/VKA (N=263)	
Any event	86	(9.7%)	31	(11.8%)
MSSO: Cholestasis and jaundice of hepatic origin				
Any event	2	(0.2%)	0	(0.0%)
Cholestasis	1	(0.1%)	0	(0.0%)
Jaundice	1	(0.1%)	0	(0.0%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions				
Any event	11	(1.2%)	1	(0.4%)
Ascites ~	1	(0.1%)	0	(0.0%)
Hepatic failure	1	(0.1%)	0	(0.0%)
Hepatic lesion	1	(0.1%)	0	(0.0%)
Hepatic steatosis	4	(0.5%)	1	(0.4%)
Hepatotoxicity	1	(0.1%)	0	(0.0%)
Liver disorder	3	(0.3%)	0	(0.0%)
MSSO: Liver infections				
Any event	1	(0.1%)	0	(0.0%)
Hepatitis B	1	(0.1%)	0	(0.0%)
MSSO: Liver neoplasms, benign				
Any event	5	(0.6%)	1	(0.4%)
Hemangioma of the liver	3	(0.3%)	0	(0.0%)
Hepatic cyst	2	(0.2%)	1	(0.4%)
MSSO: Liver neoplasms, malignant and unspecified				
Any event	1	(0.1%)	0	(0.0%)
Hepatic neoplasm malignant recurrent	1	(0.1%)	0	(0.0%)
MSSO: Liver-related investigations, signs and symptoms				
Any event	69	(7.8%)	31	(11.8%)
ALT increased	39	(4.4%)	16	(6.1%)
Ascites ~	1	(0.1%)	0	(0.0%)
AST increased	27	(3.1%)	15	(5.7%)
Blood ALK PHOS increased	9	(1.0%)	2	(0.8%)
Blood bilirubin increased	3	(0.3%)	0	(0.0%)

GGT increased	33 (3.7%)	9 (3.4%)
Hepatic enzyme increased	5 (0.6%)	8 (3.0%)
Hepatic function abnormal	2 (0.2%)	1 (0.4%)
Hepatomegaly	0 (0.0%)	1 (0.4%)
Hypoalbuminemia	0 (0.0%)	1 (0.4%)
Liver function test abnormal	1 (0.1%)	0 (0.0%)
Transaminases increased	2 (0.2%)	2 (0.8%)

Key: ALK PHOS = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; MSSO = Maintenance Service and Support Organization; VKA = vitamin K antagonist

Note: All treatment-emergent events regardless of time after last study medication are included

Note: Incidence = # of events / # at risk, where:

of events = # of subjects reporting the event reporting the event after start of treatment

at risk = # of subjects in reference population.

Note: Sorted alphabetically first by search category then by MedDRA preferred term.

Note: MedDRA preferred terms marked with ~ are allocated to multiple search categories.

When analyzed separately by individual study, the incidence of any treatment-emergent hepatic disorder adverse event was lower on rivaroxaban (11.5%) compared with heparin/VKA (23.0%) in Study 11223. However, in study 11528, the incidence of any treatment-emergent hepatic disorder adverse event was much higher on rivaroxaban (7.7%) compared with heparin/VKA (1.5%) (See Table below).

BAY 59-7939 / PHASE II TREATMENT OF DEEP VEIN THROMBOSIS		TABLE T/3.1.2 BY-STUDY INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS FOR MSSO MEDDRA SEARCH CATEGORY 'HEPATIC DISORDERS' POPULATION: SUBJECTS VALID FOR SAFETY ANALYSIS SN 11528			GLOBAL INTEGRATED ANALYSES		PAGE 1 12MAR2008
SEARCH CATEGORY MEDDRA PREFERRED TERM	BAY 59-7939 20 MG OD	BAY 59-7939 30 MG OD	BAY 59-7939 40 MG OD	BAY 59-7939 TOTAL	(LMW) HEPARIN / VKA		
ANY BELOW MENTIONED SEARCH CATEGORY							
ANY EVENT	8 (5.93%)	10 (7.46%)	13 (9.56%)	31 (7.65%)	2 (1.46%)		
MSSO: Cholestasis and jaundice of hepatic origin (SMQ)							
ANY EVENT	1 (0.74%)	0 (0.00%)	0 (0.00%)	1 (0.25%)	0 (0.00%)		
Jaundice	1 (0.74%)	0 (0.00%)	0 (0.00%)	1 (0.25%)	0 (0.00%)		
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage- related conditions (SMQ)							
ANY EVENT	0 (0.00%)	3 (2.24%)	3 (2.21%)	6 (1.48%)	0 (0.00%)		
Ascites ~	0 (0.00%)	0 (0.00%)	1 (0.74%)	1 (0.25%)	0 (0.00%)		
Hepatic failure	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (0.25%)	0 (0.00%)		
Hepatic steatosis	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (0.25%)	0 (0.00%)		
Hepatotoxicity	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (0.25%)	0 (0.00%)		
Liver disorder	0 (0.00%)	0 (0.00%)	2 (1.47%)	2 (0.49%)	0 (0.00%)		
MSSO: Liver neoplasms, benign (SMQ)							
ANY EVENT	1 (0.74%)	0 (0.00%)	0 (0.00%)	1 (0.25%)	0 (0.00%)		
Haemangioma of liver	1 (0.74%)	0 (0.00%)	0 (0.00%)	1 (0.25%)	0 (0.00%)		
MSSO: Liver neoplasms, malignant and unspecified (SMQ)							
ANY EVENT	0 (0.00%)	0 (0.00%)	1 (0.74%)	1 (0.25%)	0 (0.00%)		
Hepatic neoplasm malignant recurrent	0 (0.00%)	0 (0.00%)	1 (0.74%)	1 (0.25%)	0 (0.00%)		
MSSO: Liver related investigations, signs and symptoms (SMQ)							
ANY EVENT	6 (4.44%)	7 (5.22%)	11 (8.09%)	24 (5.93%)	2 (1.46%)		
Alanine aminotransferase increased	4 (2.96%)	2 (1.49%)	1 (0.74%)	7 (1.73%)	0 (0.00%)		
Ascites ~	0 (0.00%)	0 (0.00%)	1 (0.74%)	1 (0.25%)	0 (0.00%)		
Aspartate aminotransferase increased	1 (0.74%)	1 (0.75%)	1 (0.74%)	3 (0.74%)	1 (0.73%)		
Blood alkaline phosphatase increased	1 (0.74%)	0 (0.00%)	1 (0.74%)	2 (0.49%)	0 (0.00%)		
Gamma-glutamyltransferase increased	5 (3.70%)	5 (3.73%)	5 (3.65%)	15 (3.70%)	1 (0.73%)		
Hepatic enzyme increased	0 (0.00%)	0 (0.00%)	2 (1.47%)	2 (0.49%)	0 (0.00%)		
Hepatic function abnormal	0 (0.00%)	0 (0.00%)	2 (1.47%)	2 (0.49%)	0 (0.00%)		

Deaths

There was one liver-related death (Subject 11223-506006) that occurred in Study 11223 in the Phase 2 DVT treatment studies. This case was discussed in the previous section.

Serious Adverse Events

The incidence of hepatic disorder serious adverse events was similar between the 2 treatment groups (see Table below). Overall, 7 subjects (0.8%) administered rivaroxaban and 4 subjects (1.5%) administered the comparator reported serious adverse events. The majority of serious adverse events were laboratory abnormalities, which occurred in 4 subjects (0.5%) receiving rivaroxaban compared with 4 subjects (1.5%) receiving the comparator.

In Study 11223, there were 4 (0.8%, 1 hepatitis B and LFT abnormalities) and 4 (3.2%, all LFT abnormalities) subjects reporting a hepatic disorder serious adverse event on rivaroxaban and heparin/VKA respectively.

In Study 11528, there were 3 (0.7%, 4 events: jaundice, ascites, hepatic failure, hepatic neoplasm malignant recurrent) and 0 (0%) subjects reporting a hepatic disorder serious adverse event on rivaroxaban and heparin/VKA respectively.

**Incidence of Serious Treatment-Emergent Adverse Events from MSSO Search
Categories of Hepatic Disorders in Phase 2 Treatment Studies in Venous Thromboembolism
(Subjects Valid for Safety in Studies 11223 and 11258)**

MSSO Search Category/ MedDRA Preferred Term	Total Rivaroxaban (N=883)	Heparin/VKA (N=263)
Any event	7 (0.8%)	4 (1.5%)
MSSO: Cholestasis and jaundice of hepatic origin		
Any event	1 (0.1%)	0 (0.0%)
Jaundice	1 (0.1%)	0 (0.0%)

MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions

Any event	2 (0.2%)	0 (0.0%)
Ascites ~	1 (0.1%)	0 (0.0%)
Hepatic failure	1 (0.1%)	0 (0.0%)

MSSO: Liver infections

Any event	1 (0.1%)	0 (0.0%)
Hepatitis B	1 (0.1%)	0 (0.0%)

MSSO: Liver neoplasms, malignant and unspecified

Any event	1 (0.1%)	0 (0.0%)
Hepatic neoplasm malignant recurrent	1 (0.1%)	0 (0.0%)

MSSO: Liver-related investigations, signs and symptoms

Any event	4 (0.5%)	4 (1.5%)
ALT increased	1 (0.1%)	3 (1.1%)
Ascites ~	1 (0.1%)	0 (0.0%)
AST increased	2 (0.2%)	2 (0.8%)
Blood ALK PHOS increased	1 (0.1%)	0 (0.0%)
GGT increased	2 (0.2%)	0 (0.0%)
Hepatic enzyme increased	0 (0.0%)	1 (0.4%)
Liver function test abnormal	1 (0.1%)	0 (0.0%)

Key: ALK PHOS = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; MSSO = Maintenance Service and Support Organization; VKA = vitamin K antagonist

Note: All treatment-emergent events regardless of time after last study medication are included

Note: Incidence = # of events / # at risk, where:

of events = # of subjects reporting the event after start of treatment
at risk = # of subjects in reference population

Note: Sorted alphabetically first by search category then by MedDRA preferred term.

Note: MedDRA preferred terms marked with ~ are allocated to multiple search categories.

Adverse Events Leading to Study Discontinuation

In Phase 2 treatment studies in VTE, 3 subjects (0.3%) administered rivaroxaban discontinued from the study due to liver-related adverse events, including 2 subjects with increased laboratory values and 1 subject with hepatitis B. No subjects treated with heparin/VKA discontinued early due to adverse events.

7.3.4.4.2.3 Atrial Fibrillation Studies (Studies 11390, 11866, and 12024)

Three Phase 2 studies in subjects with atrial fibrillation were conducted in Japan. One of the Phase 2 studies was uncontrolled (Study 11390), and the other 2 studies used warfarin as the active control. Each of the studies was approximately 1 month in duration. Subjects with transaminases ≥ 2 x ULN were excluded from enrollment in these studies.

Clinical Laboratory Measurements

In the Phase 2 studies in subjects with atrial fibrillation, liver-related laboratory assessments were performed at the intervals indicated in the following table.

**Schedule of Liver-related Laboratory Assessments in Phase 2 Studies in Atrial Fibrillation
(Studies 11390, 11866, and 12024)**

Study	Screen	Day 1	Day 14	Day 28	Follow-up ^a
11390	X	X		X	X
11866	X	X	X	X	X
12024	X	X		X	X

^a 28 (±7) days after the last dose of study medication

Liver-related Laboratory Values

Treatment-emergent laboratory abnormalities are presented individually for the 3 studies in atrial fibrillation below. A laboratory abnormality was defined in the protocol as a value that exceeded the upper limit of normal range. Additional analyses at higher thresholds (i.e., 3x ULN) were not done.

In Study 11866, subjects administered rivaroxaban had a higher incidence of ALT and AST levels above the upper limit of normal compared with subjects administered warfarin (see table below). The highest incidence of treatment-emergent high laboratory abnormalities for ALT was observed in the rivaroxaban 10 mg group (19.0%) as compared to warfarin (4%). Two subjects receiving rivaroxaban experienced both increases of AST > 2 x ULN and ALT > 2 x ULN; 1 subject (Subject 200060005) in the 15 mg od group had the peak levels of AST (307 U/L, > 7 x ULN) and ALT (557 U/L, > 12 x ULN) at Visit 2 (Day 14), and 1 subject (Subject 200060004) in the 20 mg od group had the peak levels of AST (146 U/L, > 3 x ULN) and ALT (328 U/L, > 7 xULN) at Visit 3 (Day 28). The AST and ALT levels returned to the normal range within 21 days after the last dose of the study medication. Their total and direct bilirubin levels were normal during the study period.

**Table 2-19: Incidence of Treatment-emergent Increased Laboratory Abnormalities (>1x ULN)
(Subjects Valid for Safety Analyses in Study 11866)**

Laboratory Test	RIVA 10 mg od (N=26)	RIVA 15 mg od (N=25)	RIVA 20 mg od (N=24)	Warfarin od (N=27)
Alanine aminotransferase	4/21 (19.0%)	3/19 (15.8%)	3/22 (13.6%)	1/25 (4.0%)
Aspartate aminotransferase	3/23 (13.0%)	2/18 (11.1%)	1/21 (4.8%)	2/23 (8.7%)
Total bilirubin	2/23 (8.7%)	3/22 (13.6%)	2/22 (9.1%)	4/25 (16.0%)
Gamma-glutamyltransferase	1/16 (6.3%)	1/11 (9.1%)	0/15 (0.0%)	2/19 (10.5%)
Alkaline phosphatase	1/23 (4.3%)	0/23 (0.0%)	0/23 (0.0%)	1/25 (4.0%)

Key: od = once daily; RIVA = rivaroxaban

Note: Incidence rate = # of events / # at risk, where:

of events = # of subjects reporting the abnormality after start of treatment to 7 days after the last dose of study drug, and

at risk = # of subjects with readings before and after the start of treatment who did not report the abnormality before treatment

Note: When more than 1 measurement was available for a subject at baseline, the last value was used for analysis.

Note: When more than 1 measurement was available for a subject postbaseline, the maximum value was used for analysis.

In Study 12024, there were few events of any laboratory abnormality >1x ULN (see Table below). One subject (4.3%) administered rivaroxaban 10 mg bid had an ALT value above the upper limit of normal compared with 2 subjects (8.3%) administered warfarin.

**Incidence of Treatment-emergent Increased Laboratory Abnormalities (>1x ULN)
(Subjects Valid for Safety Analyses in Study 12024)**

Laboratory Test	RIVA 2.5 mg bid (N=24)	RIVA 5 mg bid (N=26)	RIVA 10 mg bid (N=24)	Warfarin od (N=26)
Alanine aminotransferase	0/21 (0.0%)	0/25 (0.0%)	1/23 (4.3%)	2/24 (8.3%)
Aspartate aminotransferase	0/18 (0.0%)	1/25 (4.0%)	1/21 (4.8%)	0/24 (0.0%)
Total bilirubin	0/20 (0.0%)	2/26 (7.7%)	0/23 (0.0%)	0/24 (0.0%)
Gamma-glutamyltransferase	1/10 (10.0%)	1/24 (4.2%)	0/15 (0.0%)	0/13 (0.0%)
Alkaline phosphatase	2/18 (11.1%)	0/25 (0.0%)	0/23 (0.0%)	0/24 (0.0%)

Key: bid = twice daily; od = once daily; RIVA = rivaroxaban

Note: Incidence rate = # of events / # at risk, where:

of events = # of subjects reporting the abnormality after start of treatment to 7 days after the last dose of study drug, and
at risk = # of subjects with readings before and after the start of treatment who did not report the abnormality before treatment

Note: When more than 1 measurement was available for a subject at baseline, the last value was used for analysis. When more than 1 measurement was available for a subject postbaseline, the maximum value was used for analysis.

ALT or AST >3x ULN With a Concurrent Total Bilirubin >2x ULN

In Studies 11390, 11866, and 12024, there were no subjects with ALT or AST levels >3xULN concurrent with a total bilirubin level >2x ULN.

Hepatic Disorder Adverse Events

Treatment-emergent Adverse Events

In Study 11390, INR increased in 3 subjects who received rivaroxaban 20 mg bid and GGT increased in 1 subject who received rivaroxaban 10mg bid (see table below).

Incidence of Treatment-emergent Hepatic Disorder Adverse Events (Subjects Valid for Safety Analyses in Study 11390)

System Organ Class MedDRA Preferred Term	RIVA 10 mg bid (N=25)	RIVA 20 mg bid (N=11)	Total (N=36)
Investigations			
International normalized ratio increased	0 (0%)	3 (27%)	3 (8%)
GGT increased	1 (4%)	0 (0%)	1 (3%)

Key: bid = twice daily; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; RIVA = rivaroxaban

Note: Includes only treatment-emergent events that occurred up to 7 days after the last dose of study medication.

Note: Incidence = # of events / # as risk, where:

of events = # of subjects reporting the abnormality after the start of treatment
at risk = # of subjects with readings before and after start of treatment who did not report the abnormality before treatment

In Study 11866, few events were reported and all events were LFT abnormalities.

Incidence of Treatment-emergent Hepatic Disorder Adverse Events (Subjects Valid for Safety Analyses in Study 11866)

System Organ Class MedDRA Preferred Term	RIVA 10 mg od (N=26)	RIVA 15 mg od (N=25)	RIVA 20 mg od (N=24)	Warfarin od (N=27)
Hepatobiliary disorders				
Hepatic function abnormal	0 (0.0%)	1 (4.0%)	1 (4.2%)	0 (0.0%)
Investigations				
ALT increased	2 (7.7%)	0 (0.0%)	1 (4.2%)	2 (7.4%)
AST increased	1 (3.8%)	0 (0.0%)	0 (0.0%)	2 (7.4%)
Blood bilirubin increased	0 (0.0%)	1 (4%)	0 (0.0%)	0 (0.0%)
GGT increased	0 (0.0%)	1 (4%)	0 (0.0%)	0 (0.0%)
Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; od = once daily; RIVA = rivaroxaban				
Note: Includes only treatment-emergent events that occurred up to 7 days after the last dose of study medication.				
Note: Incidence = # of events / # as risk, where: # of events = # of subjects reporting the abnormality after the start of treatment # at risk = # of subjects with readings before and after start of treatment who did not report the abnormality before treatment				

In Study 12024 (see table below), hepatic cirrhosis was reported in 1 subject in the rivaroxaban group and 1 alcoholic liver disease was reported in the warfarin group.

**Incidence of Treatment-emergent Hepatic Disorder Adverse Events
(Subjects Valid for Safety Analyses in Study 12024)**

System Organ Class MedDRA Preferred Term	RIVA 2.5 mg bid (N=24)	RIVA 5 mg bid (N=26)	RIVA 10 mg bid (N=24)	Warfarin od (N=26)
Hepatobiliary disorders				
Hepatic cirrhosis	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Alcoholic liver disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Investigations				
Blood bilirubin increased	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GGT increased	0 (0.0%)	1 (3.8%)	1 (4.2%)	0 (0.0%)
Key: bid = twice daily; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; od = once daily; RIVA = rivaroxaban				
Note: Includes only treatment-emergent events that occurred up to 7 days after the last dose of study medication.				
Note: Incidence = # of events / # as risk, where: # of events = # of subjects reporting the abnormality after the start of treatment # at risk = # of subjects with readings before and after start of treatment who did not report the abnormality before treatment				

The hepatic cirrhosis was reported in a 78-year-old woman (12024-200050002) who had medical history of chronic hepatitis (1995), hepatitis B carrier (1995), and hepatic cirrhosis (2005). Rivaroxaban 2.5 mg BID began on (b) (4) and continued for 8 days. On (b) (4), the patient visited the hospital for having left abdominal pain. Ascites retention was confirmed by ultrasonograph. The study drug was withdrawn. On (b) (4), she was hospitalized and was diagnosed with aggravation of hepatic cirrhosis (ascites retention), considered serious due to important medical event. ALT was normal. She was treated and was transferred to another hospital on (b) (4). No additional information was available because the subject refused to provide further information. The investigator considered the event as not related to the study drug.

Deaths

No deaths and liver-related deaths were reported in the 3 Phase 2 studies in subjects with atrial fibrillation.

Serious Adverse Events

Two subjects receiving rivaroxaban had hepatic disorder serious adverse events: one had abnormal hepatic function and another one had hepatic cirrhosis (discussed above). No serious adverse events were reported in the warfarin group.

Abnormal hepatic function was reported in a 70-year-old woman who had a medical history of hypertension, chronic heart failure, hypertrophic cardiomyopathy and angina pectoris. The subject received BAY 59-7939 15 mg od from 26 Aug 2006 to 15 Sep 2006. On (b) (4) she presented with ALT 557 U/L (> 10xULN), AST 307 U/L, LDH 388 U/L, GGT 50 U/L, but no elevation of bilirubin (T-Bil 0.8 mg/dL). On (b) (4), ALT decreased to 311 U/L and rivaroxaban was discontinued permanently due to this event. Abdominal ultrasound investigation and CT were performed but showed no abnormality. Echocardiography, ECG or Chest X-rays showed no significant change, compared to the investigations performed prior to initiating the study medication. On (b) (4) ALT and AST returned to the normal ranges. The investigator assessed the event as study drug-related.

Adverse Events Leading to Study Discontinuation

The same two subjects discussed under Serious Adverse Events above had serious hepatic disorder adverse events that led to study discontinuation.

7.3.4.4.3 Ongoing Studies

ALT >3x ULN Concurrent With TB>2x ULN

There were total of 27 subjects who had ALT >3 xULN concurrent with total bilirubin >2xULN identified in ongoing studies based on 6-month safety update based on cutoff date of 31 October 2008 for J-ROCKET-AF; cutoff date of 5 December 2008 for other studies. Only ATLAS ACS TIMI 46 and EINSTEIN DVT/PE studies were open-label studies and other studies are blinded studies.

In ATLAS ACS TIMI 46 study, 3 cases with ALT> 3xULN concurrent with TB>2xULN were reported in the placebo group (see Table below). Among the 3 cases, 1 subject had sepsis with hypotension, multi-organ failure and subsequently died; 2 subjects had pancreatitis with elevated LFTs.

**ATLAS ACS TIMI 46: ALT >3x ULN Concurrent With TB>2x ULN Cases
(All in Placebo group)**

Age/ sex	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment
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44/F	91	108	ALT 134/ TB 11	Sepsis on Day 91. Bradycardia, hypotension, worsening liver failure and multi-organ failure on Day 108. Subject died from multi-organ failure including liver failure and lower respiratory tract infection on Day 109.	Not related
57/M	32	32	ALT 561/ TB 3.3	Acute pancreatitis on Day 32	-
66/M	19	125	ALT 596/ TB 3.5	Pancreatitis on Day 125.	-

In EINSTEIN DVT/PE study, 3 cases with ALT > 3xULN concurrent with TB > 2xULN were reported in the rivaroxaban group (see Table below). One subject had dilated cardiomyopathy and later was transferred to another hospital for terminal care. One subject had cancers and subsequently died. The remaining one subject had acute severe hepatitis with liver failure and subsequently died. The patient's narrative and available Liver Advisory Panel assessment are included following these tables.

**EINSTEIN DVT/PE: ALT > 3x ULN Concurrent With TB > 2x ULN Cases
(All in Rivaroxaban Group)**

Age/ sex	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment
77/F White 400011004	169	(b) (4)	ALT 698/ TB 4.1	Hospitalized for dilated cardiomyopathy on Day 166. Discharged from hospital on 183 to another hospital for terminal care. None of these events had resolved as of [REDACTED]	-
63/F 11702- 16018- 1005	18	(b) (4)	ALT 5371/ TB 67 mmol/L	Hospitalized for dyspnea and asthenia on Day 16. Severe acute hepatitis and liver insufficiency was diagnosed on Day 18. Patient died on Day 26.	Likely drug-induced toxic injury by one member.
71/M White 220131004	35	(b) (4)	ALT 513/ TB 5.4	Gastric cancer with liver metastasis was found. Subject died on Day 56. No autopsy was performed.	-

Sixteen subjects with ALT > 3xULN concurrent with TB > 2xULN were reported from ROCKET-AF study including 6 additional cases submitted in 6-month safety update. Three were reported in the J-ROCKET-AF study. Both studies are blinded studies. Two cases in ROCKET-AF were unblinded and both had received warfarin. One case in J-ROCKET-AF study was unblinded and had received rivaroxaban.

**ROCKET-AF: ALT >3x ULN Concurrent With TB>2x ULN Cases
(Blinded)**

Age/ sex	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment
58/M White 100338	46	(b) (4)	ALT 647/ TB 3.6	Acute hepatitis C was diagnosed.	Not related
78/M White 100650	200	(b) (4)	ALT 156/ TB 3.8	Metastatic pancreatic carcinoma to liver was diagnosed. Died on Day 331.	-
71/M White 100966	45	(b) (4)	ALT 1797/ TB 6.1	Hospitalized for worsening heart failure on Day 33. Resolved on Day 83.	-
48/M Asian 101271	96	(b) (4)	ALT 443/ TB 13.1	Hospitalized for CHF on Day 93. Resolved on Day 127.	Not related
62/F American Indian/Alaskan native 101773	32	(b) (4)	ALT 1457/ TB 12.1	Acute hepatitis B was diagnosed. ALT was normal on Day 107. Subject received warfarin.	-
87/F Asian 104083	104	(b) (4)	ALT 104/ TB 2.5	Resolved 1 week later on study drug.	-
84/M White 100044	462	(b) (4)	ALT 167/ TB 2.4	Cardiac failure congestive on Day 454. Subject received warfarin.	-
73/M White 103861	178	(b) (4)	ALT 222/ TB 2.5	Resolved on Day 211.	-
79/M White 105428	168	(b) (4)	ALT 218/ TB 4.9	Gallstone/obstructive hepatitis was diagnosed.	-
72/M Asian 109730	22	(b) (4)	ALT 553/ TB 2.8	Cardiac failure congestive on Day 23. Resolved on Day 40.	-

**Table 19: Individual Subjects With ALT >3x ULN and Total Bilirubin >2x ULN
(Subjects Available for Safety in ROCKET-AF)(Continued)**

Subject ID Age/Sex	TTD (days)	Peak Laboratory Values ^b	Corresponding Peak Laboratory Ratios ^a	Comments
104111 Figure 2 in Study 11630 76/female	359	ALT = 250 U/L (Day 307) AST = 295 U/L (Day 307) TB = 6.61 mg/dL (Day 307) DB = 2.98 mg/dL (Day 307) AP = 384 U/L (Day 307)	7.81 8.68 5.38 7.29 2.84	Cholangitis (inflammatory disease because of obstruction in biliary ducts) reported on Day 307.
105059 Figure 2 in Study 11630	225	ALT = 147 U/L (Day 224) AST = 133 U/L (Day 224) TB = 5.80 mg/dL (Day 224) DB = 1.20 mg/dL (Day 224) AP = 148 U/L (Day 224)	12.25 11.08 4.83 6.00 0.78	Upper GI bleed Day 223 and cardiogenic shock Day 225. Subject died on Day 225.
103820 Figure 2 in Study 11630 80/male	351	ALT = 177 U/L (Day 353) AST = 260 U/L (Day 353) TB = 8.10 mg/dL (Day 353) DB = 3.60 mg/dL (Day 353) AP = 153 U/L (Day 353)	3.54 6.19 6.75 9.00 1.28	Cholecystitis on Day 42 and bile duct obstruction on Day 352.
106725 Figure 2 in Study 11630 58/female	222	ALT = 366 U/L (Day 219) AST = 102 U/L (Day 219) TB = 2.63 mg/dL (Day 219) DB = 1.35 mg/dL (Day 219) AP = 137 U/L (Day 219)	10.76 3.00 2.14 3.29 1.11	Abnormal liver function test reported on Day 219. Abdominal ultrasound showed liver enlargement and fat hepatosis. Additional information being sought.
109103 Figure 2 in Study 11630 60/female	82	ALT = 371 U/L (Day 77) AST = 332 U/L (Day 77) TB = 4.78 mg/dL (Day 77) and 5.63 mg/dL (Day 78) DB = 3.56 mg/dL (Day 77) and 4.42 mg/dL (Day 78) AP = 199 U/L (Day 77)	6.75 8.97 3.98 4.69 11.87 14.73 1.46	Cholecystitis and pancreatitis reported on Day 76. Treatment code broken by investigator; subject received warfarin.
110588 Figure 2 in Study 11630 66/female	85	ALT = 701 U/L (Day 62) AST = 2185 U/L (Day 62) TB = 3.53 mg/dL (Day 62) AP = 407 U/L (Day 62)	10.78 59.05 3.53 2.99	Cardiogenic shock on Day 60.

**J-ROCKET-AF: ALT >3x ULN Concurrent With TB>2x ULN Cases
(Blinded)**

Age/ sex	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment
81/M Asian 200600003	121	(*)	ALT 445/ TB 3.6	Gallbladder stone detected on Day 125. Resolved on Day 146.	-
65/M Asian 200940010	77	(*)	ALT 388/ TB 3.7	Abdominal pain on Day 76. Resolved on Day 106.	-
66/M	12	(4)	ALT 340/	Nausea started Day 7. Perihepatic	-

Asian 201310004			TB 9.3	ascites by CT on Day 22. Diagnosed of suspected drug-induced liver disorder on day 22. Resolved Day 94. Treatment code broken by investigator; subject received rivaroxaban.	
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Two additional blinded cases were reported in MAGELLaN study in medically ill patients.

Table 31: Individual Subjects With ALT >3x ULN and Total Bilirubin >2x ULN
(Subjects Valid for Safety in MAGELLaN)

Subject ID Age/Sex	Total Treatment Duration (days)	Peak Laboratory Values ^b	Corresponding Peak Laboratory Ratios ^a	Possible Alternative Etiologies for Lab Findings
280130001 Figure 2 in Study 12839 72/female	28	ALT = 520 U/L (Day 28); 429 U/L (Day 29) AST = 405 U/L (Day 27) and 252 U/L (Day 28) TB = 2.2 mg/dL (Day 28); 3.0 mg/dL (Day 29) DB = 1.6 mg/dL (Day 28); 2.3 mg/dL (Day 29) AP = 29 U/L (Day 29)	12.68 10.46 10.95 6.81 1.83 2.47 5.40 7.50 0.21	Cardiac and renal insufficiency, fatal multiple organ failure. Subject died on Day 29. Treatment code broken; subject received enoxaparin.
440070002 Figure 2 in Study 12839 67/male	2	ALT = 8078 U/L (Day 3); 478 U/L (Day 9) AST = 17384 U/L (Day 3); 86 U/L (Day 9) TB = 7.0 mg/dL (Day 9) DB = 7.8 mg/dL (Day 3); 3.9 mg/dL (Day 9)	179.51 11.12 496.69 2.32 5.48 26.10 12.09	History of heart failure and elevated AST, ALT and TB levels starting 7 months prior to the first dose of study drug. At baseline, subject had pneumonia with Troponin T and pro-BNP levels increased consistent with acute coronary syndrome and CHF.

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = direct bilirubin; TB = total bilirubin; AP = alkaline phosphatase

^a Ratio = lab value divided by the corresponding Upper Limit of Normal (ULN). Ratio provided when ULN available.

^b More than 1 laboratory value could be provided when peak elevations for analytes occur on different days.

For subject 11702-16018-1005 who developed severe acute hepatitis and liver insufficiency and subsequently died in EINSTEIN DVT/PE study, the following is the patient's narrative.

11702-16018-1005

This is a 63 year-old female originally from Madagascar and moving to France in 1995. She had a medical history of hypertension (since 1994), severe asthma on oral corticosteroids for 10 years, severe asthma exacerbation requiring intubation (1997), pulmonary emphysema, recent asthma exacerbation (11/2007). The subject had echocardiography in December 2006 which showed normal left and right chambers, normal cardiac valves, left ventricular relaxation dysfunction, and a non-significant pericardial effusion of 5 mm. She had a 34 pack year history of cigarette use, discontinued one year previously. She had no past history of liver disease or alcohol abuse (EtOH occasional) but did have an increased GGT. Corticosteroid-induced diabetes had been recently diagnosed.

The subject received rivaroxaban 15 mg bid from (b) (4) for acute multi-segmental PE in right lower lobe detected by CT scan on (b) (4). The patient received heparin on (b) (4) prior to enrollment. On enrollment on (b) (4), lab showed ALT 49, TB 12 micromol/L, and GGT 441. The patient showed clinical improvement and had been discharged on (b) (4).

In the time between (b) (4) 2008 the patient had episodes of disorientation at home and increase of dyspnea according the patient's daughter. Deroxat (paroxetine) had been started on (b) (4) because of reactional depression.

On (b) (4) Day 16) the patient had been re-admitted due to increase of dyspnea and deep asthenia. Upon admission, the patient showed tachycardia and new respiratory exacerbation without clinical signs of right heart failure. The blood pressure in admission was 120/80 mmHg and O2 Sat was 96% at room air. Neither episode of acute hypotension nor signs of cardiac decompensation were described. She was treated for asthma exacerbation and improved with a decrease of the wheezing. No liver function tests were done.

On (b) (4) (Day 18), lab showed ALT 5371 UL, AST 10506 U/L, TB 67 micromol/L, AP 151 U/L, GGT 538 U/L, PT < 10%, FV <10%, D-dimer >4000, platelet 121,000 (decreased from 301,000 on (b) (4) B-type natriuretic peptide (BNP; norm < 100pg/ml): 1610, and Creatinine 180 µmol/L (increased from (b) (4)). Severe acute hepatitis and liver insufficiency was diagnosed. Rivaroxaban was stopped.

On (b) (4) (b) (4) she was transferred to surgical ICU of another hospital with the diagnosis of acute liver failure potentially related to study drug and consideration for liver transplant. The BP was 109/68 mmHg during the transfer. Abdominal ultrasound reported "The ultrasonographic appearance was in support of hepatitis with a layered appearance of the gall bladder wall on the hepatic side. Discovery of a tumor mass 6 cm diameter at the upper pole of the right kidney." Thoracoabdominal CT showed right segmental pulmonary embolism (suspect of left lingular subsegmental thrombosis) and 6 cm tumor mass in right kidney, highly suspicious of malignancy. Hepatitis serology test showed previous hepatitis B (positive HBcAb and negative HBsAg) and negative for hepatitis C. Transthoracic Echocardiography (TTE) showed LA surface area = 40 cm², E/A >1, PAPS = 50-55 mmHg, LVEF 40%, sub-aortic gradient 7 cm at maximum, RV/RA dilatation, chambers free of any visible thrombi; no pericardial effusion. Upon arrival, the patient had a BP of 100/70, HR of 107 bpm, a regular sinus rhythm, conjunctival icterus, hepato-jugular reflux and hematomas and petechia at the puncture site. The patient was afebrile and no hepatomegaly was observed. Lung radiographic and laboratory findings showed no abnormalities except for a high white blood cell count and moderate renal insufficiency.

On (b) (4) (b) (4) TTE showed hypokinetic left ventricle with a heart-rate dependent flow.

On (b) (4) resumption of anti-coagulant therapy with unfractionated heparin 12000 U/24h, in a context of pulmonary embolism, with probable thrombogenic renal cancer.

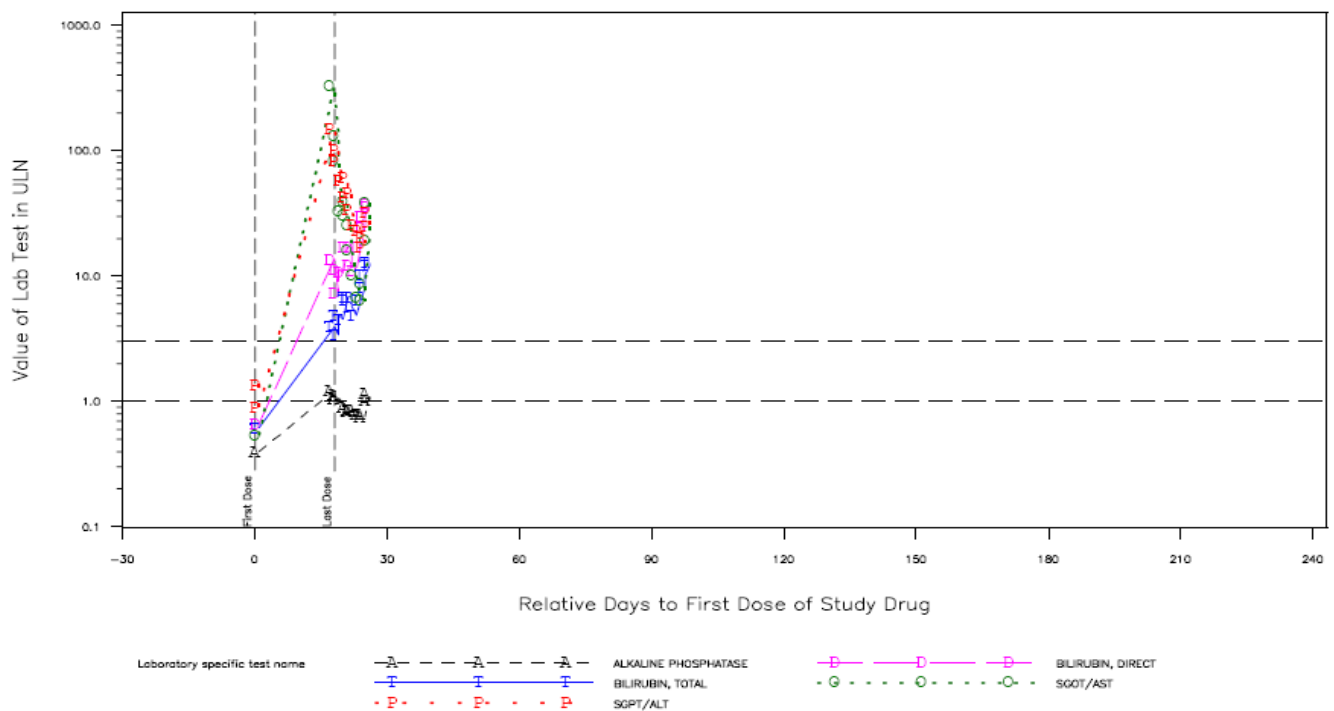
On (b) (4) TTE (pt on dobutamine) showed LV fraction of 34%, E/A >1 and obstructed PAP of 11; systolic PAP of 36 mmHg, VTI = 5.4 and an estimated cardiac output of 2.2 L/min. Lack of any increased troponin levels and lack of significant changes in ECG were noted by physician.

On (b) (4) the patient experienced another episode of myocardial failure with agitation and hypotension; and at the end of TTE, the patient suffered from cardiac arrest through asystole which was treated immediately with recovery of precarious hemodynamic condition at 15 minutes of resuscitation and followed by multiple organ failure. TTE showed dilated cardiopathy with increased pressures (i.e. LVEF = 30%)

On (b) (4), the patient died with multi-organ failure.

Autopsy was performed on (b) (4) concluded “Principle observations: hematoma on the anterior aspect of the kidney opposite the tumor process. Cardiac liver. Probable thrombosis of the ilio-femoral veins, the vena cava was patent.” Under liver, it stated “Congested liver with dilation of sinusoid cavities”. Additional heart and lung report showed “Heart: massive dilation of the right ventricle and left ventricular hypertrophy, adipose involution of the right ventricular wall, and partially of the left ventricle, compatible with arrhythmia-inducing right ventricular dysplasia (ARVD); Coronary arteries: lesions of atheroma and 40% stenosis of the left coronary artery and the anterior IV artery, without occlusion, without recent thrombosis, absence of a recent or old ischemic area; Lungs: recent thrombus of a segmental artery of the right lower lobe grafted onto an organized old thrombus, sequelae of chronic bronchial inflammation”. Microscopy examination stated “The hepatic parenchyma was the seat of a hemorrhagic necrosis in the central lobe area and a macrovacuolar steatosis. There was no argument in favor of a drug-related hepatitis. The kidney had partly undergone autolysis. We observed a few obsolete glomeruli. Moreover, there was a slight lymphocytic inflammatory infiltrate, evoking chronic interstitial nephropathy. We observed an old organizing hematoma in the perirenal fat with presence of a very large number of foamy macrophages. There was no tumor cell proliferation.”

The following figure shows the liver-related laboratory values over time.



The following are assessments made by members of Liver Advisory Panel:

(b) (4)

In conclusion, rivaroxaban causality is **unlikely**. The most probable cause is ischemic hepatitis mainly based on the clinical and biological evolution observed after January 14th. Moreover, the cause of death is clearly related to cardiac failure. However, it is impossible to definitively exclude rivaroxaban causality in the liver function tests perturbation observed on (b) (4) since no episode of cardiac failure, hypotension was described at that time.

The histopathological findings in the liver as well as in the kidney are highly suggestive of circulatory failure.

Indeed, hemorrhagic necrosis in the centrilobular areas of the liver, minimal thickening of the terminal hepatic veins and mild centrilobular perisinusoidal fibrosis, with minimal inflammatory infiltration, absence of lesions of the hepatocytes in the periportal areas and absence of portal or periportal fibrosis, are consistent with acute cardiac failure, possibly surimposed to mild liver injury secondary to chronic cardiac failure.

The lesions observed in the renal parenchyma are also consistent with such an hypothesis.

There is no positive histopathological argument favoring hepatotoxicity on the present liver sample obtained at necropsy. Although the centrilobular predominance of hepatocellular necrosis is suggestive of drug induced injury, hemorrhage is rare, and there usually are other lesions such as the presence of apoptotic hepatocytes and more pronounced portal and lobular inflammatory infiltration than was observed in the present case. Also, eosinophils and epithelioid and giant cell granulomas are expected, particularly if the hepatotoxicity is to be explained by an immunoallergic mechanism.

Statement dated [REDACTED]

CONCLUSION :

Case of acute liver failure followed by death. Death was largely related to severe cardiac dysfunction.

The role of the study drug appears very unlikely on the clinical presentation and the very important findings made at autopsy and subsequent histological liver examination which strongly argue for a liver ischemia caused by cardiac dysfunction.

(b) (4)

The initial episode of acute hepatitis occurs on [REDACTED]. The major increase in serum transaminases with a ratio AST/ALT >> 1 associated with very high LDH and CK, followed by a very rapid drop of these enzymes are in favour of a tissue ischemia in line with acute renal failure. The absence of hypotensive episode and cardiac distress between [REDACTED] does not allow proving an ischemic event, definitely. However, there are evidences in the literature showing that such events may be missed (extensively reviewed in [REDACTED] and [REDACTED]). The centrilobular predominance of hepatocellular necrosis may be consistent of drug induced injury. However, the number of examples with such features, without significant inflammatory infiltration is finally very limited, mainly paracetamol overdosage or directly toxic compounds or mushroom. Indeed, in these cases, the pattern is a kind of biochemical hepatectomy related to the acute but very short exposure to a toxic agent. This may explain the rapid improvement of liver enzymes and renal condition provided the lesion is not too severe and if there are no other aggravating factors.

In case of acute ischemia in a patient with normal heart function, there is a relatively good prognosis even for extensive lesion. In contrast, when the cardiac function is limited combining ischemia and stasis because of right cardiac failure, this may trigger an irreversible decompensation usually fatal. It is the picture that we can observe in this case. The liver and kidney samples obtained at the time of autopsy (11 days after the first event) mainly showed signs of circulatory failure. The autopsy revealed that the right heart ventricle was much deteriorated (ICU opinion) so that cardiac failure is the very likely cause of death (ICU opinion).

It would be very important that [REDACTED] may review also the cardiac macroscopy and histology.

I agree that the role of the study drug cannot be excluded.

[REDACTED]
Statement dated [REDACTED]

Liver

The lobular architecture is intact, with the usual relation between portal tracts and central veins. Severe centrilobular necrosis and hemorrhage is present, but inflammation is sparse. Moderate macrovesicular steatosis is noted. The portal tracts appear normal.

Impression: The morphologic appearance is consistent with toxic liver injury of the predictable type. Such toxins include carbon tetrachloride, acetaminophen and poisonous mushrooms. The pathologic changes also resemble those seen in patients who have experienced profound shock, although those lesions are usually not as severe. The term ischemic hepatitis has also been employed. Clinical correlation is recommended.

Statement date (b) (4)

According to the clinical records, on (b) (4) the patient was conscious and oriented, with a Glasgow score of 15. Her blood pressure was 110/80 and the oxygen saturation was 98%. She had regular heart sounds and moderate tachycardia. Nevertheless, she was clearly in acute liver failure and suffered from renal insufficiency. Total bilirubin was 68. Platelets were 89,000, with abnormally high D-Dimers.

The clinical and laboratory data are not consistent with hemorrhagic centrilobular necrosis of the liver secondary to shock. Such lesions usually follow severe and sustained hypotension, which was not present in this case at the time of acute liver failure. A diagnosis of drug-induced toxic injury of the liver is far more likely. Please feel free to call upon me for any further information.

(b) (4)

Conclusion: All evidence supports ischemic hepatitis occurring in a patient with chronic heart failure and severe asthma who had a superimposed pulmonary embolization event. I could not find documentation of an episode of definite hypotension although I suspect such occurred. The patient had required dobutamine further supporting the conclusion of severe circulatory collapse. I do not think the study drug had a role in causing the hepatic injury.

7.3.4.4.4 Summary

The following table summarizes the number of cases with ALT >3xULN concurrent with TB >2xULN in all completed studies. There were 14 (0.15%) cases in the rivaroxaban group and 9 (0.13%) in the control group. In RECORD phase 3 trials, 7 cases (0.11%) in the rivaroxaban group and 3 (0.05%) in the enoxaparin group were considered to be possibly related to rivaroxaban by at least one member of the Liver Advisory Panel. Two of 14 subjects in the rivaroxaban group subsequently died with liver failure as compared to none in the enoxaparin group. One death was considered to be drug-induced cholestasis. Another death was considered to be hepatitis B infection but the autopsy findings of liver tissues raised concerns for possible toxic origin of lesions. In both cases, the role of rivaroxaban could not be excluded.

An additional 27 cases of ALT >3xULN concurrent with TB >2xULN were reported in 5 ongoing studies. These included 4 cases in subjects received rivaroxaban, 3 in subjects received placebo, and 3 in subjects received warfarin, and 17 still blinded cases. One subject in the rivaroxaban group in ongoing studies died with liver failure and the autopsy findings again raised concerns of likely drug-induced toxic injury by liver advisory member.

In the RECORD studies, serious treatment-emergent ALT increased was reported more often in the rivaroxaban group (17, 0.27%) as compared to the enoxaparin group (11, 0.18%) although the rate of ALT >3x ULN was lower with rivaroxaban (152, 2.48%) than with enoxaparin (227, 3.70%). Because enoxaparin control has been known to cause benign liver enzyme elevation and

such elevations are fully reversible (NDA 20-164, Lovenox labeling), the comparison of liver enzyme elevation between the two treatments would not eliminate the concerns of possible serious liver toxicity for rivaroxaban.

Previous experience with EXANTA (ximelagatran) that causes drug-induced liver injury suggested even short term tolerance does not necessarily predict long term safety (NDA 21-686, Medical Review, Dr. Ruyi He, M.D., 9/27/04; Cardiovascular and Renal Drug Advisory Committee Transcript, 9/10/04). In the current application, 92% of study patients were exposed to <35 days of rivaroxaban treatment and only 6% (635 patients) were exposed to rivaroxaban for 3 months based on completed studies. Therefore, the long-term safety data from ongoing studies, using a control that has not been shown to increase liver enzymes, such as warfarin, will be needed to fully evaluate the hepatotoxicity for rivaroxaban.

ALT >3x ULN Concurrent With TB>2x ULN in Completed Studies

	Rivaroxaban	Control
RECORD 1-4	9/6131 (0.15%)	7/6131 (0.11%)
Possible related	7/6131 (0.11%)	3/6131 (0.05%)
Phase 2 VTE Prophylaxis Studies	4/1700 (0.2%)	2/379 (0.5%)
Phase 2 VTE Treatment Studies	1/824 (0.1%)	0/235 (0%)
Phase 2 Atrial Fibrillation Studies	0/158 (0%)	0/76 (0%)
Phase 1 Studies	0/497 (0%)	0/180 (0%)
Total	14 /9310 (0.15%)	9/7001 (0.13%)
Liver-related deaths	2/9310 (0.02%)	0

7.2.5 Submission Specific Primary Safety Concerns

Hepatic adverse events were discussed in the above section.

7.4 Supportive Safety Results

7.2.1 Common Adverse Events

The following table presents the common treatment-emergent adverse events that reported in ≥2% of subjects in the rivaroxaban group in RECORD 1-4 Studies. Overall, there were 68% of rivaroxaban subjects and 69% of enoxaparin subjects who reported at least one treatment-emergent adverse event. The most frequent events occurring at an incidence of at least 2% of

subjects were: nausea (788[12.7%] rivaroxaban and 797 [12.9%] enoxaparin subjects); pyrexia (719 [11.6%] rivaroxaban and 712 [11.5%] enoxaparin subjects); vomiting (605 [9.8%] rivaroxaban and 610 [9.8%] enoxaparin subjects); constipation (573 [9.3%] rivaroxaban and 596 [9.6%] enoxaparin subjects), and deep vein thrombosis (258 [4.2%] rivaroxaban and 450 [7.3%] enoxaparin subjects).

Adverse events that were reported more frequently on rivaroxaban compared to enoxaparin were peripheral edema, dizziness, pruritus, pain in extremity, urinary retention, muscle spasms, and wound secretion. Adverse events reported more frequently on enoxaparin compared to rivaroxaban were chest pain, ALT increase, AST increase, GGT increase, arthralgia, and DVT.

Common AEs that occurred $\geq 2\%$ in the Rivaroxaban group in RECORD 1-4 Studies

Preferred Term	Rivaroxaban (N=6183)	Enoxaparin (N=6200)
Any AEs	4179 (67.59%)	4306 (69.45%)
Nausea	788 (12.74%)	797 (12.85%)
Pyrexia	719 (11.63%)	712 (11.48%)
Vomiting	605 (9.78%)	610 (9.84%)
Constipation	573 (9.27%)	596 (9.61%)
Peripheral edema	419 (6.78%)	409 (6.60%)
Anemia postoperative	352 (5.69%)	355 (5.73%)
Procedural pain	322 (5.21%)	345 (5.56%)
Hypotension	313 (5.06%)	315 (5.08%)
Insomnia	307 (4.97%)	326 (5.26%)
Dizziness	259 (4.19%)	243 (3.92%)
Deep vein thrombosis	258 (4.17%)	450 (7.26%)
Anemia	244 (3.95%)	244 (3.94%)
Pruritus	225 (3.64%)	202 (3.26%)
Pain in extremity	203 (3.28%)	167 (2.69%)
Diarrhea	158 (2.56%)	182 (2.94%)
Hemoglobin decreased	157 (2.54%)	166 (2.68%)
Urinary retention	156 (2.52%)	149 (2.40%)
Headache	153 (2.47%)	151 (2.44%)
Muscle spasms	148 (2.39%)	115 (1.85%)
Tachycardia	146 (2.36%)	149 (2.40%)
Wound secretion	146 (2.36%)	106 (1.71%)
ALT increased	134 (2.17%)	183 (2.95%)

7.2.2 Laboratory Findings

Laboratory safety data from the 2 THR studies (RECORD 1 and 2) and 2 TKR studies (RECORD 3 and 4) are presented separately since the testing schedule was slightly different. The following table shows the incidence of high ($>1\times\text{ULN}$) non-liver-related abnormalities in the THR and TKR studies, respectively.

Rivaroxaban and enoxaparin were generally similar with respect to showing elevations in laboratory abnormalities except for creatinine and urea. The incidences of high creatinine and urea abnormalities were higher on rivaroxaban compared to enoxaparin (based on treatment-emergent analysis). This pattern was present in the hip replacement studies (RECORD 1 and 2) and the knee replacement studies (RECORD 3 and 4). It was also noted that the incidence of high amylase was slightly higher with rivaroxaban than with enoxaparin in both hip and knee replacement studies.

**Pooled Treatment-emergent Incidence Rates of High (>1x ULN) Laboratory Abnormalities^a
(Subjects Valid for Safety in RECORD 1 and 2)**

Category Laboratory Variable	Rivaroxaban (N=3437)		Enoxaparin (N=3453)	
Hematology				
Hematocrit	5/3300	(0.15%)	8/3307	(0.24%)
Hemoglobin	6/3318	(0.18%)	6/3321	(0.18%)
White blood cells	1861/3072	(60.58%)	1891/3115	(60.71%)
Neutrophils (total)	1567/1906	(82.21%)	1568/1907	(82.22%)
Lymphocytes	83/2085	(3.98%)	109/2090	(5.22%)
Monocytes	467/1950	(23.95%)	465/1952	(23.82%)
Eosinophils	333/1955	(17.03%)	330/1967	(16.78%)
Basophils	166/2018	(8.23%)	150/2020	(7.43%)
Platelets	1995/3191	(62.52%)	1976/3200	(61.75%)
Blood Chemistry				
Glucose, unspecified	1105/3056	(36.16%)	1062/3039	(34.95%)
Uric Acid	92/3219	(2.86%)	92/3213	(2.86%)
Calcium	32/3318	(0.96%)	43/3323	(1.29%)
Sodium	22/3353	(0.66%)	17/3366	(0.51%)
Potassium	152/3289	(4.62%)	148/3286	(4.50%)
Creatinine	291/2819	(10.32%)	224/2789	(8.03%)
Urea	287/3107	(9.24%)	231/3079	(7.50%)
Albumin	0/3366	(0%)	0/3380	(0%)
Lactate dehydrogenase	1440/3153	(45.67%)	1560/3177	(49.10%)
Amylase	508/3086	(16.46%)	477/3090	(15.44%)
Lipase	438/3104	(14.11%)	416/3112	(13.37%)

^a High is above upper limit of normal

Note: The schedule Day 0 visit is used as baseline. If earlier visits are present, the highest value up to and including Day 0 is used as baseline.

Note: Incidence rate = # of events / # at risk, where:

of events = # of subjects reporting the abnormality post-baseline

at risk = # of subjects with baseline and post-baseline readings who did not report the abnormality at baseline

Note: Measurements taken more than 2 days after stop of double-blind treatment are not included

**Pooled Treatment-emergent Incidence Rates of High (>1x ULN) Laboratory Abnormalities^a
(Subjects Valid for Safety in RECORD 3 and 4)**

Category Laboratory Variable	Rivaroxaban (N=2746)		Enoxaparin (N=2747)	
Hematology				
Hematocrit	2/2631	(0.08%)	1/2609	(0.04%)
Hemoglobin	2/2639	(0.08%)	2/2628	(0.08%)
White blood cells	1301/2506	(51.92%)	1334/2514	(53.06%)
Neutrophils (total)	1329/1887	(70.43%)	1310/1869	(70.09%)
Lymphocytes	30/1952	(1.54%)	31/1939	(1.60%)
Monocytes	265/1883	(14.07%)	281/1857	(15.13%)
Eosinophils	210/1844	(11.39%)	226/1799	(12.56%)
Basophils	81/1949	(4.16%)	75/1921	(3.90%)
Platelets	1615/2567	(62.91%)	1574/2546	(61.82%)
Blood Chemistry				
Glucose, unspecified	912/2322	(39.28%)	942/2347	(40.14%)
Uric Acid	76/2525	(3.01%)	73/2504	(2.92%)
Calcium	14/2646	(0.53%)	25/2635	(0.95%)
Sodium	22/2668	(0.82%)	25/2664	(0.94%)
Potassium	151/2623	(5.76%)	137/2625	(5.22%)
Creatinine	280/2163	(12.94%)	248/2146	(11.56%)
Urea	234/2428	(9.64%)	188/2424	(7.76%)
Albumin	0/2691	(0%)	0/2690	(0%)
Lactate dehydrogenase	1611/2404	(67.01%)	1628/2413	(67.47%)
Amylase	285/2451	(11.63%)	263/2454	(10.72%)
Lipase	321/2485	(12.92%)	318/2500	(12.72%)

^a High is above upper limit of normal

Note: The schedule Day 0 visit is used as baseline. If earlier visits are present, the highest value up to and including Day 0 is used as baseline.

Note: Incidence rate = # of events / # at risk, where:

of events = # of subjects reporting the abnormality post-baseline

at risk = # of subjects with baseline and post-baseline readings who did not report the abnormality at baseline

Note: Measurements taken more than 2 days after stop of double-blind treatment are not included

The following tables show the frequency of creatinine and urea abnormalities >1x, 1.5x, and 2x ULN at specified time points. The Day 0 laboratory assessment was done on the day prior to surgery. The Day 1 laboratory assessment was done on the day of surgery (after surgery but prior to first tablet intake). After Day 1, the assessments reflect laboratory assessments made on study drug at any time through the follow-up period. The tables below include all subjects regardless of whether they had a baseline abnormality or not (post-baseline analysis).

In THR studies, after Day 1, the frequency of creatinine abnormalities was comparable in both groups but the frequency of urea abnormalities remained higher in the rivaroxaban group than the enoxaparin group (see table below). However, there were more subjects with creatinine and urea abnormalities at baseline and at Day 1 in the enoxaparin group than in the rivaroxaban group. The similar prevalence of creatinine abnormalities between the two groups after Day 1 further confirms a higher incidence of creatinine and urea abnormalities with rivaroxaban than with enoxaparin.

**Creatinine and Urea Postbaseline Laboratory Abnormalities by Time Windows and Visits
(Subjects Valid for Safety in RECORD 1 and 2)**

Laboratory Abnormality Visit/Time Window	Rivaroxaban		Enoxaparin	
	N/D	(%)	N/D	(%)
Creatinine >1x ULN				
Day 0	556/3411	(16.30%)	604/3433	(17.59%)
Day 1	191/3344	(5.71%)	244/3354	(7.27%)
After Day 1	683/3361	(20.32%)	680/3347	(20.32%)
Creatinine >1.5x ULN				
Day 0	38/3411	(1.11%)	55/3433	(1.60%)
Day 1	12/3344	(0.36%)	26/3354	(0.78%)
After Day 1	82/3361	(2.44%)	81/3347	(2.42%)
Creatinine >2x ULN				
Day 0	9/3411	(0.26%)	11/3433	(0.32%)
Day 1	3/3344	(0.09%)	3/3354	(0.09%)
After Day 1	24/3361	(0.71%)	28/3347	(0.84%)
Urea >1x ULN				
Day 0	262/3411	(7.68%)	314/3435	(9.14%)
Day 1	65/3344	(1.94%)	85/3354	(2.53%)
After Day 1	477/3361	(14.19%)	443/3347	(13.24%)
Urea >1.5x ULN				
Day 0	15/3411	(0.44%)	23/3435	(0.67%)
Day 1	5/3344	(0.15%)	4/3354	(0.12%)
After Day 1	58/3361	(1.73%)	54/3347	(1.61%)
Urea >2x ULN				
Day 0	5/3411	(0.15%)	1/3435	(0.03%)
Day 1	2/3344	(0.06%)	0/3354	(0.00%)
After Day 1	14/3361	(0.42%)	7/3347	(0.21%)

Key: D = denominator; N = numerator; ULN = upper limit of normal

In the TKR studies, after Day 1, the frequency of creatinine and urea abnormalities in all categories except urea >2x ULN remained higher on rivaroxaban compared with enoxaparin (see Table below). Again, it was noted that there were more subjects with creatinine and urea abnormalities at baseline and at Day 1 in the enoxaparin group than in the rivaroxaban group. This further confirms a higher incidence of creatinine and urea abnormalities with rivaroxaban than with enoxaparin.

**Creatinine and Urea Postbaseline Laboratory Abnormalities by Time Windows and Visits
(Subjects Valid for Safety in RECORD 3 and 4)**

Laboratory Abnormality Visit/Time Window	Rivaroxaban		Enoxaparin	
	N/D	(%)	N/D	(%)
Creatinine >1x ULN				
Day 0	534/2721	(19.63%)	556/2723	(20.42%)
Day 1	277/2669	(10.38%)	296/2668	(11.09%)
After Day 1	722/2673	(27.01%)	683/2666	(25.62%)
Creatinine >1.5x ULN				
Day 0	62/2721	(2.28%)	45/2723	(1.65%)
Day 1	22/2669	(0.82%)	20/2668	(0.75%)
After Day 1	105/2673	(3.93%)	90/2666	(3.38%)
Creatinine >2x ULN				
Day 0	5/2721	(0.18%)	7/2723	(0.26%)
Day 1	3/2669	(0.11%)	2/2668	(0.07%)
After Day 1	25/2673	(0.94%)	22/2666	(0.83%)
Urea >1x ULN				
Day 0	267/2721	(9.81%)	274/2723	(10.06%)
Day 1	93/2669	(3.48%)	101/2668	(3.79%)
After Day 1	445/2673	(16.65%)	392/2666	(14.70%)
Urea >1.5x ULN				
Day 0	26/2721	(0.96%)	19/2723	(0.70%)
Day 1	10/2669	(0.37%)	10/2668	(0.37%)
After Day 1	57/2673	(2.13%)	53/2666	(1.99%)
Urea >2x ULN				
Day 0	3/2721	(0.11%)	3/2723	(0.11%)
Day 1	1/2669	(0.04%)	1/2668	(0.04%)
After Day 1	16/2673	(0.60%)	16/2666	(0.60%)

Key: D = denominator; N = numerator; ULN = upper limit of normal

In the pooled RECORD studies, any serious treatment-emergent “renal and urinary disorders” was reported in 13 (0.21%) and 10 (0.16%) subjects on rivaroxaban and enoxaparin, respectively. Serious “renal failure acute” was reported in 6 (0.10%) and 5 (0.08%) subjects on rivaroxaban and enoxaparin, respectively. Serious “renal failure” was reported in 0 and 2 (0.03%) subjects on rivaroxaban and enoxaparin, respectively. Serious “renal impairment” was reported in 1 (0.02%) and 0 subjects on rivaroxaban and enoxaparin, respectively. Serious “urinary retention” was reported in 4 (0.06%) and 0 subjects on rivaroxaban and enoxaparin. Serious “hematuria” was reported in 1 (0.02%) and 0 subjects on rivaroxaban and enoxaparin.

In the RECORD studies, any treatment-emergent “renal and urinary disorders” was reported in 333 (5.39%) and 309 (4.98%) subjects on rivaroxaban and enoxaparin, respectively. The most frequent adverse events reported more with rivaroxaban than with enoxaparin were urinary retention [156 (2.52%) and 149 (2.40%)], dysuria [55(0.89%) and 33(0.53%)], hematuria [33 (0.53%) and 16 (0.26%)], pollakiuria [30 (0.49%) and 25 (0.40%)], urogenital hemorrhage [4 (0.06%) and 0 (0.00%)], and renal impairment [3 (0.05%) and 1 (0.02%)] for rivaroxaban and enoxaparin, respectively. The term “renal failure” was reported in 1 (0.02%) and 7 (0.11%) subjects on rivaroxaban and enoxaparin, respectively. “Renal failure acute” was reported in 6 (0.10%) and 8 (0.13%) subjects on rivaroxaban and enoxaparin, respectively.

The following tables show the incidence of low (<1x LLN) non-liver-related abnormalities in the THR and TKR studies, respectively. Rivaroxaban and enoxaparin were generally similar with respect to occurrence of low laboratory abnormalities.

**Pooled Treatment-emergent Incidence Rates of Low (<1x LLN) Laboratory Abnormalities^a
(Subjects Valid for Safety in RECORD 1 and 2)**

Category Laboratory Variable	Rivaroxaban (N=3437)		Enoxaparin (N=3453)	
Hematology				
Hematocrit	2478/2629	(94.26%)	2537/2679	(94.70%)
Hemoglobin	2575/2750	(93.64%)	2649/2810	(94.27%)
White blood cells	118/3291	(3.59%)	128/3291	(3.89%)
Neutrophils (total)	64/2039	(3.14%)	96/2061	(4.66%)
Lymphocytes	1648/1935	(85.17%)	1619/1925	(84.10%)
Monocytes	377/1889	(19.96%)	406/1895	(21.42%)
Eosinophils	535/910	(58.79%)	556/905	(61.44%)
Basophils	94/179	(52.51%)	92/178	(51.69%)
Platelets	339/3278	(10.34%)	345/3274	(10.54%)
Blood Chemistry				
Glucose, unspecified	156/3318	(4.70%)	149/3333	(4.47%)
Uric Acid	459/3288	(13.96%)	516/3321	(15.54%)
Calcium	2502/3293	(75.98%)	2525/3320	(76.05%)
Sodium	321/3299	(9.73%)	278/3300	(8.42%)
Potassium	297/3264	(9.10%)	330/3297	(10.01%)
Creatinine	453/3282	(13.80%)	517/3298	(15.68%)
Urea	43/3366	(1.28%)	35/3371	(1.04%)
Albumin	1242/3356	(37.01%)	1272/3373	(37.71%)
Lactate dehydrogenase	65/3303	(1.97%)	59/3313	(1.78%)
Amylase	381/3275	(11.63%)	393/3280	(11.98%)
Lipase	110/3357	(3.28%)	94/3371	(2.79%)

^a Low is below lower limit of normal

Note: The schedule Day 0 visit is used as baseline. If earlier visits are present, the lowest value up to and including Day 0 is used as baseline.

Note: Incidence rate = # of events / # at risk, where:

of events = # of subjects reporting the abnormality post-baseline

at risk = # of subjects with baseline and post-baseline readings who did not report the abnormality at baseline

Note: Measurements taken more than 2 days after stop of double-blind treatment are not included

Note: Hematology lab tests were done locally and therefore the LLN could vary from site to site. If the LLN includes 0, a subject would not be considered evaluable in a treatment-emergent analysis of low laboratory abnormalities. Consequently the denominator for certain lab tests (i.e. basophils) are markedly lower than for other lab tests.

**Pooled Treatment-emergent Incidence Rates of Low (<1x LLN) Laboratory Abnormalities^a
(Subjects Valid for Safety in RECORD 3 and 4)**

Category Laboratory Variable	Rivaroxaban (N=2746)		Enoxaparin (N=2747)	
Hematology				
Hematocrit	1930/2107	(91.60%)	1987/2143	(92.72%)
Hemoglobin	1997/2180	(91.61%)	2026/2202	(92.01%)
White blood cells	44/2624	(1.68%)	70/2594	(2.70%)
Neutrophils (total)	38/1959	(1.94%)	29/1938	(1.50%)
Lymphocytes	1336/1846	(72.37%)	1336/1818	(73.49%)
Monocytes	275/1622	(16.95%)	296/1622	(18.25%)
Eosinophils	364/839	(43.38%)	399/823	(48.48%)
Basophils	32/112	(28.57%)	35/109	(32.11%)
Platelets	170/2616	(6.50%)	173/2608	(6.63%)
Blood Chemistry				
Glucose, unspecified	112/2603	(4.30%)	102/2604	(3.92%)
Uric Acid	260/2659	(9.78%)	265/2667	(9.94%)
Calcium	1635/2642	(61.88%)	1685/2634	(63.97%)
Sodium	439/2618	(16.77%)	451/2641	(17.08%)
Potassium	317/2610	(12.15%)	314/2594	(12.10%)
Creatinine	189/2657	(7.11%)	216/2664	(8.11%)
Urea	27/2688	(1.00%)	38/2689	(1.41%)
Albumin	656/2688	(24.40%)	657/2688	(24.44%)
Lactate dehydrogenase	20/2670	(0.75%)	26/2655	(0.98%)
Amylase	422/2599	(16.24%)	459/2594	(17.69%)
Lipase	133/2680	(4.96%)	132/2680	(4.93%)

^a Low is below lower limit of normal

Note: The schedule Day 0 visit is used as baseline. If earlier visits are present, the lowest value up to and including Day 0 is used as baseline.

Note: Incidence rate = # of events / # at risk, where:

of events = # of subjects reporting the abnormality post-baseline

at risk = # of subjects with baseline and post-baseline readings who did not report the abnormality at baseline

Note: Measurements taken more than 2 days after stop of double-blind treatment are not included

Laboratory parameters of special interest were lipase and platelets.

Lipase was of interest in the Phase 3 RECORD program because the Phase 2 orthopedic surgery database suggested a trend towards an increased incidence of lipase and amylase laboratory abnormalities relative to enoxaparin. The following table shows that the incidences of lipase abnormalities at various thresholds (e.g. >3, >5, >8x ULN) are generally similar between rivaroxaban and enoxaparin groups. The incidence of “lipase increased” reported as an adverse event by investigators was 50 (0.81%) versus 45 (0.73%) subjects on rivaroxaban and enoxaparin, respectively. The adverse event term “pancreatitis” occurred in 1 (<0.1%) and 2 (<0.1%) rivaroxaban and enoxaparin subjects, respectively. The incidence of the adverse event term “acute pancreatitis” occurred in 1 (<0.1%) and 3 (<0.1%) rivaroxaban and enoxaparin subjects, respectively.

The incidences of low platelet abnormalities at various thresholds (e.g. < 30, < 50, < 80 or < 100) are generally similar between rivaroxaban and enoxaparin, respectively (see Table below). “Platelet count decreased” reported as an adverse event occurred in 7 (0.1%) and 7(0.1%) rivaroxaban and enoxaparin subjects, respectively.

**Incidence Rates of Prespecified Treatment-emergent Laboratory Abnormalities
(Subjects Valid for Safety in pooled RECORD 1-4 studies)**

Laboratory Variable Limit	Rivaroxaban (N=6183)		Enoxaparin (N=6200)	
	N/D	%	N/D	%
Lipase				
>3x ULN	137/6061	(2.26%)	152/6082	(2.50%)
>5x ULN	70/6073	(1.15%)	83/6088	(1.36%)
>8x ULN	43/6076	(0.71%)	45/6090	(0.74%)
Platelets				
<30 GIGA/L	3/6040	(0.05%)	4/6033	(0.07%)
<50 GIGA/L	6/6039	(0.10%)	7/6032	(0.12%)
<80 GIGA/L	32/6032	(0.53%)	29/6024	(0.48%)
<100 GIGA/L or <baseline/2	152/6023	(2.52%)	157/6015	(2.61%)

Key: ULN = upper limit of normal; N = numerator, D = denominator

Note: The schedule Day 0 visit is used as baseline. If earlier visits are present, the lowest value up to and including Day 0 is used as baseline.

Note: Incidence rate = # of events / # at risk, where # of events = # of subjects reporting the abnormality post-baseline # at risk = # of subjects with baseline and post-baseline readings who did not report the abnormality at baseline

Note: All measurements after the start of study medication are included regardless of onset relative to the last dose of study medication.

7.2.3 Vital Signs

Vital sign data from the 2 THR studies and 2 TKR studies are presented separately in the following table since the testing schedule was slightly different. The effects of rivaroxaban and enoxaparin on systolic blood pressure, diastolic blood pressure, and heart rate are generally similar.

Vital Sign Measurements^a
(Subjects Valid for Safety in Pooled RECORD 1 & 2, and Pooled RECORD 3 & 4)

Study				
Parameter	Rivaroxaban		Enoxaparin	
Change period	N	Mean ± SD	N	Mean ± SD
RECORD 1 and 2				
Diastolic BP (mm Hg)				
Baseline	3397	80.26 ± 10.13	3415	80.43 ± 9.93
Change from baseline (Day 1)	3384	-8.90 ± 13.64	3406	-9.21 ± 13.55
Change from baseline (Day 6 ^b)	3269	-5.99 ± 11.83	3276	-5.93 ± 11.26
Change from baseline (Day 13 ^b)	3186	-4.28 ± 11.47	3174	-4.25 ± 11.52
Change from baseline (Day 65 ^c)	3026	-0.53 ± 12.01	3012	-0.50 ± 11.50
Systolic BP (mm Hg)				
Baseline	3397	136.11 ± 18.23	3415	136.5 ± 17.98
Change from baseline (Day 1)	3385	-12.59 ± 21.51	3406	-13.24 ± 21.57
Change from baseline (Day 6)	3270	-8.62 ± 18.59	3277	-8.29 ± 18.09
Change from baseline (Day 13)	3186	-7.39 ± 18.30	3175	-7.76 ± 18.06
Change from baseline (Day 65)	3027	-2.43 ± 18.40	3012	-2.77 ± 18.17
Heart rate (bpm)				
Baseline	3381	73.50 ± 9.78	3402	73.77 ± 10.04
Change from baseline (Day 1)	3363	1.07 ± 12.69	3389	0.85 ± 12.85
Change from baseline (Day 6)	3245	3.69 ± 11.20	3254	3.34 ± 11.57
Change from baseline (Day 13)	3167	2.54 ± 10.80	3147	2.20 ± 11.12
Change from baseline (Day 65)	3016	1.38 ± 10.78	3005	1.11 ± 10.73
RECORD 3 and 4				
Diastolic BP (mm Hg)				
Baseline	2724	79.76 ± 10.16	2724	79.93 ± 10.37
Change from baseline (Day 1)	2718	-7.19 ± 13.47	2721	-7.17 ± 13.77
Change from baseline (Day 6)	2613	-5.52 ± 11.76	2601	-5.46 ± 12.18
Change from baseline (Day 13)	2532	-3.03 ± 11.61	2527	-3.02 ± 11.87
Change from baseline (Day 42)	2474	-0.91 ± 11.19	2464	-1.01 ± 11.92
Systolic BP (mm Hg)				
Baseline	2724	136.54 ± 17.09	2724	136.67 ± 17.66
Change from baseline (Day 1)	2718	-8.28 ± 21.35	2721	-8.11 ± 21.76
Change from baseline (Day 6)	2613	-5.90 ± 18.71	2601	-6.06 ± 18.96
Change from baseline (Day 13)	2532	-4.36 ± 18.44	2527	-4.51 ± 18.47
Change from baseline (Day 42)	2474	-3.21 ± 18.14	2464	-3.03 ± 18.54
Heart rate (bpm)				
Baseline	2723	74.48 ± 10.26	2716	74.00 ± 10.51
Change from baseline (Day 1)	2714	0.31 ± 13.27	2711	0.82 ± 13.22
Change from baseline (Day 6)	2610	4.58 ± 12.40	2593	5.15 ± 12.64
Change from baseline (Day 13)	2525	3.14 ± 11.73	2517	3.51 ± 12.08
Change from baseline (Day 42)	2467	2.21 ± 11.23	2460	2.39 ± 11.54

^a Vital sign measurements in subjects with at least 1 baseline and 1 postbaseline vital signs assessment.

^b (± 2 days)

^c (± 5 days)

Key: BP = blood pressure; od = once daily

Note: Day 0 visit is used as baseline.

Note: Since more than 1 measurement is available for a subject at the same visit (postbaseline), the mean value is used for analysis.

7.2.4 Electrocardiograms (ECGs)

Routine electrocardiographic safety monitoring was not done in the Phase 3 RECORD studies. A thorough Phase 1 QT study (Study 11275) was performed and is being reviewed by clinical pharmacology.

7.2.5 Special Safety Studies

N/A

7.2.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.2.1 Dose Dependency for Adverse Events

In the Phase 2 orthopedic VTE prophylaxis dose-ranging studies there was an increased risk of bleeding events with increasing rivaroxaban dose. No non-bleeding events appeared to be related to rivaroxaban dose. Only one dose of rivaroxaban was studied in the phase 3 trials.

7.2.2 Time Dependency for Adverse Events

No specific time of dependency for adverse events was clearly identified.

7.2.3 Drug-Demographic Interactions

According to subgroup analysis, in certain subgroups, such as Asian subjects, subjects with body weight ≤ 50 kg or > 110 kg, BMI < 18.5 or ≥ 40 , the risk of major or non-major clinically relevant bleeding event appears to be higher with rivaroxaban as compared to other groups.

In the RECORD phase 3 trials, it was noted that there were significantly higher incidence of ALT $> 3 \times \text{ULN}$ and TB $> 2 \times \text{ULN}$ in the rivaroxaban group (4, 0.65%) than in the enoxaparin group (1, 0.16%) in Asians. The four Asians in the rivaroxaban group were from China, Indonesia, India and Sri Lanka, respectively. The one Asian in enoxaparin group was from India. There were also higher incidences of ALT $> 10 \times \text{ULN}$ and $> 20 \times \text{ULN}$ with rivaroxaban than with enoxaparin in Asians. The differences between the two treatment groups were not seen for other liver-related abnormalities. If Asians are more susceptible to possible liver injury will need further investigation.

7.2.4 Drug-Disease Interactions

Hepatic impairment:

A phase 1 study in subjects with Child Pugh A and B was conducted and is under review by Clinical pharmacology. According to the sponsor, the study showed no difference in pharmacokinetic or pharmacodynamic response in healthy subjects compared to subjects classified as Child Pugh A. Subjects classified as Child Pugh B had more pronounced pharmacokinetic and pharmacodynamic effects. Subjects classified as Child Pugh C were not studied in Phase 1 studies.

In the Phase 3 RECORD studies, subjects with significant liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis) were to be excluded from enrollment. However, some subjects with elevated liver enzymes (e.g. ALT or AST) were enrolled. There were no apparent differences in liver safety for the subjects entering the trial with elevated ALT or AST values compared with those with normal values.

One rivaroxaban subject with HBsAg positive at baseline detected by retention sample in a phase 2 trial developed fulminant liver failure and subsequently died. Another rivaroxaban subject in phase 3 RECORD trial was diagnosed with hepatitis C by serology tests. Because of the temporal association between rivaroxaban treatment and the occurrence of these events, concern is raised for possible virus activation by rivaroxaban treatment.

Renal impairment:

A phase 1 study in subjects with renal impairment was conducted and is under review by Clinical pharmacology.

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 (C_{max} and AUC) was increased and the overall inhibition of FXa activity was increased by 1.5-, 1.9- and 2.0-fold respectively, compared to healthy subjects with normal renal function (creatinine clearance >80 mL/min). In addition, the increased overall exposure was associated with an increased sensitivity of prothrombin time prolongation. Patients with creatinine clearance <15 mL/min were not studied.

In the Phase 3 RECORD studies, subjects with a severe renal impairment were to be excluded from the studies. However, 57 subjects (29 in the rivaroxaban group and 28 in the enoxaparin group) with creatinine clearance <30 mL/min were enrolled in the Phase 3 RECORD studies. Major or non-major clinically relevant bleeding was reported in 3 (10.34%) subjects in the rivaroxaban group and 1 (3.57%) subjects in the enoxaparin group in patients with creatinine clearance <30 mL/min although the number of patients was relatively small in this subpopulation.

A total of 380 and 409 subjects with creatinine clearance 30 to <50 mL/min (moderate renal impairment) were included in the rivaroxaban and enoxaparin groups, respectively, of the RECORD studies. Major or non-major clinically relevant bleeding was reported in 10 (2.63%) subjects in the rivaroxaban group and 13 (3.18%) subjects in the enoxaparin group in patients with creatinine clearance 30 to <50 mL/min.

7.2.5 Drug-Drug Interactions

Phase 1 drug-drug interactions studies involving coadministration of rivaroxaban and ketoconazole, ritonavir, clarithromycin or erythromycin were conducted and are under review by clinical pharmacology.

Rivaroxaban is eliminated both metabolically (primarily CYP3A4 mediated) and renally (primarily active secretion).

In the 4 RECORD studies the influence of 6 classes of co-medication use (CYP3A4 or P-gp inhibitors, NSAIDs, opioid, statin, nitrate and antiplatelet agents) on post-tablet major or non-major clinically relevant bleeding event and any bleeding event rates per 100 patient-weeks for rivaroxaban and enoxaparin was explored.

In pooled RECORD studies, there were about 70% of study patients on NSAIDs, 94% on opioids, 18% on statins, 4% on nitrates, 9% on platelet aggregation inhibitors or ASA, and 8% on CYP-3A4 or P-gp inhibitors. The number of subjects with use of these co-medications between the day of surgery and the end of the risk period is well balanced for the rivaroxaban and enoxaparin/placebo group (see Table below).

Number and Proportion (%) of Subjects with Use ^a of Co-medication In RECORD 1, 2, 3, and 4 Pool (Safety Population with Surgery and Tablet Intake)		
Concomitant Drug(s)	Rivaroxaban 10 mg od (N=6093)	Enoxaparin / Placebo (N=6107)
NSAIDs	4396 (72%)	4432 (73%)
Opioids	5714 (94%)	5740 (94%)
Statins	1092 (18%)	1028 (17%)
Nitrates	260 (4%)	283 (5%)
Platelet aggregation inhibitors or ASA	563 (9%)	526 (9%)
CYP-3A4 or P-gp inhibitors	467 (8%)	465 (8%)
^a Time under concomitant drug use or <u>up to 2 days</u> after last intake of concomitant drug considered time of co-medication use		

The analyses focus on treatment emergent adjudicated bleeding events ('major and non-major clinically relevant' and 'any bleeding') after first tablet intake (rivaroxaban or matching placebo). The at-risk period for which bleeding events and person time are accumulated, extends from the day of surgery until the last day of study medication intake + 2 days or event onset date, whatever is first. The use of co-medications is a time-dependent covariate and a subject may be on and off the co-medications of interest in the evaluated risk period. If a subject experienced a bleeding event while receiving the listed co-medication (up to 2 days after co-medication discontinuation), the event would be counted as occurring with co-medication use. If an event occurred while a subject was not taking the listed co-medication, the event would be counted as occurring without co-medication use. The table also includes data on the proportion of patient-time accumulated by subjects using the listed co-medication relative to the total time of rivaroxaban exposure.

The following table presents the proportion of person-time within the three time intervals

“day 1-3”, “day 4-7” and “>day 7” and the overall risk period. It shows that the proportion of NSAID and Opioid exposed person-time decreases over time, while the proportion of exposed person-time is more constant over time for the other 4 drug classes.

Proportion of Person-Time with Use of Co-medication in Time Windows after Surgery RECORD 1, 2, 3, and 4 Pool (Safety Population with Surgery and Tablet Intake)

Concomitant Drug(s) / Treatment Group	Day 1 - 3	Day 4 – 7	After Day 7	Total Risk Period
Total Number of Patient-Weeks at Risk ^a				
Rivaroxaban 10 mg od	2593	3321	15717	21631
Enoxaparin / Placebo	2602	3329	15621	21552
Proportion (%) of Person Time ^b with Concomitant Use of				
NSAIDs				
Rivaroxaban 10 mg od	62%	51%	29%	36%
Enoxaparin / Placebo	62%	52%	28%	36%
Opioids				
Rivaroxaban 10 mg od	91%	60%	26%	39%
Enoxaparin / Placebo	92%	60%	27%	40%
Statins				
Rivaroxaban 10 mg od	17%	17%	14%	15%
Enoxaparin / Placebo	15%	16%	13%	14%
Nitrates				
Rivaroxaban 10 mg od	3%	3%	3%	3%
Enoxaparin / Placebo	4%	3%	2%	3%
Plat.Agg. Inhibitors or ASA				
Rivaroxaban 10 mg od	3%	4%	5%	5%
Enoxaparin / Placebo	3%	4%	4%	4%
CYP3A4 or P-gp inhibitors				
Rivaroxaban 10 mg od	7%	6%	4%	5%
Enoxaparin / Placebo	6%	6%	4%	5%

a Person time from analysis of any bleeding event.

b Time (at risk) under concomitant drug use or up to 2 days after last intake of concomitant drug considered time of co-medication use.

The following tables lists the number of subjects, major or clinically relevant non-major bleeding events, crude bleeding rate, as well as bleeding rate per patient time analysis for each co-medication use in the two treatment group. It appears that the subjects with concomitant use of NSAIDs, opioids, statins, and nitrates experienced more major or clinically relevant non-major bleeding events than those without use of these medications in the rivaroxaban group, as well as in the enoxaparin group.

BAY 59-7939 (RIVAROXABAN) / PHASE III
PREVENTION OF VENOUS THROMBOEMBOLISM

GLOBAL INTEGRATED ANAL

TABLE 14.3.5/10.1.1
INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND
WITH CO-MEDICATION: NSAID

POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PL)
POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: NSAID

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	4392	92	2.09	7981.3	1.15	{ 0.93, 1.41}
	NO	4956	81	1.63	14148.9	0.57	{ 0.45, 0.71}
ENOXAPARIN / PLACEBO	YES	4422	64	1.45	7938.3	0.81	{ 0.62, 1.03}
	NO	5027	66	1.31	14161.4	0.47	{ 0.36, 0.59}

BAY 59-7939 (RIVAROXABAN) / PHASE III
PREVENTION OF VENOUS THROMBOEMBOLISM

GLOBAL INTEGRATED ANAL

TABLE 14.3.5/10.2.1
INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND
WITH CO-MEDICATION: OPIOID

POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PL)
POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: OPIOID

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	5714	130	2.28	8700.4	1.49	{ 1.25, 1.77}
	NO	4376	43	0.98	13429.7	0.32	{ 0.23, 0.43}
ENOXAPARIN / PLACEBO	YES	5738	93	1.62	8842.1	1.05	{ 0.85, 1.29}
	NO	4366	37	0.85	13257.6	0.28	{ 0.20, 0.38}

BAY 59-7939 (RIVAROXABAN) / PHASE III
PREVENTION OF VENOUS THROMBOEMBOLISM

GLOBAL INTEGRATED ANALYSE

TABLE 14.3.5/10.3.1
INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND EX
WITH CO-MEDICATION: STATIN

POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PLACE
POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: STATIN

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	1091	39	3.57	3359.0	1.16	{ 0.83, 1.59}
	NO	5189	134	2.58	18771.1	0.71	{ 0.60, 0.85}
ENOXAPARIN / PLACEBO	YES	1028	24	2.33	3028.6	0.79	{ 0.51, 1.18}
	NO	5268	106	2.01	19071.1	0.56	{ 0.46, 0.67}

BAY 59-7939 (RIVAROXABAN) / PHASE III
 PREVENTION OF VENOUS THROMBOEMBOLISM
 TABLE 14.3.5/10.4.1
 GLOBAL INTEGRATED ANALYSE
 INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND EX
 WITH CO-MEDICATION: NITRATE
 POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PLACE
 POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: NITRATE

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	258	8	3.10	663.6	1.21	{ 0.52, 2.37}
	NO	5932	165	2.78	21466.6	0.77	{ 0.66, 0.90}
ENOXAPARIN / PLACEBO	YES	283	7	2.47	586.7	1.19	{ 0.48, 2.46}
	NO	5962	123	2.06	21513.0	0.57	{ 0.48, 0.68}

BAY 59-7939 (RIVAROXABAN) / PHASE III
 PREVENTION OF VENOUS THROMBOEMBOLISM
 TABLE 14.3.5/10.6.1
 GLOBAL INTEGRATED ANALY
 INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND
 WITH CO-MEDICATION: CYP3A4 OR P-GP INHIBITORS
 POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PL
 POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: CYP3A4 OR P-GP INHIBITORS

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	465	12	2.58	1068.9	1.12	{ 0.58, 1.96}
	NO	5830	161	2.76	21061.3	0.76	{ 0.65, 0.89}
ENOXAPARIN / PLACEBO	YES	464	2	0.43	1019.4	0.20	{ 0.02, 0.71}
	NO	5859	128	2.18	21080.3	0.61	{ 0.51, 0.72}

BAY 59-7939 (RIVAROXABAN) / PHASE III
 PREVENTION OF VENOUS THROMBOEMBOLISM
 TABLE 14.3.5/10.5.1
 GLOBAL INTEGRATED ANALY
 INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND
 WITH CO-MEDICATION: PLAT.AGGR. INHIBITORS OR ASA
 POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PLA
 POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: PLAT.AGGR. INHIBITORS OR ASA

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	554	8	1.44	1025.6	0.78	{ 0.34, 1.54}
	NO	5983	165	2.76	21104.6	0.78	{ 0.67, 0.91}
ENOXAPARIN / PLACEBO	YES	518	5	0.97	843.6	0.59	{ 0.19, 1.38}
	NO	6014	125	2.08	21256.1	0.59	{ 0.49, 0.70}

The following table shows the relative rate of major or non-major clinically relevant bleeding events in subjects using the listed co-medication relative to non-use in both the rivaroxaban and enoxaparin groups from the RECORD studies.

In the rivaroxaban group, it suggests that patients with concomitant use of opioid and statin had 2.5 and 1.5-fold higher risk of major or clinical relevant non-major bleeding, respectively, as compared to those without use of these medications. The relative rate with use of opioids versus no use for major or non-major clinically relevant bleeding was nearly 2 fold on rivaroxaban (2.52) compared to enoxaparin (1.31). The relative rate with use of statin versus no use major or non-major clinically relevant bleeding was also higher on rivaroxaban (1.52) compared to enoxaparin (1.26).

Patients with concomitant use of NSAIDs, nitrates, platelet aggregation inhibitors or ASA, and CYP3A4 or Pgp inhibitors also had a slightly higher rate of major or clinical relevant non-major bleeding as compared to those without use of these medications in the rivaroxaban group but the increase was not statistically significant.

For concomitant use of CYP3A4 or Pgp inhibitors, the relative rate of major or clinical relevant non-major bleeding with use versus no use was 5-fold higher on rivaroxaban group (1.22) compared to enoxaparin (0.25). It was noted that only 2 subjects with bleeding event from the enoxaparin/placebo group under concomitant use of CYP3A4 or Pgp inhibitors. A total of 458 rivaroxaban subjects used a CYP3A4 inhibitor at any time during the study. The most common CYP3A4 inhibitors used were cimetidine (n = 118), diltiazem (n = 103), verapamil (n = 101), and amiodarone (n = 52). A total of 128 rivaroxaban subjects used a Pgp inhibitor at any time during the study. The most common Pgp inhibitor used was verapamil (n = 101).

For concomitant use of CYP3A4 or P-gp inhibitors, the rate ratio in the rivaroxaban group appears also higher for any bleeding (RR=1.41, 95% CI: 0.98 – 2.01) compared to the enoxaparin/placebo group (RR=0.83, 95% CI: 0.52 – 1.34).

For concomitant use of ‘platelet aggregation inhibitors or ASA’, the rivaroxaban group shows rate ratios comparable to the enoxaparin/placebo group for both bleeding endpoints.

The Relative Rate of Post-Tablet Major or Non-major Clinically Relevant Bleeding events per 100 Patient-Weeks with Use versus no Use of Concomitant Medications (Post-Tablet Safety Population)

Co-Medication	Rivaroxaban		Enoxaparin	
	% Patient-time exposed to co-medication	Relative Rate Use vs No use (95% CI)	% Patient-time exposed to co-medication	Relative Rate Use vs No use (95% CI)
NSAIDS	36%	1.28 (0.94 to 1.73)	36%	0.90 (0.63 to 1.28)
OPIOID	39%	2.52 (1.72 to 3.71)	40%	1.31 (0.87 to 1.96)
STATIN	15%	1.52 (1.07 to 2.17)	14%	1.26 (0.81 to 1.95)
NITRATE	3%	1.45 (0.72 to 2.94)	3%	1.71 (0.81 to 3.63)
ANTI-PLATELET	5%	1.11 (0.55 to 2.25)	4%	1.13 (0.47 to 2.75)
CYP3A4 or P-gp INHIBITOR	5%	1.22 (0.68 to 2.18)	5%	0.25 (0.06 to 1.02)

Source: Table: 14.3.5/11.1, PH-35415 5.3.5.3.4-4784

Note: Time under concomitant drug use or up to 2 days after the last intake of concomitant drug considered time of comedication use.

Note: Relative Rate (Rate Ratio) estimate stratified by time after surgery (Days 1-3, Days 4-7, and after Day 7)

7.6 Additional Safety Explorations

7.2.1 Human Carcinogenicity

The carcinogenicity studies in rat and mouse are ongoing.

7.2.2 Human Reproduction and Pregnancy Data

According to the sponsor, rivaroxaban has not shown any evidence of a primary teratogenic potential, but animal reproduction studies have shown pronounced maternal toxicity (e.g. hemorrhagic complications) with secondary effects on fetal development. Due to the intrinsic risk of bleeding and evidence that rivaroxaban crosses the placenta, and since in rats, rivaroxaban is secreted into breast milk, rivaroxaban is contraindicated in pregnant or nursing women. Pharmacology/Toxicology review is pending.

7.2.3 Pediatrics and Effect on Growth

The safety and effectiveness of rivaroxaban in pediatric patients has not been studied. The RECORD study protocols excluded subjects under the age of 18 years from clinical trials.

7.2.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There have been no reports of accidental or intentional overdose in the rivaroxaban clinical study program. Doses of up to 30 mg bid (a total of 60 mg per day) have been studied in Phase 2 studies. In a single-dose Phase 1 escalation study, a ceiling effect with no further increase in

average exposure was reached at a supra-therapeutic dose of 50 mg rivaroxaban even when taken with food. This effect is most probably the result of the limited solubility of rivaroxaban.

Overdose following administration of rivaroxaban may lead to hemorrhagic complications due to its pharmacodynamic properties. Administration of activated charcoal up to 8 hours after overdose may reduce the absorption of rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable. There are no specific antidotes available for rivaroxaban.

No potential for drug dependence or drug abuse has been noted for rivaroxaban.

No study has been conducted to evaluate the rebound effect of rivaroxaban treatment. In Phase 3 RECORD studies, during the off-treatment period, there were 17 (0.28%) cardiovascular events in the rivaroxaban group as compared to 14 (0.23%) in the enoxaparin group. Among those patients, 11 (66%) events (4 MI, 3 stroke and 4 cardiovascular death) in the rivaroxaban group and 2 (14%) events (1 cardiovascular death and 1 unexplained death) in the enoxaparin group occurred within 10 days after the last dose of treatment; 7 (41%) events (2 MI, 2 stroke, and 3 CV deaths) in the rivaroxaban group and 1 (7%) events (CV death) in the enoxaparin group occurred within 5 days after the last dose of treatment. There were more ischemic stroke events in the rivaroxaban group (6, 0.10%) than in the enoxaparin group (1, 0.02%) during the off treatment period. The earlier occurrence of cardiovascular events and a higher incidence of ischemic stroke during off-treatment raise concerns of possible rebound effect for rivaroxaban after the treatment is withdrawn.

7.7 Additional Submissions

N/A

8 Postmarketing Experience

According to 6-month Safety Update, since the approval of rivaroxaban (Xarelto®) in Canada on 16 September and in Europe on 30 September 2008, postmarketing surveillance with a data cutoff of 5 December, 2008, has identified 2 spontaneous cases of adverse experiences (both from Germany). These cases are described briefly below. An estimate of the total number of patients treated with rivaroxaban as of 5 December 2008 is not available.

Patient #200828853 [REDACTED], was a 70-year-old man with a history of arterial hypertension, type 2 diabetes mellitus, and gonarthrosis, who received 10 mg Xarelto for 9 days after knee total endoprosthesis surgery. The patient was also receiving ibuprofen and ibuhexal. On the 9th day of treatment, the patient experienced bleeding of the sigmoid colon (hemoglobin went from 9.4 g/dl to 7.2 g/dl), for which he received 2 to 3 units of packed red cells; Xarelto was discontinued. Additionally, the patient experienced an increase in renal parameters (laboratory data not provided), which improved after discontinuation of Xarelto and ibuprofen. An increased GGT was reported and was considered serious, but no relationship assessment is available. The physician considered the bleeding sigmoid colon and the increased renal values to be serious and

possibly related to Xarelto and ibuprofen, although the increase in renal laboratory values was also considered possibly related to ibuhexal.

Patient #200829844 (b) (4) was a 66-year-old man who was under treatment with Xarelto (duration of treatment and dose not available) and experienced perianal bleeding; Xarelto was withdrawn and bleeding stopped the next day. Two days later, the patient had a recurrence of perianal bleeding and he was advised to undergo an endoscopic colonoscopy/rectoscopy.

CLINICAL PHARMACOLOGY REVIEW

NDA	22-406
Drug Substance	Xarelto (rivaroxaban) tablets (Factor Xa inhibitor)
Applicant	Johnson & Johnson
Indication	Prophylaxis of DVT & PE
Type of Submission	Briefing document for Advisory Committee Meeting March 19, 2009
Date of Submission	N/A
Reviewer	Joseph A. Grillo, Pharm.D., Primary CP Reviewer Christoffer Tornoe, Ph.D. CP/PM Reviewer Rosane Charlab Orbach, Ph.D. CP/PG Reviewer

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EXECUTIVE SUMMARY

- Xarelto (rivaroxaban) is a competitive, selective, and direct oral Factor Xa inhibitor that can be orally administered.
- Dose-dependent inhibition of FXa activity and prolongation of the prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® were observed in humans. The offset of the pharmacodynamic effect (24-48 hours) parallels the pharmacokinetic half-life.
- The proposed dose of 10 mg qd is appropriate given the shallow ER relationship for effectiveness and steep increase in the risk of major bleeding with increasing total daily dose seen for rivaroxaban compared to enoxaparin.
- Clinically relevant increases in drug exposure and related toxicity are likely in the patients with renal impairment, hepatic impairment, and/or moderate/strong CYP3A4 or P-gp inhibitors. Clinically relevant pharmacodynamic drug interactions were noted when rivaroxaban was combined with either enoxaparin or clopidogrel.
- Given rivaroxaban's steep ER relationship for major bleeding and the risk of higher exposure in the special populations noted above, without the ability for downward dose adjustment a part of the target population will not be able to utilize this drug. FDA has recommended that the applicant develop a lower strength or scored 10 mg tablet.
- The absorption of rivaroxaban is almost complete at the proposed dose (T_{\max} 2-4 hours). The pharmacokinetics of rivaroxaban are linear up to 15 mg qd (no significant accumulation observed). Approximately 50% of an orally administered dose undergoes metabolic degradation by the CYP3A4/3A5 pathway, CYP2J2 pathway, and hydrolytic cleavage. The remainder is excreted unchanged via P-gp/BCRP-mediated, active, renal secretion (~36%) and in the feces (~7%). The half-life of rivaroxaban is 5-9 hours in healthy subjects.
- In healthy, elderly subjects (65-80 years of age), a higher rivaroxaban exposure was noted with terminal half-lives between 11 and 13 h. There were no clinically relevant differences in rivaroxaban exposure in studies evaluating the effect of body weight or sex on pharmacokinetics. Japanese subjects were found to have an apparent higher dose-normalized rivaroxaban exposure compared to other ethnic groups. The reason for this difference requires further exploration.
- Administration of the 10-mg rivaroxaban tablet with food suggests the absence of a significant food effect. Studies evaluating the effect of the concomitant use of an H_2 receptor antagonist or chelating agent (i.e., antacid) did not suggest a clinically relevant effect on rivaroxaban exposure.

BACKGROUND

Xarelto (rivaroxaban) is a competitive, selective, and direct oral Factor Xa (FXa) inhibitor that can be orally administered and is under development for the indication of prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing total hip replacement (THR) or knee replacement surgery. The proposed dosage regimen is 10 mg daily (QD) for 14 (knee) or 35 days (THR).

In vitro studies suggest rivaroxaban competitively inhibits human free FXa and also inhibits prothrombinase activity and clot-associated FXa activity. *In vitro* studies also reveal that the onset of inhibition of FXa activity appears rapid and that rivaroxaban is a reversible inhibitor, with a mean lifetime of 200 seconds. This appears to be agreement with the K_i of rivaroxaban for FXa.

1.1 Dose-Response Relationship

The efficacy of rivaroxaban was evaluated in over 6000 patients participating in 4 randomized clinical trials of prevention of venous thromboembolism (VTE) following THR (RECORD 1 & 2) or knee replacement (RECORD 3 & 4 studies) surgery. Rivaroxaban demonstrated superiority over the low molecular weight heparin enoxaparin in the primary endpoint (total VTE) in all four studies. There are no short term safety concerns from a clinical pharmacology perspective; however, safety signals suggesting possible hepatotoxicity were noted by the Clinical reviewer. Three deaths that may be related to hepatotoxicity have been reported. These deaths were in women > 60 years of age who received doses greater than proposed by the applicant. From a clinical pharmacology perspective, the potential for increased liver exposure of rivaroxaban in the setting of age induced renal insufficiency in these patients can not be ruled out. This safety issue is being extensively evaluated in the current pivotal trials and ongoing studies by the Clinical reviewer.

Dose-dependent inhibition of FXa activity and prolongation of the prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® were observed in humans. The relationship between prothrombin time and rivaroxaban plasma concentration appears linear. In general, prolongation of the prothrombin time reached half of the maximum effect within 0.5-1 hours and maximum effect within 2-4 hours after administration of a tablet. The offset of pharmacodynamic effect (24-48 hours) appears to parallel the pharmacokinetic half-life (i.e., 5 to 9 hours in healthy subjects).

There is clear evidence of an exposure-response (ER) relationship for the safety and effectiveness of rivaroxaban compared to enoxaparin using total daily dose as the predictor (Figure). The proposed dose of 10 mg qd is appropriate given the shallow ER relationship for effectiveness and steep increase in the risk of major bleeding with increasing total daily dose.

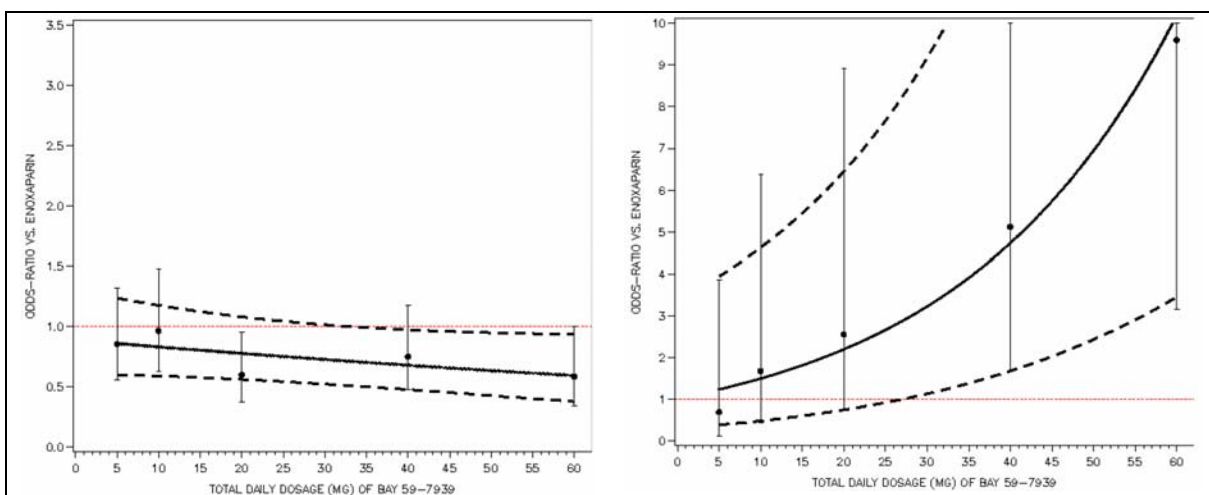


Figure 4: (Left) Total venous thrombotic events odds ratio curve of rivaroxaban vs enoxaparin and (Right) post-operative major bleeding odds ratio curve of rivaroxaban vs enoxaparin with total daily dose for studies 10942, 10944, and 10945-safety population.

Source: Applicant's Figure 4.3 and 5.1 in clinical overview on pages 41 and 64.

The applicant chose not to explore genetic differences that may affect the ER relationship because it states that known genetically determined deficiencies of factor X that might affect the response to rivaroxaban are rare. FDA agrees with this position in principle; however, other polymorphisms/mutations in coagulation factors and hemostasis-related genes may affect the ER relationship.

1.2 Effect of Rivaroxaban on the QTc

The applicant reports that it performed study, in accordance with International Conference on Harmonisation (ICH) E14 guidance, to evaluate the effect of rivaroxaban on the QTc and the results suggest that the potential for pro-arrhythmic risk unlikely. This conclusion is pending confirmation by the FDA Interdisciplinary Review Team for QT Studies (IRT).

1.3 Pharmacodynamic Drug Interactions

Several studies that evaluated rivaroxaban's potential to interact with other drugs that influence the coagulation system (i.e., pharmacodynamics) were submitted in support of this application. Co-administration of rivaroxaban with acetylsalicylic acid, naproxen, diclofenac, clopidogrel, or warfarin showed additive but not potentiating effects on bleeding time prolongation in a rat tail transection model. Confirmatory studies in humans suggest that coadministration of rivaroxaban with enoxaparin resulted in clinically relevant additive pharmacodynamic effects (~50% increase as measured by anti-Factor Xa assay). Increased bleeding time (approximately double) following concomitant administration of rivaroxaban and aspirin or naproxen was observed, but this does not appear to be clinically relevant.

Rivaroxaban in combination with clopidogrel does not appear to have a relevant effect on Factor Xa, PT, aPTT, and HepTest[®] as compared to rivaroxaban alone based on the

reports from two clinical studies. However, a clinically relevant increase in bleeding time was noted in both of these studies. One study reported a clinically relevant increase in 6/14 subjects receiving combined therapy (i.e., 4.8 to 8.5 fold change). Increased inhibition of thrombocyte aggregation was reported with combined treatment in comparison to rivaroxaban alone. In a follow up study a ~6 fold increase in bleeding time was noted in 4/13 subjects following concomitant administration of rivaroxaban and clopidogrel. The remaining 9/13 subjects in this study exhibited similar bleeding times to control. Rivaroxaban exposure, platelet aggregation, P-selectin, or GPIIb/IIIa receptor levels did not appear to correlate with the higher bleeding time reported in this study. The applicant did not address potential pharmacogenomic causes which warrant further investigation.

PHARMACOKINETICS

Population models of the pharmacokinetics of rivaroxaban suggest it is best described by an oral, two-compartment model with elimination from the central compartment. Rivaroxaban appears to exhibit linear pharmacokinetics up to 15 mg and shows no significant accumulation following repeat dosing. Interindividual variability (coefficient of variation) reported in the pharmacokinetics studies submitted in support of this application ranges from 30% to 40%.

1.4 Distribution

The volume of distribution at steady-state (V_{ss}) is approximately 50 L (0.62 L/kg). Rivaroxaban is characterized *in vitro* as a substrate of both P-glycoprotein (P-gp) and the active transport protein “breast cancer resistance protein” (BCRP). It is highly bound to plasma proteins (92% to 95%) and appears to exhibit reversible binding that is not concentration dependent. Albumin is the main binding component. Displacement of rivaroxaban from protein binding sites (*in vitro* at therapeutic rivaroxaban concentrations in human plasma) was observed at high salicylic acid concentrations (corresponding to single oral doses of 4 – 5 g aspirin orally). This resulted in a ~12% increase of fraction unbound that does not appear to be clinically relevant. The human plasma-to-blood partition coefficient is 1.40.

1.5 Metabolism

Rivaroxaban is expected to exhibit almost complete absorption following administration of a 10 mg tablet (~80% to 100%). Approximately 50% of an orally administered dose undergoes metabolic degradation (CYP3A4/3A5 (~18%), CYP2J2 (~14%), and hydrolytic cleavage (~14%) based on *in vitro* studies), and the rest is excreted unchanged via P-gp/BCRP mediated active renal secretion (~36%) and in the feces (~7%). The terminal half-life of rivaroxaban is approximately 5-9 hours in healthy subjects and 11-13 hours in the healthy elderly. The average systemic plasma clearance of rivaroxaban is approximately 10 L/h and appears to lack significant first-pass extraction.

1.6 Excretion

In the [^{14}C]rivaroxaban mass balance study, about 94% of the radioactive dose administered was recovered in the excreta within 7 days following administration of a 10

mg solution (45.8 μ Ci). Urinary excretion accounted for approximately 66% of the total dose, and approximately 36% of the dose is excreted as unchanged active drug. Fecal/biliary excretion accounted for approximately 28% of the total dose. Unchanged drug was the main compound in circulating plasma.

1.7 Population-Based Approaches

Population approaches to describe rivaroxaban pharmacokinetics (pop-PK) have been prospectively implemented into the applicant's clinical development program. Although differently reflected in the various pharmacokinetics models, the important patient covariates identified to influence rivaroxaban pharmacokinetics were: 1) Renal function (creatinine clearance) was found to affect rivaroxaban clearance and 2) Body weight was a significant covariate for rivaroxaban volume of distribution.

EXTRINSIC AND INTRINSIC FACTORS AFFECTING PHARMACOKINETICS AND PHARMACODYNAMICS

The extrinsic and intrinsic factors affecting rivaroxaban pharmacokinetics and pharmacodynamics are summarized in Table 4 below.

Table 4: ANOVA results – Point estimates and 90% confidence intervals for pharmacokinetic parameters, percent inhibition of Factor Xa activity and relative prolongation PT (values are Test/Reference).

Reference	Test	AUC(0-t _n)	C _{max} or E _{max}
Pharmacokinetics			
Renal impairment			
subjects with normal renal function	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)
Hepatic impairment			
subjects with 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)
Drug interactions			
<u>strong inhibitors of both CYP3A4 and P-gp</u>			
RIVA 10 mg alone	RIVA + ritonavir 600mg tid	2.53 (2.34 - 2.74)	1.55 (1.41 - 1.69)
	RIVA + ketoconazole 400mg od	2.58 (2.36 - 2.82)	1.72 (1.61 - 1.83)
	RIVA + ketoconazole 200mg od	1.82 (1.59 - 2.08)	1.53 (1.27 - 1.85)
<u>strong inhibitor of CYP3A4 and weak-to-moderate inhibitor of P-gp</u>			
RIVA 10 mg alone	RIVA + clarithromycin 500mg bid	1.54 (1.44 – 1.64)	1.40 (1.30 – 1.52)
<u>weak-to-moderate inhibitor of CYP3A4 and P-gp</u>			
RIVA 10 mg alone	RIVA + erythromycin 500mg tid	1.34 (1.23 - 1.46)	1.38 (1.21 - 1.48)
Percent inhibition of Fxa			
Renal impairment			
subjects with normal renal function	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 (0.991-1.27)
Hepatic impairment			
subjects with 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 PT			
Renal impairment			
subjects with normal renal function	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)
Hepatic impairment			
subjects with 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)	1.401 (1.28–1.54)

Fxa: Factor Xa; CL_{CR}: creatinine clearance; PT: prothrombin time; RIVA: rivaroxaban
A 10-mg rivaroxaban dose was used in the different studies.

Source: Applicant's Table 2 in fda-response-05-dec-2008.pdf

1.8 Extrinsic Factors

Seventeen drug-drug interaction studies were submitted in support of this application and the relevant finding are outlined in Table 4. Given rivaroxaban is eliminated via both metabolism and active renal secretion of unchanged drug, the effect of CYP3A4/weak P-

gp inhibitors (e.g., erythromycin) and pure P-gp inhibitors (e.g., digoxin) did not result in clinically relevant changes in rivaroxaban exposure. Also, studies evaluating the concurrent use of rivaroxaban with CYP3A4 substrates (e.g., midazolam) or CYP3A4/P-gp substrates did not result in a clinically relevant change in exposure. However, studies evaluating the effect of moderate or strong inhibitors of both metabolism (i.e., CYP3A4) and active secretion (i.e., P-gp and BCRP) suggest a clinically relevant increase in systemic exposure and relevant pharmacodynamic parameters of rivaroxaban. The concomitant use of rivaroxaban with strong CYP3A4/P-gp inducers was also evaluated by the applicant. In this study, the strong CYP3A4 and P-gp inducer rifampicin led to a significant decrease in rivaroxaban elimination half-life and exposure by approximately 50%. In addition, reduced pharmacodynamic effects of rivaroxaban (i.e., inhibition of Factor Xa activity and prolongation of PT, aPTT and HepTest read-out) were noted compared to rivaroxaban alone.

The applicant did not explore genetic differences in metabolism because it believes they are unlikely to be of clinical significance for rivaroxaban because rivaroxaban elimination is not dependent on one single route of elimination. While FDA agrees in principle, it notes that polymorphisms in CYP3A4, CYP3A5, CYP2J2, P-gp, & BCRP have been described.

1.9 Intrinsic Factors

Renal Impairment

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 (C_{max} and AUC) was increased and the overall inhibition of FXa activity was increased by 1.5-, 1.9- and 2.0-fold respectively, compared to healthy subjects with normal renal function (creatinine clearance >80 mL/min). In addition, the increased overall exposure was associated with an increased sensitivity of prothrombin time prolongation. It is important to note that patients with creatinine clearance <15 mL/min were not studied. The unbound fraction of rivaroxaban did not appear to be affected by renal impairment. The potential effect of concurrent renal impairment and the use of a moderate/strong CYP3A4 inhibitors on rivaroxaban exposure is of particular concern given this interaction can result in an increased exposure greater than the sum of its parts and this interaction was not evaluated or modeled by the applicant.

Hepatic Impairment

Cirrhotic subjects with mild liver impairment (Child-Pugh Grade A) exhibited ~1.2 fold increase for AUC and related pharmacodynamics, which were comparable to the healthy control group. In cirrhotic subjects with moderate hepatic impairment (Child-Pugh Grade B with baseline prothrombin time prolongations), rivaroxaban plasma concentrations (2.3 fold for AUC on average) and related pharmacodynamic effects were significantly increased compared to subjects with normal hepatic function. Cirrhotic subjects with severe hepatic impairment (Child Pugh Grade C) were not studied. The unbound fraction

of rivaroxaban was not consistently altered by hepatic impairment and is considered inconclusive.

Age

In healthy elderly subjects (65-80 years of age) higher mean rivaroxaban AUC values were observed in males (52%) and females (39%) when compared to young subjects of the same sex. This was accompanied by an increase in C_{\max} by 35% in both sexes and terminal half-lives between 11 and 13 h. Observations in subjects older than 75 years confirmed these results, showing approximately 41% higher AUC values in comparison to young subjects. This difference is likely due to reduced (apparent) total body clearance and renal clearance.

Ethnicity and Other Factors

Differences in rivaroxaban exposure was observed between the various investigated ethnic groups (i.e., Caucasian, African-American, Hispanic, Japanese, and Chinese, were evaluated). Japanese subjects were found to have an apparent higher dose-normalized rivaroxaban C_{\max} and AUC compared to other ethnic groups (see Figure 5).

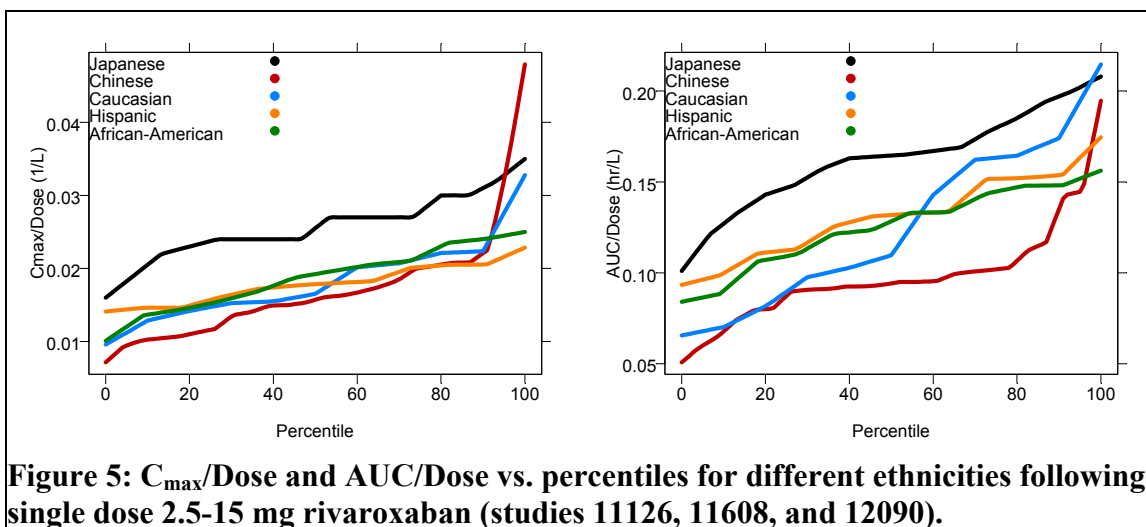
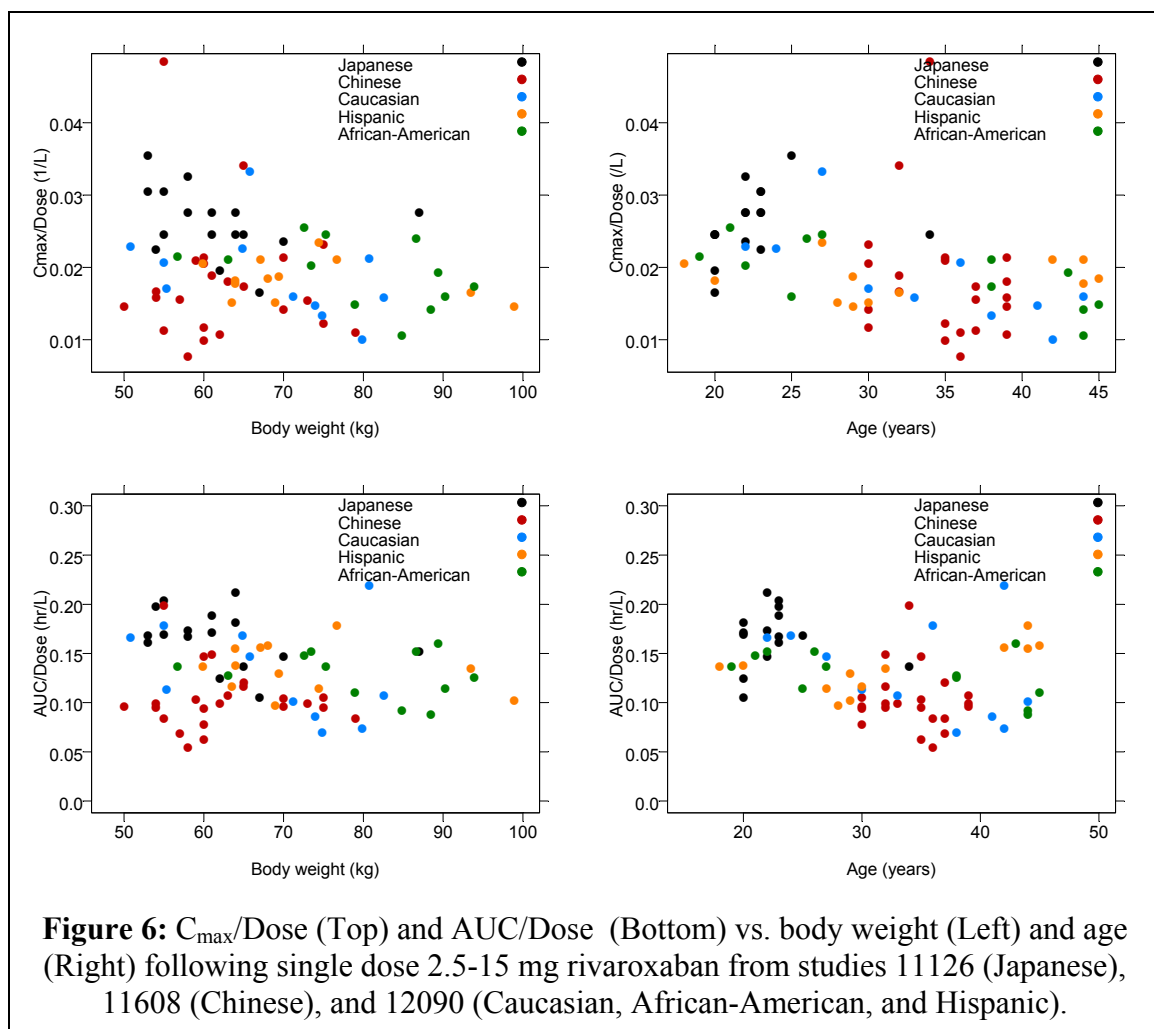


Figure 5: C_{\max}/Dose and AUC/Dose vs. percentiles for different ethnicities following single dose 2.5-15 mg rivaroxaban (studies 11126, 11608, and 12090).

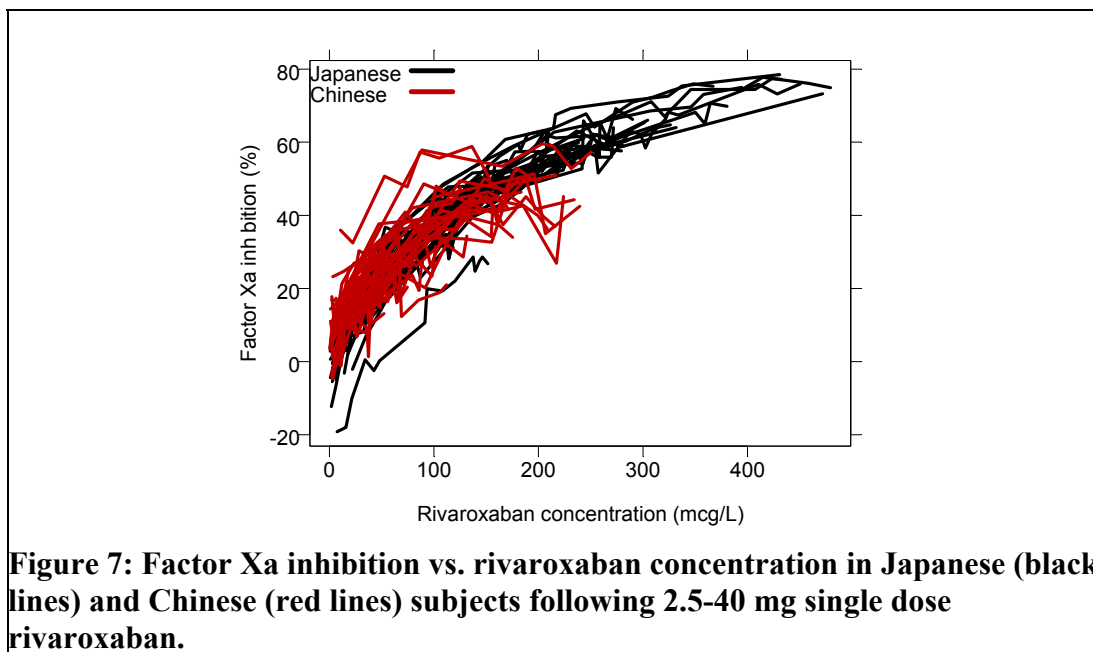
The only differences in demographic covariates for Japanese compared to other ethnicities are body weight and age where the Japanese were the youngest and lightest subjects potentially explaining the higher exposure (see Figure 6). However, the median exposure in Japanese was approx. 50% higher compared to Chinese subjects weighing the same as Japanese. The Japanese were approximately 10 years younger than the Chinese (mean age of 23 and 34 years for Japanese and Chinese subjects in studies 11126 and 11608, respectively). One would expect the younger Japanese subjects to clear the drug faster since age was found to be a covariate for clearance in the population PK analysis using phase 2 and 3 data and thus have lower exposure (AUC). However, the opposite finding was observed in studies 11126 and 11608 where Japanese subjects have approx. 50% higher median $C_{max}/Dose$ and $AUC/Dose$ compared to the Chinese. In conclusion, the observed differences in exposure between Japanese and other ethnicities are unlikely due to demographic differences but rather inter-ethnicity differences.



These findings are not due to outliers, as almost all Japanese dose-normalized C_{max} and AUC percentiles were higher than for the other ethnic groups.

No inter-ethnicity differences were identified for Factor Xa inhibition between Japanese (study 11126) and Chinese (study 11608) subjects after adjusting for exposure

differences following 10 mg single dose rivaroxaban (see Figure 7). This further suggests that the ethnicity pharmacokinetics differences are not due to assay or study differences since the same pharmacokinetic/pharmacodynamic relationship is observed in Japanese and Chinese subjects. FDA has requested that the applicant provide an additional explanation (including potential pharmacogenetic differences) for the higher exposure in the Japanese population.



1.10 Safety of Proposed Single Strength Formulation in Light of Extrinsic and Intrinsic Factors

The applicant is currently proposing to market only a single unscored 10 mg tablet of rivaroxaban. As described above, clinically relevant increases in drug exposure and related pharmacodynamics are likely in the patients with renal impairment, hepatic impairment, and/or moderate/strong CYP3A4 or P-gp inhibitors. Further, a steep ER relationship for rivaroxaban (Figure) for major bleeding draws additional concern. Information submitted by the applicant (Table 5) indicates a greater than 4 fold increase in major bleeding (0.7% vs. 4.3%) when exposure is increased two fold from the proposed dose. This suggests that even a 1.5 fold increase in exposure may double the risk of major bleeding.

Table 5: Incidence of Total VTE, Major VTE , Major Bleeding and Any Bleeding Events by Dose Group (Phase 2 Once-Daily Study 11527)

Outcome	RIVA 5 mg od n/N (%)	RIVA 10 mg od n/N (%)	RIVA 20 mg od n/N (%)	RIVA 30 mg od n/N (%)	RIVA 40 mg od n/N (%)	ENOX 40 mg od 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; od = once daily; RIVA = rivaroxaban

Major bleeding events are defined as a fatal bleeding event, 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, or clinically overt extrasurgical site bleeding leading to transfusion of ≥ 2 units of whole blood or packed cells.

Source: Applicant's Table 1 in *fda-response-05-dec-2008.pdf*

Therefore, without the ability for downward dose adjustment it is apparent that a part of the target population will not be able to utilize this drug and inappropriate use of the current strength in these special populations could pose an additional risk for medication error. Since there is very little accumulation with 10 mg qd dosing of rivaroxaban, it is not possible to lower the daily exposure in these patients by shifting from daily (QD) to every other day (QOD) dosing (see Figure 8). Therefore FDA has recommended that the applicant develop a lower strength or scored 10 mg tablet (makes tablet splitting possible) to make downward dose adjustments possible in patients with increased exposure due to intrinsic and extrinsic factors.

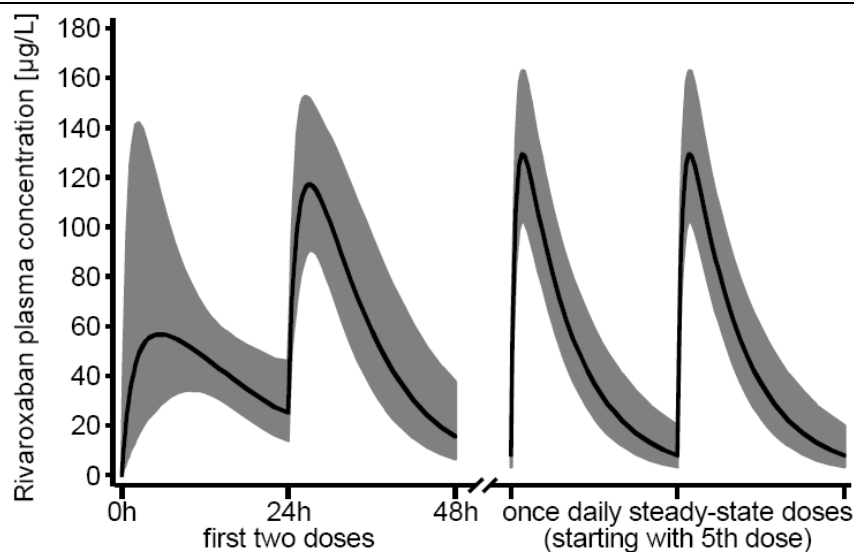


Figure 8: Rivaroxaban plasma-concentration vs time profile for the 10 mg od dosing regimen used in OdIXa-HIP OD trial [geometric mean/SD of individually posthoc estimated plasma concentration/time curves; n=131-140] (Study PK000131).

Source: Applicant's Figure 3.7 in clinical pharmacology summary on pages 187.

BIOPHARMACEUTICS

1.11 Absorption, Bioavailability and Relative Bioequivalence

According to the criteria of the Biopharmaceutical Classification System (BCS), rivaroxaban is a low solubility, high permeability compound (ie, Class 2). At this time the sponsor is proposing to market the 10 mg strength tablet only. Although the relative bioavailability of the 10 mg tablet was not studied, the applicant's estimate of 80% to 100% appears reasonable given information regarding the absolute bioavailability of the 5 mg tablet and dose ranging studies suggesting dose proportionality at doses less than 15 mg.

The absolute bioavailability of the 5-mg tablet dose compared to intravenous administration appears complete (112%) based on AUC. The bioavailability of the 5-mg tablet relative to the oral solution was close to 100% based on AUC, but the C_{max} was only 50% and related pharmacodynamic effects were more pronounced after administration of the solution. In addition, the BA for a 20 mg strength tablet is 66%. The applicant suggests this discrepancy may be related to a decrease in absorption as a result of the limited aqueous solubility of rivaroxaban (rivaroxaban solubility (5 – 7 mg/L, pH-independent). Given the nonlinearity seen at higher doses of the phase 1 dose ranging studies, flip-flop pharmacokinetics is possible but still unconfirmed. Although the relative bioavailability of the 10 mg tablet was not studied, the applicant's estimate of 80% to 100% appears reasonable given information regarding the absolute bioavailability of the 5 mg tablet and dose ranging studies suggesting dose proportionality at doses less than 15 mg.

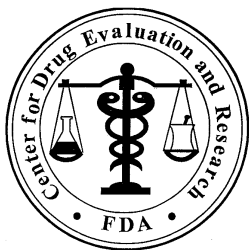
Following oral administration of 5 – 10 mg solution the T_{\max} of rivaroxaban is approximately 30 min and approximately 2 – 4 h following the administration of a 1.25 to 80 mg as tablet. Particle size does not appear to effect rivaroxaban exposure. Preliminary reports suggest absorption is dependent on the site of drug release in the GI tract with moderately lower concentrations reported when the drug is released as granules in proximal small intestine, distal small intestine, and ascending colon.

1.12 Food effect and Other Extrinsic Factors

Administration of the proposed 10-mg rivaroxaban tablet with food (high-calorie/high-fat meal) suggests the absence of a significant food effect at this dose. However, after multiple once- and twice-daily doses administered with food, more complete absorption of these higher strength tablet formulations (e.g., 20 mg or greater) that are not planned to be marketed at this time. The effect of changes in gastric pH (i.e., H_2 receptor antagonist ranitidine, 150 mg bid) or concomitant use of chelating agents (i.e., the antacid aluminum hydroxide / magnesium hydroxide (Maalox[®]), 10 ml) on rivaroxaban exposure (30 mg single dose) were evaluated in healthy volunteers. The results of these studies did not suggest a clinically relevant drug interaction, based on the pharmacokinetic and pharmacodynamic parameters reported. It is important to note; however, that these studies were conducted using the 30 mg strength. In light of the differences seen between the absorption of tablet strengths greater than 15 mg, this information regarding the proposed 10 mg strength can not be considered conclusive.

1.13 Analytical Methods

Bioanalytical methods used to for the qualification and quantification of rivaroxaban in human plasma and urine used in the clinical pharmacology and biopharmaceutics studies submitted in support of this application appear to have been appropriately validated.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 13, 2009
To: Rafel (Dwayne) Rieves, M.D., Director
Division of Medical Imaging and Hematology Products (DMIHP)
Through: Solomon Iyasu, M.D., M.P.H. Director
Division of Epidemiology (DEPI)
Office of Surveillance and Epidemiology (OSE)
From: Kate Gelperin, M.D., M.P.H.
Medical Epidemiologist
Division of Epidemiology
Subject: Ongoing evaluation of potential severe liver injury signal in
rivaroxaban clinical trials
Drug Name(s): Rivaroxaban, BAY 59-7939
Submission Number: NDA 22-406 submitted in July 2008
Application NDA 22-406
Type/Number:
Applicant/sponsor: Bayer/Johnson & Johnson
OSE RCM #: 2008-2019

1 INTRODUCTION

This review follows a request from the Division of Medical Imaging and Hematology Products (DMIHP) to review and comment on a potential signal for severe drug-induced liver injury identified by the OND medical reviewer during the mid-cycle review process, and to provide relevant background information regarding previous regulatory experience with hepatotoxicity signal detection, assessment, and subsequent considerations of the balance of potential therapeutic benefit(s) versus defined hepatotoxicity risk(s).

Rivaroxaban (BAY 59-7939) is a highly selective direct factor Xa inhibitor with oral bioavailability. There are three active INDs for rivaroxaban: IND 64,892 (VTE); IND 75,931 (ACS); and IND 75,238 (A Fib). The proposed indication for the current application is prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. The proposed dose is 10 mg once daily.

2 MATERIAL REVIEWED

The following materials were considered for this review:

- Dr. Min Lu's FDA mid-cycle clinical review slides dated December 2, 2008
- Proposed package insert dated July 28, 2008
- Sponsor's laboratory datasets submitted to FDA January 22 and 30, 2009
- Cases reviewed by Sponsor's expert panel (LAP), Miami, February 17-18, 2008
- Sponsor's ISLS 6-month Safety Update dated February 2, 2008; Document No. EDMS-PSDB-9405338:2.0

3 RESULTS OF REVIEW

3.1 Overview of Clinical Program

The rivaroxaban clinical program (excerpted from Dr. Min Lu's mid-cycle review slides with cut-off date September 10, 2008) includes the following:

- **Completed studies:** N=10,600 (Rivaroxaban exposure)
 - 4 phase 3 studies (RECORD 1-4): n=6183
 - 9 phase 2 studies: n=3300 (2 VTE Tx and 3 AF)
 - 51 phase 1 studies: n=1117
- **Ongoing studies:** N=16,965 enrolled (as of September 10, 2008); N=34,236 planned
 - 5 phase 3 studies:
 - 2 VTE Tx: n=3160 enrolled, n=7500 planned
 - 2 AF: n=10,008 enrolled, n=15,200 planned
 - 1 Medically ill: n=316 enrolled, n=8000 planned
 - 1 phase 2 study: ACS n=3462 enrolled, n=3500 planned
 - 1 phase 1 study: CHF n=19 enrolled, n=36 planned

3.2 FDA Safety Concerns – Potential Severe Liver Injury

3.2.1 Safety issue identified during rivaroxaban mid-cycle review

The DMIHP medical officer's mid-cycle review identified a major concern with potential severe and/or fatal drug-induced liver injury with rivaroxaban. In the completed studies, severe liver injury (defined as a concurrent increase of total bilirubin [TBL] >2x ULN and alanine aminotransferase [ALT] >3x ULN) was observed in 14/9310 (0.15%) rivaroxaban-treated patients, and 9/7001 (0.13%) patients in comparator groups, as described in Dr Lu's review. Seven cases of severe liver injury in the RECORD studies were considered to be possibly related to rivaroxaban therapy by at least one member of the sponsor's expert panel of hepatologists.

Members of the sponsor's expert panel of hepatologists considered that some cases of severe liver injury in completed and ongoing clinical trials, including at least two deaths, were possibly related, or of uncertain relationship to rivaroxaban. As presented in the mid-cycle clinical review, at least two cases of fatal liver injury for which a possible contribution of rivaroxaban has not been ruled out occurred after fewer than 30 days of drug exposure.

3.2.2 Previous FDA experience with signal detection for severe liver injury with anticoagulant drug development for short-term versus long-term indications

Previous FDA experience with assessment of severe drug-induced liver injury due to ximelagatran, an anticoagulant drug (direct thrombin inhibitor) developed for similar indications, found no cases of severe liver injury in the short-term (orthopedic) clinical trials; however, a strong signal was subsequently identified in long-term (atrial fibrillation) trials.

After full evaluation of the signal, it was determined that 37/6948 (0.5%) ximelagatran-treated patients experienced severe liver injury versus 5/6230 (0.08%) patients randomized to warfarin (relative risk 6.6; 95% confidence interval 2.6 – 16.9). An expert causality assessment of severe liver injury cases was conducted by the sponsor, and determined that study drug may have caused or contributed to the severe liver injury in 19/6948 ximelagatran-treated patients compared to 2/6230 patients in the comparator groups (relative risk 8.5; 95% confidence interval 2.0 – 36.6).

Although a signal for severe liver injury was not detected in short-term orthopedic trials with ximelagatran, analysis of long-term data showed that initial signs of liver injury were observed within the first 30 days of ximelagatran administration for six study subjects who went on to develop severe liver injury, of which four cases were considered by the sponsor to be causally related to ximelagatran administration.

A full consideration of the balance of drug benefit(s) versus risk of severe or fatal liver injury was conducted at a public Advisory Committee meeting, which determined that potential benefits of ximelagatran did not outweigh the risks. Based on this decision, the drug was not approved in the US, and subsequently the sponsor decided to withdraw ximelagatran from marketing worldwide.

3.3 Laboratory Datasets from Ongoing Rivaroxaban Clinical Trials (blinded data)

Initial inspection of clinical laboratory datasets by Dr. Ted Guo (biostatistician) from ongoing clinical trials received from the sponsor on January 30, 2009 show the following counts of cases (numbers of patients) of potential severe liver injury in ongoing clinical trials (defined as concurrent maximum ALT >3x ULN and maximum TBL >2x ULN). Please note that there were multiple measurements over the course of the trial for each patient. The greatest values of ALT and TBL of the patient were used to determine potential severe liver injury. Missing data in ALT and TBL did not affect the values of the maximum ALT and TBL. The effect of missing data has not been investigated. Therefore, these patient counts are preliminary, and current findings could potentially be somewhat biased.

Open-label long-term EINSTEIN DVT/PE (Study #11702) – ongoing

Treatment	#Patients	Mean Rx Duration in days	# Cases potential severe liver injury in available data
BAY 59-7939	1682	150	3
ENOXAPARIN 1 mg/kg s.c. / Vitamin K-antagonist p.o.	1673	154	1

Blinded long-term ROCKET-AF (Study #11630; comparator warfarin) – ongoing

Treatment labeled as	#Patients	Mean Rx Duration in days	# Cases potential severe liver injury in available data
Dummy A (BLINDED)	5495	233	8
Dummy B (BLINDED)	5492	229	12

Blinded long-term J-ROCKET-AF (Study #12620; comparator warfarin) – ongoing

Treatment labeled as	#Patients	Mean Rx Duration in days	# Cases potential severe liver injury in available data
BLINDED	1185	201	3

4 DISCUSSION

Instances in clinical trials (even very few of them) of transaminase elevation accompanied by elevated bilirubin (in the absence of biliary obstruction), have been associated with, and have often predicted, post-marketing serious liver injuries (fatal or requiring transplant). Drug-induced hepatocellular jaundice is considered a serious lesion, with an estimated mortality of at least 10%. The reason is that hepatocellular injury great enough to interfere with bilirubin excretion involves a large fraction of the liver cell mass.

An FDA Office of Drug Safety review which was included in the background package for the ximelagatran Advisory Committee meeting in September 2004 is included for reference as an appendix to this memo.

5 RECOMMENDATIONS

A potential signal for severe liver injury associated with rivaroxaban therapy has not been fully characterized at this time. Complete risk assessment, fully evaluating safety data from long term clinical trials, should be undertaken in order to inform decisions about the balance of therapeutic benefit versus risk with rivaroxaban.

APPENDIX—DRUG-INDUCED LIVER INJURY

A. Brief regulatory history: withdrawals and risk management

During the past ten years, two drugs, DURACT (bromfenac) and REZULIN (troglitazone), have been withdrawn from marketing in the US because they were associated with an unacceptable risk of severe drug-induced liver injury (DILI) in the absence of a clear counter-balancing benefit. In both cases, attempts were made to manage the risk of hepatotoxicity while keeping the drug available for therapeutic use. In the case of bromfenac, approved by FDA in 1997 for use as a short-term analgesic (ten days or less), severe DILI was generally observed only in patients who took the drug for more than 30 days,⁴⁷ however, despite attempts to regulate the duration of therapy by clear statements in product labeling, prescribers did not adequately heed this information and more than 50 cases of severe DILI were reported, prompting market withdrawal in 1998. In the case of troglitazone, approved by FDA in 1997 for glucose control in patients with type 2 diabetes, reports of fatal liver injury received by FDA shortly after marketing prompted a black box warning and a series of Dear Healthcare Professional letters recommending monthly transaminase monitoring. Despite these measures, transaminase monitoring was not regularly performed.⁴⁸ Moreover, in some patients, liver injury still progressed to fatal liver failure despite stopping the drug in response to monthly transaminase monitoring due to rapid progression of liver injury to a state of irreversibility.⁴⁹ Troglitazone was withdrawn from the US market in March 2000, after 94 cases of drug-induced liver failure had been reported, most of which were fatal. A more complete discussion of troglitazone is provided in Section D of this Appendix, under the heading Specific Examples.

Also during the past ten years, there have been instances where regulatory action prompted by concern about severe DILI included risk management actions which stopped short of market withdrawal. Examples include CYLERT (pemoline) and TROVAN (trovafloxacin).

Pemoline was approved by FDA in 1975 for ADHD with recommendations in the Precautions section to monitor transaminase levels periodically due to a 1% to 2% incidence of drug-induced liver injury. Reports of acute liver failure (ALF) led to a series of black box warnings and Dear Healthcare Professional letters in 1996 and 1999, shifting the drug to second line therapy and recommending baseline and bi-weekly transaminase monitoring. Although compliance with these recommendations was assessed to be poor,⁵⁰ the use of pemoline dropped off substantially over the next five years,⁵¹ and no additional drug-related cases of liver failure were subsequently reported to FDA.⁵²

⁴⁷ Fontana RJ, McCashland TM, Benner KG, et al. Acute liver failure associated with prolonged use of bromfenac leading to liver transplantation. *Liver Transpl Surg* 1995;5:480-4.

⁴⁸ Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess M. Liver enzyme monitoring in patients treated with troglitazone. *JAMA* 2001;286:831-33.

⁴⁹ Graham DJ, Green L, Senior JR, Noujeh P. Troglitazone-induced liver failure: a case study. *Am J Med* 2003;114:299-306.

⁵⁰ Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A study of compliance with FDA recommendations for pemoline (Cylert). *J Am Acad Child Adolesc Psychiatry* 2002, 41(7):785-790.

⁵¹ FDA/CDER/ODS/DSRCS Review of the Proposed Risk Management Communication Plan for Cylert (pemoline) dated January 16, 2004.

⁵² Racoosin JA. FDA/CDER/Division of Neuropharmacological Drug Products (HFD-120) memorandum to Patient Information Sub-Committee Members, dated February 6, 2004.

Trovafloxacin (a fluoroquinolone antibiotic) received FDA approval in 1997. During the first two years of marketing in the US, there were over 100 cases of clinically symptomatic liver toxicity, including 14 cases of ALF. An analysis of drug utilization based on data from IMS Health, National Disease and Therapeutic Index™ (NDTI™)⁵³ showed that during the period from 1998 to 1999, approximately 91% of trovafloxacin prescriptions were for five days or longer, with only about 5% of prescriptions for 20 days or longer.⁵⁴ A lag was noted between completion of trovafloxacin therapy and onset of liver symptoms in six of 14 probable ALF cases, which ranged from five to 20 days.⁵⁵ Survival analysis was conducted on the spontaneous reports, and showed that the relative risk of ALF with trovafloxacin was elevated from the start of therapy, and increased with increasing duration of exposure.⁵⁶ A Public Health Advisory in 1999 warned about severe hepatotoxicity, restricted use to certain very severe infections, and announced that the manufacturer would restrict trovafloxacin distribution to inpatient facilities only.⁵⁷

Examples of drugs never marketed in the US because of hepatotoxicity include ibufenac, perhexilene, dilevalol (a beta blocker), tasosartan (an angiotensin II receptor antagonist), and Fialuridine (FIAU).⁵⁸ In the case of dilevalol, the application was refused in 1990 based on findings of >3x ULN transaminase elevations and modest bilirubin elevation (>2 mg/dL) in a few patients, accompanied by an increased incidence of 3-fold transaminase elevation compared to placebo.⁵⁹

B. Range of issues: timing, tempo and reversibility of hepatotoxicity

Drug-induced liver injury is an important cause of fulminant liver failure. The Acute Liver Failure Study Group found that, between 1998 and 2000, 52% of all cases of ALF in the United States were due to drug-induced liver injury.⁶⁰

Drug-induced liver disease can be predictable (dose-related, occurring at doses exceeding recommendations) or unpredictable (idiosyncratic, and occurring in susceptible individuals at usual therapeutic doses).⁶¹ Idiosyncratic liver injuries occur with a pattern that is consistent for each drug and for each drug class.⁶²

⁵³ IMS Health, National Disease and Therapeutic Index, 1998-March 1999, extracted 6/99.

⁵⁴ FDA/CDER/OPDRA/DDRE Review of Trovan® (trovafloxacin and alatrofloxacin) and acute liver failure, dated July 12, 1999.

⁵⁵ *ibid.*

⁵⁶ *ibid.*

⁵⁷ Public Health Advisory (1999) Trovan (trovafloxacin / alatrofloxacin mesylate) and risk of liver failure. FDA June 9, 1999. Available from: <http://www.fda.gov/cder/news/trovan/trovan-advisory.htm>

⁵⁸ Center for Drug Evaluation and Research (CDER). Drug-induced liver toxicity. Clinical White Paper. November 2000. (Accessed June 1, 2004, at <http://www.fda.gov/cder/livertox/default.htm>.)

⁵⁹ *ibid.*

⁶⁰ Ramkumar D, LaBrecque DR. Drug-induced liver disease and environmental toxins. In: Hepatology A Textbook of Liver Disease. Fourth Edition. Zakim D and Boyer TD, (Eds.) Saunders, Philadelphia, 2003.

⁶¹ *ibid.*

⁶² Lee WM. Drug-induced hepatotoxicity. *N Engl J Med* 2003;349:474-85.

As Lee has proposed in a recent review of drug-induced liver injury,⁶³ most idiosyncratic drug reactions result from a succession of unlikely events, a “multihit” process. This implies that a “series of events that first involve intracellular disruption, cell necrosis, or apoptosis, followed by activation of the immune sequence, might explain the features of idiosyncratic drug reactions: their rarity, their severity, and their resolution despite continued use of the drugs by patients with phenotypes that appear to be adaptive.”⁶⁴

Timing: Risk vs. duration of treatment (hazard rate over time)

Idiosyncratic reactions are characterized by a variable delay or latency period, typically ranging from 5 to 90 days from the initial ingestion of the drug, and are frequently fatal if the drug is continued once the reaction has begun.⁶⁵ The relationship of onset of liver injury with duration of drug exposure is not predictable. An increased risk of severe DILI has been found to be positively associated with increasing duration of therapy for several drugs including trovafloxacin,⁶⁶ troglitazone,⁶⁷ pemoline,⁶⁸ and bromfenac.⁶⁹

Tempo and reversibility of injury

The range of tempos of injury is a characteristic both of individual drugs and patients. Rapid acceleration of liver injury in some individuals may preclude an absolute protective value of standardized periodic transaminase monitoring.⁷⁰

A key issue in effective intervention to prevent fatal liver injury is “recoverability” at time of sign or symptom onset. This refers to a “point of irreversibility”, after which there is an inexorable progression to liver failure and often death. The contrast between isoniazid liver injury (chronic parenchymal injury)⁷¹ and that characteristic of troglitazone⁷² demonstrates the contrast between a situation where stopping the drug at the time of symptom onset most often prevents progression to irreversible injury, and one where it does not in many cases. Drugs that can cause severe DILI generally demonstrate a range of responses, with varying proportions of patients who recover whether or not the drug is stopped, versus the proportion of patients who go on to develop irreversible injury.

⁶³ *ibid.*

⁶⁴ *ibid.*

⁶⁵ *ibid.*

⁶⁶ Graham DJ, Ahmad SR, Piazza-Hepp T. (2002) Spontaneous reporting – USA. In: Mann RD and Andrews EB, (eds), *Pharmacovigilance*, John Wiley and Sons, Ltd.

⁶⁷ Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. *Am J Med* 2003;114:299-306.

⁶⁸ Safer DJ, Zito JM, Gardner JE. Pemoline hepatotoxicity and postmarketing surveillance. *J Am Acad Child Adolesc Psychiatry*. 2001 Jun;40(6):622-9.

⁶⁹ Fontana RJ, McCashland TM, Benner KG, et al. Acute liver failure associated with prolonged use of bromfenac leading to liver transplantation. *Liver Transpl Surg* 1995;5:480-4.

⁷⁰ Avigan M. Responses to a signal of drug-induced hepatotoxicity. FDA/CDER/ODS/DDRE presentation at Drug-Induced Hepatotoxicity Workshop, January 28, 2003, Washington, DC.

⁷¹ Ramkumar D, LaBrecque DR. 2003. *op cit.*

⁷² Graham DJ, Green L, Senior JR, Nourjah P. 2003. *op cit.*

Dose-related hepatotoxicity

Acetaminophen is an example of a drug with predictable dose-related toxic effects. At higher doses, acetaminophen can rapidly cause hepatocyte injury. Acetaminophen toxicity produces the most common form or cause of ALF in the US, accounting for 39% of cases in a recent survey of tertiary care centers,⁷³ both after attempted suicide by acetaminophen overdose and after unintentional overdose, in which use of the drug for pain relief in excess of the recommended dose has occurred over a period of days.⁷⁴

C. Experience with clinical trial data

Possible “signals” for severe DILI are abnormalities (signs or symptoms) that reflect ongoing liver injury 1) in the same individual if drug is continued, and 2) in other drug-treated individuals due to a common mechanism of toxicity.⁷⁵ Signals can be generated in clinical trials by subjects with clinically mild reversible drug-induced liver injury.

The observation that “instances (even very few of them) of transaminase elevation accompanied by elevated bilirubin (even if obvious jaundice was not present) have been associated with, and have often predicted, post-marketing serious liver injuries (fatal or requiring transplant)” was first made by Dr. Hyman Zimmerman,⁷⁶ and has been dubbed “Hy’s Law”.⁷⁷ The ominous implications of Hy’s Law proved to be true for bromfenac, dilevalol, troglitazone, and trovafloxacin, even though no cases of life-threatening serious injury were seen for any of these drugs pre-marketing.⁷⁸

Zimmerman noted that drug-induced hepatocellular jaundice is a serious lesion, with mortality ranging from 10 to 50 percent.⁷⁹ More recent mortality estimates continue to regard the combination of pure hepatocellular injury and jaundice as ominous, with about 10-15% of patients who show such findings as a result of drug-induced injury going on to die⁸⁰. The explanation for this outcome is that hepatocellular injury great enough to interfere with bilirubin excretion must involve a large fraction of the liver cell mass.⁸¹

Increased transaminases alone – examples

Clinical trials with statins have generally shown an imbalance in transaminase elevations (ALT >3x ULN) between active drug and placebo. However, extensive marketed experience with the

⁷³ Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care center in the United States. *Ann Intern Med* 2002;137:947-54.

⁷⁴ Lee WM. 2003. *op cit*.

⁷⁵ Avigan M. 2003. *op cit*.

⁷⁶ Center for Drug Evaluation and Research (CDER). Drug-induced liver toxicity. Clinical White Paper. November 2000. (Accessed June 1, 2004, at <http://www.fda.gov/cder/livertox/default.htm>.)

⁷⁷ Reuben A. Hy’s Law. *Hepatology* 2004 Feb;39(2):574-8.

⁷⁸ CDER. Drug-induced liver toxicity. 2000. *op cit*.

⁷⁹ Zimmerman HJ. Drug-induced liver disease. In: Hepatotoxicity The Adverse Effects of Drugs and Other Chemicals on the Liver. Appleton-Century-Crofts, New York, 1978, 1999.

⁸⁰ CDER. Drug-induced liver toxicity. 2000. *op cit*.

⁸¹ *ibid*.

older statins (e.g., simvastatin), as well as several large morbidity and mortality trials⁸², have shown that serious liver injury occurs rarely, not exceeding background, with several of these drugs. For instance, during clinical trials with lovastatin, ALT > 3x ULN occurred in 2.6% and 5.0% of patients on doses of 20 mg and 80 mg/day, respectively. The elevations are reversible with continuing therapy and are dose related. Postmarketing, lovastatin exposure is estimated worldwide to be 24 million patient-years. Rare cases of liver failure have been reported at a rate of approximately 1/1.14 million patient years, which is approximately equal to the background rate of idiopathic ALF.⁸³

Increased Hy's cases – examples

Troglitazone is an example where “Hy’s cases” observed during clinical trials portended a significant postmarketing issue with severe DILI and fatal liver failure. Troglitazone is discussed below in Section D.

D. Specific Examples – long-term indications (chronic therapy)

Troglitazone

In the clinical trials which led to troglitazone’s approval by the FDA in 1997,⁸⁴ there were no cases of liver failure in 2510 patients. In the NDA database (N=2510), 1.9% of troglitazone-treated patients had ALT >3x ULN, 1.7% had ALT >5x ULN, and 0.2% (5 patients) had ALT >30x ULN (two of whom also experienced jaundice). The median duration of troglitazone therapy before peak ALT elevation was 121 days. In 1997, NIH sponsored a large Diabetes Prevention Program⁸⁵ designed to determine whether non-insulin-dependent diabetes mellitus can be prevented or delayed in persons with impaired glucose tolerance. Study groups included intensive lifestyle intervention with diet and exercise, metformin or troglitazone with standard diet and exercise, and a control group. The troglitazone arm was discontinued in 1998 due to reports of severe hepatotoxicity.⁸⁶ In the NIH Diabetes Prevention Trial (N=585), 3.0% of troglitazone-treated subjects had ALT >3x ULN, 1.5% had ALT >8x ULN, and two patients had ALT >30x ULN. One of these patients developed liver failure and died, despite receiving a liver transplant. The second patient recovered. The median duration of troglitazone therapy before initial ALT elevation was 126 days, and to peak elevation was 143 days.⁸⁷

In response to worrisome and continuing reports of ALF associated with troglitazone use, a series of “Dear Healthcare Professional” letters were sent to practicing physicians between 1997

⁸² Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;360:7-22.

⁸³ Tolman K. The liver and lovastatin. *Am J Cardiol* 2002;89:1374-1380.

⁸⁴ FDA Center for Drug Evaluation and Research. Medical review of troglitazone – efficacy supplement, NDA 20-720, Dr. Robert Misbin, March 12, 1999. www.fda.gov/cder/foi/nda/99/20720S12S14_Rezulim.htm (accessed July 12, 2004).

⁸⁵ Muniyappa R, El-Atat F, Aneja A, McFarlane SI. The diabetes prevention program. *Current Diabetes Reports* 2003 Jun; 3(3):221-2.

⁸⁶ *ibid.*

⁸⁷ FDA Center for Drug Evaluation and Research. Medical review of troglitazone – efficacy supplement, NDA 20-720, Dr. Robert Misbin, March 12, 1999. www.fda.gov/cder/foi/nda/99/20720S12S14_Rezulim.htm (accessed July 12, 2004).

and 1999, warning about severe liver injury and recommending monthly transaminase monitoring. Unfortunately, transaminase monitoring was not regularly performed.⁸⁸ Moreover, an analysis of 94 cases of liver failure which were reported spontaneously to the FDA showed that the progression from normal hepatic functioning to irreversible liver injury occurred within one month in 19 patients who were indistinguishable clinically from the 70 patients who had an unknown time course to irreversibility. Of the 89 cases of ALF, only 11 (13%) recovered without liver transplantation. The onset of injury began from three days to after more than two years of troglitazone use. Progression from jaundice to hepatic encephalopathy, liver transplantation, or death was rapid, averaging 24 days. The authors concluded that “progression to irreversible liver injury probably occurred within a one-month interval in most patients, casting doubt on the value of monthly monitoring” of serum transaminase levels as a means of preventing severe DILI.⁸⁹

A marked increase in risk with each month of troglitazone use was demonstrated by Graham⁹⁰ in an analysis of interval-specific hazard rates (per million person-years) for each month of continued troglitazone use, based on ALF cases reported to the FDA (numerator) and the estimated person-years of troglitazone exposure for that corresponding month of use (denominator). A table in that report is reproduced below,⁹¹ and shows the cumulative risk of ALF calculated as “1-survival probability” for each month of continued use, derived from the life-table analysis, and expressed in the form of “1 case per x persons treated” for each month of continued use (slide 29 in the original document).

This analysis of troglitazone data through the close of 1999 showed that the interval-specific hazard rate was substantially elevated above the expected background rate of one per million person-years beginning with the first month of troglitazone use. The cumulative risk of ALF increased from one case per 131,000 users at one month of use to one case per 7,000 users with 18 months of continued troglitazone use.⁹²

⁸⁸ Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess M. Liver enzyme monitoring in patients treated with troglitazone. *JAMA* 2001;286:831-833.

⁸⁹ Graham DJ, Green L, Senior JR, Noujeh P. Troglitazone-induced liver failure: a case study. *Am J Med* 2003;114:299-306.

⁹⁰ Graham DJ, Green L. Final Report: Liver Failure Risk with Troglitazone (Rezulin). FDA/CDER/ODS/DDRE consult, dated December 19, 2000.

⁹¹ *ibid*, page 20.

⁹² *ibid*, page 20.

Interval-Specific Hazard Rates ($\times 10^{-6}$ pyrs) and Cumulative Risk of
Liver Failure with Rezulin, by Duration of Use^a

Months Use	Cases	Int Hazard	Cum Risk (1 per "x")
1	9	89	131K
2	5	58	79K
3	9	117	44K
4	14	206	25K
5	13	216	17K
6	8	149	14K
7	3	62	13K
8	10	230	10K
9	2	52	10K
10	2	57	9K
11	2	64	9K
12	2	72	9K
13	1	40	8K
14			
15			
16			
17	2	135	8K
18	1	79	7K

^aDuration missing
for 11 cases

29

Table reproduced from Graham DJ, Green L. Final Report: Liver Failure Risk with Troglitazone (Rezulin). FDA/CDER/ODS/DDRE consult, dated December 19, 2000.

More recently, the incidence of hospitalized idiopathic acute liver injury and ALF in troglitazone-treated patients was estimated in an observational retrospective cohort study using claims data from a large multistate health care organization.⁹³ The inception cohort included 7568 patients who began troglitazone during the study period. A total of 4020 person-years of exposure were observed. The incidence rates per million person-years of acute idiopathic liver injury (95% CI) were as follows: hospitalization with jaundice (n=4), 995 per million person-years (271, 2546); ALF (n=1), 240 per million person-years (6.3, 1385). This represents a marked increase in risk compared to estimated background rates of hospitalization for idiopathic acute liver injury (22 per million person-years) and ALF (1 per million person-years).⁹⁴

Although the pathogenesis of troglitazone toxicity is not understood,⁹⁵ experience with troglitazone provides a clear example of a situation where "Hy's Law" cases observed during clinical trials prior to approval were predictive of a high risk of severe DILI and ALF post marketing. Troglitazone was withdrawn from the US market in March 2000, after 94 cases of drug-induced liver failure had been reported.⁹⁶

⁹³ Graham DJ, Drinkard CR, Shatin D. Incidence of idiopathic acute liver failure and hospitalized liver injury in patients treated with troglitazone. *Am J Gastroenterol* 2003;98(1):175-9.

⁹⁴ *ibid.*

⁹⁵ Lee WM. 2003. *op cit.*

⁹⁶ Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. *Am J Med* 2003;114:299-306.

Isoniazid

Isoniazid remains a first-line agent against tuberculosis, even though increased levels of aminotransferase are observed in 15 to 30 percent of patients who take the medication and one in 1000 patients will have severe hepatic necrosis.^{97 98} Recent experience in public health clinics has shown that risk of severe hepatotoxic reactions to isoniazid can be effectively minimized by instructing patients to stop drug and immediately report symptoms of liver injury as soon as they occur.⁹⁹ In a recent 7-year survey from a public health tuberculosis clinic in Seattle, WA, a total of 11,141 consecutive patients who started a regimen of isoniazid preventive therapy for latent TB infection were followed to determine the rate of developing signs and symptoms of hepatotoxicity during clinically monitored therapy.¹⁰⁰ Monitoring for the safety of isoniazid was done by a clinical evaluation for symptoms rather than by transaminase monitoring because many patients experience a transient rise in serum transaminase levels during isoniazid therapy. During the 7-year study period, eleven patients (0.1%) experienced hepatotoxic reactions while receiving isoniazid. All eleven patients had highly elevated serum transaminase levels and nine (82%) patients were hyperbilirubinemic. Only one patient was hospitalized because of hepatotoxicity. All eleven patients recovered without sequelae.

Similar experience was reported from a tuberculosis clinic in California, with outcomes available for 3,788 patients started on isoniazid between 1999 and 2002. Ten patients (0.3%) developed isoniazid-associated liver injury, none of whom required hospitalization or died. The authors conclude that clinical evaluation as the primary monitoring method for most patients taking isoniazid is effective. High rates of asymptomatic transaminase elevations in isoniazid-treated patients limit the utility of routine periodic monitoring in detecting clinically meaningful liver injury that will progress to irreversibility.¹⁰¹

Pemoline

Pemoline (Cylert®), a drug for the treatment of ADHD, was approved by the FDA in 1975 as a Schedule IV stimulant. At the time of approval, hepatic enzyme abnormalities were noted in 1% to 2% of patients, leading to recommendations in the precautions section to monitor transaminase levels periodically. Postmarketing, cases of liver injury, including ALF, were reported. An analysis of 13 cases of fulminant liver failure in children treated with pemoline which had been reported to the FDA prior to 1996 found that the median duration of pemoline use prior to symptomatic liver disease was about 13 months, with the shortest duration among the 13 cases being six months.¹⁰²

⁹⁷ Lee WM. 2003. *op cit*.

⁹⁸ Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999;281:1014-18.

⁹⁹ *ibid*.

¹⁰⁰ *ibid*.

¹⁰¹ LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. *Am J Respir Crit Care Med* 2003;168:443-7.

¹⁰² FDA/CDER/Epidemiology Branch. Report on Fulminant Hepatic Failure with Pemoline (Cylert), dated April 17, 1996.

These reports of serious DILI and ALF prompted a labeling change in 1996 (black box warning) and a Dear Healthcare Professional letter, shifting the drug from first-line to second-line therapy for ADHD. In June 1999 another labeling change and Dear HCP letter was issued, with new recommendations for baseline and bi-weekly transaminase monitoring. Compliance with labeling recommendations was subsequently assessed, and was found to be poor in a retrospective cohort study using administrative claims data.¹⁰³ Recently, use of this drug has dropped sharply since there are several therapeutic alternatives. A search of the AERS safety database (covering the period from June 1999 through January 2004) indicates that no unconfounded cases of liver failure associated with pemoline therapy administered after June 1999 have been received by the FDA.¹⁰⁴ An analysis of drug utilization^{105,106} shows that the use of the drug (brand and generic) has decreased substantially over the last six years such that domestic use in 2003 (171,000 prescriptions) was about 22% of its use in 1998 (773,000 prescriptions).

E. Specific Examples – short- or intermediate-term indications

Bromfenac

Bromfenac (Duract®) was approved by FDA in 1997 for use as a short-term analgesic for periods of 10 days or less. Although no cases of serious liver injury were seen in clinical trials, the product was approved only for short term use because a higher incidence of transaminase elevations were observed in patients treated long-term in clinical trials. Bromfenac was never approved as a treatment for chronic conditions such as osteoarthritis or rheumatoid arthritis.¹⁰⁷ However, when used off label in such patients, need for chronic pain relief increased the risk of longer term use, despite precautions in the label.

During clinical trials, bromfenac use was associated with transaminase elevations in approximately 15% of patients, and elevations >3x ULN were seen in 2.7% of patients at some time during treatment. In contrast, the incidence of such elevations was <0.4% during short-term therapy. In longer term trials, marked elevations more than 8x ULN occurred in 0.4% of patients.¹⁰⁸

Post-approval, reports of hepatic failure, including four deaths and eight cases requiring liver transplant, were received. All but one of these cases involved the use of bromfenac for more than ten days, the maximum recommended duration of treatment. In response to the reports, FDA and the company strengthened the warnings in the US package insert (USPI) with a black box warning, and the company issued a Dear HCP letter. Despite these efforts, the FDA and the

¹⁰³ Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A study of compliance with FDA recommendations for pemoline (Cylert). *J Am Acad Child Adolesc Psychiatry* 2002; 41(7):785-790.

¹⁰⁴ Racoosin JA. FDA/CDER/Division of Neuropharmacological Drug Products (HFD-120) memorandum to Patient Information Sub-Committee Members, dated February 6, 2004

¹⁰⁵ FDA/CDER/ODS/DSRCS. Update to ODS/DSRCS Review of the Proposed Risk Management Communication Plan for Cylert® (pemoline), NDAs 16-832 and 17-703, dated January 16, 2004.

¹⁰⁶ Data source - IMS Health, National Prescription Audit Plus™, 1997-2003, extracted 1/04.

¹⁰⁷ FDA Talk Paper. Wyeth-Ayerst Laboratories announces the withdrawal of Duract from the market. Available from: <http://www.fda.gov/bbs/topics/ANSWERS/ANS00879.html>.

¹⁰⁸ Product Information: Duract®, bromfenac. Wyeth Laboratories, Philadelphia, PA, 1998.

company continued to receive reports of severe injuries and death with long-term use of bromfenac.¹⁰⁹

Four patients with severe bromfenac hepatotoxicity were identified at three tertiary care centers participating in the US Acute Liver Failure Study Group. Bromfenac had been administered for a minimum of 90 days at usual dosages to four women who presented with severe, symptomatic hepatocellular injury with associated hypoprothrombinemia. Despite supportive measures, all the subjects developed progressive liver failure over 5 to 37 days, leading to liver transplantation in three patients and death in one patient while awaiting transplantation. The authors concluded that the “poor outcomes in this series, coupled with the inability to identify individuals at risk for severe, idiosyncratic bromfenac hepatotoxicity preclude further use of bromfenac in the medical community.”¹¹⁰

Given the availability of other therapies, in 1998 FDA and the company concluded that it would not be practical to implement the restrictions necessary to ensure the safe use (less than ten days) of bromfenac, and that the drug should be withdrawn from the market.¹¹¹

Analysis of drug utilization during the two years prior to bromfenac’s withdrawal from the market (1997-1998), shows that 55-60% of bromfenac mentions in outpatient office visits were for intended therapy of 10 days or less, based on information from an IMS Health, National Disease and Therapeutic Index (NDTITM)¹¹², which reflects the intention of the physician at the time of prescribing. Approximately 10-20% of mentions were for more than 10 days of intended treatment and 25-30% had “unspecified” intended duration, suggesting that an even higher percentage of mentions could have been for more than 10 days of intended treatment. Among those physicians mentioning bromfenac during an office-based visit, the intended duration of therapy ranged from one to 90 days, with the most mentions occurring for 10 days of therapy (approximately 21%).¹¹³

Trovafloxacin

Following the marketing of trovafloxacin (a fluoroquinolone antibiotic) in 1998, FDA began receiving reports of patients with serious liver reactions.¹¹⁴ During pre-marketing clinical trials with trovafloxacin (N = 7000), there were no reports of liver failure. Post-marketing, FDA received reports of over 100 cases of clinically symptomatic liver toxicity, including 14 cases of ALF, many of which were fatal and/or required liver transplant. Trovafloxacin-associated liver

¹⁰⁹ FDA Risk Intervention Examples. Appendix G. Available from: <http://www.fda.gov/oc/tfrim/AppendixG.html>.

¹¹⁰ Fontana RJ, McCashland TM, Benner KG, et al. Acute liver failure associated with prolonged use of bromfenac leading to liver transplantation. The Acute Liver Failure Study Group. *Liver Transpl Surg* 1999;5:480-4.

¹¹¹ FDA Talk Paper. Wyeth-Ayerst Laboratories announces the withdrawal of Duract from the market. Available from: <http://www.fda.gov/bbs/topics/ANSWERS/ANS00879.html>.

¹¹² Data source - IMS Health, National Disease and Therapeutic IndexTM, April 1994-March 2000, extracted 6/04.

¹¹³ FDA/CDER/ODS/DSRCS Review of average length of a prescription and average intended duration of therapy for ketorolac and bromfenac, dated July 13, 2004.

¹¹⁴ Public Health Advisory (1999) Trovan (trovafloxacin / alatrofloxacin mesylate) and risk of liver failure. FDA June 9, 1999. Available from: <http://www.fda.gov/cder/news/trovan/trovan-advisory.htm>.

failure appeared to be unpredictable, occurring after as few as two days exposure, but with a substantially increased risk noted in patients receiving the drug for longer than two weeks.¹¹⁵

Time-to event analysis (life-table estimation) showed an association between risk of developing ALF and duration of therapy with trovafloxacin. A background incidence rate for ALF due to idiopathic causes was estimated at one case per million per year. Based on the 14 reports of ALF received by the FDA over a two year period, the relative risk of ALF with trovafloxacin was shown to be above background from the start of therapy, and to increase rapidly with increasing duration of exposure.¹¹⁶

A Public Health Advisory was issued by the FDA in 1999 which effectively restricted use of this drug to hospitalized patients with certain serious life or limb-threatening infections. The efficacy of liver function monitoring in acceptably monitoring the risk of severe liver injury associated with trovafloxacin was considered uncertain. The manufacturer of trovafloxacin agreed to direct distribution of trovafloxacin only to pharmacies in inpatient health care facilities (i.e., hospitals and long-term nursing care facilities).¹¹⁷

F. Synopsis - RiskMAP tools for drugs that induce liver injury - track record of efficacy

Transaminase Monitoring

A rationale of regular serum transaminase monitoring is predicated on full characterization of the timing and tempo of liver injury as well as a high level of compliance by patients and physicians. In fact, the utility of transaminase monitoring in preventing severe DILI has never been convincingly demonstrated. Moreover, transaminase monitoring has been shown to be ineffective as a risk minimization tool in the case of troglitazone, isoniazid, and lovastatin (as described in previous sections of this review). Transaminase monitoring is ineffective when the tempo of liver injury is such that inexorable progression occurs even after the drug has been stopped in response to a signal of transaminase elevation. The foremost requirement that determines the usefulness of transaminase monitoring in preventing frank liver injury is that “the time interval between onset of liver chemistry abnormality and subsequent liver injury must exceed the screening interval.”¹¹⁸

This was not the case with troglitazone. An analysis of spontaneously reported cases of ALF associated with troglitazone showed that “progression to irreversible liver injury probably occurred within a one-month interval in most patients, casting doubt on the value of monthly monitoring” of serum transaminase levels as a means of preventing severe DILI.¹¹⁹ In addition,

¹¹⁵ *Ibid.*

¹¹⁶ Graham DJ, Ahmad SR, Piazza-Hepp T. (2002), *op cit.*

¹¹⁷ *Ibid.*

¹¹⁸ Adams PC, Arthur MJ, Boyer TD, DeLeve LD, et al. Screening in liver disease: Report of an AASLD Clinical Workshop. *Hepatology* 2004;39:1204-1212.

¹¹⁹ Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. *Am J Med* 2003;114:299-306.

despite a series of “Dear Healthcare Professional” letters recommending monthly monitoring, transaminase monitoring was not regularly performed.¹²⁰

With regard to the utility of transaminase monitoring as a method of minimizing risk of liver injury, Lee concluded in a recent review article¹²¹ that “monitoring is unlikely to be effective in the case of a rare adverse reaction. Monitoring is seldom performed consistently, and even if it were, it provides no guarantee of safeguarding the patient, since many drug reactions develop abruptly.” Rapid acceleration of liver injury in some individuals may preclude an absolute protective value of standardized periodic transaminase monitoring.¹²²

Limited Duration of Therapy

Hepatotoxicity was generally only observed with bromfenac in patients who took the drug for more than 30 days; however, despite attempts to regulate the duration of therapy by clear statements in product labeling, prescribers often did not heed this information and fatal liver injuries still occurred (as described previously in this review).¹²³

Although not primarily for reasons of hepatotoxicity, the USPI for Toradol (ketorolac tromethamine tablets) includes a boxed warning which states that the duration of use is “not to exceed 5 days because of the increased risk of serious adverse events.” An analysis (using data from IMS NPA^{Plus}™)¹²⁴ of the average length of a prescription for oral ketorolac during the five year period from June 1999 to May 2004 showed a fairly consistent pattern, ranging from 5.1 to 7.3 days. Analysis of the average intended duration of therapy (using data from IMS NDTI™)¹²⁵ for oral ketorolac for patients seen by office-based physicians showed that, from May 2001 to April 2002, approximately 82% of prescribers intended patients to take ketorolac for a 5 day or less course of therapy. In 15% of mentions the intended duration of therapy was not specified.¹²⁶ It is not known whether, or to what extent, computer-based real-time notifications to retail pharmacists from pharmacy benefit managers (PBMs) regarding prescription days supplied in excess of recommendations (non-reimbursable claims) may influence appropriate duration of therapy for this product.

Restricted Access and/or Restricted Distribution

A Public Health Advisory was issued by the FDA in 1999 which effectively restricted use of trovafloxacin to hospitalized patients with certain serious life or limb-threatening infections. The efficacy of liver function monitoring in acceptably monitoring the risk of severe liver injury

¹²⁰ Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess M. Liver enzyme monitoring in patients treated with troglitazone. *JAMA* 2001;286:831-833.

¹²¹ Lee WM. 2003. *op cit*.

¹²² Avigan M. 2003. *op cit*.

¹²³ FDA Talk Paper. Wyeth-Ayerst Laboratories announces the withdrawal of Duract from the market. *op cit*.

¹²⁴ Data source - IMS Health, National Prescription Audit Plus™, June 1999- May 2004, extracted 6/04.

¹²⁵ Data source - IMS Health, National Disease and Therapeutic Index, May 2001-April 2004, extracted 6/04.

¹²⁶ FDA/CDER/ODS/DSRCS Review of average length of a prescription and average intended duration of therapy for ketorolac and bromfenac, dated July 13, 2004.

associated with trovafloxacin was considered uncertain. The manufacturer of trovafloxacin agreed to distribute trovafloxacin only to pharmacies in inpatient health care facilities (i.e., hospitals and long-term nursing care facilities).¹²⁷ These actions have resulted in a substantial decrease in trovafloxacin utilization, and a corresponding decrease in spontaneous reports of liver failure caused by this drug (there have been none reported to FDA since 1999).

Because of potential serious liver injury, as well as potential fetal damage if taken during pregnancy, Tracleer (bosentan), a drug recently approved for the treatment of pulmonary arterial hypertension in patients with Class III or IV heart failure, is only available through the Tracleer Access Program. FDA approval of this drug was contingent on several actions by the sponsor including 1) developing an enhanced prescriber educational program; 2) developing a program which ensures complete registration of all patients receiving Tracleer; 3) developing a program to provide complete registration and certification of practitioners who prescribe Tracleer; 4) developing a comprehensive program to track and report to CDER all severe liver injuries; and, 5) developing a monitoring program to facilitate on an annual basis an assessment of risk management goals.

The Tracleer™ Access Program (TAP) provides a toll free line to physicians with initial information about Tracleer, a site to report adverse events, and customer service. Following the toll-free call, a completed patient enrollment form is faxed to TAP to initiate the prescription, allowing a one month supply (with refills), providing patient information and including physician certifications. Each specialty distributor must agree to a defined set of rules to sell Tracleer, including insertion of patient reminders in the monthly prescription, generating a letter to the prescribing physician stating the prescription has been filled, calling the patient prior to shipment of the next month's medication supply and asking whether they've had a blood draw for liver tests, calling the physician if the patient has not had a test within the last month, and determining the reason if a planned refill does not occur. The patient enrollment form contains a statement: "I certify that I am prescribing Tracleer for this patient for a medically appropriate use in the treatment of pulmonary arterial hypertension, as described in the Tracleer full prescribing information. I have reviewed the liver and pregnancy warnings with the patient and commit to undertaking appropriate blood testing for monitoring liver function in this patient and testing for pregnancy (if the patient is a female of child-bearing potential)". This statement is followed by a place for the physician's signature.¹²⁸

Labeling

A recent study of FDA-approved product labeling for identified hepatotoxic drugs indicated that the Physicians Desk Reference for the year 2000 included black box warnings for severe liver toxicity for eleven non-generic drugs.

¹²⁷ *Ibid.*

¹²⁸ FDA/CDER. Regulatory Briefing for Tracleer (bosentan). dated October 23, 2001.

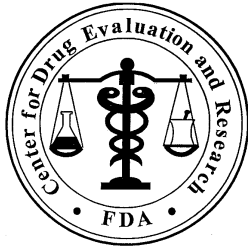
The labels for an additional 52 drugs were found to include Warnings or Precautions about liver failure and/or necrosis.¹²⁹ The utility of Warnings or Precautions in communicating risk information in an effort to prevent liver injury has not been systematically evaluated. However, several studies of particular drugs have found that product labeling may not meaningfully affect physician behavior.^{130 131 132}

¹²⁹ Willy ME, Li Z. What is prescription labeling communicating to doctors about hepatotoxic drugs? A study of FDA approved product labeling. *Pharmacoepi Drug Saf* 2004;13:201-206.

¹³⁰ Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride. *JAMA* 2000; 284:3036-9.

¹³¹ Walker AM, Bortnichak EA, Lanza L, Yood RA. The infrequency of liver function testing in patients using nonsteroidal anti-inflammatory drugs. *Arch Fam Med* 1995; 4:24-29.

¹³² Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess M. 2001. *op cit*.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 12, 2009
To: Rafel (Dwayne) Rieves, M.D., Director
Division of Medical Imaging and Hematology Products (DMIHP)
Through: Claudia Karwoski, Pharm.D., Acting Director
Division of Risk Management (DRISK)
Office of Surveillance and Epidemiology (OSE)
From: Rivaroxaban Risk Management Team

Scientific Lead:

Kathryn O'Connell, MD, PhD, Medical Officer (DRISK/OSE)

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Mary Dempsey, Risk Management Coordinator (DRISK/OSE)

Subject: Review of "Safety Surveillance Plan"
Drug Name(s): Rivaroxaban
Submission Number: Original NDA July 28, 2008
Application: NDA 022406
Type/Number:
Applicant/sponsor: Bayer/Johnson & Johnson
OSE RCM #: 2008-2019

1 INTRODUCTION

This review follows a request from the Division of Medical Imaging and Hematology Products (DMIHP) to review and comment on the proposed “safety surveillance plan” for rivaroxaban dated July 28, 2008 and submitted to OSE for consultation on December 17, 2008.

Rivaroxaban (BAY 59-7939) is a highly selective, direct factor Xa (FXa) inhibitor. The proposed indication is prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing total hip replacement (THR) or total knee replacement (TKR) surgery. The proposed dosing is 10 mg by mouth once daily for up to 35 days, and use does not require therapeutic blood monitoring. If approved as such, it may be appealing for broader use “off-label” in patients requiring long term anticoagulation. The sponsor is currently studying longer-term exposure indications, such as prevention of stroke and non-central nervous system systemic embolism in patients with nonvalvular atrial fibrillation.

2 MATERIAL REVIEWED

The following materials were reviewed:

- Sponsor’s proposed safety surveillance plan dated July 28, 2008
- Dr. Min Lu’s FDA mid-cycle clinical review slides dated December 2, 2008
- Proposed package insert dated July 28, 2008

3 RESULTS OF REVIEW

3.1 Overview of Clinical Program

There are two pivotal studies for each indication under current NDA review, THR and TKR. All four are randomized, double-blind, double-dummy, active-controlled studies. The active comparator for both indications was subcutaneous enoxaparin, which is approved and labeled for prophylaxis after both THR and TKR. The primary efficacy endpoint was a composite of all cause death, non-fatal PE, and proximal and/or distal DVT.

According to the sponsor’s submission, subjects were included who were scheduled for elective primary or revision THR or TKR procedures. Bilateral procedures were allowed if done during the same surgery. Exclusion criteria most relevant to this review were: 1) active bleeding or high risk of bleeding contraindicating treatment with low molecular weight heparin, and 2) acute clinical hepatitis, chronic active hepatitis, or cirrhosis. Liver panel testing was done on days 1, 6, 13, 36 or 42, and 65.

A total of 10,600 rivaroxaban subjects were evaluated for safety in 64 completed studies to date across all indications. Approximately 7,000 of these subjects were exposed to

rivaroxaban for at least 12 days. The total patient denominators for adverse event analysis in the THR/TKR pivotal studies are rivaroxaban, 6183 and enoxaparin, 6200.

Regarding efficacy, the review division medical officer's mid-cycle analysis pointed out that rivaroxaban showed statistically significant efficacy for the major endpoint, venous thrombosis, compared to the comparator in 3 of the 4 pivotal studies (all cause death shown as a safety endpoint):

No. events (%)	THR trial 1 (rivaroxaban vs enoxaparin)	THR trial 2 (rivaroxaban vs enoxaparin)	TKR trial 1 (rivaroxaban vs enoxaparin)	TKR trial 2 (rivaroxaban vs enoxaparin)
<i>Venous thrombosis</i>	1.1 vs. 3.7	2.0 vs. 9.3	9.6 vs. 18.9	6.9 vs. 10.1
Death all cause	0.3 vs. 0.3	0.2 vs. 0.7	0 vs. 0.2	0.2 vs. 0.3

3.2 Safety Concerns

3.2.1 Sponsor's Safety Concerns

The sponsor identified two safety concerns:

- Identified risk: Bleeding events
Major bleeding was defined as bleeding that was fatal, into a critical organ, required re-operation, clinically overt extra-surgical site bleeding associated with a drop in hemoglobin ≥ 2 g/dL, or clinically overt extra-surgical site bleeding requiring transfusion of ≥ 2 units blood. These events occurred in less than 1% of subjects and the rates were similar for subjects in the rivaroxaban and enoxaparin arms.
- Potential risk: Transient elevation of liver laboratory tests
Of "transient elevation of liver laboratory tests", the application states: "...cases of ALT levels >3 x ULN concurrent with total bilirubin levels >2 x ULN have been observed. The incidence of such cases is balanced on rivaroxaban and enoxaparin and most frequently occur after surgery within the first 2 weeks of study medication administration. The occurrence of such cases is most likely a consequence of surgery (i.e., reduced blood flow during surgery, hypoperfusion of liver) and associated medical procedures (i.e., blood transfusion and anesthesia)".

3.2.2 FDA Safety Concerns

The review division medical officer's mid-cycle review identified three major concerns:

- Bleeding events
- Cardiovascular events (ischemic stroke)
- Hepatic events

Hepatic events are the focus of this post-marketing risk management review. Bleeding is an expected consequence of products that decrease clotting, and is normally managed through recommendations and information in the professional package insert. Ischemic strokes, recorded for 12 rivaroxaban patients vs. 7 in the comparator arm, are a clinical review issue related to both safety and efficacy, since the intended effect is anti-coagulation.

In the pivotal trials for THR/TKR, the overall death rate was higher in the comparator arm (0.21% vs. 0.40%). However, the FDA mid-cycle clinical review of the entire safety database showed that there were 3 deaths from liver failure in which rivaroxaban could not be excluded. Two of these cases occurred within the 30 day window of treatment duration proposed for the indications under review. In addition, there were six “possibly related” Hy’s law cases¹ among rivaroxaban patients in the THR/TKR trials compared to three in the enoxaparin² comparator arm.

3.3 Sponsor’s Safety Surveillance Plan

The sponsor submitted a “safety surveillance plan” including a pharmacovigilance plan whose stated objective is “...to systematically³ 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”. As such, the pharmacovigilance plan is routine adverse event monitoring and reporting as per appropriate Regulations. In addition, the “safety surveillance plan” includes a risk mitigation strategy to minimize off-label use. Specifically, the objectives are:

- Rivaroxaban prescribed only for short term VTE prophylaxis in patients undergoing THR or TKR
- Rivaroxaban prescribed only for the recommended duration of therapy (14 days for TKR and 35 days for THR)
- Rivaroxaban not to be prescribed for unapproved indications

¹ FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation [DRAFT]. October 2007. *Hy’s law cases have the following components - 1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo. 2. Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN). 3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.*

² The labeling for enoxaparin includes the following information in the ‘Side Effects’ section: “Elevations of Serum Aminotransferases: Asymptomatic increases in aspartate (AST [SGOT]) and [alanine](#) (ALT [SGPT]) [aminotransferase](#) levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in [bilirubin](#). Since aminotransferase determinations are important in the [differential diagnosis](#) of myocardial infarction, [liver disease](#), and pulmonary emboli, elevations that might be caused by drugs like Lovenox should be interpreted with caution.”

³ “systematically” is not defined

To meet these objectives, the sponsor proposes the following risk management elements:

- Professional labeling. The risk of hepatotoxicity is described primarily as elevations in liver function tests in the Adverse Reactions section. The sponsor proposes to contraindicate rivaroxaban use in patients with “hepatic disease associated with coagulopathy associated with clinically significant bleeding risk.” No liver monitoring plan was proposed in the labeling.
- “Targeted educational and outreach programs”. In summary, pertinent healthcare professionals (orthopedic surgeons, hematologists, hospitalists, and anesthesiologists, hospital and retail pharmacists, and nurses) will receive a launch information sheet/mass mailing. In addition, a product website, formulary kit, in-service programs, and toll-free medical information line will be developed. None of the materials were submitted. In absence of the materials, it is difficult to determine if they will serve an educational purpose or function primarily to advertise and promote rivaroxaban.

4 DISCUSSION

The sponsor has proposed a risk management program consisting of routine measures such as labeling, education (with targeted detailing by the sales force), and spontaneous adverse event reporting to assure appropriate prescribing consistent with the proposed indication. The routine nature of the sponsor’s proposal is explained by their conclusion to the pharmacovigilance submission: “...a Risk Minimization Action Plan is not needed for rivaroxaban because routine risk assessment and risk minimization measures, targeted educational activities and outreach programs can adequately address all the potential safety risks”.

A formal risk management plan⁴ that exceeds routine labeling and pharmacovigilance can be required if FDA finds additional measures are necessary to ensure that the benefits of the product outweigh the risks. In making this determination, the FDA Amendments Act (FDAAA) requires FDA to consider a number of factors including the estimated size of the population likely to use the drug, the seriousness of the disease or condition that is to be treated with the drug, the expected benefit of the drug, the expected or actual duration of treatment with the drug, and the seriousness of the known or potential adverse events that may be related to the drug.

⁴ A formal risk management plan is called a “Risk Evaluation and Mitigation Strategy” or REMS. On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act (FDAAA) which amends the Federal Food, Drug and Cosmetic Act (FDCA) to authorize FDA to require a risk evaluation and mitigation strategy (REMS) when it is determined that additional measures are necessary to ensure the benefits of a drug outweigh the risks. (section 505-1(a)(1)).

Clearly, this assumes that the risks in question are manageable with available tools. Thus, REMS might not be appropriate in situations where the risk-benefit ratio is not acceptable for marketing with only routine risk management *and* the risks cannot be mitigated with a formal risk management plan. .

If FDA's review is consistent with the sponsor's interpretation of rivaroxaban's safety database, we would not recommend any risk mitigation strategy other than routine measures. If, on the contrary, it is concluded that the observed liver injury cases are likely causally related to rivaroxaban use, or if the data relevant to a potential signal for severe drug-induced liver injury have not been fully characterized and assessed, then the sponsor's proposal would not be considered adequate to address the risk of drug induced liver injury (DILI).

The question then becomes whether the risk of DILI can be mitigated by a formal risk management plan. There are three main categories of risk management tools: Patient labeling (Medication Guides), Communication Plans, and Elements to Assure Safe Use (ETASU), which often involving some degree of restricted distribution.

- A **Medication Guide** for rivaroxaban could serve to alert patients to the warning signs of liver injury, thus increasing the timeliness of drug discontinuation and medical attention. However, it is unlikely that this strategy would prevent DILI, since some patients in the trials developed serious hepatic dysfunction despite robust clinical and laboratory monitoring.
- **Education/Communication Plans** are also unlikely to succeed at managing this severe potential toxicity. Education, in the absence of strategies to assure safe use, would encourage but not ensure safe use. Traditional risk communication tools such as labeling and Dear Healthcare Professional letters have been shown to have little impact on prescribing behavior or compliance with recommended laboratory monitoring^{5,6,7,8} For example, troglitazone was withdrawn from the market due to hepatotoxicity after several labeling changes and Dear Healthcare Professional Letters did not achieve meaningful or sustained improvement in liver enzyme testing.⁶
- **Elements to Assure Safe Use** may include any number of strategies such as mandatory prescriber, pharmacy, and/or patient enrollment in a program based on certification of education or special experience, required laboratory monitoring, and other measures to assure safe use. These strategies offer additional measures to mitigate harm, but are contingent on having an identifiable at-risk group and/or

⁵ Willy M, et al. *A study of compliance with FDA recommendations for pemoline (Cylert)*. J Am Acad Child Adolesc Psychiatry. 2002 Jul;41(7):785-90.

⁶ Graham D, et al. *Liver enzyme monitoring in patients treated with troglitazone*. JAMA. 2001 Aug 15;286(7):831-3.

⁷ Smalley W, Shatin D, Wysowski D, Gurwitz J, Andrade S, et al. *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*. JAMA 2000;284(23):3036-3039.

⁸ Weatherby LB, Nordstrom BL, Fife D, Walker AM. *The Impact Of Wording in "Dear Doctor" Letters and In Black Box Labels*. Clin Pharmacol Ther. 2002;72:735-742.

methodology to monitor for preventable harm. As noted above, some patients in the rivaroxaban trials developed serious hepatic dysfunction despite robust clinical and laboratory monitoring. Generally, the effectiveness of transaminase monitoring in preventing severe DILI in the post-marketing setting has not been convincingly demonstrated. This may reflect the fact that for some products, rapid acceleration of liver injury limits the protection afforded by periodic transaminase monitoring. Programs currently in place to manage hepatotoxic risk through periodic monitoring⁹ in the post-approval setting were implemented after considering a variety of factors. These include severity of the indicated disease and expected clinical benefit, availability of other treatment options, and severity of the hepatotoxic risk observed during drug development (for example, transient elevation of laboratory tests versus frank liver failure and/or death).

Limiting treatment duration through a risk management program could be a useful tool if there is a window of safe use that does not preclude efficacy. This might be an effective option for this product if suspect cases for rivaroxaban did not exist in the short-term use indications. Until/if a causal role for rivaroxaban in Hy's cases occurring within the 30-day exposure window is ruled out, limiting use to 30 days is not a useful risk mitigation strategy for this product.

5 RECOMMENDATIONS

If future safety data from on-going clinical trials indicate that rivaroxaban is likely causally associated with severe DILI, a formal risk management program with safe use strategies should be considered *if* the data identify the at-risk subpopulation and/or a monitoring approach that will prevent serious adverse hepatobiliary events. In the absence of such directive information, we believe additional risk management measures for rivaroxaban will not effectively minimize the risk of hepatotoxicity.

⁹ Tracleer (bosentan) Access Program (TAP) and Letairis (ambrisentan). Education and Access Program (LEAP); both programs address the risk of hepatotoxicity and teratogenicity, Promacta (eltrombopag) CARES program addresses the risk of hepatotoxicity along with a number of other risks. These 3 drugs carry Boxed Warnings with regard to the risk for hepatotoxicity.