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APPLICATION NUMBER:

022406Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW
ADDENUM TO April 6, 2009 REVIEW

NDA: **22-406**	Submission Date(s): **12/30/10**
Brand Name	**XARELTO® immediate release tablets**
Generic Name	**rivaroxaban**
Primary Reviewer	**Joseph A. Grillo, Pharm.D.**
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OCP Division	**5**
ORM division	**OND/OODP/DHP**
Applicant	**Johnson & Johnson Pharmaceutical Research and Development, L.L.C (J&J)**
Relevant IND(s)	**64,892**
Submission Type; Code	**Resubmission NME NDA (SDN 70), Priority Review [original OCP NME NDA review 4/6/2009]**
OCP Briefing Date	**None [original submission: March 25, 2009]**
Formulation; Strength(s)	**10 mg immediate release tablets**
Indication	**The prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.**

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1 Executive Summary

The original NDA application was submitted on July 22, 2008, for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. A clinical pharmacology review dated April 6, 2009, found the original application acceptable provided post-marketing related issues were addressed. A complete response letter was issued on May 27, 2009, due to Clinical and Quality related issues. Although there were no clinical pharmacology related deficiencies, the agency did proactively communicate potential a post-marketing related issue regarding the need to develop a lower strength tablet for patients with Child Pugh class B hepatic impairment without coagulopathy, concurrently taking rivaroxaban with a P-gp and strong CYP3A4 inhibitor, and concurrently taking rivaroxaban with a P-gp and mild or moderate CYP3A4 inhibitor with mild-moderate renal impairment.

In its formal response the applicant states that it does not consider using a lower rivaroxaban dose for the treatment of Child Pugh class B patients without coagulopathy appropriate because its analysis suggests higher baseline prothrombin time (PT) and greater sensitivity between rivaroxaban plasma concentrations and PT in this population. However, the clinical relevance of the increased baseline PT and higher sensitivity in this population is not clear. There was no relationship observed between PT levels and proportion of patients with major bleeding in the 11527 and RECORD studies. Furthermore, FDA found that using the expected concentrations from a phase 2 study (11527), at the proposed clinical dose, the expected difference in PT ratio (PTR) following exposure matching in Child Pugh class B patients appears to be within the range seen in the combined analysis of the Phase 3 RECORD studies. In addition, both PT and PTR were considered to have poor predictive value for bleeding risk in the applicant's safety analysis of the RECORD studies. Therefore, FDA is not persuaded by the applicant's argument against exposure matching in this population.

In addition, the applicant does not consider using a lower rivaroxaban dose (5 mg QD) for patients concurrently receiving Xarelto and a P-gp and strong CYP3A4 inhibitor appropriate. This is because applicant's simulations suggest that steady state, trough concentration (C_{trough}) are estimated to be approximately 6-times higher in patients taking 5 mg QD dose with strong CYP3A4 and P-gp inhibitor compared to patients taking 10 mg QD alone. The applicant's simulation analysis was limited by holding the apparent volume of distribution (Vd/F) constant in its model and decreasing only apparent clearance (CL/F) to drive change in exposure causing prolonged elimination half-life and higher trough levels. However, both Vd/F and CL/F were reduced with minimal change in half-life in drug interaction studies with these combined inhibitors.

FDA simulations of this scenario were also conducted using the same method except reducing both CL/F and Vd/F to that observed in the applicant's drug interaction studies. The resulting simulations did not support the 6-fold change in steady-state C_{trough} concentrations following exposure matching. Therefore, FDA is not persuaded by the applicant's argument against exposure matching in this population.

FDA continues to recommend that the availability of lower dose strengths of rivaroxaban is the best option to allow a larger patient population to receive this treatment and this issue should still be considered as a post marketing commitment. Until a lower dose formulation is developed FDA supports avoidance language in the labeling for these populations.

1.1 Recommendation

From a clinical pharmacology perspective, this resubmission of the original application is ACCEPTABLE provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the applicant commits to the following post marketing commitments addressing clinical pharmacology related safety concerns with rivaroxaban treatment.

1.2 Post Marketing Requirements

None

1.3 Post Marketing Commitments

1.3.1 Develop and propose a 5 mg dosing form (tablet) or scored 10 mg tablet to allow for proper dose titration when rivaroxaban needs to be co-administered in patients at risk for clinically relevant changes in rivaroxaban exposure. The 5 mg dose form should be sufficiently distinguishable from the 10 mg tablet. Full chemistry, manufacturing and controls (CMC) information for the 5 mg dosage form including the batch data and stability data, labels, updated labeling, and updated environmental assessment section is required in a prior approval supplement.

Protocol submission Date: 45 days from date of action.

Submission Date: 6 months after FDA agreement to submitted protocol.

1.3.2 The applicant should evaluate the effect of renal impairment (i.e., mild, moderate, severe) plus the concurrent use of P-gp and moderate inhibitors of CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in volunteers so that appropriate dosing recommendations can be developed in these populations following the development of the 5 mg tablet formulation.

Protocol submission Date: We note the applicant has submitted a draft protocol with this NDA application and request that it be resubmitted for FDA review under the IND within 10 business days of this action.

Submission Date: 6 months after FDA agreement to submitted protocol.

1.4 Comments to the Applicant

1.4.1 The FDA suggests that the applicant evaluate the effect of a P-gp inhibitor with limited CYP3A4 inhibitory activity (e.g., quinidine) on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in healthy subjects. This study will explore the involvement of P-gp in rivaroxaban elimination so that appropriate dosing recommendations can be created following the development of the 5 mg tablet formulation.

1.5 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The original NDA application was submitted on July 22, 2008, for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. A clinical pharmacology review dated April 6, 2009, found the original application acceptable provided post-marketing related issues were addressed. A complete response letter was issued on May 27, 2009, due to Clinical and Quality related issues. Although there were no clinical pharmacology related deficiencies, the agency did proactively communicate a potential post-marketing related issue regarding the need for the development of a lower strength tablet for the following patients:

- Child Pugh class B hepatic impairment without coagulopathy

- Concurrently taking rivaroxaban with a P-gp and strong CYP3A4 inhibitor
- Concurrently taking rivaroxaban with a P-gp and mild or moderate CYP3A4 inhibitor with mild-moderate renal impairment

This resubmission includes a response to the clinical pharmacology issue regarding the need for a lower dose formulation for Xarelto in the above populations. These responses were evaluated in this review.

In its formal response the applicant states that it does not consider using a lower rivaroxaban dose for the treatment of Child Pugh class B patients without coagulopathy appropriate because its analysis of pharmacodynamic response from the dedicated hepatic impairment study suggests greater sensitivity between rivaroxaban plasma concentrations and prothrombin time (PT) in this population. Sensitivity was derived from the slope of the exposure response plot of PT versus rivaroxaban concentration.

FDA evaluated the applicant's proposal and PT analysis and added an analysis of the ratio of PT to baseline (PTR) to rivaroxaban concentration to focus on sensitivity rather than baseline differences. The baseline PT was greater in Child Pugh class B patients (16.2 seconds) compared to healthy subjects (13.0 seconds). In addition, relationship between PT and major bleeding was explored using the data from the 11527 and RECORD studies. The FDA analysis found the following:

- Using the expected concentrations from a phase 2 study (11527), at the proposed clinical dose and assuming exposure matching between Child Pugh class B patients and healthy subjects, where the Child Pugh class B patients where given half the dose of the healthy subjects, FDA estimated the expected PTR for each group from the linear equation describing this relationship. The expected median PTR was ~1.61 in the C-P class B patients compared to ~1.34 in the health subjects. This PTR range for exposure matched C-P class B patients is within the range reported by the applicant for the PTR seen in the combined analysis of the RECORD studies.
- There was no relationship observed between steady state PT levels and proportion of patients with major bleeding in 11527 and RECORD studies.
- The applicant's integrated safety summary reports that it found no relationship between PT or PTR and relevant bleeding risk.

Based on this analysis, FDA is not persuaded by the applicant's argument against exposure matching in this population.

The applicant also states that it does not consider using a lower rivaroxaban dose for patients concurrently receiving Xarelto and a P-gp and strong CYP3A4 inhibitor appropriate. This is because its simulations suggest that steady state, C_{trough} concentrations for 5 mg rivaroxaban co-administered with a P-gp and strong CYP3A4 inhibitor are estimated to be approximately 6-times higher as compared to steady-state C_{trough} concentrations for 10 mg rivaroxaban administered alone. Simulations were performed by the applicant using PK data of patients receiving rivaroxaban 10 mg once daily as obtained from the Phase 2 dose ranging study 11527 and inhibiting CL/F by a factor of 0.39 (observed in the Phase 1 drug interaction studies with ritonavir and ketoconazole) and leaving Vd/F constant.

The applicant's decision to decrease CL/F but hold the Vd/F constant in its model results in prolonged half-life with clearance driving the change in exposure. This is in contrast to data from five drug interaction studies with combined P-gp and CYP3A4 inhibitors of various potencies showing both Vd/F and CL/F as prominent factors causing increase in exposures such that half-life was minimally changed. FDA repeated the applicant's simulations using the same method except reducing CL/F by a factor of 0.39 and Vd/F by a factor of 0.48 as observed in the Phase 1 drug interaction studies with ritonavir and ketoconazole. These simulations did not support the significant change in steady-state C_{trough} concentrations

following exposure matching that was proposed by the applicant. Based on the simulations, the plasma concentration-time profiles were similar for patients taking 5 mg QD with concomitant strong CYP3A4 and P-gp inhibitor compared to 10 mg QD alone resulting in overlapping steady state C_{trough} levels. Furthermore, the half life was increased by 1.25-fold which is consistent with the observations of the phase 1 drug interaction studies.

Based on this analysis and the limitations of the applicant's approach, FDA is not persuaded by the applicant's argument against exposure matching in this population. The applicant also acknowledged the need to better understand the potential complex interaction of concurrent rivaroxaban use with a P-gp and mild or moderate CYP3A4 inhibitor with mild-moderate renal impairment. It also affirmed its plan to conduct a drug interaction study in the special population of patients with mild or moderate renal impairment concomitantly receiving erythromycin, a combined CYP3A4 (moderate) and P-gp inhibitor.

Therefore, FDA was not persuaded by the applicant's arguments against exposure matching in the Child Pugh class B hepatic impairment without coagulopathy and with concurrent rivaroxaban use with a P-gp and strong CYP3A4 inhibitor. FDA agrees with the applicants plan to study the potential complex interaction of concurrent rivaroxaban use with a P-gp and mild or moderate CYP3A4 inhibitor with mild-moderate renal impairment. FDA continues to recommend that the availability of lower dose strengths of rivaroxaban is the best option to allow a larger patient population to receive this treatment and this issue should still be considered as a post marketing commitment. Until a lower dose formulation is developed FDA supports avoidance language in the labeling for these populations.

Signatures

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2 Question Based Review

2.1 Pertinent Regulatory Background

2.2 The original NDA application was submitted on July 22, 2008, for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. A complete response letter was issued on May 27, 2009. For further details on this submission and for review material relevant to the labeling, post-marketing comments, and suggestions from the Agency see the clinical pharmacology review dated April 6, 2009.

In the Complete Response letter, the FDA identified concerns over the clinical investigator Inspections from the RECORD studies, insufficient clinical data to fully characterize the potential risk for serious hepatotoxicity, and the adequacy of the drug substance and product information. Although there were no clinical pharmacology related deficiencies, the Agency did proactively communicate potential post-marketing related issue regarding the need for the development of a lower strength tablet for the following patients:

- Child Pugh class B hepatic impairment without coagulopathy
- Concurrently taking rivaroxaban with a P-gp and strong CYP3A4 inhibitor
- Concurrently taking rivaroxaban with a P-gp and mild or moderate CYP3A4 inhibitor with mild-moderate renal impairment

FDA provided additional clarification regarding this clinical pharmacology related issue in a 6/9/2009 meeting with the applicant. The applicant also requested a type C meeting with FDA, which was held on October 14, 2010, to obtain guidance from the Agency on the design of a proposed study to evaluate this complex DDI scenario involving the concurrent use of rivaroxaban with a P-gp and mild or moderate CYP3A4 inhibitor in patients with mild-moderate renal impairment.

This resubmission includes a response to the Clinical and Quality related deficiencies as well as the clinical pharmacology issue regarding the need for a lower dose formulation for Xarelto. Specifically the applicant submitted a response to the need for a lower dose formulation in each of the populations listed above with supplemental pop-PK based simulation reports and a revised protocol to evaluate the complex DDI scenario.

2.3 General Attributes

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.4 General Clinical Pharmacology

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.5 Intrinsic Factors

2.5.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.5.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are

not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.5.2.1 Elderly

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.5.2.2 Pediatric patients

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.5.2.3 Gender

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.5.2.4 Race

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.5.2.5 Renal impairment

See Section 2.6.2.2 and the 4/6/2009 clinical pharmacology review of the original NDA.

2.5.2.6 Hepatic impairment

In its formal response to the May 27, 2009, CR action included in this submission the applicant states that it does not consider exposure matching by using a lower rivaroxaban dose for the treatment of Child Pugh (CP) class B patients without coagulopathy appropriate. This is because the applicant's analysis of pharmacodynamic response from the dedicated hepatic impairment study (11003) reported a steeper PK/PD relationship between rivaroxaban plasma concentrations and prothrombin time (PT) in Child Pugh class B patients (i.e., 7.8 seconds/(100 µg/L) for Child Pugh class B patients versus 3.1 seconds/(100 µg/L) for healthy subjects with normal hepatic function). Sensitivity is derived from the slope of the exposure response plot of PT versus rivaroxaban concentration (Table 1).

Table 1: Descriptive statistics of individual slopes of linear relation between PT or PT ratio (PTR) and rivaroxaban concentration

Parameter	Prothrombin time (seconds)		
	CPA	CPB	Healthy
PT			
Mean Slope	0.0380	0.0784	0.0308
Mean Intercept	13.3	16.2	13.0
PTR			
Mean Slope	0.0029	0.0048	0.0024
Mean Intercept	1	1	1

$ raw dataset from the Applicant's study report 11003

FDA evaluated the applicant's proposal and analysis of the data from study 11003. As expected, a difference in the baseline PT between Child Pugh class B patients (16.2 seconds) and healthy subjects (13.0 seconds) is apparent. In order to focus on the sensitivity rather than baseline differences, FDA also obtained the slope describing the relationship between the ratio of PT to baseline (PTR) and rivaroxaban concentration in hepatic impairment and healthy subjects (Table 1) using the applicant's method of analysis. FDA also derived the expected PTR, based on the linear equation from the exposure response analysis of study 11003, using exposure data (i.e., C_{max}) from the

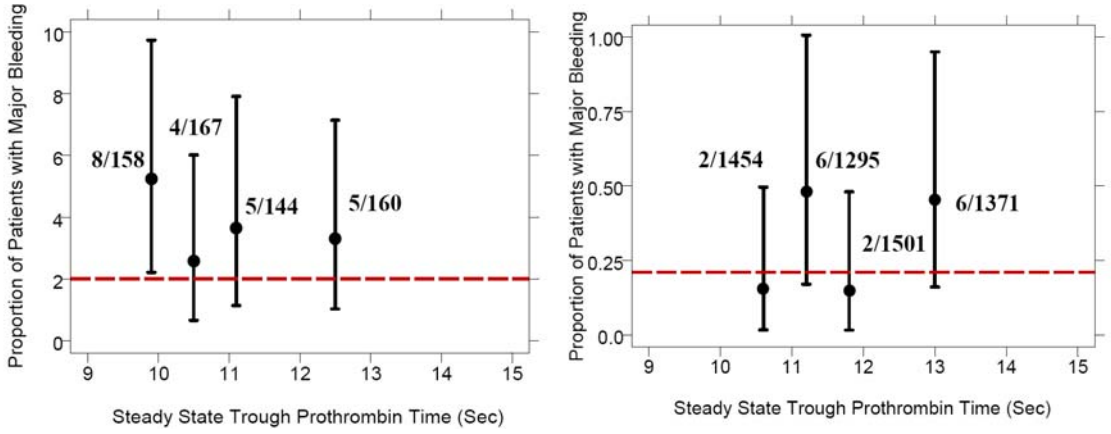
phase 2b study #11527 where 135 patients received Xarelto dosed at 10 mg daily. The results of this analysis are presented in Table 2.

Table 2: Estimated PTR for hepatic impairment patients and healthy subjects using phase 2 C_{max} estimates from study 11527[#] and the linear relation between PTR and rivaroxaban concentration from study 11003

Parameter	Concentration (μg/L)	Prothrombin time ratio (PTR)		
		CPA	CPB	Healthy
Study 11527 dosed 10 mg qd (n=135)				
5th Percentile	125	1.28	1.45	1.26
25th Percentile	111	1.34	1.55	1.31
Median	154	1.38	1.61	1.34
75th Percentile	91.4	1.46	1.75	1.41
95th Percentile	196	1.58	1.96	1.52

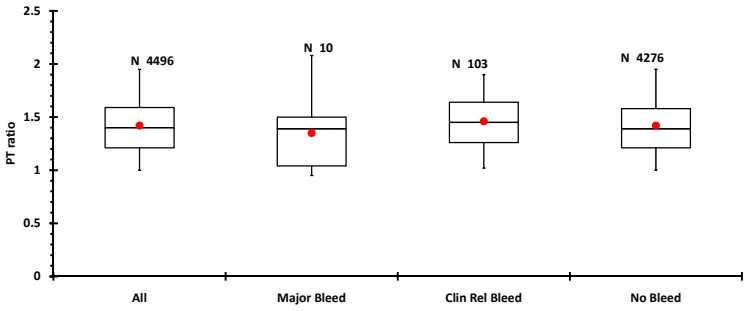
[#]Applicant's pop-PK report PK000131 for 135 patients receiving a Xarelto dose of 10 mg daily

Assuming exposure matching between Child Pugh class B patients and healthy subjects, where the Child Pugh class B patients where given half the dose of the healthy subjects (i.e., 5 mg daily), the expected median PTR (25^{th} , 75^{th}) would be approximately 1.61 (1.55,1.75) in the Child Pugh class B patients compared to approximately 1.34 (1.31, 1.41) in the health subjects. This difference is not likely to affect bleeding risk since the applicant's integrated safety summary reports found no relationship between PT or PTR and relevant bleeding risk. Plotting the major bleeding episodes versus the quartiles for PT from the Phase 2 11527 study and RECORD studies did not change this conclusion (Figure 1). Further, the PTR range for exposure matched Child Pugh class B patients is within the range reported by the applicant for the PTR seen in the RECORD studies (Figure 2) and submitted in support of the proposed safety of this drug. Further,



**The vertical black bars represent the mean with 95% confidence interval. Proportion of patients with major bleeding are demonstrated as black circles at the median PT of each quartile. The numbers against each quartile are the number of patients with major bleeding/total number of patients. The horizontal dashed red line represents the proportion of patients with major bleeding in the placebo arm (enoxaparin).*

Figure 1: PT-major bleeding relationship for study 11527 (left) and the combined analysis of RECORD studies (right).*



#Boxes report median (25th, 75th) and whiskers represent 5th and 95th percentiles for PTR. The red dot represents the mean PTR
$ Day 6 PTR measurements from PH35408 study report table 14.4/5

Figure 2: PTR versus bleeding risk from the combined analysis of data from the RECORD studies#,$

Therefore, FDA is not persuaded by the applicant's argument regarding this issue since the expected difference in PT ratio following exposure matching in Child Pugh class B patients appears unlikely to increase bleeding risk since the change is within the range observed in the phase 3 clinical studies and both PT and PTR are considered to have poor predictive value for bleeding risk. FDA still supports the original analysis from the 4/6/2009 clinical pharmacology review suggesting that the availability of a lower dose formulation (e.g., 5 mg tablet) will allow Child Pugh class B patients without coagulopathy to receive rivaroxaban (see Figure 5 in Section 4.1). The development of a lower dose formulation should still be considered as a post marketing commitment.

2.5.2.7 What pregnancy and lactation use information is there in the application?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.6 Extrinsic Factors

2.6.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.6.2 Drug-drug interactions

2.6.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.6.2.2 Is there a basis to suspect complex drug-drug-disease interactions?

Yes. The possibility for a significant change in exposure with the use of a combined CYP3A4 (weak to moderate) and P-gp/BCRP inhibitor in patients with renal impairment that may increase bleeding risk exists based on simulations from both the applicant and FDA. The applicant requested a type C meeting with FDA, which was held on October 14, 2010, to obtain guidance from the Agency on the design of a proposed study to evaluate this complex DDI scenario.

In its formal response to the May 27, 2009, CR action included in this submission the applicant acknowledged the need to better understand this potential complex interaction and affirmed it's plan to conduct a drug interaction study in the special population of patients with mild or moderate renal impairment concomitantly receiving erythromycin, a combined CYP3A4 (moderate) and P-gp inhibitor.

The applicant reports that based on its simulations using a population pharmacokinetic approach, it anticipates that combined use of a drug that would inhibit non-renal clearance by 30% and inhibit active renal clearance by 45% in patients with mild or moderate renal impairment may result in an approximate 2 and 2.4 fold increase in plasma AUC, respectively, when compared to subjects.

Using a physiologically based (PBPK) modeling approach FDA reached similar results, but also found that this complex DDI may be more pronounced in the elderly (**Table 3**).[1]

Table 3: Change in rivaroxaban exposure relative to combined CYP3A4/P-gp inhibition and renal impairment

Scenario	AUC_R of Rivaroxaban			
Observed		CL_{cr} (mL/min)		
		50-80	30-49	15-29
Reported exposure change	1.0	1.4[b]	1.5[b]	1.6[b]
+Erythromycin[a]	1.3			
		Renal Impairment		
Simulated	control	mild	moderate	severe
Young				
- Erythromycin	1.0	1.6	1.9	2.1
+ Erythromycin	1.2	1.9	2.4	2.6
Elderly				
- Erythromycin	1.0 (1.3[c])	1.5 (2.0[c])	1.7 (2.2[c])	1.8 (2.3[c])
+ Erythromycin	1.2 (1.6[c])	1.9 (2.5[c])	2.2 (2.9[c])	2.3 (3.0[c])

a=data from study 11865; b= data from study 11002; c= relative to young control

The Applicant proposes cautionary wording in the labeling regarding the use of Xarelto in this potential complex DDI scenario. FDA disagrees with this proposal since both the applicant and FDA simulations suggest the possibility of exposure changes consistent with those of other factors resulting in avoidance language due to concern regarding bleeding risk. In addition, since 53% of patients participating in the RECORD studies were greater than 65 years of age, the FDA simulations suggesting even greater exposure changes in the elderly a particular concern for the population that will likely use this drug for the proposed indication. Therefore, FDA recommends that the concomitant use of Xarelto with a combined weak to moderate inhibitor of CYP3A4 and an inhibitor of P-gp and/or BCRP (e.g., verapamil, erythromycin, diltiazem, dronedarone quinidine, ranolazine, amiodarone, felodipine, and azithromycin) should be avoided in patients with any degree of renal impairment.

The reviewer agrees with the Applicants plan to study this issue and continues to recommend that this issue be a post marketing commitment. Since this NDA submission is not the forum for FDA to provide comments on the draft protocol submitted by the applicant related to this issue, FDA recommends that the applicant resubmit it under the Xarelto IND for review and comment by the Agency.

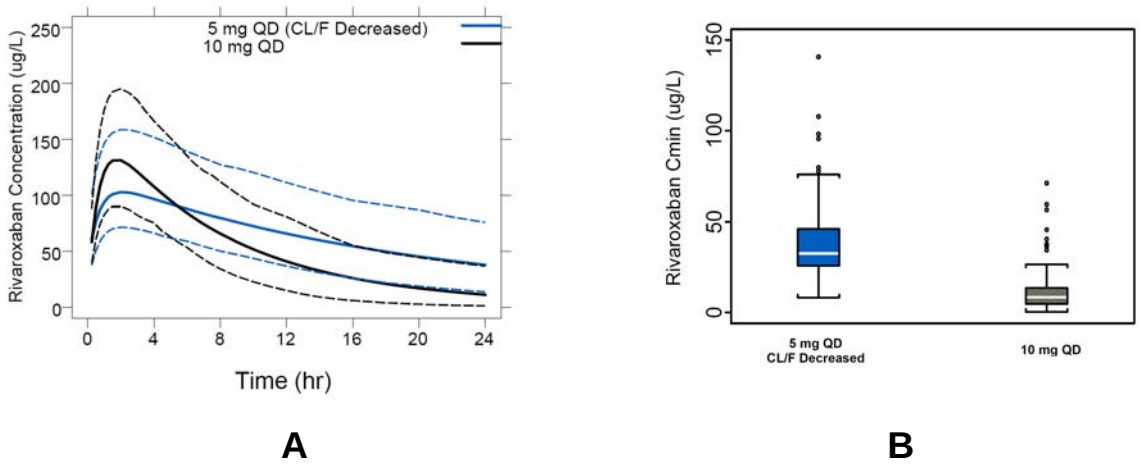
[1] P Zhao, L Zhang, JA Grillo, Q Liu, J M Bullock, YJ Moon, et.al. Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review. *Clin Pharmacol Ther* 2011;89:259-67.

2.6.2.3 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.6.2.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

In its formal response to the May 27, 2009, CR action included in this submission, the applicant states that it does not consider the use a lower rivaroxaban dose for patients concurrently receiving Xarelto and a P-gp and strong CYP3A4 inhibitor appropriate. This is because the applicant's simulations suggest that steady state, C_{trough} concentrations for 5 mg rivaroxaban co-administered with a P-gp and strong CYP3A4 inhibitor are estimated to be approximately 6-times higher compared to steady-state C_{trough} concentrations for 10 mg rivaroxaban administered alone (Figure 3).. The applicant's simulations were performed using the PK data of patients receiving rivaroxaban 10 mg once daily from the Phase 2 dose ranging study 11527 and inhibiting clearance (both oxidative metabolism (CYP3A4) and renal secretion (P-gp)) to the extent observed in the Phase 1 drug interaction studies with ritonavir (11935) and ketoconazole (11936).



**Inhibition effect was accomplished by reducing clearance by a factor of 0.39 and leaving Vd/F constant.*
[#] Simulated plasma concentration profile in patients (n=135) taking 10 mg QD without strong CYP3A4 and P-gp inhibitor (black) compared to the same patients (n=135) taking 5 mg QD with strong CYP3A4 and P-gp inhibitor (blue). The solid blue and black lines represent the mean while the dashed blue and black lines are the 5th and 95th percentiles.
[$] Predicted steady state Cmin levels in patients (n=135) with 5 mg QD dose taking strong inhibitors of both CYP3A4 and P-gp (blue) compared to observed steady state trough levels in same patients (n=135) taking 10 mg QD without strong CYP3A4 and P-gp inhibitor (grey).

Figure 3: Applicant's Simulated Steady-State Plasma-Concentration Time Profiles[#] (A) and expected trough concentrations[$] (B) of Rivaroxaban in Patients receiving 5 mg rivaroxaban Daily With Inhibition* of Oxidative Metabolism (i.e., CYP3A4) and Renal Secretion (i.e. P-gp) Versus 10 mg Rivaroxaban Daily Without Inhibition

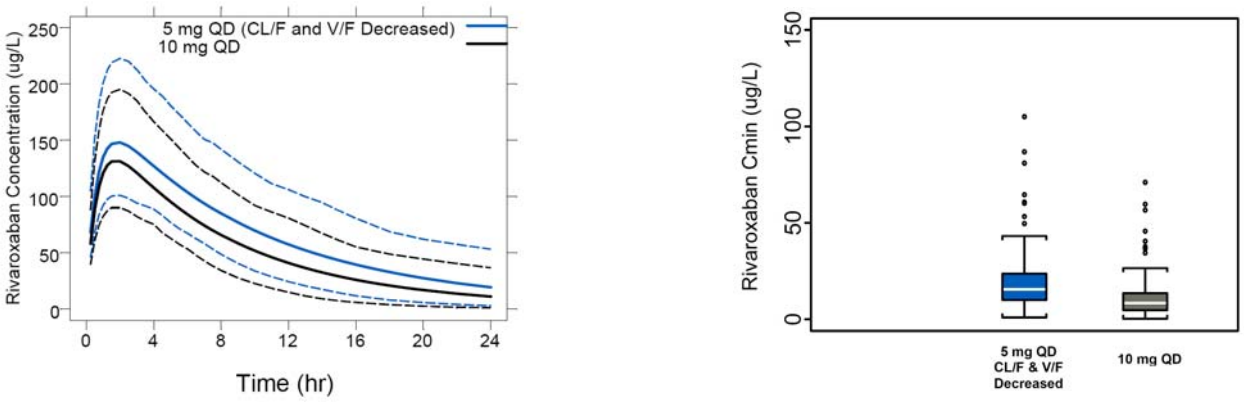
In evaluating the applicant's simulations, FDA noted that in reducing clearance to that seen in the 11935 and 11936 studies (i.e., 0.39-fold) the applicant left the volume of distribution (Vd/F) constant. This causes half-life to be prolonged and thus results in higher trough levels. In contrast, data from five drug interaction studies with combined P-gp and CYP3A4 inhibitors of various potencies, submitted in the original NDA application, show both Vd/F and CL/F as prominent factors causing increase in exposures such that half-life was minimally changed. The rationale for this change in Vd/F is not clear from available information regarding rivaroxaban, but the contribution of a yet unidentified influx transporter (e.g., OAT, OATP, OCT, etc.) can not be ruled out since many of the drugs in Table 4 may also affect these transporters.

Table 4: Relative change in rivaroxaban exposure and relevant PK parameters following concurrent use with combined P-gp and CYP3A4 inhibitors of various potencies

DDI Study*	Ratio INH+Rivaroxaban/Rivaroxaban alone				
	AUC	C_{max}	CL	$T_{1/2}$	Vd
Ketoconazole 200 mg	1.8	1.5	0.54	0.78	0.42
Ketoconazole 400 mg	2.6	1.7	0.39	1.37	0.53
Ritonavir	2.5	1.55	0.4	1.21	0.48
Clarithromycin	1.5	1.4	0.66	0.85	0.55
Erythromycin	1.3	1.3	0.75	0.86	0.64

*Data from Applicant's study reports 10992, 11936, 11935, 11865, 12612

FDA repeated the applicant's simulations using the same method except both CL/F and Vd/F were adjusted to the extent as observed in the Phase 1 drug interaction study with ritonavir (11935) and ketoconazole (11936). CL/F and Vd/F were reduced by a factor of 0.39 and 0.48, respectively. These simulations did not suggest a significant change in steady-state C_{trough} concentrations for 5 mg rivaroxaban co-administered with a P-gp and strong CYP3A4 inhibitor as compared to steady-state C_{trough} concentrations for 10 mg rivaroxaban administered alone (Figure 4).. Furthermore, the half-life was increased by 1.25-fold which is consistent with the observations of the dedicated phase 1 drug interaction studies in Table 4 . Additional information regarding this FDA analysis can be found in Section 4.1.



**Inhibition effect was accomplished by reducing clearance by a factor of 0.39 and Vd by a factor of 0.48, respectively.*
[#] Simulated plasma concentration profile in patients (n=135) taking 10 mg QD without strong CYP3A4 and P-gp inhibitor (black) compared to the same patients (n=135) taking 5 mg QD with strong CYP3A4 and P-gp inhibitor (blue). The solid blue and black lines represent the mean while the dashed blue and black lines are the 5th and 95th percentiles.
[$] Predicted steady state Cmin levels in patients (n=135) with 5 mg QD dose taking strong inhibitors of both CYP3A4 and P-gp (blue) compared to observed steady state trough levels in same patients (n=135) taking 10 mg QD without strong CYP3A4 and P-gp inhibitor (grey).

Figure 4: FDA's Simulated Steady-State Plasma-Concentration Time Profiles[#] (A) and expected trough concentrations[$] (B) of Rivaroxaban in Patients receiving 5 mg rivaroxaban Daily With Inhibition* of Oxidative Metabolism (i.e., CYP3A4) and Renal Secretion (i.e. P-gp) Versus 10 mg Rivaroxaban Daily Without Inhibition

Therefore, FDA is not persuaded by the applicant's argument regarding this issue given the limitations of its simulations noted above. FDA still supports the original analysis from the 4/6/2009 clinical pharmacology review suggesting that the availability of a lower dose formulation (e.g., 5 mg tablet) will allow patients concurrently receiving Xarelto and a P-gp and strong CYP3A4 inhibitor to receive rivaroxaban (see Figure 4 in Section 4.1). The development of a lower dose formulation should still be considered as a post marketing commitment.

2.6.2.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

In its formal response to the May 27, 2009, CR action included in this submission the applicant proposes that labeling should recommend that no dose adjustment be recommended in subjects with normal renal function or subjects with mild to moderate renal impairment receiving strong pure P-gp inhibitors. Since FDA is unaware of any approved drugs that are pure strong P-gp inhibitors this proposal seems reasonable.

Since FDA does not believe sufficient evidence exists at this time to accurately and consistently qualify the potency of a P-gp inhibitor (e.g., strong, moderate weak), it disagrees with the applicant's use of these terms in labeling and recommends they be removed.

FDA continues to suggest that the applicant evaluate the effect of a P-gp inhibitor with limited CYP3A4 inhibitory activity (e.g., quinidine) on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in healthy subjects. This study will provide additional information to support estimates, derived from ADME or DDI studies where the true effect of P-gp could not be clearly identified, regarding the involvement of P-gp or possibly other transporters in rivaroxaban elimination so that appropriate dosing recommendations can be created following the development of the 5 mg tablet formulation.

Additional information regarding P-gp transporters can be found in the 4/6/2009 clinical pharmacology review of the original NDA.

2.6.2.6 Are there other metabolic/transporter pathways that may be important?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.6.2.7 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.6.2.8 What other co-medications are likely to be administered to the target patient population?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.6.2.9 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.6.2.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.6.2.11 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.6.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.7 General Biopharmaceutics

See the 4/6/2009 clinical pharmacology review of the original NDA.

2.8 Analytical Section

See the 4/6/2009 clinical pharmacology review of the original NDA.

3 Detailed Labeling Recommendations

The following are pages excepted from the applicant's proposed labeling that relate to clinical pharmacology. The FDA recommendations are in grey.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 Appendices

4.1 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRIC REVIEW

Application Number	22406
Submission Date	30 Dec 2010
Compound (Dosing Regimen)	Rivaroxaban 10 mg tablet taken once daily
Clinical Division	DDOP
Primary PM Reviewer	Nitin Mehrotra, Ph.D.
PM Team Leader	Christine Garnett, Pharm.D.

Table of Contents

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

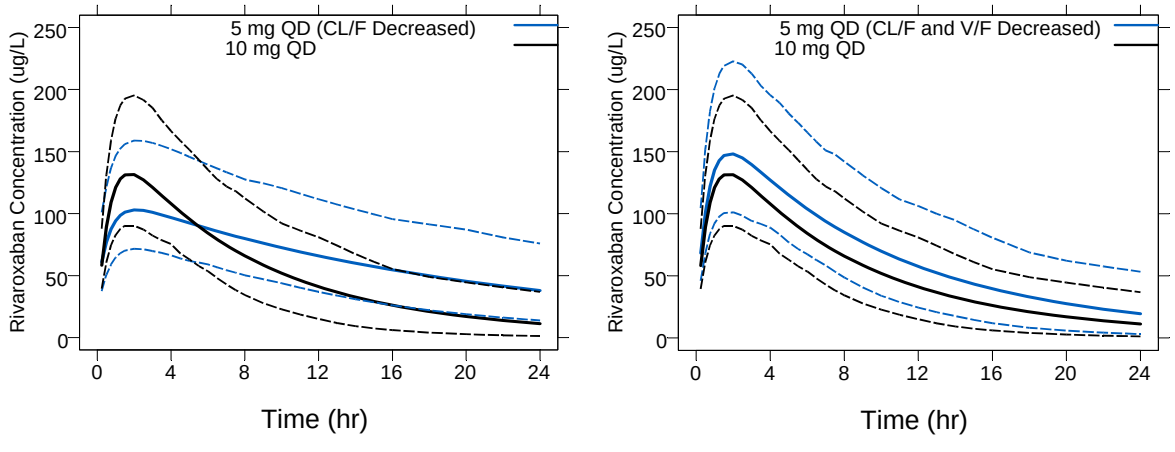
The following key questions were addressed in this pharmacometric review.

1.1.1 Is the sponsor's rationale for not recommending 5 mg QD dose of rivaroxaban in patients taking concomitant strong CYP3A4 and PgP inhibitors (e.g. ketoconazole, ritonavir etc) appropriate?

No. The sponsor's justification is based on PK simulations that assume individual clearance of each patient is reduced by a factor of 0.39 (**Figure 1**, left). This assumption is not supported by the phase 1 drug interactions studies with ketoconazole and ritonavir. In these studies, the mean rivaroxaban AUC was increased by ~2.6-fold, however, there was minimal change in half-life. This implies that volume of distribution (V/F) is also decreased.

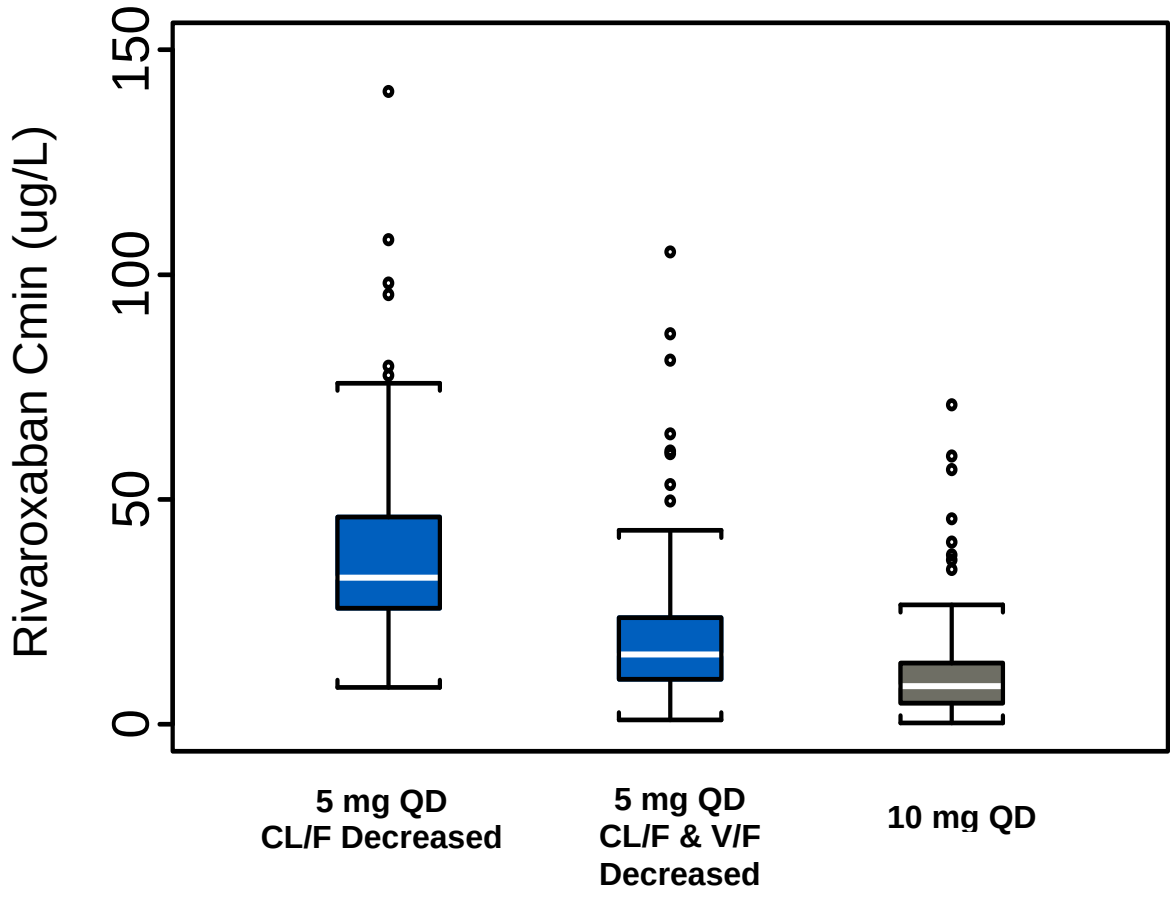
Based on sponsor's PK simulations, the half life is increased by ~2.6 fold and steady state C_{min} levels are 3.4-fold higher in patients taking 5 mg QD dose with strong CYP3A4 and P-gp inhibitor compared to patients taking 10 mg QD dose without any strong CYP3A4 and P-gp inhibitor (**Figure 2**). As a result, the sponsor concluded that it is not appropriate to administer a lower dose (5 mg QD) of rivaroxaban to patients taking strong inhibitors of both CYP3A4 and P-gp. We do not agree with this conclusion because the simulations are not consistent with phase 1 data where in the presence of strong CYP3A4 and P-gp inhibitors, the half-life was only increased by 1.2- to 1.4-fold.

Figure 1: Sponsor's (left) and FDA Reviewer's (right) simulated plasma concentration profile in patients (n=135) taking 10 mg QD without strong CYP3A4 and P-gp inhibitor (black) compared to the same patients (n=135) taking 5 mg QD with strong CYP3A4 and P-gp inhibitor (blue). The solid blue and black lines represent the mean while the dashed blue and black lines are the 5th and 95th percentiles.



FDA repeated the pharmacokinetic simulations with reducing the individual estimates of both CL/F and V/F by factor of 0.39 and 0.48, respectively, as observed in the phase 1 drug interaction studies with strong CYP3A4 and P-gp inhibitors (**Figure 1**, right). The results show that the plasma concentration-time profiles were similar for the two scenarios with overlapping steady state C_{min} values (**Figure 1**, right and **Figure 2**). Furthermore, the half life was increased by 1.25-fold which is consistent with the observations of the dedicated phase 1 drug interaction studies.

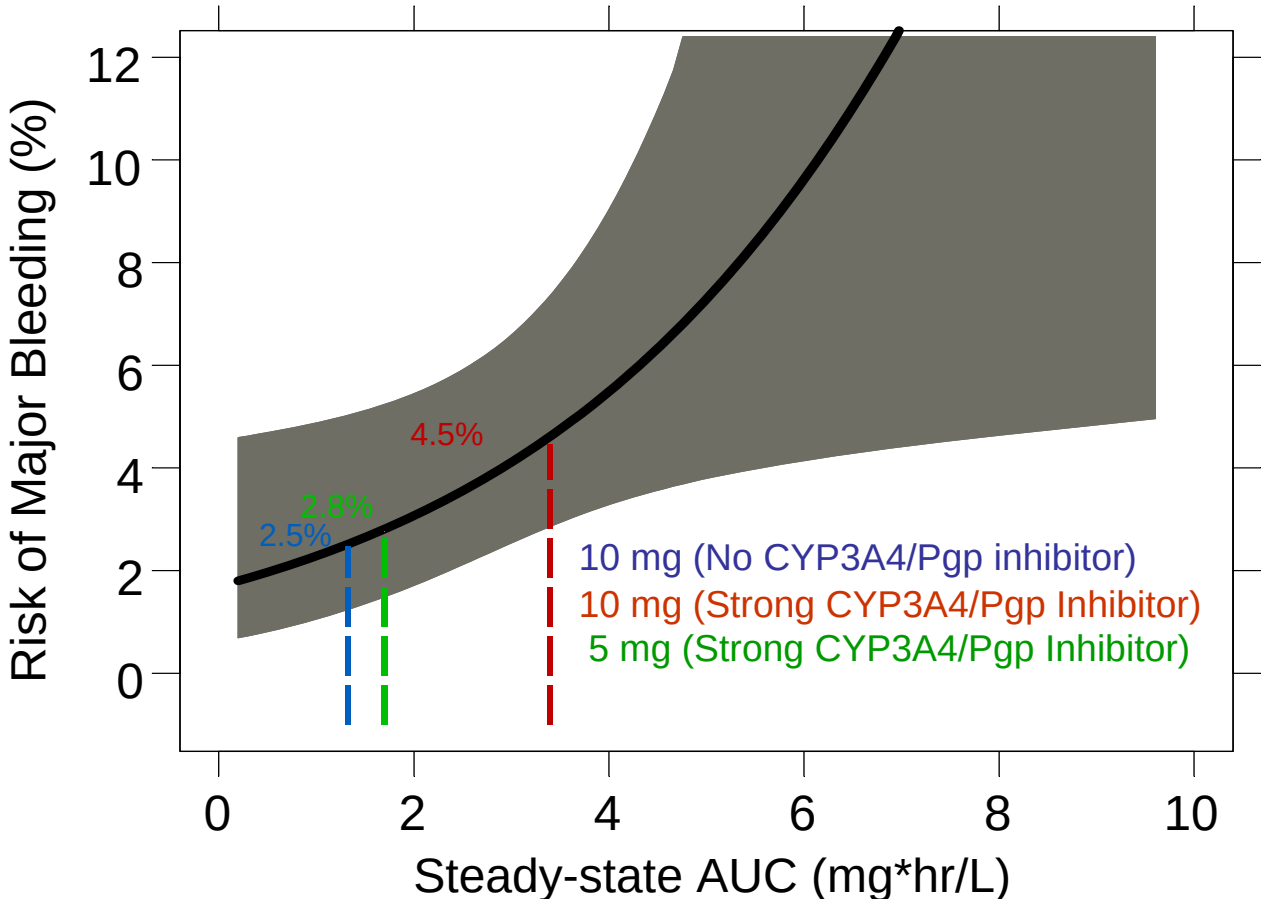
Figure 2: Predicted steady state C_{min} levels in patients (n=135) with 5 mg QD dose taking strong inhibitors of both CYP3A4 and P-gp (blue) compared to observed steady state trough levels in same patients (n=135) taking 10 mg QD without strong CYP3A4 and P-gp inhibitor (grey).



Thus, we would continue to recommend that the availability of a lower dose of 5 mg would enable matching exposure and risk of major bleeding in patients taking strong inhibitors of both CYP3A4 and P-gp. A significant exposure-major bleeding relationship was established with increased risk of major bleeding with increasing exposures (For details refer to clinical pharmacology review in DAARTs by Drs. Grillo and Tornoe dated 4/2/2009). The mean AUC (exposure) in normal patients receiving 10 mg was approximately 1300 ug*h/ml (1.3 mg*hr/ml) with a risk of major bleeding of 2.5%. A patient taking concomitant strong CYP3A4 and P-gp inhibitor will have 2.6-fold increase in exposure and the risk of major bleeding increases to 4.5%. By administering 5 mg to a patient taking concomitant strong CYP3A4 and P-gp inhibitor, the exposure will be

similar (slightly higher) than a normal patient and the risk of major bleeding is reduced to 2.8% (**Figure 3**).

Figure 3: Risk of major bleeding vs. steady state AUC. The figure is modified from the FDA's presentation at the CRD advisory committee meeting (March 19, 2009).

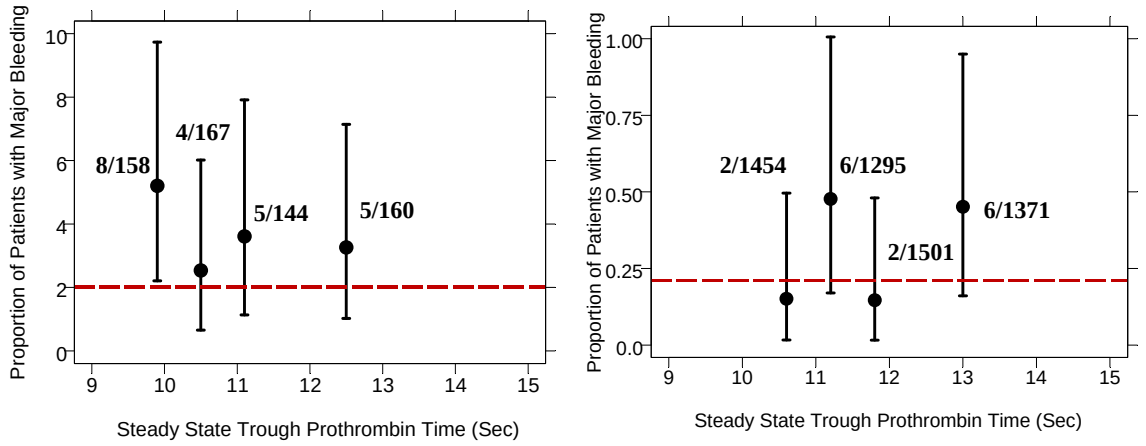


1.1.2 Is the sponsor's rationale for not recommending 5 mg QD dose of rivaroxaban in patients with moderate hepatic impairment (Child Pugh B) appropriate?

No. The sponsor presents an argument that subjects with moderate hepatic impairment have higher baseline prothrombin time (PT) (approximately 3 sec higher) and a steeper concentration-PT relationship (1.7-fold higher slope) compared to subjects with normal hepatic function patients. However, the clinical relevance of the increased baseline PT and higher sensitivity in moderate hepatic impairment is not clear. PT-major bleeding relationship was explored for dose ranging study 11527 (5-40 mg QD) and for the four

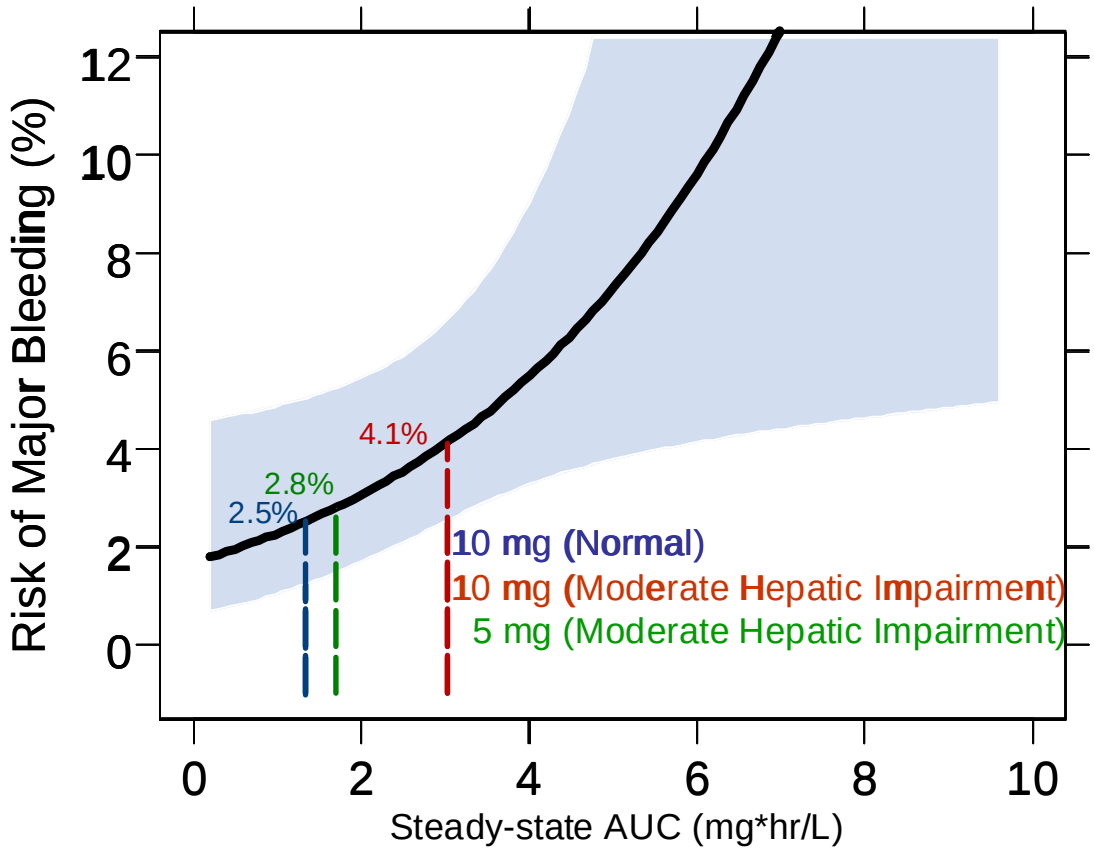
pivotal registration trials (combined analysis using RECORD 1, 2, 3 and 4 at 10 mg QD dose level). There was no relationship observed between steady state trough PT levels and proportion of patients with major bleeding across the PT range observed in 11527 and RECORD studies (**Figure 4**). The 5th and 95th percentiles of steady state trough PT in 11527 and RECORD studies were 9.6, 14.5 sec and 10.3, 14.4 sec, respectively.

Figure 4: PT-major bleeding relationship for study 11527 (left) and RECORD studies (right). The vertical black bars represent the mean with 95% confidence interval. Proportion of patients with major bleeding are demonstrated as black circles at the median PT of each quartile. The numbers against each quartile are the number of patients with major bleeding/total number of patients. The horizontal dashed red line represents the proportion of patients with major bleeding in the placebo arm (enoxaparin).



Thus, we would continue to recommend a lower dose of 5 mg QD in moderate hepatic impairment in order to match exposures and risk of major bleeding (**Figure 5**).

Figure 5: Risk of major bleeding vs. steady state AUC. The figure is taken from the FDA's presentation at the CRD advisory committee meeting (March 19, 2009).



1.2 Label Statements

There are no new labeling statements proposed based on the current analysis. The analysis was conducted to support our previous recommendation to use 5 mg QD dose of rivaroxaban in specific populations (patients taking concomitant strong CYP3A4 and P-gp inhibitor or patients with moderate hepatic impairment). For detailed labeling recommendations from the first review cycle of the NDA, please refer to clinical pharmacology review dated 4/2/2009 by Drs. Joe Grillo and Chris Tornoe in DAARTS.

2 Pertinent Regulatory Background

Rivaroxaban is a selective Factor Xa (FXa) inhibitor that can be orally administered. The proposed indication is for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery at the dose of 10 mg QD.

Original application for this NDA was submitted in 2008. The efficacy of rivaroxaban was evaluated in over 6000 patients participating in 4 randomized clinical trials of prevention of venous thromboembolism (VTE) following total hip replacement (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 the four studies. Exposures in several specific populations (e.g. moderate or severe hepatic impairment, patients taking strong CYP3A4 and P-gp inhibitors, severe renal impairment etc) were increased. Furthermore, significant exposure-response relationship was identified for major bleeding. Thus, a dose adjustment in some of the specific populations was identified as an appropriate way to match exposures and risk of major bleeding. FDA recommended the sponsor to develop a lower strength tablet to address this need.

The sponsor received complete response from FDA for the application for issues related to clinical site inspections, product quality and the potential risk of liver toxicity. Although, there were no clinical pharmacology issues related to complete response, FDA asked sponsor to provide a description of their plan to develop a lower strength formulation to address the dose modification in specific populations outlined above.
The current submission is a complete response from the sponsor in which the sponsor provides argument against use of lower dose (5 mg QD) in patients with moderate hepatic impairment or concomitant use of strong CYP3A4 and P-gp inhibitors.

3 Results of Sponsor's Analysis

3.1 Rationale for not recommending 5 mg QD dose in specific populations

3.1.1 Patients with concomitant administration of strong inhibitors of CYP3A4 and P-gp

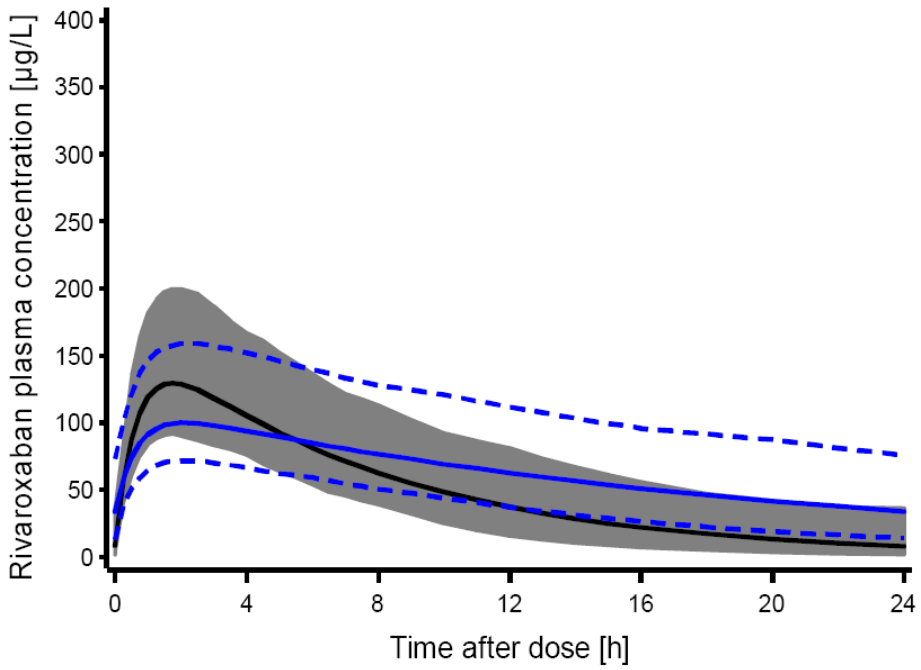
In subjects with normal renal function, co administration of 10 mg rivaroxaban with strong inhibitors of both CYP3A4 and P-gp (i.e., ketoconazole and ritonavir) resulted in plasma rivaroxaban AUC increases of more than two-fold and prolonged $t_{1/2}$ values of 1 to 2 hours. The use of strong inhibitors of both CYP3A4 and P-gp was not allowed in the Phase 3 Record program; hence very limited to no clinical data are available.
In order to evaluate the appropriateness of a potential dose reduction to 5 mg in subjects receiving strong inhibitors of both pathways, simulations were performed using PK data of patients receiving rivaroxaban 10 mg once daily as obtained from the Phase 2 dose ranging study 11527 and inhibiting both oxidative metabolism (CYP3A4) and renal secretion (P-gp) to the extent as observed in the Phase 1 drug interaction study with ritonavir and ketoconazole. The results of these simulations suggest that a dose-reduction to 5 mg rivaroxaban once daily in subjects with a combined strong inhibition of both CYP3A4 and P-gp results in plasma rivaroxaban concentration-time profiles that differ from those of subjects receiving 10 mg rivaroxaban once daily alone. This was done by a multiplication of individual CL values by a factor 0.39 (i.e. reduction by a factor of about 2.6) and simulating the concentration-time profile with 5 mg QD dose. These simulations suggest that concomitant administration of 5 mg rivaroxaban with a strong inhibitor of

both CYP3A4 and P-gp would result in a prolonged elimination half-life, and greater accumulation following multiple-dosing compared to 10 mg rivaroxaban alone (**Figure 6**). At steady state, C_{min} concentrations for 5 mg rivaroxaban coadministered with a strong inhibitor of both CYP3A4 and P-gp are estimated to be approximately 6-times higher as compared to steady-state C_{min} concentrations for 10 mg rivaroxaban administered alone (

Figure 7).
The sponsor therefore does not consider a lower dose of 5 mg in this specific situation to be appropriate, and recommends that strong inhibitors of both CYP3A4 and P-gp (such as ketoconazole and ritonavir) not be used with rivaroxaban in the general patient population, not even at a lower dose.

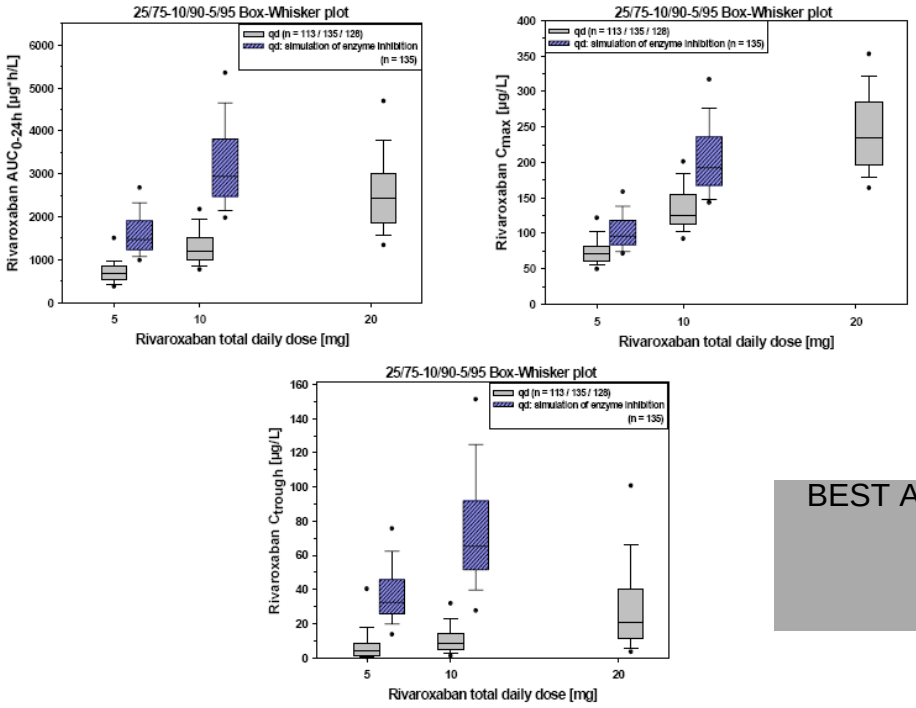
(Source: Section 4, Rivaroxaban: Complete Response to FDA Letter of May 27, 2009.pdf and clinical-pk-supportive-calculations-and-simulations.pdf)

Figure 6: Simulated steady-state plasma-concentration time profiles of rivaroxaban in patients receiving 5 mg rivaroxaban once daily with inhibition of oxidative metabolism (i.e., CYP3A4) and renal secretion (i.e. P-gp) (blue curves) versus patients receiving 10 mg rivaroxaban once daily without inhibition (black curve with shaded area) as observed in the phase 2 dose-ranging study 11527 (Report PK000131).



(Source: Figure 1, clinical-pk-supportive-calculations-and-simulations.pdf)

Figure 7: Estimated rivaroxaban steady-state AUC, C_{max} and C_{trough} in patients receiving 5 or 10 mg rivaroxaban once daily with inhibition of oxidative metabolism (i.e., CYP3A4) and renal secretion (i.e. P-gp) versus observed rivaroxaban steady-state exposure parameters in patients receiving 5 to 20 mg rivaroxaban once daily without inhibition as observed in the phase 2 dose-ranging study 11527 (Report PK000131).



(Source: Figure 2, clinical-pk-supportive-calculations-and-simulations.pdf)

Reviewer's Comments:

- *Sponsor used incorrect assumptions for simulation which contradicts the results of the phase 1 drug interaction studies with strong CYP3A4 and P-gp inhibitors (ketoconazole and ritonavir). In these drug interaction studies, the increase in 2.6-fold AUC was due to both reduction in apparent clearance and volume of distribution. However, in the simulations, sponsor only reduced the individual estimates of clearance and not volume of distribution which resulted in an increase in steady state trough levels and half-life by 3.4 and 2.6-fold, respectively. It is important to note that half-life of rivaroxaban was only increased by 1.2-1.4 fold in the drug interaction studies with strong CYP3A4 and P-gp inhibitors.*

- *Reviewer repeated the analysis using correct assumptions and concluded that exposure matching is possible by reducing the dose to 5mg QD in patients taking strong inhibitors of both CYP3A4 and P-gp.*

3.1.2 Patients with moderate hepatic impairment

The effect of hepatic impairment on rivaroxaban PK was studied in subjects with mild or moderate hepatic impairment according to the Child Pugh classification (Study 11003); coagulopathy is not part of the C-P classification, but PT prolongation is. Baseline PT values in healthy subjects with normal hepatic function and cirrhotic patients with mild hepatic impairment [Child Pugh class A] were comparable (mean: 12.6 seconds and 13.1 seconds, respectively), whereas baseline PT was significantly prolonged in all cirrhotic patients with moderate hepatic impairment [Child Pugh classB] (mean: 16.0 seconds). In the Child Pugh class A subjects, no difference in PK or PD (i.e., Factor Xa and PT) response was observed when compared to healthy subjects. In the Child Pugh class B subjects, rivaroxaban mean AUC was increased 2.3-fold compared to subjects with normal hepatic function. The increase in plasma rivaroxaban AUC seen in the Child Pugh class B subjects was driven by both reduced hepatic and renal clearance (the C-P class B subjects had a reduced renal elimination of rivaroxaban similar to that seen in subjects with moderate renal impairment as reported in Study 11002). Furthermore, PT both at baseline and during treatment with rivaroxaban was more pronounced in Child Pugh class B subjects due to the underlying hepatic disease which impairs the ability of the liver to synthesize clotting factors. This led to a increased pharmacodynamic response and a steeper PK/PD relationship between rivaroxaban plasma concentrations and PT in Child Pugh class B patients (7.8 seconds/(100 μg/L) for C-P class B patients versus 3.1 seconds/(100 μg/L) for healthy subjects with normal hepatic function).

Although coagulopathy may or may not be present at the time of classification or diagnosis of Child Pugh class B patients, these patients may be predisposed for developing coagulopathy. Given that Child Pugh class B patients have significant liver disease, they are likely to have higher plasma exposures of rivaroxaban and an increased pharmacodynamic response. In the Phase 3 RECORD program, subjects with a medical history of hepatic disease were included; however, no information is available regarding their categorization according to the Child Pugh classification. Patients, with known significant hepatic disease (i.e., acute clinical hepatitis, chronic active hepatitis, liver cirrhosis) were excluded from these clinical trials. The Sponsor therefore does not consider it appropriate to use a lower rivaroxaban dose for the treatment of Child Pugh class B patients without coagulopathy and recommends that rivaroxaban use be contraindicated in patients with Child Pugh class B hepatic impairment.

(Source: Section 4, Rivaroxaban: Complete Response to FDA Letter of May 27, 2009.pdf)

Reviewer's Comments:

- *The slope estimates reported by the sponsor are based on a stage two approach where individual slopes were calculated for each patient first and mean of slopes was calculated thereafter. Sponsor also conducted non-linear mixed effects modeling using the same data and came up with a slightly different estimates of slopes for normal and moderate hepatic impaired subjects. Based on the population PK analysis, the slope for subjects with moderate hepatic impairment and normal subjects was 8.2 and 4.9 sec/(100 μg/L), respectively such that slope for moderate hepatic impaired subject was 1.7-fold of the normal healthy subject.*
- *Sponsor did not support their argument with PT-bleeding relationship to show if higher PT values possible in moderate hepatic impairment results in higher risk of bleeding. Reviewer explored relationship between PT and major bleeding.*
- *Sponsor also evaluated concentration-PT relationship for the study 11527 which was the dose ranging study (5-40 mg QD dose) in patients undergoing hip replacement. The slope for these patients without any hepatic impairment was much shallow (0.8 sec/ (100 μg/L), ppk-000131 study report) compared to what was observed in the other studies. This might suggest that concentration-PT relationship is different between healthy subjects and patients. Since, this is the most relevant patient population, it implies that the PT would remain relatively unchanged over a wide range of rivaroxaban concentrations.*

4 Reviewer's Analysis

4.1 PK simulations and PT-major bleeding relationship

4.1.1 Objectives

The two main objectives of the reviewer's analysis were:

- Repeat sponsor's simulations with correct assumptions (decrease in both apparent clearance and volume of distribution).
- Explore PT-major bleeding relationship for the dose ranging study (study 11527, 5-40 mg QD dose) and phase 3 trials (RECORD 1, 2, 3 and 4).

4.1.2 Methods

PK Simulations in subjects taking concomitant strong CYP3A4 and P-gp inhibitors: Individual estimates of the clearance and volume of distribution were scaled by a factor of 0.39 and 0.48, respectively as observed in the drug interaction studies. Individual concentration-time profiles were then generated and steady state C_{max}, C_{min} and AUC (0-24h) were estimated.

PT-major bleeding relationship:
PT-major bleeding relationship was explored for:

- Phase 2 dose ranging study (study 11527, 5 to 40 mg QD) and
- Combined analysis using 4 pivotal registration trials at one dose level of 10 mg QD. The data from RECORD 1, 2, 3 and 4 was pooled for the analysis.

Steady state trough PT values were used for the analysis. PT values were divided into quartiles and the proportion of patients with major bleeding was plotted against median of each quartile.

4.1.3 Datasets

The datasets utilized for the analysis are summarized below**.**

Study Number	Name	Link to EDR
11527	beev01.xpt	\\cdsesub1\EVSPROD\NDA022406\\0000\m5\datasets\11527\analyses\beev01.xpt
	lab.xpt	\\cdsesub1\EVSPROD\NDA022406\\0000\m5\datasets\11527\analyses\lab.xpt
	patinfo.xpt	\\cdsesub1\EVSPROD\NDA022406\\0000\m5\datasets\11527\analyses\patinfo.xpt
RECORD 1, 2, 3 and 4	beev01.xpt	\\cdsesub1\EVSPROD\NDA022406\\0008\m5\datasets\iss\analysis\beev01.xpt
	patinfo.xpt	\\cdsesub1\EVSPROD\NDA022406\\0008\m5\datasets\iss\analysis\patinfo.xpt
	lab11354.xpt	\\cdsesub1\EVSPROD\NDA022406\\0008\m5\datasets\iss\analysis\lab11354.xpt
	lab11355.xpt	\\cdsesub1\EVSPROD\NDA022406\\0008\m5\datasets\iss\analysis\lab11355.xpt
	lab11356.xpt	\\cdsesub1\EVSPROD\NDA022406\\0008\m5\datasets\iss\analysis\lab11356.xpt
	lab11357.xpt	\\cdsesub1\EVSPROD\NDA022406\\0008\m5\datasets\iss\analysis\lab11357.xpt

4.1.4 Software

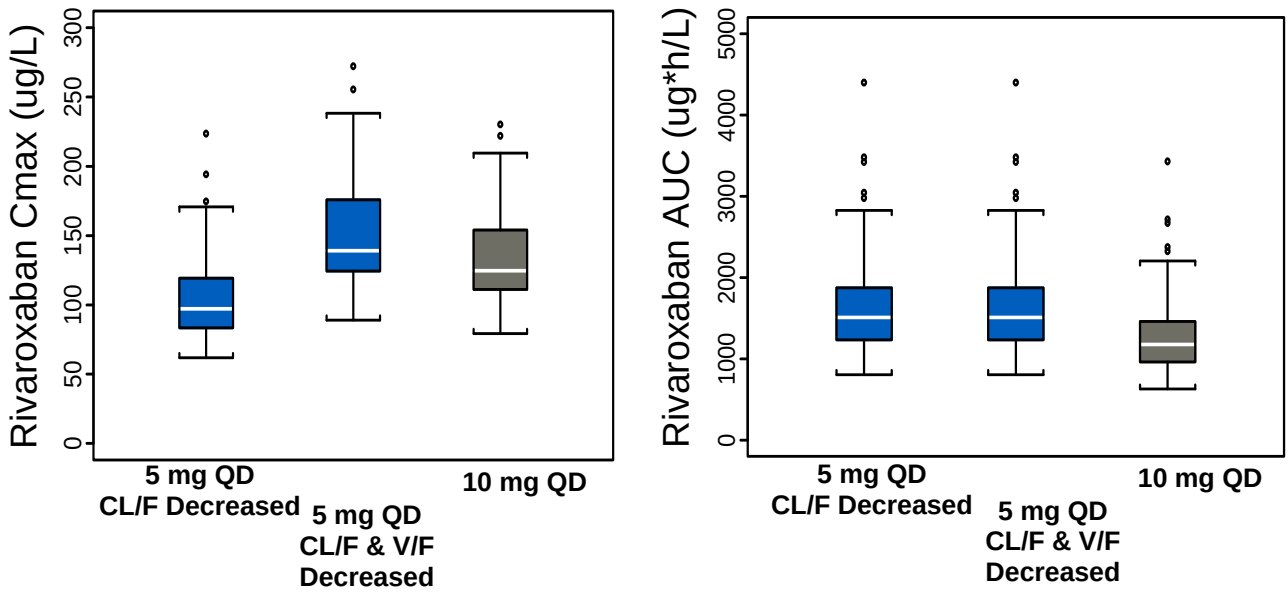
NONMEM version 6, SAS 9.2 and TIBCO Spotfire S-Plus 8.1were used for analyses.

4.1.5 Results

The reduction of dose to 5 mg QD in patients taking concomitant strong inhibitors or CYP3A4 and P-gp is reasonable. It results in overlapping steady state trough levels (**Figure 2**) and comparable C_{max} and AUC (**Figure 8**). Furthermore, as seen in **Figure 3**,

reduction of dose in this specific patient population will result in similar (slightly higher risk of major bleeding).

Figure 8: Predicted steady state C_{max} and AUC in patients with 5 mg QD dose taking strong inhibitors of both CYP3A4 and P-gp (blue) compared to observed steady state trough levels in same patients (n=135) taking 10 mg QD without strong CYP3A4 and P-gp inhibitor (grey**).**



PT-major bleeding relationship could not be identified for rivaroxaban in this patient population. Thus clinical relevance of higher PT levels in patients with moderate hepatic impairment is not clear.

4.2 Referenced Scientific Papers

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/s/

JOSEPH A GRILLO
06/03/2011

NITIN MEHROTRA
06/03/2011

CHRISTINE E GARNETT
06/03/2011

JULIE M BULLOCK
06/03/2011

NAM ATIQUR RAHMAN
06/03/2011

ONDQA (Biopharmaceutics) Review

NDA:	22-406
Submission Date:	12/27/2010; 03/17/2011; 4/28/2011
Product:	XARELTO^{TM} (Rivaroxaban) tablets, 10 mg
Type of Submission:	Sponsor's Complete Response
Sponsor:	Johnson & Johnson
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: The original New Drug Application (NDA 22-406) is for an immediate release 10-mg oral tablet of Rivaroxaban (XARELTO^{TM}) for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery filed July 29th, 2008, by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) on behalf of Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI). The Agency issued a Complete Response action letter dated 27 May, 2009 for the original submission citing several deficiencies. The purpose of this report is to review the sponsor's response to the Agency's recommendation of changing the dissolution specifications for the proposed product (b) (4) to *Q* = (b) (4) *at **15** minutes.*

In response to an information request communication dated March 17, 2011 from the Agency, the sponsor provided an explanation requesting the Agency to grant a specification of (b) (4). Upon review of the sponsor's explanation, the Agency issued another information request letter dated April 8, 2011, asking the sponsor that they need to adhere to the Agency's previously suggested dissolution specification of *Q* = (b) (4) *at **15** minutes.*

In the communication dated April 28, 2011, the sponsor agreed to the dissolution specification of *Q*= (b) (4) *in 15 minutes* for both Bayer and Johnson & Johnson-manufactured rivaroxaban 10 mg drug product, using the dissolution methodology described in the dossier and as summarized below.

Recommendation:

*As per the recommendation by the Agency for dissolution method and specification in the original submission review (put in DARRT on 4/1/2009), review of the CR response (put in DARRT on 3/23/2011) and the IR letter dated 4/28/2011, the sponsor via communication dated April 28, 2011, agreed to the dissolution specification of **Q** =* (b) (4) ***in 15 minutes** for both Bayer and Johnson & Johnson-manufactured rivaroxaban 10 mg drug product, using the dissolution methodology described in the dossier and as summarized below:*

Apparatus	USP apparatus 2 (paddle)
Dissolution medium	900 mL acetate buffer pH 4.5 + 0.2 % SDS
Rotation speed	75 rpm
Analytical procedure	HPLC with UV/VIS detection or UV/VIS spectrophotometry Both analytical procedures lead to the same results and may thus be used interchangeably.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

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/s/

TAPASH K GHOSH
05/02/2011

PATRICK J MARROUM
05/02/2011

ONDQA (Biopharmaceutics) Review

NDA:	22-406
Submission Date:	12/27/2010; 03/17/2011
Product:	XARELTO™ (Rivaroxaban) tablets, 10 mg
Type of Submission:	Sponsor's Complete Response
Sponsor:	Johnson & Johnson
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: The original New Drug Application (NDA 22-406) is for an immediate release 10-mg oral tablet of Rivaroxaban (XARELTO™) for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery filed July 29th, 2008, by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) on behalf of Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI). The Agency issued a Complete Response action letter dated 27 May, 2009 for the original submission citing several deficiencies. The purpose of this report is to review the sponsor's response to the Agency's recommendation of changing the dissolution specifications for the proposed product (b) (4) to *Q* = (b) (4) *at **15** minutes.*

In an information request communication dated March 17, 2011 from the Agency, the sponsor explained that based on data obtained from the dissolution results (generated from release data from Bayer commercial scale batches BXA1JPG, BXA1JPJ and BXA1JPH), two out of three batches (66%) would require stage 2 testing. Specific reference was made to Tables 6, 7 and 8 of that report which provided individual dissolution data at 15 minutes showing that 2 of the 3 batches have values (shown in circles) that fell below the FDA proposed dissolution limit of NLT (b) (4) at the 15 minute time point.

In further support of this statement, there was a statistical analyses performed by the sponsor on these 3 commercial-scale Bayer batches, along with 7 commercial-scale batches from J&J's Gurabo site. An excerpt of the relevant statistical data is attached in Appendix A.

The sponsor mentioned that the stability results do not contain dissolution profile data encompassing a 15 minute time point; instead the data were generated based on the originally proposed dissolution time point (b) (4). Therefore, there are no bulk stability data available from Bayer on these particular batches.

Discussion:

The dissolution data at 15 minutes showing that 2 of the 3 batches have values (shown in circles) below the FDA proposed dissolution limit of NLT (b) (4) at the 15 minute time point, as pointed out by the sponsor, are individual data. The sponsor needs to keep in mind that a dissolution specification should be made based on mean data, not the

individual data. The mean dissolution data from three commercial batches meets the Agency's recommendation of *Q* = (b) (4) *at **15** minutes.*

Also, based on the statistical/simulation analysis performed by the sponsor, a Q of (b) (4) at 15 minutes will result in a Stage I (S1) failure rate around 63 % with overall lot rejection less than 1 in 1000 for Bayer and J&J (Table 2). This lot rejection rate is extremely low and therefore does not justify Q of (b) (4).

Overall, for the indication of prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE), a tighter quality control is recommended for rivaroxaban (XARELTO^{TM}) to assure optimal therapeutic effect.

Recommendation:

As recommended in the original submission review (put in DARRT on 4/1/2009), the Agency wants to uphold the same recommendation as outlined below:

While the sponsor's selection and validation of the dissolution methodology is acceptable, the sponsor's proposed dissolution specifications, especially two different specifications for two different facilities (Bayer and J and J) for an identical product is not acceptable.

In light of the release data of the pilot and commercial batches, the Agency proposes the following in-vitro dissolution specification for both Bayer and J and J manufacturing facilities:

Q = (b) (4) ***at 15 minutes*** *using the following dissolution methodology:*

Apparatus	USP apparatus 2 (paddle)
Dissolution medium	900 mL acetate buffer pH 4.5 + 0.2 % SDS
Rotation speed	75 rpm
Analytical procedure	HPLC with UV/VIS detection or UV/VIS spectrophotometry Both analytical procedures lead to the same results and may thus be used interchangeably.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

DISSOLUTION RESULTS:

The dissolution curves of batches for the validation batches (commercial scale) only are shown. The dissolution profiles were generated under representative conditions.

The batches are:

10 mg	batch no. BX01XZH	(b) (4)	pilot scale
10 mg	batch no. BX01XZJ		pilot scale
10 mg	batch no. BX01XZK		pilot scale
10 mg	batch no. BX02CCX		pilot scale
10 mg	batch no. BX02E15		pilot scale
10 mg	batch no. BXA1JPG		commercial scale
10 mg	batch no. BXA1JPJ		commercial scale
10 mg	batch no. BXA1JPH		commercial scale

Table 6: Rivaroxaban coated tablet 10 mg, batch BXA1JPG, USP Paddle, 900 mL, buffer pH 4.5 + 0.2 % SDS, 75 rpm

Sampling time [min.]	Single values [%]	Mean [%]	Standard deviation	Confidence interval (95 %)
15	(b) (4)		1.3	± 1.4
30			0.7	± 0.7
45			0.6	± 0.6
60			0.6	± 0.7

Figure 6: Rivaroxaban coated tablet 10 mg, batch BXA1JPG

(b) (4)

Table 7: Rivaroxaban coated tablet 10 mg, batch BXA1JPJ, USP Paddle, 900 mL, buffer pH 4.5 + 0.2 % SDS, 75 rpm

Sampling time [min.]	Single values [%]	Mean [%]	Standard deviation	Confidence interval (95 %
15	[redacted]	(b) (4)	1.9	± 1.9
30			1.2	± 1.3
45			1.3	± 1.4
60			1.2	± 1.2

Figure 7: Rivaroxaban coated tablet 10 mg, batch BXA1JPJ

Table 8: Rivaroxaban coated tablet 10 mg, batch BXA1JPH, USP Paddle, 900 mL, buffer pH 4.5 + 0.2 % SDS, 75 rpm

Sampling time [min.]	Single values [%]	Mean [%]	Standard deviation	Confidence interval (95 %)
15	[redacted]	(b) (4)	2.1	± 2.2
30			1.4	± 1.5
45			1.0	± 1.1
60			0.8	± 0.9

Figure 8: Rivaroxaban coated tablet 10 mg, batch BXA1JPH

Reviewer's Comment:

While the sponsor's selection and validation of the dissolution methodology is acceptable, the sponsor's proposed dissolution specifications, especially two different specifications for two different facilities (Bayer and J and J) for an identical product is not acceptable.

In light of the release data of the pilot and commercial batches, the Agency proposes the following in-vitro dissolution specification for both Bayer and J and J manufacturing facilities:

Q = (b) (4) ***at 15 minutes*** *using the following dissolution methodology:*

Apparatus	USP apparatus 2 (paddle)
Dissolution medium	900 mL acetate buffer pH 4.5 + 0.2 % SDS
Rotation speed	75 rpm
Analytical procedure	HPLC with UV/VIS detection or UV/VIS spectrophotometry Both analytical procedures lead to the same results and may thus be used interchangeably.

Appendix A

Extract of Rivaroxaban 10 mg Tablets – Statistical Analysis of Release Data for 15 minutes Dissolution: Stage 1 – 3 Failure Rates at Various Q-Specifications for Gurabo and Bayer Lots (28May2009)

SUMMARY

Dissolution data at release (obtained at 15, 30, 45 and 60 minutes) from three commercial scale batches of rivaroxaban 10 mg tablets (BXA1JPG, BXA1JPH, BXA1JPJ), manufactured at Bayer's Leverkusen site, were statistically analyzed in 2009 by Johnson & Johnson's Global Development Organization. The resultant report also contained statistical analyses on seven (7) commercial scale rivaroxaban 10 mg drug product batches manufactured by Johnson & Johnson (J&J), namely: 7CG1745-X, 7CG1747-X, 7CG1748-X, 7CG1751-X, 7MG4060-X, 7MG4061-X, and 7MG4062-X.

Dissolution profiles were performed on three commercial scale batches of rivaroxaban 10 mg tablets (BXA1JPG, BXA1JPH, BXA1JPJ), manufactured at the Bayer Leverkusen, Germany site. Dissolution data were collected at 15, 30, 45 and 60 minutes time points. Estimates of mean dissolution and variability related to manufacturing (process lot-to-lot) and analytical method (vessel-to-vessel) were estimated through an analysis of variance model. Estimates of overall variability were as follows in Table 1 below:

Table 1

Dissolution time	Bayer	
	(b) (4)	RSD
15		2.0
30		1.7
45		1.4
60		1.2

METHOD OF ANALYSIS AND RESULTS

A. Estimation of Mean and Variance across all Dissolution Time Points

At each of 15, 30, 45 and 60 minutes, estimates of mean dissolution and variability related to manufacturing (process lot-to-lot) and analytical method (vessel-to-vessel) were estimated by manufacturer, through a random-effects analysis of variance model with lot as a random effect.

All available dissolution time points (15, 30, 45 and 60) were used to the dissolution profile using an exponential decay model on the lot means. In addition, the relationship between mean and variance (both at the lot and vessel level) was charactertzed through linear regression modeling using all available dissolution time points (15, 30, 45 and 60).

B. Stage I -3 Failure Rate Calculation at 15 Minutes

Given a set of Q-specification limits, the risk of failure (as per USP rules) for a randomly chosen future lot, was estimated for the 15 minutes dissolution time point. A simulation approach was used to evaluate risks of lot rejection at each stage and overall. Rates for Stage 2 and 3 are conditional on the previous Stage failures (e.g. Stage 2 rates reflect the rate of failure among the lots that failed previous Stage 1). Fixed process mean and variance components as estimated by the data at hand, were assumed.

Based on the simulation results, a Q of (b) (4) at 15 minutes will result in a Stage I (S1) failure rate around 63Yo with overall lot rejection less than 1 in 1000 for Bayer and J&J. Table 2 lists the results of the failure rate calculations.

Based on the simulation results, a Q of (b) (4) at 15 minutes will result in a Stage I (S1) failure rate around 63 % with overall lot rejection less than 1 in 1000 for Bayer and J&J. Table 2 lists the results of the failure rate calculations.

Table 2: S1, S2, S3 and Overall Failure Rate estimates by Manufacturer

Dataset	Dissolution Time (min.)	Mean	SE LOT	SE Vessel	Q+5 (%)	Failure Rates (%)			Overall Lot Rejection Rate per 1000 lots
						S1	S2/S1	S3/S2	
Bayer (3 Lots)		(b) (4)			(b) (4)				
	15		1.0	1.8		63	<<1	<<1	<1
Gurabo (7 lots)									
	15		1.8	3.2		63	<<1	<<1	<1
N.B. <<1 means much less than 1									

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/s/

TAPASH K GHOSH
03/23/2011

PATRICK J MARROUM
03/23/2011

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-406**	**Brand Name**	**XARELTO™ immediate release tablets**
OCPB Division (I, II, III)	**5**	**Generic Name**	**rivaroxaban**
Medical Division	**OND/OODP/DMIHP**	**Drug Class**	**Direct factor Xa inhibitor**
OCPB Reviewer	**Joseph A. Grillo, Pharm.D.**	**Indication(s)**	
		• **The prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.**	
OCPB Team Leader	**Young Moon Choi, Ph.D.**	**Dosage Form**	**Immediate release tablets**
		Dosing Regimen	
		• **10 mg tablet taken once daily with or without food.**	
Date of Submission	**7/28/08**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**4/11/09**	**Sponsor**	**Johnson & Johnson Pharmaceutical Research and Development, L.L.C**
PDUFA Due Date	**5/28/09**	**Priority Classification**	**Standard Review**
Division Due Date	**TBD**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		
Isozyme characterization:		**11**		
Blood/plasma ratio:	**X**			
Plasma protein binding:	**X**	**2**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		
multiple dose:	**X**	**1**		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**			
fasting / non-fasting multiple dose:	**X**			
Drug-drug interaction studies -		**17**		
In-vivo effects on primary drug:	**X**			
In-vivo effects of primary drug:	**X**			
In-vitro:				
Subpopulation studies -				
ethnicity:	**X**	**8**		
gender:	**X**	**1**		
pediatrics:				

body weight:	**X**	**1**		
geriatrics:	**X**	**2**		
renal impairment:	**X**	**1**		
hepatic impairment:	**X**	**1**		
PD:				
Phase 2:	**X**	**2**		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	**X**	**4**		
Phase 3 clinical trial:	**X**	**4**		
Unrelated to proposed indication	**X**	**5**		
Population Analyses -				
Data rich:				
Data sparse:	**X**	**8**		
II. Biopharmaceutics				
Absolute bioavailability:	**X**	**2**		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**10**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**3**		
Dissolution:				
(IVIVC):				
Bio-wavier				
BCS class	**X**	**1**		
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
In vitro PD bridge study				
Literature References	**X**	**9**		
Reports/Meta-analysis	**X**	**122**		
Total Number of Studies		**96 (218 with Refs)**		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	
Comments sent to firm ?	**X**	• **Please provide datasets in SAS transfer format for studies 11273, 10924, 10846, 10989, 11937, 11125, 11197, 10990, 10998, 10996, 10997, 11032, 11321, 11322, 11938, 10842, 10847, 10991, 11529, 11569, 10850, 11568, 11002, 11003, 11126, 11127, 11325, 12026, 11608, 11609, 11708, 12090, 11000, 11001, 10993, 10999, 12359, 10992, 11936, 11935, 11865, 12680, 10848, 11123, 11124, 11279, 11864, 12089, 12612, 11140, PH-34980, & PH-34982.** • **Please provide a table of all clinical pharmacology & biopharmaceutics studies containing** Product, Formulation/Formulation Code, Drug Substance Batch Number, Drug Product Batch Number, site of manufacture. • **Please provide a table of all clinical pharmacology & biopharmaceutics studies containing validated analytical method(s) used in each study, cross reference to the validation report, overview of the methodology, LLQ , Validated Range , Within-run Precision, Between-run Precision, Accuracy , Stability in Human Plasma , Processed Extract Stability.**
QBR questions (key issues to be considered)	• **Ethnicity (Japanese)** • **Need for Dose adjustment in moderate/severe RI & HI** • **Need for Dose adjustment for CYP 3A4 & PGP in the absence of RI** • **Pharmacogenomics**	
Other comments or information not included above	**None**	
Primary reviewer Signature and Date	**/s/ Joseph A. Grillo, Pharm.D.**	
Secondary reviewer Signature and Date	**/s/ Young Moon Choi, Ph.D.**	

CC: NDA 22-291, HFD-850(Electronic Entry or Lee), HFD-160(CSO), HFD-860(TL, DD, DDD), CDR (B. Murphy)

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/s/

Joseph Grillo
9/2/2008 09:32:57 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: **22-406**	Submission Date: **7/28/08**
Brand Name	**XARELTO™ immediate release tablets**
Generic Name	**rivaroxaban**
Reviewer	**Joseph A. Grillo, Pharm.D.**
Team Leader	**Young Moon Choi, Ph.D.**
Pharmacometrics Primary Reviewer & TL	**Christoffer Tornoe , Ph.D.**
Pharmacometrics Secondary Reviewer & TL	**Yaning Wang, Ph.D.**
Pharmacogenomics Reviewer	**Rosane Charlab Orbach, Ph.D.**
Pharmacogenomics Director	**Issam Zineh, Pharm.D.**
SIMCYP & Drug Metabolism	**Ping Zhao, Ph.D.**
OCPB Division	**5**
ORM division	**OND/OODP/DMIHP**
Sponsor	**Johnson & Johnson Pharmaceutical Research and Development, L.L.C**
Relevant IND(s)	**64,892**
Submission Type; Code	**Standard Review**
OCP Briefing Date	**April 1, 2009**
Formulation; Strength(s)	**10 mg immediate release tablets**
Indication	**The prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.**

Table of Contents

1 Executive Summary

Xarelto (rivaroxaban) is a competitive, selective, and direct Factor Xa (FXa) inhibitor that can be orally administered. The proposed indication is for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.

The efficacy of rivaroxaban was evaluated in over 6000 patients participating in 4 randomized clinical trials of prevention of venous thromboembolism (VTE) following total hip replacement (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 hepatotoxicty were noted by the Clinical reviewer.

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 severe renal impairment, moderate or severe hepatic impairment, and/or concurrent use of strong CYP3A4 or Pgp inhibitors. Patients with mild to severe renal impairment who are concurrently taking moderate/strong CYP3A4 or Pgp inhibitors are expected to also be at risk for clinically relevant increases in exposure. Clinically relevant decreases in drug exposure and related risk of VTE are likely in the patients with concurrent use of moderate/strong CYP3A4 or Pgp inducers. Clinically relevant pharmacodynamic drug interactions were noted when rivaroxaban was combined with enoxaparin, warfarin or clopidogrel.

Given rivaroxaban's steep ER relationship for major bleeding and the risk of higher or lower exposure in the special populations noted above, without the ability for downward dose adjustment some of these populations will not be able to utilize this drug. FDA has recommended that the applicant develop a lower strength or scored 10 mg tablet to address this need. A dose increase (20 mg with food) is recommended if concurrent CYP3A4 or Pgp inducer use can not be avoided.

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is ACCEPTABLE provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the sponsor commits to the following post marketing commitments addressing clinical pharmacology related safety concerns with rivaroxaban treatment.

1.2 Post Marketing Requirements

1.2.1 Develop and propose a 5 mg dosing form (tablet) or scored 10 mg tablet to allow for proper dose titration when rivaroxaban needs to be co-administered in patients at risk for clinically relevant changes in rivaroxaban exposure. The 5 mg dose form should be sufficiently distinguishable from the 10 mg tablet. Full chemistry, manufacturing and controls (CMC) information for the 5 mg dosage form including the batch data and stability data, labels, updated labeling, and updated environmental assessment section is required in a prior approval supplement.
Protocol submission Date: 45 days from date of action.
Submission Date: 6 months after FDA agreement to submitted protocol.

1.2.2 The applicant should evaluate the effect of renal impairment (i.e., mild, moderate, severe) plus the concurrent use of moderate inhibitors of CYP3A4 and Pgp on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in volunteers so that appropriate dosing recommendations can be developed in these populations following the development of the 5 mg tablet formulation.
Protocol submission Date: 45 days from date of action.
Submission Date: 6 months after FDA agreement to submitted protocol.

1.2.3 The applicant should evaluate the effect of a pure Pgp inhibitor (e.g., quinidine) on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in healthy subjects. This study will explore the involvement of Pgp in rivaroxaban elimination so that appropriate dosing recommendations can be created following the development of the 5 mg tablet formulation.
Protocol submission Date: 45 days from date of action.
Submission Date: 6 months after FDA agreement to submitted protocol.

1.3 Comments to the applicant

- The FDA suggests that the sponsor evaluate the effect of moderate hepatic impairment on the safety of rivaroxaban following administration of a 5 mg dose in subjects representative of the intended patient population so that appropriate dosing recommendations can be developed in this population following the development of the 5 mg tablet formulation.
- The FDA suggests that the sponsor evaluate the effect of administering a 20 mg dose (i.e., two 10 mg tablets) to subjects concurrently receiving a strong CYP3A4 inducer (e.g., rifampicin) on the safety of rivaroxaban in subjects representative of the intended patient population so that appropriate dosing recommendations can be developed in this population.
- Since it is plausible that the pharmacokinetics differences seen in the Japanese population may be explained, at least in part, by genetic differences in any or all of the genes involved in rivaroxaban pharmacokinetics. The FDA suggests that the sponsor consider an evaluation of candidate SNPs or haplotypes in order to rule out this cause of variability.

1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Xarelto (rivaroxaban) is a competitive, selective, and direct oral FXa inhibitor that can be orally administered. The proposed indication is for the prophylaxis of DVT and PE in patients undergoing hip replacement surgery or knee replacement surgery.

The efficacy of rivaroxaban was evaluated in over 6000 patients participating in 4 randomized clinical trials of prevention of 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 hepatotoxicty were noted by the Clinical reviewer. Three deaths that may be related to hepatotoxicity have been reported.

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 relationship between exposure and PT prolongation appears linear.

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 severe renal impairment, moderate or severe hepatic impairment, and/or concurrent use of moderate/strong CYP3A4 or Pgp inhibitors. Patients with mild to severe renal

impairment who are concurrently taking moderate/strong CYP3A4 or Pgp inhibitors are expected to also be at risk for clinically relevant increases in exposure. Clinically relevant decreases in drug exposure and related risk of VTE are likely in the patients with concurrent use of moderate/strong CYP3A4 or Pgp inducers. Clinically relevant pharmacodynamic drug interactions were noted when rivaroxaban was combined with enoxaparin, warfarin or clopidogrel.

Given rivaroxaban's steep ER relationship for major bleeding and the risk of clinically relevant higher or lower exposure at the proposed dose in the special populations noted above, without the ability for dose titration some of these special populations will not be able to utilize this drug. FDA has recommended that the applicant develop a lower strength or scored 10 mg tablet to address this need. A dose increase (20 mg with food) is recommended if concurrent CYP3A4 or Pgp inducer use can not be avoided.

The absorption of rivaroxaban is almost complete at the proposed dose (T_{max} 2-4 hours). The pharmacokinetics of rivaroxaban is 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 Pgp/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. However, increased bleeding risk was noted with extremes of body weight in the phase 3 trials. 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 by the applicant.

Administration of the 10-mg rivaroxaban tablet with food suggests the absence of a significant food effect. A relevant food effect was reported for the rivaroxaban 20 mg tablet (increase in rivaroxaban mean AUC by 39%, in mean Cmax by 76%). A clinically relevant effect on rivaroxaban exposure was not reported following concomitant use of an H_2 receptor antagonist antacid at the proposed dose.

Signatures

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Clinical Pharmacology Reviewer, DMIHP Team
Division of Clinical Pharmacology 5

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Team Leader, DMIHP Team
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Pharmacometrics Division

Yaning Wang, Ph.D.
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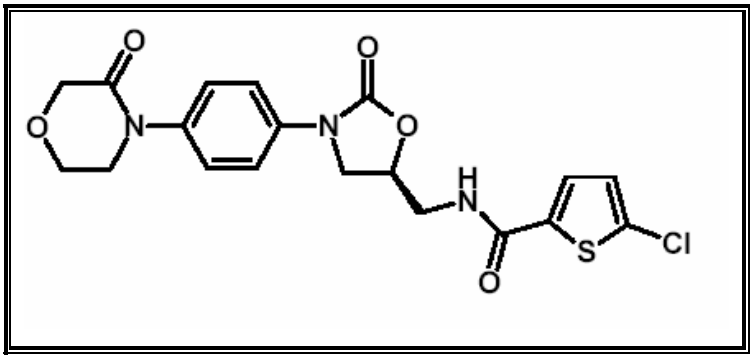
Issam Zineh, Pharm.D.
Director
Pharmacogenomics Team

Nam Atiqur Rahman, Ph.D.
Division Director
Division of Clinical Pharmacology 5

2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?



Established name:	rivaroxaban
Molecular Weight:	435.89
Molecular Formula:	$C_{19}H_{18}ClN_3O_5S$
Chemical Name:	5 Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide
Description:	Odorless, non-hygroscopic, white to yellowish powder.
Chirality:	Pure (S)-enantiomer.
Solubility/ pH-Value:	Rivaroxaban is practically insoluble in water. A saturated solution in water gives a pH-value of 5.2.
pKa-Values:	Rivaroxaban is practically insoluble in water. Determination of pKa is therefore not possible. From calculations (b) (4) the following pKa values were estimated: pKa1 = 13.4 (b) (4)
Partition Coefficient:	The partition coefficient of rivaroxaban was determined in octanol/water at room temperature. (b) (4)
Density:	(b) (4)

Each Xarelto tablet contains 10 mg of rivaroxaban. The inactive ingredients of Xarelto are: Microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and Opadry® Pink (b) (4), a proprietary film coating mixture containing polyethylene glycol 3350, hypromellose, titanium dioxide, and ferric oxide red.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The activated serine protease FXa plays a central role in blood coagulation (Figure 1). It is activated by both the intrinsic and extrinsic coagulation pathways. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin.

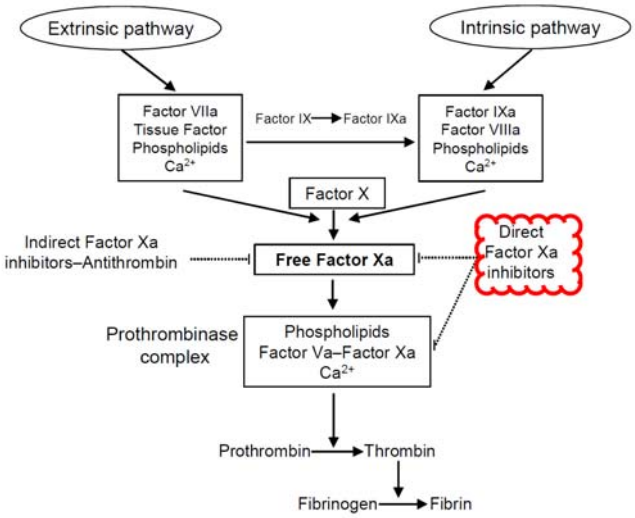


Figure 1: Schematic representation of the coagulation cascade, illustrating the pivotal role of Factor Xa, and the differing mechanisms of action of direct and indirect Factor Xa inhibitors.
Source: Applicants Figure 1-1 in "2.7.2 Summary of Clinical Pharmacology Studies" page 13

Rivaroxaban is a competitive, selective, and direct oral Factor Xa inhibitor. *In vitro* studies suggest rivaroxaban competitively inhibits human free FXa (Ki 0.4 ± 0.02 nM) and also inhibits prothrombinase activity (IC_{50} 2.1 ± 0.4 nM) and clot-associated FXa activity (IC_{50} 92 ± 4 nM). *In vitro* studies also report that the onset of inhibition of FXa activity (k_{on}) was $1.7x10^{7}$ M^{-1} s^{-1} and that rivaroxaban is a reversible inhibitor, with a mean lifetime of 200 s (k_{off} $5×10^{-3}$ s^{-1}). The values for k_{on} and k_{off} appear to be agreement with the Ki of rivaroxaban for FXa (0.4 nM).

The proposed indication for rivaroxaban is for the prophylaxis of DVT and PE in patients undergoing hip replacement surgery or knee replacement surgery.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

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

The duration of treatment depends on the individual risk of the patient for venous thromboembolism, which is determined by the type of orthopedic surgery.

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

The use of doses of more than 10 mg of once daily or treatment beyond 35 days is not recommended.

During this review cycle, the FDA requested the sponsor to develop a lower dose tablet or scored 10 mg tablet to permit dose titration in the special populations at risk for clinically relevant higher or lower rivaroxaban drug exposure at the proposed dose (See Section 2.2.4.4.1 for additional information). To date, the sponsor has regarded this modification as unnecessary.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

This application is supported by 44 human clinical studies, 8 population pharmacokinetic (pop-PK) studies, 13 *in vitro* studies, and 16 biopharmaceutics studies as shown in Figure 2. A general description of the human clinical studies is provided in Section 4.2 and a review of relevant clinical studies in detail is provided in Section 4.3.

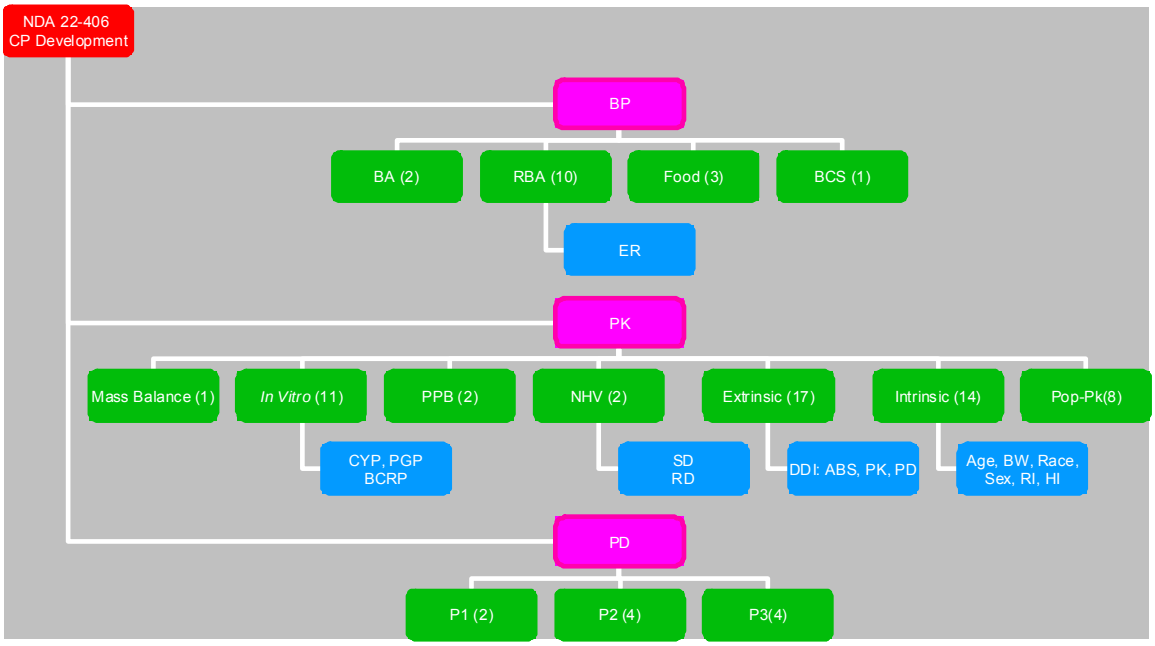


Figure 2: Clinical Pharmacology Studies Submitted in Support of NDA 22-460

The clinical efficacy and safety of rivaroxaban was evaluated in the **RE**gulation of **C**oagulation in **OR**thopedic Surgery to prevent **D**VT and PE (RECORD) program, which includes 4 randomized, double-blind, Phase 3 comparative trials with enoxaparin (RECORD 1 [Study 11354], RECORD 2 [Study 11357], RECORD 3 [Study 11356], and RECORD 4 [Study 11355]). The 4 pivotal RECORD studies were designed to be similar in methodology and identical in the efficacy and safety parameters measured. The rivaroxaban dose and start time were the same in all studies.

Treatment with rivaroxaban was 10 mg once daily for 35±4 days in the 2 THR studies (RECORD 1 and 2), and treatment with subcutaneous enoxaparin was 40 mg once daily for either 36±4 days (RECORD 1) or for 13±2 days followed by placebo until Day 35 (RECORD 2). The first dose of rivaroxaban was administered on Day 1, at least 6 to 8 hours after surgery (wound closure), and the first dose of enoxaparin was administered the evening before surgery. In the TKR studies, treatment with rivaroxaban was 10 mg once daily for 12±2 days, and treatment with subcutaneous enoxaparin was either 40 mg once daily for 13±2 days (RECORD 3) or 30 mg twice daily for 12±2 days (RECORD 4). In each of the studies, the first dose of rivaroxaban was administered on Day 1, at least 6

to 8 hours after surgery (wound closure), and the first dose of enoxaparin was to be administered the evening before surgery in RECORD 3 and 12 to 24 hours after surgery (wound closure) in RECORD 4.

The primary efficacy endpoint in each of the individual RECORD studies was the incidence of total VTE that was defined as the composite of any DVT (asymptomatic or symptomatic), non-fatal PE, or all cause death. Prior to initiation of the RECORD program, 3 categories of adverse events of special interest were identified prospectively and proactively monitored during the studies. These included: bleeding events, hepatic disorder adverse events, and cardiovascular events. 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 extra-surgical site bleeding associated with a >2 g/dL decrease in hemoglobin concentration and clinically overt extrasurgical site bleeding requiring transfusion of >2 units of whole blood or packed cells.

Four Phase 2 studies comparing the efficacy and safety of rivaroxaban with enoxaparin in the prevention of VTE following either THR (Studies 10942, 10944, and 11527) or TKR (Study 10945) were submitted. These studies were multicenter, randomized, open-label (Study 10942 only) or double-blind, active comparator controlled, parallel group trials designed to compare the efficacy and safety of rivaroxaban versus enoxaparin in men or women aged ≥18 years. The total daily doses of rivaroxaban administered in each of the 4 Phase 2 studies were similar; however, bid dosing was used in Studies 10942, 10944, and 10945 (total daily dose ranged from 5 to 60 mg) and once daily dosing (total daily dose ranged from 5 to 40 mg) was used in Study 11527. Bilateral venography was also performed in these studies at the end of the treatment period. The duration of dosing was shorter at 8-9 days. Although in most respects similar, there were differences in the definition of major bleeding as the program progressed from Phase 2 to Phase 3. In Phase 2, bleeding events that warranted treatment cessation were included.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

For the investigation of pharmacodynamics in phase 1 and 2 studies, factor Xa activity, prothrombin time (PT), prothrombin time ratio (PTINR), HepTest and activated partial prothrombin time (aPTT) were determined. The basis for selecting the PD response endpoints are as follows:

- The serine protease Factor Xa (FXa) plays a central role in the blood coagulation, as it acts at the convergence point of the intrinsic and extrinsic coagulation pathways. FXa catalyzes the conversion of prothrombin to thrombin; one molecule of FXa results in the generation of more than 1000 thrombin molecules. Inhibition of FXa blocks this burst of thrombin- generation, thereby diminishing thrombin-mediated activation of coagulation. Inhibition of Factor Xa activity was measured in almost all Phase 1 trials. It is important to note that in at least one study (10848) differerent results were apparent when inhibition of Factor Xa activity was assessed using the assay that has been used during the whole Phase 1 program compared to the anti-Factor Xa activity, an assay which is used to monitor LMWHs. The relevance of this finding is unclear.
- Preclinical data have also demonstrated that the global clotting tests PT and aPTT are useful in following the effect of rivaroxaban. PT is a global clotting test that is used for the assessment of the extrinsic pathway of the blood coagulation cascade. The test is sensitive for deficiencies of Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. The aPTT is a screening test for the intrinsic pathway and is sensitive for deficiencies of Factors I, II, V, VIII, IX, X, XI and XII.

- HepTest® was also applied in Phase 1 studies, as it is useful for indirect inhibitors of Factor Xa like LMWHs. This test has been developed to monitor heparin and especially low-molecular weight heparins (LMWH). It is based on the inhibition of free Factor Xa in the first step.

The basis for selecting the primary efficacy endpoint is that venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious condition that is a common cause of mortality and morbidity. Patients undergoing major orthopedic surgery, including total hip replacement (THR) and total knee replacement (TKR) surgeries, represent a group that is at a particularly high risk for VTE. Therefore, in the individual RECORD studies, the primary efficacy endpoint (total VTE or composite endpoint) was a composite of the incidences of any DVT (proximal and/or distal), nonfatal PE or death from all causes appears reasonable.

In the Phase 2 studies, the primary efficacy endpoint was also the total VTE composite and appears reasonable.

The pharmacogenomics reviewer agrees (see Section 4.4.2) with the applicant's statement that "In addition, genetically determined deficiencies of factor X that might affect the response to rivaroxaban are one of the most uncommon inherited coagulation disorders." at this time. Given the complexity of coagulation and fibrinolysis, multiple genetic variants may influence the phenotype of an individual, and the potential clinical implication is unknown.

However, it is conceivable that additional (b) (4) mutations in coagulation factors other than genetically determined deficiencies of factor X could potentially affect the response to rivaroxaban. (b) (4)

(b) (4)

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the active moieties in the plasma (or other biological fluid) appear to have been appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships.

In vitro, the metabolites M-13, M-15, M-16, M-17 and M-18 do not appear to inhibit FXa up to 100 µM. The metabolites M-1 and M-4 appear to be relatively weak inhibitors showing inhibition in the micromolar range. The active metabolite M-7 (IC_{50} 89 ± 15 nM) was 130-fold less potent than rivaroxaban (IC_{50} 0.68 ± 0.17 nM). The active metabolite M-2 (IC_{50} 2.3 ± 0.2 nM) was 3-fold less potent than rivaroxaban. Therefore, these metabolites were not routinely assessed.

2.2.4 Exposure-response

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 hepatotoxicty were noted by the Clinical reviewer. Three deaths that may be related to

(b) (4)

hepatotoxicity have been reported. These deaths were in women > 60 years of age who received doses greater then 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.

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Dose-dependent inhibition of FXa activity and prolongation of the prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® were observed in humans (Figure 3). In Phase 1 dose escalation studies FXa was inhibited in a dose-dependent way closely following the PK profile. Other global clotting tests were also affected in a dose-dependent way. The most sensitive one which is also following a linear correlation to plasma concentration is prothrombin time (PT Neoplastin®). Although the activated partial thomboplastin time (aPTT) and HepTest® are also prolonged dose-dependently, their correlations to plasma concentrations either do not discriminate well due to a flat slope of the correlation curve or follow a curvilinear relationship.

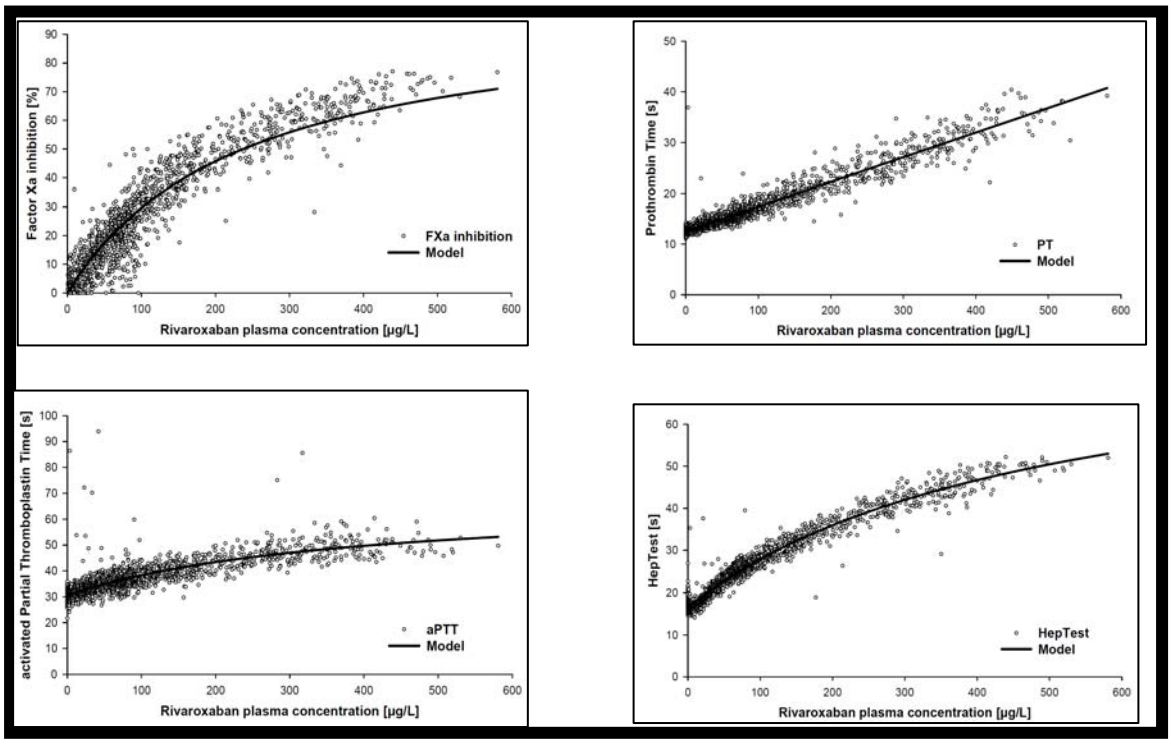


Figure 3: Correlation between rivaroxaban plasma concentrations and FXa activity PT, aPTT and HepTest® in healthy subjects (Study 10847)

Source: Applicants Figures 3-8, -9,-10, -11 in "2.7.2 Summary of Clinical Pharmacology Studies" pages 191-194

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).

A shallow dose/exposure-response relationship was observed for effectiveness (composite endpoint consisting of any deep vein thrombosis (DVT), non-fatal pulmonary

embolism (PE), or death from all causes) in the dose-ranging study 11527 for prevention of VTE in patients undergoing elective total hip replacement where doses from 5 to 40 mg qd were administered (Figure 4). No increase in effectiveness was observed beyond 10 mg qd.

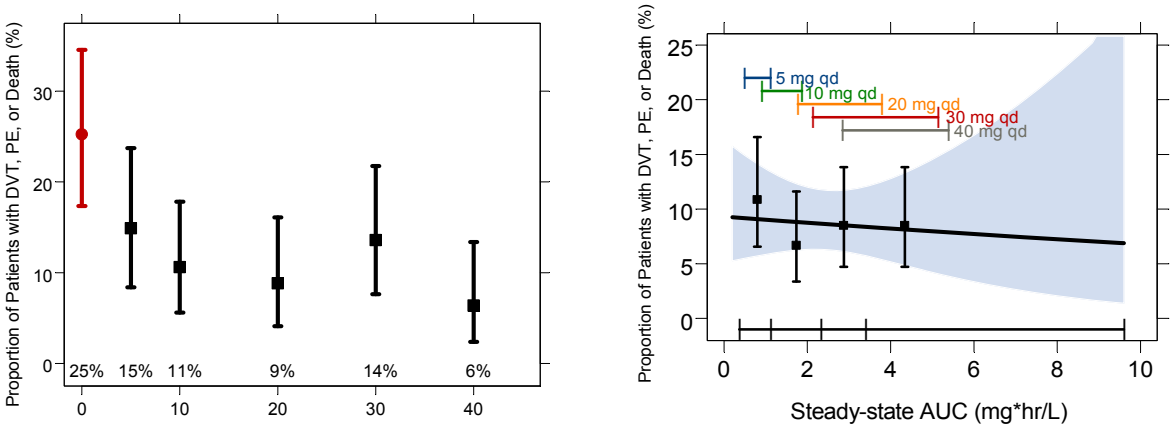


Figure 4: Proportion of patients with DVT, PE, or death vs. (Left) dose and (Right) steady-state AUC_{0-24} quartiles and associated 95% CI in dose-ranging study 11527 receiving 5-40 mg qd (per protocol population). The horizontal black bar shows the steady-state AUC_{0-24} quartiles and the colored bars illustrate the predicted 10-90th AUC and C_{max} percentiles following different dose regimens.

A logistic regression model of pooled data from phase II studies 010942, 010944, and 010945 also suggest a similar shallow dose response relationship relative to enoxaparin for total VTE in the per protocol population in these three twice daily dosing studies combined (Figure 5). A similar pattern was observed in the once daily dosing study 011527.

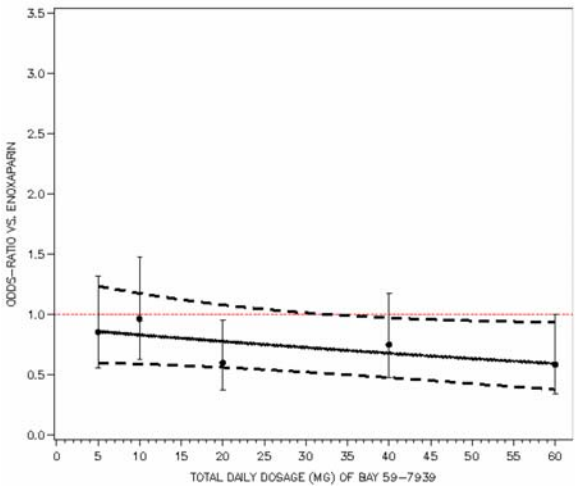


Figure 5: Total venous thrombotic events odds ratio curve of rivaroxaban vs enoxaparin with total daily dose for studies 10942, 10944, and 10945-per protocol population.
Source: Applicant's Figure 4.3 and 5.1 in clinical overview on pages 41 and 64.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

A steep increase in the risk of major bleeding from 0.7% for 10 mg qd (proposed therapeutic dose) to 6.1% for 40 mg qd was observed in the dose-ranging study 11527 whereas only 1.9% receiving the active comparator enoxaparin 40 mg experienced major bleeding event. The proposed therapeutic dose of 10 mg qd is adequate from a safety point of view with similar risk of major bleeding as the comparator (Figure 6).

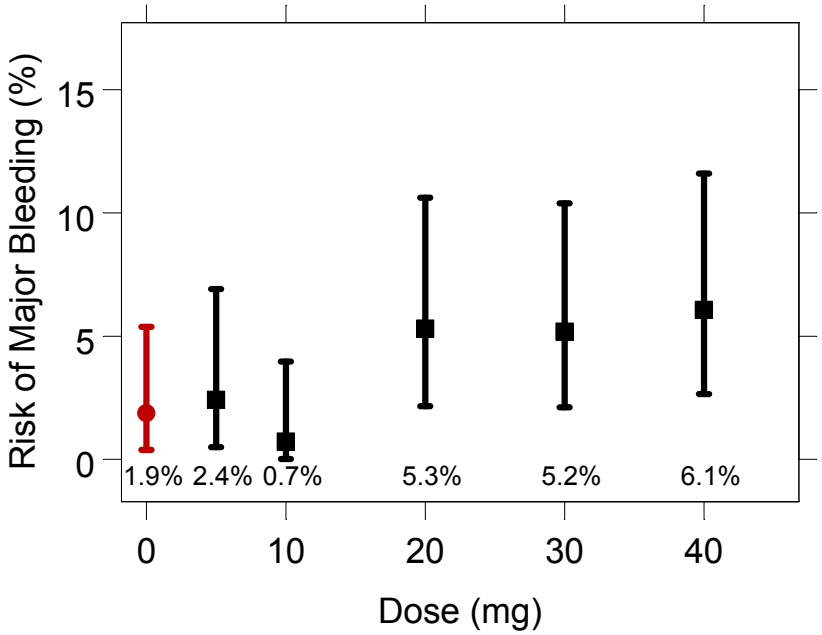


Figure 6: Risk of major bleeding and associated 95% CI vs. dose in dose-ranging study 11527 receiving 5-40 mg qd rivaroxaban (black) and enoxaparin 40 mg (red) (safety population).

The risk of major bleeding was found to increase with increasing exposure (AUCss,0-24 or Cmax,ss) (Figure 7). The mean exposure percentile following 10 mg qd is associated with a 2.5% risk of major bleeding while a 2-fold increase in exposure due to intrinsic and extrinsic factors (Table 3) will increase the risk of major bleeding by 50%.

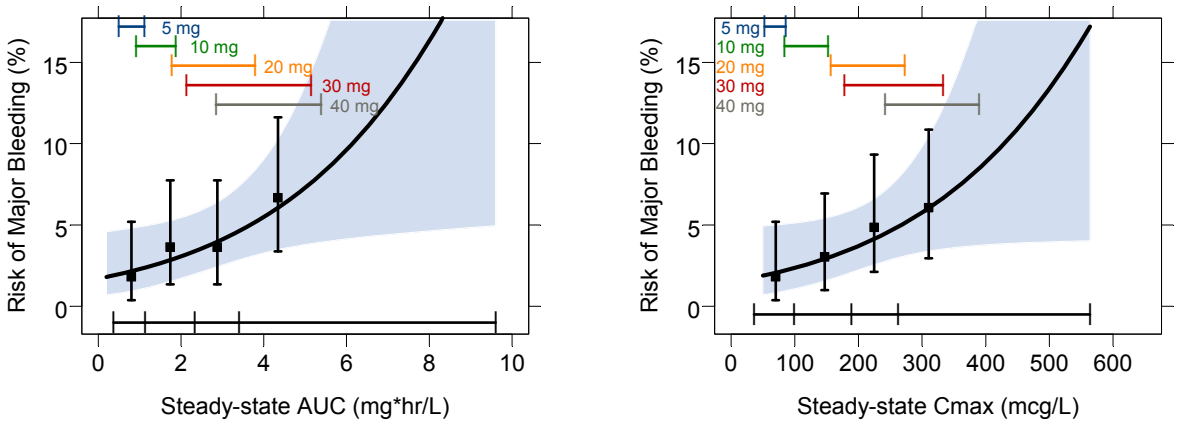


Figure 7: Risk of major bleeding vs. median quartile steady-state (Left) AUC_{0-24} and (Right) C_{max}. The horizontal black bar shows the steady-state AUC_{0-24} quartiles and the colored bars illustrate the predicted 10-90th AUC and C_{max} percentiles following different dose regimens.

A steep increase in the risk of major bleeding with increasing total daily dose was observed in the dose-ranging studies 10944 and 10945 for prevention of VTE in patients undergoing elective total hip and knee surgery where doses from 2.5 to 30 mg bid were administered (Figure 8). A similar pattern was observed in the once daily dosing study 011527.

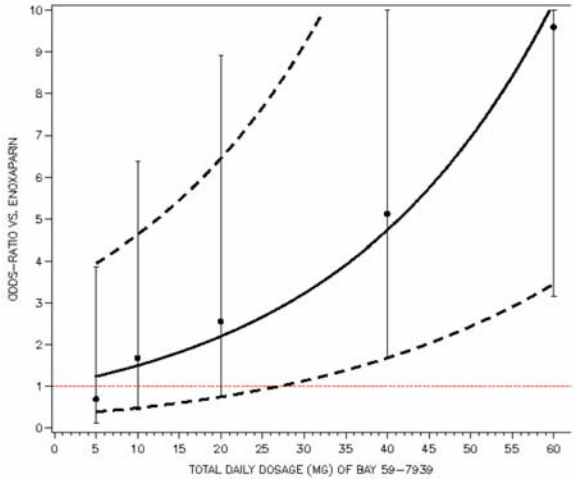


Figure 8: Total venous thrombotic events odds ratio curve of rivaroxaban vs enoxaparin with total daily dose for studies 10942, 10944, and 10945-safety population.
Source: Applicant's Figure 4.3 and 5.1 in clinical overview on pages 41 and 64.

The most common treatment emergent adverse events reported in Phase 1 studies are listed in Table 1. The majority (85%) of adverse events among rivaroxaban subjects were mild in severity. A clear dose response relationship was not apparent. An approximately two-fold incidence of an increase in ALT concentration was apparent in the rivaroxaban subjects compared to placebo at the proposed dose of 10 mg daily.

Table 1: Incidence of Treatment-emergent Adverse Events Occurring in at Least 2% of Subjects (Subjects Valid for Safety in Phase 1 Studies)

MedDRA primary SOC MedDRA preferred term	Rivaroxaban <10 mg n=64	Rivaroxaban 10 mg n=437	Rivaroxaban >10 mg n=616	Rivaroxaban All n=1117	Placebo n=181
Any system organ class					
Any event	12 (18.8%)	165 (37.8%)	234 (38.0%)	411 (36.8%)	49 (27.1%)
Gastrointestinal disorders					
Any event	2 (3.1%)	34 (7.8%)	48 (7.8%)	84 (7.5%)	8 (4.4%)
Diarrhea	0 (0.0%)	13 (3.0%)	14 (2.3%)	27 (2.4%)	3 (1.7%)
General disorders and administration site conditions					
Any event	2 (3.1%)	27 (6.2%)	36 (5.8%)	65 (5.8%)	4 (2.2%)
Fatigue	0 (0.0%)	19 (4.3%)	10 (1.6%)	29 (2.6%)	3 (1.7%)
Infections and infestations					
Any event	1 (1.6%)	16 (3.7%)	33 (5.4%)	50 (4.5%)	4 (2.2%)
Nasopharyngitis	1 (1.6%)	12 (2.7%)	24 (3.9%)	37 (3.3%)	1 (0.6%)
Investigations	2 (3.1%)	36 (8.2%)	34 (5.5%)	72 (6.4%)	9 (5.0%)
Any event					
ALT increased	0 (0.0%)	10 (2.3%)	11 (1.8%)	21 (1.9%)	2 (1.1%)
Nervous system disorders					
Any event	7 (10.9%)	77 (17.6%)	93 (15.1%)	177 (15.8%)	12 (6.6%)
Dysgeusia	1 (1.6%)	9 (2.1%)	5 (0.8%)	15 (1.3%)	0 (0.0%)
Headache	6 (9.4%)	63 (14.4%)	84 (13.6%)	153 (13.7%)	8 (4.4%)
Skin and subcutaneous tissue disorders					
Any event	3 (4.7%)	9 (2.1%)	21 (3.4%)	33 (3.0%)	7 (3.9%)
Erythema	2 (3.1%)	2 (0.5%)	6 (1.0%)	10 (0.9%)	2 (1.1%)
Vascular disorders					
Any event	2 (3.1%)	8 (1.8%)	17 (2.8%)	27 (2.4%)	7 (3.9%)
Hematoma	0 (0.0%)	1 (0.2%)	12 (1.9%)	13 (1.2%)	5 (2.8%)

Key: ALT = alanine aminotransferase; MedDRA = Medical Dictionary of Regulatory Activities; SOC = system organ class;
Note: Only treatment-emergent adverse events that occurred up to 30 days after the last dose of study drug. are included.
Note: Incidence rate = # 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 first by System Organ Class (alphabetical order) then by Preferred Term (coded order).
Note: Each subject is assigned to the dose group with the longest treatment duration. In case of equal duration the highest dose was assigned.
Note: Placebo subjects are subjects who received only placebo during the study.
Source: Table 14.04.A2, PH-34980 5.3.5.3.1-83

Source: Applicant's Table 3-3 in Integrated Summary of Safety on page118.

Reviewing rates of high (above upper limit of normal) lab abnormalities by dose groups in the Phase I Studies (**Table 2**), suggest that a there is higher incidence of increased AST, ALT, and total bilirubin in the rivaroxaban treated population, at the proposed 10 mg daily dose, compared to placebo. A clear dose response relationship can not be concluded, however; a trend is apparent.

Table 2: Incidence rates of high (above upper limit of normal) lab abnormalities by dose groups (subjects valid for safety analysis)

Laboratory Value	Rivaroxaban <10 MG (N=64)	Rivaroxaban 10 MG (N=437)	Rivaroxaban >10 MG (N=616)	Placebo (N=181)
SGOT/AST	4 / 63 (6.3%)	28 / 412 (6.8%)	27 / 607 (4.4%)	4 / 181 (2.2%)
SGPT/ALT	1 / 60 (1.7%)	38 / 403 (9.4%)	74 / 588 (12.6%)	11 / 167 (6.6%)
GGT	0 / 63 (0.0%)	9 / 372 (2.4%)	12 / 605 (2.0%)	2 / 163 (1.2%)
LDH	0 / 61 (0.0%)	5 / 380 (1.3%)	5 / 502 (1.0%)	2 / 163 (1.2%)
ALKALINE PHOSPHATASE	1 / 63 (1.6%)	4 / 416 (1.0%)	5 / 596 (0.8%)	1 / 173 (0.6%)
BILIRUBIN, TOTAL	1 / 55 (1.8%)	14 / 391 (3.6%)	21 / 547 (3.8%)	4 / 169 (2.4%)
BILIRUBIN, DIRECT	0 / 50 (0.0%)	1 / 132 (0.8%)	10 / 381 (2.6%)	3 / 109 (2.8%)
BILIRUBIN, INDIRECT	1 / 12 (8.3%)	0 / 36 (0.0%)	10 / 167 (6.0%)	0 / 27 (0.0%

Source: Applicant's Table 14.10.D1 in Pooled analysis of safety of rivaroxaban (BAY 59-7939) in subjects included in Phase I clinical trials on page 214.

Safety data from the phase 2 dose ranging study 011527 (QD rivaroxaban dosing) report a dose related increase in "all adverse events," "serious adverse events," and "prolonged hospitalization" at rivaroxaban exposures greater that 10 mg (Figure 9). The incidence rates for the latter two parameters were also higher than that seen for enoxaparin. A similar trend was noted for any event bleeding and major bleeding (Figure 10) however; an increased incidence above enoxaparin was apparent in both cases exposures greater

that 10 mg. No obvious trend in liver function tests relative to dose were obvious from this study.

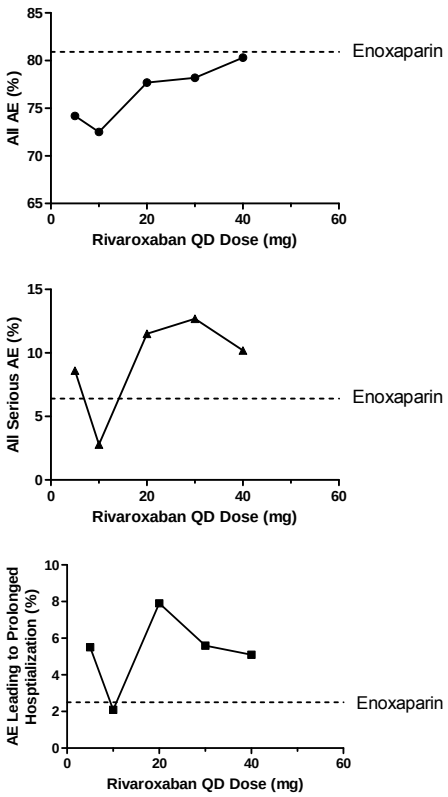


Figure 9: Reviewer Generated Graphs of the Incidence rates of All AE, SAE, and Prolonged Hospitalization (safety population) by Dose
Source: Applicant's Table 12-3 in the report for Study 011527 "Controlled, Double-Blind, Randomized, Dose-ranging Study of once-daily regimen of BAY59-7939 in the Prevention of VTE in Patients Undergoing Elective Total Hip Replacement" page 101

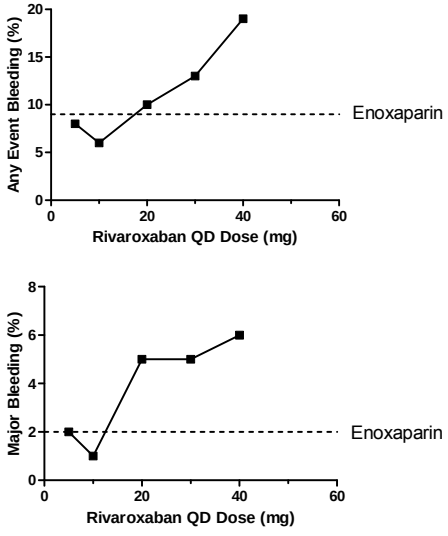


Figure 10: Reviewer Generated Graph of the Incidence Rates of Bleeding Events (safety population) by Dose
Source: Table 12-8 in Applicant's report for Study 011527 "Controlled, Double-Blind, Randomized, Dose-ranging Study of once-daily regimen of BAY59-7939 in the Prevention of VTE in Patients Undergoing Elective Total Hip Replacement" page 112

Therefore there are no obvious short term safety concerns, except for bleeding risk, from a clinical pharmacology perspective from the phase 1 and 2 studies; however, safety signals suggesting possible hepatotoxicty were noted by the Clinical reviewer in the Integrated Summary of Safety. Three deaths that may be related to hepatotoxicity have been reported. These deaths were in women > 60 years of age who received doses greater then 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.

2.2.4.3 Does this drug prolong the QT or QTc interval?

FDA Interdisciplinary Review Team for QT Studies (IRT) evaluation (see Section 4.4.3) states that no significant QT prolongation effect of BAY 59-7939 (15 mg and 45 mg) was detected in the applicant's TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between BAY 59-7939 (15 mg and 45 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that the assay sensitivity of the study was established.

IRT further states that the proposed label statement "In a thorough QT study in healthy men and women aged 50 years and older, no QTc prolonging effects were observed for XARELTOTM (15 mg and 45 mg, single dose)" is acceptable.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

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.

The reviewer has identified several special populations at risk for clinically relevant changes in exposure that may lead to reduced efficacy or increased bleeding risk. These special populations are:

- Severe renal impairment (RI)
- Mild, moderate or severe RI + CYP3A4 inhibitor
- Moderate hepatic impairment (HI), Severe HI
- Concurrent use of a moderate/strong CYP3A4 inhibitor, Pgp inhibitor, or both
- CYP3A4 inducers

During this review cycle, the FDA requested the sponsor to develop a lower dose tablet or scored 10 mg tablet to permit dose titration in these special populations that are at risk for clinically relevant changes rivaroxaban drug exposure at the proposed dose (See Section 2.2.4.4.1 for additional information). To date, the sponsor has regarded this modification as unnecessary. Therefore, the reviewer is recommending restricting the use of rivaroxaban in these populations.

2.2.4.4.1 Is 10 mg rivaroxaban qd appropriate for all patients?

The identified intrinsic and extrinsic factors affecting rivaroxaban PK/PD are summarized in Table 3.

Table 3: 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-tn)	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		
strong inhibitors of both CYP3A4 and P-gp			
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)
strong inhibitor of CYP3A4 and weak-to-moderate inhibitor of P-gp			
RIVA 10 mg alone	RIVA + clarithromycin 500mg bid	1.54 (1.44 – 1.64)	1.40 (1.30 – 1.52)
weak-to-moderate inhibitor of CYP3A4 and P-gp			
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: Sponsor's Table 2 in fda-response-05-dec-2008.pdf

Several special populations (i.e., patients with severe renal impairment, moderate-severe hepatic impairment, and strong CYP3A4 or Pgp inhibitors) have greater than 2-fold increases in drug exposure (Table 3). Please see Section 2.3 and 2.4 for additional information.

The increased exposure resulted in approx. 2-fold increase in Factor Xa inhibition and prothrombin time (PT) for moderate-severe renal impaired patients and 2.6-fold and 2.1-fold increase in Factor Xa inhibition and PT time, respectively, for Child Pugh B hepatic impaired patients.

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 severe renal impairment, moderate to severe hepatic impairment, and/or concurrent use of moderate/strong CYP3A4 or Pgp inhibitors. Further, a steep ER relationship for rivaroxaban (2.2.4.2) for major bleeding draws additional concern. Information submitted by the applicant in its phase 2 dose ranging study indicates an almost 5 fold increase in major bleeding (0.7% vs. 4.3%) when exposure is increased two fold from the proposed dose. This suggests that theoretically even a 1.5 fold increase in exposure may double the risk of major bleeding.

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 (which was found to increase the risk of major bleeding) in these patients by shifting from once daily to every other day dosing (Figure 11). It is therefore recommended that the sponsor develops a 5 mg or scored 10 mg tablet to make dose adjustments in patients with clinically relevant increases in exposure due to intrinsic and extrinsic factors.

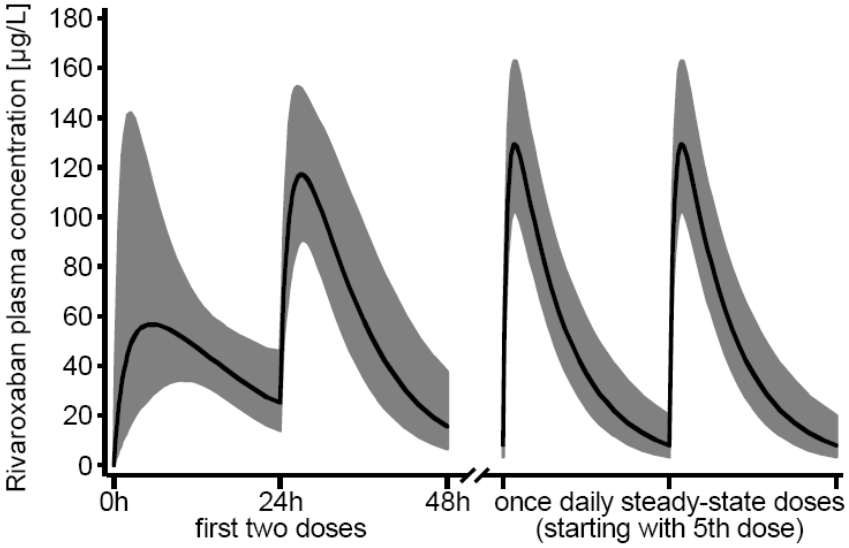


Figure 11: Rivaroxaban plasma-concentration vs time profile for the 10 mg qd dosing regimen used in OdIXa-HIP OD trial [geometric mean/SD of individually posthoc estimated plasma concentration/time curves; n=131-140] (Study PK000131).
Source: Sponsor's Figure 3.7 in clinical pharmacology summary on pages 187.

2.2.4.4.2 Is there evidence of inter-ethnicity differences in rivaroxaban PK/PD?

Yes, Japanese subjects were found to have an apparent higher dose-normalized rivaroxaban C_{max} and AUC compared to other ethnic groups (i.e., Caucasian, African-American, Hispanic, Japanese, and Chinese, were evaluated) (Figure 12).

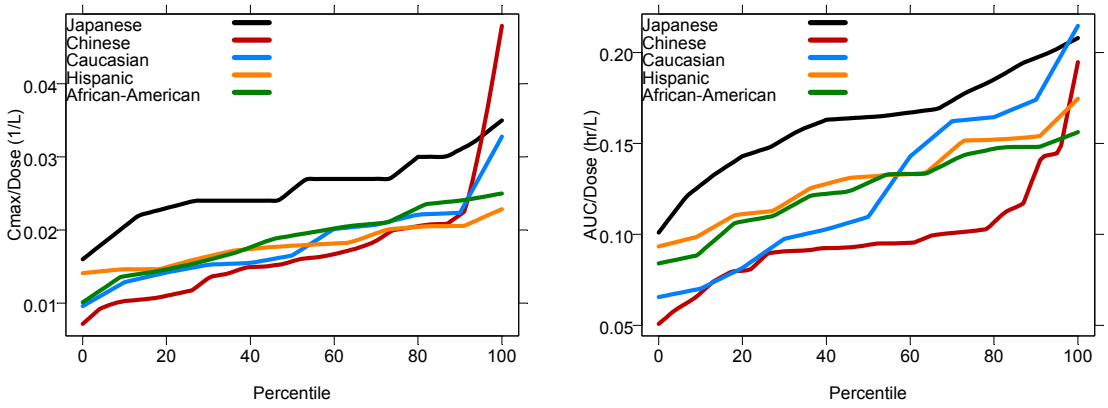
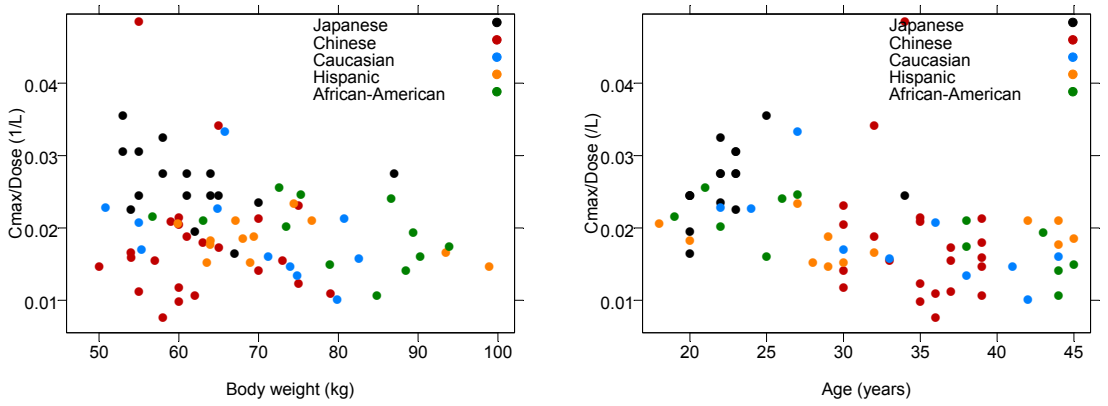


Figure 12: C_{max}/Dose and AUC/Dose vs. percentiles for different ethnicities following single dose 2.5-10 mg rivaroxaban (studies 11126, 11608, and 12090).

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 (Figure 13).

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. In conclusion, the observed differences in exposure between Japanese and other ethnicities are unlikely due to demographic differences but rather inter-ethnicity differences.



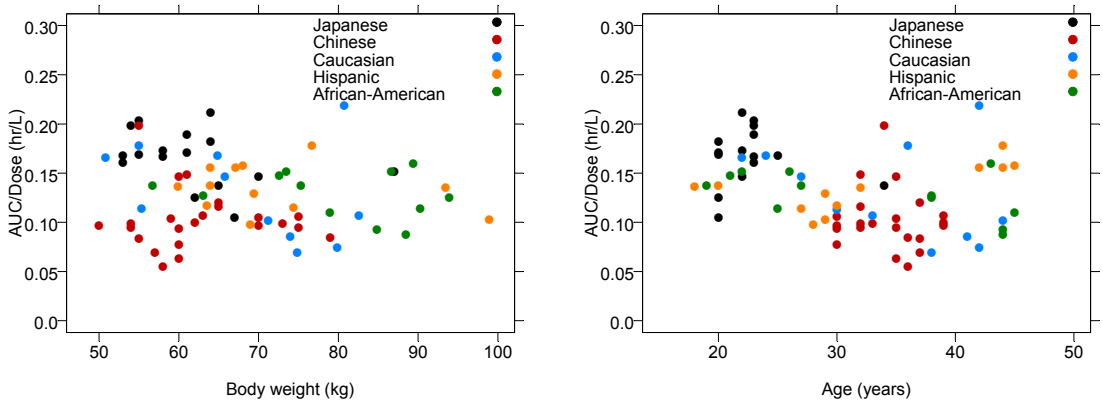


Figure 13: C_{max}/Dose (Top) and AUC/Dose (Bottom) vs. body weight (Left) and age (Right) following single dose 2.5-10 mg rivaroxaban from studies 11126 (Japanese), 11608 (Chinese), and 12090 (Caucasian, African-American, and Hispanic).

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 (Figure 14). This further suggests that the ethnicity PK differences are not due to assay or study differences since the same PK/PD relationship is observed in Japanese and Chinese subjects.

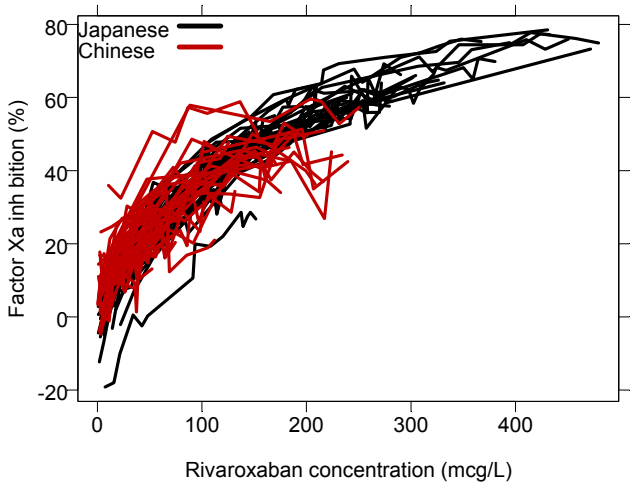


Figure 14: Factor Xa inhibition vs. rivaroxaban concentration in Japanese (black lines) and Chinese (red lines) subjects following 2.5-40 mg single dose rivaroxaban.

Further, the genes involved in rivaroxaban pharmacokinetics (CYP3A4, CYP3A5, CYP2J2, ABCG2, and ABCB1) (b) (4) may contribute to the observed inter-ethnic variability. In addition, linkage disequilibrium and haplotype structure differ for these genes across populations.

(b) (4)

(b) (4)

(b) (4)

It is therefore plausible that the pharmacokinetics differences seen in the Japanese population may be explained, at least in part, by genetic differences in any or all of the genes involved in rivaroxaban pharmacokinetics. The applicant may consider analysis of candidate SNPs or haplotypes in order to rule out this cause of variability.

Of note, the applicant indicated on a response letter to a FDA Information Request Letter of 19 February 2009 that pharmacogenomic samples were not collected in the ethnic Phase 1 studies, or in the Phase 3 RECORD program, but pharmacogenomic samples are being collected in the other large rivaroxaban Phase 3 programs.

2.2.5 PK characteristics of the drug and its major metabolite

Population models of the PK of rivaroxaban suggest it is best described by an oral, two-compartment model with elimination from the central compartment. Rivaroxaban appears to exhibit linear PK up to 15 mg and shows no significant accumulation following repeat dosing. The volume of distribution at steady-state (Vss) is approximately 50 L (0.62 L/kg). Rivaroxaban is characterized in vitro as a substrate of both P-glycoprotein (Pgp) and the active transport protein "breast cancer resistance protein" (BCRP). It is highly bound to plasma proteins (92% to 95%). Approximately 50% of an orally administered dose undergoes metabolic degradation (CYP3A4/3A5, CYP2J2, & hydrolytic cleavage). The remainder is excreted unchanged via Pgp/BCRP mediated active renal secretion and in the feces. The terminal half-live 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.

2.2.5.1 What are the single dose and multiple dose PK parameters?

The applicant conducted a randomized, single-blind, placebo-controlled, group comparison, dose-escalation study in healthy young male subjects under fasting conditions. The study investigated the safety, tolerability, and PD effects as well as the PK of rivaroxaban after single oral doses of 1.25, 5, 10, 15, 20, 30, 40, 60, and 80 mg (administered as 5-mg tablets) and 5 and 10 mg as oral solution. After administration of an oral solution, the plasma concentration time profiles reached maximal plasma concentrations (Cmax) after about 0.5 h followed by a fairly rapid decline leading to a terminal half-life of 3 – 5 h (Figure 15).

After administration of the rivaroxaban tablet releasing micronized drug substance, peak concentrations observed after 2 - 3 h. While bioavailability in terms of AUC was comparable between the two formulations, the dose-normalized Cmax was reduced by approximately 50% after administration of the tablet when compared to the solution. Mean terminal elimination half-lives were approximately 4 – 9 h hours for the 5- and 10-mg tablet doses.

(b) (4)

[5] Cusatis G, Gregorc V, Li J, Spreafico A, Ingersoll RG, Verweij J, et al. Pharmacogenetics of ABCG2 and adverse reactions to gefitinib. *J Natl Cancer Inst.* 2006 Dec 6;98(23):1739-42.

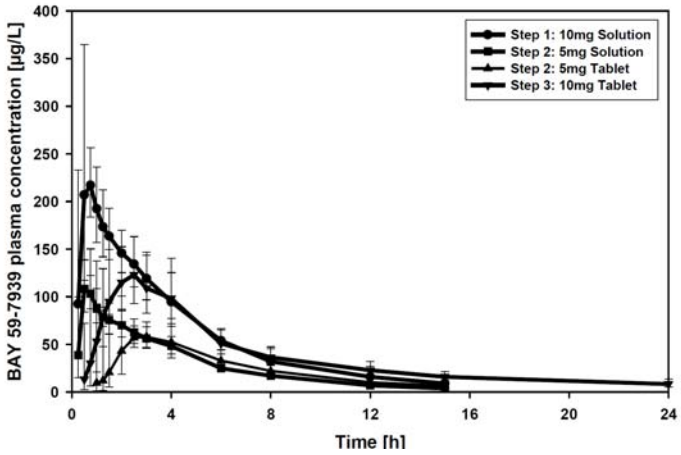


Figure 15: Plasma-concentration vs time profiles of BAY 59-7939 following administration of 5mg (N=6 each) and 10 mg (N=8 each) BAY 59-7939 either as oral solution or as tablet [geometric mean/geometric standard deviation]

Source: Applicants figure 11-11 in the report for Study # 10842 page 366

Rivaroxaban plasma concentrations increased dose-proportionally after administration of the solution (5 and 10 mg) and this was also observed for the tablets up to a dose of 15 mg (Figure 16). With higher tablet doses, dose-dependent but less than dose-proportional increases in Cmax and AUC were observed (Figure 16). In addition, an apparent lower proportion of rivaroxaban excreted unchanged in the urine (Aeur) was reported at the highest doses (60 and 80 mg) compared with the lowest dose (1.25 mg) in this study (10% vs 40%, respectively). Given this and the low aqueous solubility of this drug, flip-flop pharmacokinetics could not be ruled out.

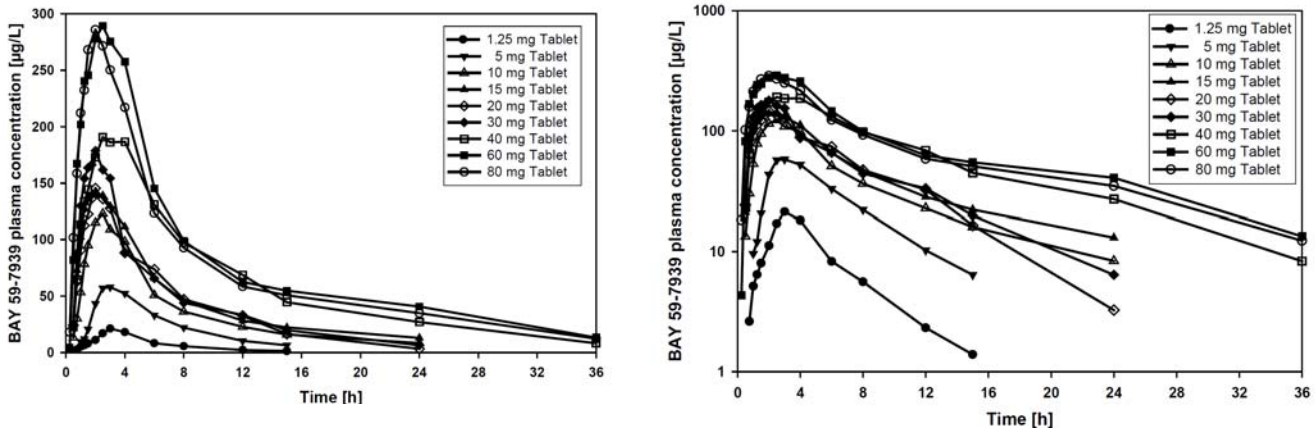


Figure 16: Plasma-concentration vs time profiles of BAY 59-7939 following administration of 1.25mg - 80mg BAY 59-7939 as tablet administrations, linear (left) & semi-logarithmic (right) scales [geometric mean, N=6-8 each]

Source: Applicants figures 11-12 and 11-13 in the report for Study # 10842 pages 366-367

The applicant conducted a randomized, placebo-controlled, single-blind, parallel-group study investigated the safety, tolerability, PD, and PK of rivaroxaban after single and multiple dose applications of rivaroxaban as immediate-release tablets: 5 mg qd, 5 mg bid, 5 mg tid, 10 mg bid, 20 mg bid, and 30 mg bid. For each subject, the study consisted of 1 dosing period. Study drug was administered *with food* on Day 1 and on Days 4 to 8. On Days 2 and 3 no study drug was administered.

The PK behavior of the drug after multiple dosing was comparable to the results obtained after single dosing (Figure 17). There was no change in the absorption kinetics of rivaroxaban after multiple-dose administration. Inter-individual variability was of moderate extent (20% to 30% for AUC and Cmax). Elimination of rivaroxaban from plasma occurred with terminal half-lives ($t_{1/2}$) of 4.3 to 5.9 h (Day 1) and 4.9 to 9.2 h (steady-state) and was not changed after multiple-dose administration.

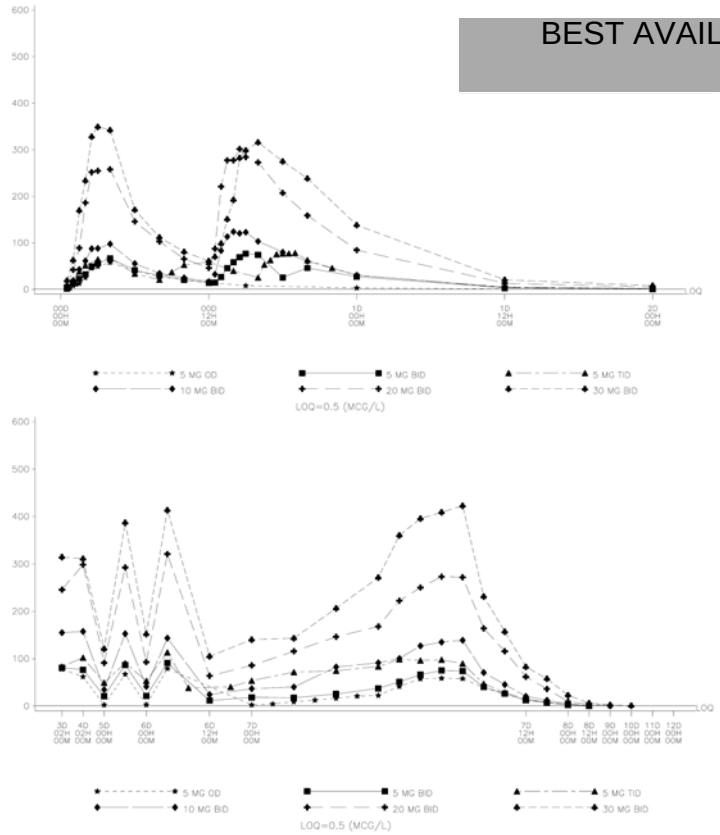


Figure 17: Plasma concentrations of BAY 59-7939 (µg/L) for each dose step displayed as geometric means from Day d 0 to Day d 2 (upper graph) and Day d 3h2 to Day d 12 (lower graph) – all subjects valid for PK (N=61)
Source: Applicants figures 11-13 and 11-14 in the report for Study # 10847 pages 97-98.

There was no significant accumulation beyond steady-state observed after qd or bid dosing of doses up to 30 mg. Morning and evening/night PK profiles within the bid/tid dosing regimens appeared to be comparable. Dose-proportional increases in AUC and Cmax were seen up to the highest dose tested (30 mg bid). This may suggest that the decreased bioavailability seen with higher doses in the fasting state single dose study may be overcome by administration of the drug with food.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

There were no significant alterations in rivaroxaban steady-state PK in VTE prevention in patient's undergoing hip or knee replacement surgery (Table 4) compared to parameters from healthy volunteers discussed above (Section 2.2.5.1), besides the anticipated effects inherent to the elderly, when compared to healthy subjects. Inter-patient variability in rivaroxaban plasma exposure at steady-state was moderate (CV % ranging from 30% to 40%). Increased variability was apparent in early post-surgery, which is likely attributable to the post-surgical conditions of the patients.

Table 4: Median post-hoc estimated rivaroxaban PK parameters in total hip replacement patients at steady state following qd- and bid dosing in ODIXa-HIP2 and ODIXa-HIP OD trials [median (5/95 percentiles)]

Parameter			Rivaroxaban total daily dose		
			5 mg	10 mg	20 mg
		n (bid/od)	114/118	114/135	109/131
C_{max}	µg/L	bid	39.8 (29.5–74.0)	64.9 (45.8–105)	142 (103–218)
		od	69.3 (49–113)	125 (91.4–196)	223 (160–360)
C_{trough}	µg/L	bid	8.37(1.55–27.9)	14.6 (4.21–39.2)	35.1 (7.85–99.7)
		od	4.50 (0.7–38.8)	9.10 (1.32–37.6)	22.3 (4.32–95.7)
AUC	µg·h/L	bid	531 (304–1287)	902 (577–1637)	2010 (1139–3757)
		od	673 (373–1603)	1170 (772–2118)	2374 (1366–4858)

Source: Applicants Table 3-2 in "2.7.2 Summary of Clinical Pharmacology Studies" page 187

Figure 18 simulates rivaroxaban plasma-concentration vs time profile for the applicants proposed 10 mg qd dosing regimen in patients based on a population based PK analysis of combined VTE prevention phase 2 studies #11527 and #10944. Relevant accumulation is not apparent.

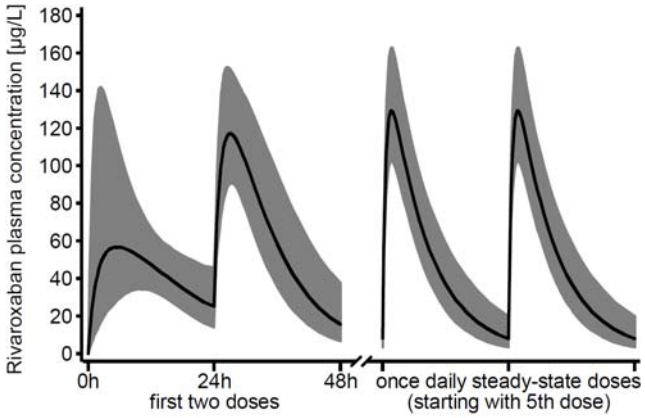


Figure 18: Rivaroxaban plasma-concentration vs time profile for the 10 mg od dosing regimen used in OdIXa-HIP OD trial [geometric mean/SD of individually posthoc estimated plasma concentration/time curves; n=131-140]
Source: Applicants Figure 3-7 in "2.7.2 Summary of Clinical Pharmacology Studies" page 187

2.2.5.3 What are the characteristics of drug absorption?

Rivaroxaban tablets contain micronized rivaroxaban drug substance and standard excipients cellulose microcrystalline, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate and sodium lauril sulfate (b) (4). Tablets of all dose strengths have been developed to be of same size (b) (4), same tablet weight (b) (4).

In vitro characteristics and *in vivo* animal data oral bioavailability of rivaroxaban is high with almost complete absorption. Relevant pre-systemic first-pass extraction is not apparent.

Following oral administration of 5 – 10 mg solution in humans 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 lower exposure reported, relative to oral tablet administration, when rivaroxaban is released as granules in proximal small intestine, distal small intestine, and ascending colon (Table 5).

Table 5: Point estimates (geometric LS-means) and 90% CI for the ratios of the primary parameters AUC_{norm} and $C_{max,norm}$ of BAY 59-7939 comparing different BAY 59-7939 formulations and administration locations (results of ANOVA; subjects valid for PK)

Group comparison	Parameter	Estimated ratio (%)	90% CI (%)
10 mg BAY 59-7939 granulate proximal small bowel/ 2 x 5 mg BAY 59-7939 tablet orally	AUC_{norm}	70.96	[51.10; 110.1]
	$C_{max,norm}$	44.45	[10.72; 94.53]
10 mg BAY 59-7939 granulate distal small bowel/ 2 x 5 mg BAY 59-7939 tablet orally	AUC_{norm}	55.48	[33.98; 97.26]
	$C_{max,norm}$	28.62	[19.50; 54.05]
10 mg BAY 59-7939 granulate ascending colon/ 2 x 5 mg BAY 59-7939 tablet orally	AUC_{norm}	25.42	[12.89; 44.05]
	$C_{max,norm}$	8.49	[3.97; 16.22]
5 mg BAY 59-7939 solution ascending colon/ 2 x 5 mg BAY 59-7939 tablet orally	AUC_{norm}	59.54	[52.45; 70.94]
	$C_{max,norm}$	41.73	[22.68; 77.95]
5 mg BAY 59-7939 solution ascending colon/ 10 mg BAY 59-7939 granulate ascending colon	AUC_{norm}	244.47	[121.2; 423.7]
	$C_{max,norm}$	487.00	[215.8; 1087]

Source: Applicants Figure 11-4 in the report for study #10924 page 50

Therefore, administration of rivaroxaban via a method that could deposit drug directly into the proximal small intestine (e.g., feeding tube) may result in reduced absorption and related drug exposure. Given this drug is intended to be used during the perioperative period when patients may be intubated and unable to take medication orally, the administration section of the labeling for rivaroxaban should state that it should not be administered via a feeding tube to patients who are unable to take the tablet formulation and additional context provided in the clinical pharmacology section. Other therapeutic options (e.g., Low Molecular Weight Heparins) are available for these patients.

2.2.5.4 What are the characteristics of drug distribution?

The volume of distribution of rivaroxaban at steady-state (Vss) is approximately 50 L (0.62 L/kg). 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. Due to its high plasma protein binding rivaroxaban is not expected to be dialyzable. 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.

The unchanged drug appears to be the main compound in human plasma based on the ADME study 10991 and accounts for at least 82 % of radioactivity in plasma. Other identified metabolites were M-1, M-4, M-5, M-7, and M-8/M-9.

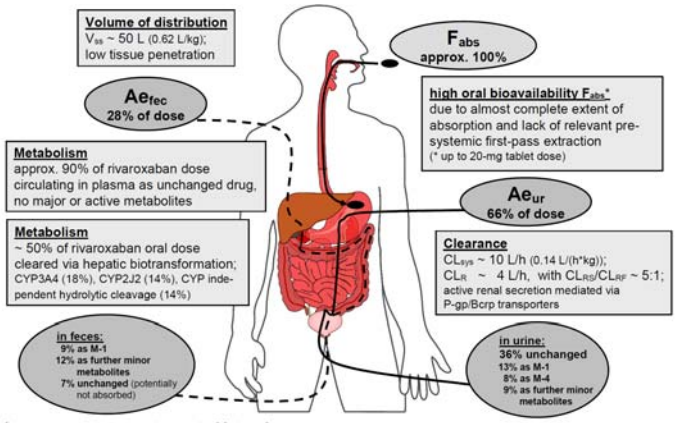
Rivaroxaban is characterized *in vitro* as a substrate of both P-glycoprotein (Pgp) and the active transport protein “breast cancer resistance protein” (BCRP). These transporters may place a role in the active secretion of rivaroxaban in the kidney. The effect of these transporters on rivaroxaban’s absorption was not apparent.

The bi-directional permeability across Pgp overexpressing LLC-PK1 (L-MDR1) cell monolayers and the influence of possible clinical relevant inhibitors was determined. Rivaroxaban was actively transported in L-MDR1 cells; the efflux ratios were 15.9 (0.5 µM), 13.1 (1 µM), 9.78 (10 µM) and 10.6 (100 µM). Comparing the efflux ratios observed for rivaroxaban to strong Pgp substrates such as taxol, which shows an efflux ratio of >108 in Pgp overexpressing cells the observed efflux appears moderate. The efflux ratios in wild-type LLC-PK1 cells was 1.5 at concentrations of 0.5 and 2 µM, respectively. By addition of 5 µM of the Pgp inhibitors ivermectin or LY 335979, the efflux of rivaroxaban in L-MDR1 cells was almost completely blocked, resulting in efflux ratios of 1.20 and 1.69, respectively.

Rivaroxaban (2 µM) exhibited a pronounced polarized transport in MDCKII cells over-expressing mouse Bcrp (Abcg2), resulting in efflux ratios ranging from 27.0 to 41.7. Rivaroxaban transport by Bcrp was not saturated up to a concentration of 20 µM. The maximum plasma concentration of rivaroxaban was 0.29 µM at the therapeutic dose level of 10 mg. The pronounced polarized transport of rivaroxaban in the MDCKII-Bcrp cells could completely be blocked by addition of the specific Bcrp inhibitor Ko 143 (5 µM) (10) and the dual Bcrp and Pgp inhibitor pantoprazol (500 µM).

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Hepatic is the major route of elimination (Figure 19). Approximately 50% of an oral dose of rivaroxaban undergoes hepatic biotransformation to reasonably inactive metabolites. Approximately 21% is eliminated as metabolites and 7% is eliminated as unchanged drug in the feces. Approximately 36% of an oral dose of rivaroxaban is eliminated renally as unchanged drug via active secretion and an additional 30% as reasonably inactive metabolites.



Ae_{ur}	amount excreted into urine
Ae_{fec}	amount excreted into bile/feces
Bcrp	breast cancer resistance protein
CL_{sys}	systemic (plasma) clearance
CL_R	renal clearance (via active secretion CL_{RS} and glomerular filtration CL_{RF})
CYP3A4	cytochrome P450 3A4
CYP2J2	cytochrome P450 2J2
F_{abs}	absolute bioavailability
M-1, M-4	metabolites M-1 and M-4 (for structures see Figure 3-3)
P-gp	P-gylcoprotein
V_{ss}	volume of distribution at steady-state

all numbers are approximate; sum of percentages is 94% (= recovery in human mass balance study)

Figure 19: Summary of rivaroxaban mass balance, excretion pattern, distribution and clearance properties in man, based on human mass balance, absolute bioavailability and renal impairment studies
Source: Applicants Figure 3-2 in "2.7.2 Summary of Clinical Pharmacology Studies" page 180

2.2.5.6 What are the characteristics of drug metabolism?

In the [^{14}C]rivaroxaban mass balance (Study 10991), about 94% of the radioactive dose administered was recovered in the excreta within 7 days following administration. Urinary excretion accounted for approximately 66% of the total dose, and approximately 36% of the dose is excreted as unchanged active drug (Figure 19). Fecal/biliary excretion accounted for approximately 28% of the total dose (Figure 19).

Eighty-nine percent of the dose administered could be attributed to known structures (Figure 20). In all investigated species the oxidative degradation of the morpholinone moiety (catalyzed via CYP3A4/3A5 and CYP2J2 and leading via cleavage of the ring [M2 metabolite] and further oxidation to metabolite M-1) was the major site of biotransformation of rivaroxaban. Furthermore, cleavage of the amide bonds and conjugation with glycine lead to formation of metabolite M-4. The corresponding (S)-oxamine derivative M-15 was further metabolized in man to the alcohol derivative M-17 and the carboxylic acid derivative M-18. No metabolic conversion of rivaroxaban to its enantiomer was observed in humans.

Figure 20: Proposed metabolites of [14C]rivaroxaban from in vitro and in vivo studies (main metabolic pathway is indicated by larger arrowheads)

Source: Applicants Figure 3-3 in "2.7.2 Summary of Clinical Pharmacology Studies" page 181

In addition to unchanged rivaroxaban, metabolite M-1 appears to be the main metabolite in the excreta of animals and man. No obvious species differences in the metabolism of rivaroxaban were reported.

The proposed metabolic pathways derived from in vivo and in vitro studies are depicted in Figure 20. An *in vitro* CYP reaction phenotyping study, suggests that CYP3A4 may be the major enzyme for M-9 formation, whereas CYP3A4 and CYP2J2 contribute to similar extents to M-2 formation. The latter 50:50 distribution is likely based on the applicants assumption that total P450 content by CYP2J2 and CYP3A4 are 1-2% and 30% (an approximately 1:30 ratio). The applicant did not sufficiently justify this 1:30 estimation and their estimation can not be considered conclusive given estimates as high as 1:80 have been reported.[6]

Taking excretion data and metabolite profiles derived from the mass balance study in man into consideration, present data from this CYP reaction phenotyping study the applicant suggests that CYP2J2 contributes to ~14% and CYP3A4/3A5 to ~18% of total rivaroxaban elimination, respectively. However, this finding is based on the same equivocal assumption regarding the 50:50 contributions of CYP3A4 and CYP2J2 to M-2 formation and also cannot be considered conclusive at this time.

In addition to this oxidative biotransformation, hydrolysis of the amide bonds (~14% of total elimination) also play an important role in the biotransformation of rivaroxaban.

2.2.5.7 What are the characteristics of drug excretion?

In the [^{14}C]rivaroxaban mass balance (Study 10991), about 94% of the radioactive dose administered was recovered in the excreta within 7 days following administration. The urinary excretion pathway appears to be more pronounced in humans than in animals (~25% [rat] and ~52% [dog]) following oral administration, with 66% of the administered radio-labeled dose excreted renally and 28% excreted via the fecal/biliary route.

Approximately 36% (Figure 19) of the dose was excreted as unchanged active drug in the urine. Metabolites M-1 and M-4, appear to be the major metabolites in urine and accounted for approximately 13% and 8% of the dose. The major constituents in human fecal extracts appear to be unchanged drug and metabolite M-1 accounting for approximately 7% and 9% of the dose.

In phase I development, the mean systemic clearance after intravenous administration of rivaroxaban was approximately 10.7 L/h (0.137 L/[h*kg]) in healthy volunteers. First pass extraction is not apparent or expected given the low clearance. Approximately 40% of rivaroxaban dose were excreted via the kidneys as unchanged drug which is comparable to the recovery reported in the mass balance study. This renal clearance is approximately 5 times the normal glomerular filtration rate of 0.75 L/h suggesting additional active secretion that may be Pgp and/or Bcrp mediated (Section 2.2.5.4). This finding also appeared consistent with systemic and renal excretion estimates from a Phase 2 prevention study in hip replacement patients (study #10944) where rivaroxaban was dosed using a twice daily (bid) regimen.

Elimination of rivaroxaban from plasma is associated with terminal half-lives of 5 to 9 h in young male healthy subjects (Study 10847); terminal half-lives in the healthy elderly increased to 11 and 13 h.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose concentration appears linear at the proposed dosing range. See section 2.2.5.1 for additional information regarding dose proportionality.

[6] Yamazaki H, Okayama A, Imai N, Guengerich FP, Shimizu M. Inter-individual variation of cytochrome P4502J2 expression and catalytic activities in liver microsomes from Japanese and Caucasian populations. *Xenobiotic*. 2006; 36(12):1201-9.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

The proposed indication does not permit chronic administration. No apparent changes were noted with multiple dosing for 14 or 35 days as proposed by the applicant.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Variability in PK from the phase I rivaroxaban clinical studies suggest that 1) the inter-individual variability (coefficient of variation) ranging from 18 to 33% for AUC, and from 16 to 39% for Cmax and 2) intra-individual variability was on average (median) 14% for AUC, and 19% for Cmax.

Possible sources of reduced reliability may include practice variability across the large number of clinical sites; increased variability in dosing and sampling times; and increased variability in subjects' underlying age related renal status. Population approaches to describe rivaroxaban pharmacokinetics (pop-PK) suggest that important patient covariates identified to influence rivaroxaban pharmacokinetics were: 1) Renal function (creatinine clearance) affecting rivaroxaban clearance and 2) Body weight affecting volume of distribution.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Results from Phase I rivaroxaban clinical studies of studies suggest that age, Japanese race, renal insufficiency, and hepatic insufficiency influence rivaroxaban exposure and response (e.g., bleeding risk). Body weight and gender do not appear to influence rivaroxaban exposure (Table 6) and response. While sample for pharmacogenetic analysis were collected in many studies, genetic polymorphism was not evaluated. Additional specific information regarding these intrinsic factors will be provided in section 2.3.2 below.

Table 6: Summary of rivaroxaban exposure data by weight and gender potentially affecting its plasma concentrations [presented as mean ratios and 90% confidence intervals (CI) for AUC and Cmax assessed in specifically designed clinical pharmacology studies

Influence of	Rivaroxaban AUC ratio [CI]	Rivaroxaban C_{max} ratio [CI]
	1.41 [1.20 - 1.66]	1.08 [0.94 - 1.25]
Weight		
≤ 50 kg vs 70-80 kg	1.14 [1.00 - 1.30]	1.24 [1.07 - 1.44]
>120 kg vs 70-80 kg	1.12 [0.98 - 1.28]	1.04 [0.90 - 1.20]
Gender (female vs. male)	0.93 [0.79 - 1.09]	0.99 [0.86 - 1.15]

Source: Applicants Figure 1-2 in "2.7.2 Summary of Clinical Pharmacology Studies" page 20

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

Several specifically designed Phase 1 studies investigating the effects of age on rivaroxaban PK and PD behavior.

Study 11529 is a randomized, single-blind, placebo-controlled, dose-escalation study in elderly (> 60 years) male and female healthy subjects to investigate the safety, tolerability, PD and PK of rivaroxaban following single-dose administration of 30, 40, and 50 mg rivaroxaban given with a standard breakfast. While the doses administered in this study are greater than those proposed by the applicant and no direct comparison to younger subjects was done, the observed reduced total body clearance (geometric mean of 8.5-11 L/H and increased half-life (geometric mean of 11-13 h) were consistent with later studies that represented intended use for rivaroxaban.

Study 11569 is a randomized, single-blind, placebo-controlled trial an investigation of the safety, tolerability, PD, and PK of a single oral dose of 10 mg rivaroxaban in male and female subjects older than 75 years compared to young (18 - 43 years) subjects of both genders. This study reported an approximately 1.5-2 fold reduction in renal clearance in the elderly male and female subjects compared to the younger subjects as well as a similar trend for reduced total body clearance and increased half-life. An increase in exposure (AUC) of approximately 40% was reported (Table 7). The difference pharmacodynamic effect (Factor Xa & PT) E_{max} and AUC showed a similar trend to that reported for the pharmacokinetic exposure differences reported in Table 7.

Table 7: LS-mean pharmacokinetic characteristics based on main effects ANOVA for study 11569

Parameter	LS-Mean	Value (90% CI)	LS-Mean	Value (90% CI)
C_{max}	Women	226.70 (204.35 – 251.45)	Old	236.80 (213.44 – 262.64)
	Men	228.20 (205.71 – 253.12)	Young	218.50 (196.95 – 242.34)
	Women/Men	0.9934 (0.8579 – 1.1503)	Old/Young	1.084 (0.9359 – 1.2549)
$C_{max,norm}$	Women	1541.0 (1365.7 – 1738.6)	Old	1710.0 (1515.2 – 1929.1)
	Men	1777.0 (1574.8 – 2004.9)	Young	1601.0 (1419.3 – 1806.9)
	Women/Men	0.8672 (0.7311 – 1.0287)	Old/Young	1.068 (0.9000 – 1.2664)
AUC	Women	1533.0 (1366.8 – 1719.0)	Old	1890.0 (1684.9 – 2119.0)
	Men	1648.0 (1469.9 – 1848.6)	Young	1337.0 (1192.4 – 1499.6)
	Women/Men	0.9299 (0.7907 – 1.0935)	Old/Young	1.4130 (1.2016 – 1.6617)
AUC_{norm}	Women	10419 (9010.1 – 12047)	Old	13643 (11799 – 15776)
	Men	12834 (11099 – 14840)	Young	9801.0 (8475.7 – 11333)
	Women/Men	0.8118 (0.6611 – 0.9969)	Old/Young	1.392 (1.1336 – 1.7095)

Source: Applicants table 11-14 in the study report for study 11569 page 61

The applicant's analysis of calculated creatinine clearance (Clcr) vs. age (Figure 21) and Clcr vs. the total and renal clearance of rivaroxaban (Figure 22) and suggestion that age related changes in renal function may play a significant role in this age effect appears reasonable given what is known about the effect of age on renal function and the renal clearance of rivaroxaban. In addition, an exploratory pop-PK analysis (PK000131) of data from two phase 2 studies (11527 and 10944) suggests a similar trend regarding the relationship between creatinine clearance and total clearance of rivaroxaban.

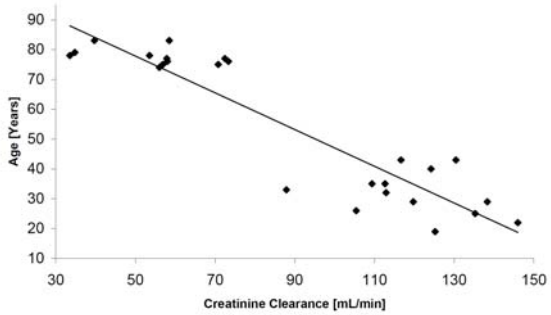


Figure 21: Individual data for calculated creatinine clearance at baseline plotted against age (all subjects treated with BAY 59-7939) from study 11569

Source: Applicants figure 11-1 in the study report for study 11569 page 41

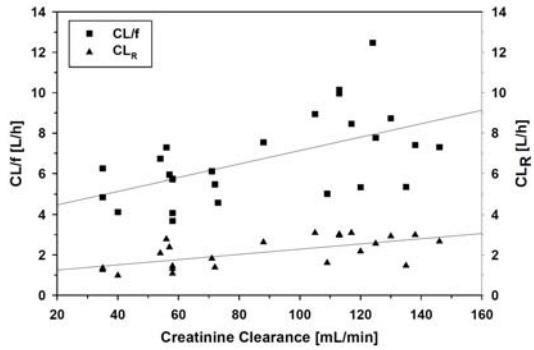


Figure 22: Individual data for total clearance (CL/f) and renal clearance (CLR) of BAY 59-7939 plotted against calculated creatinine clearance from study 11569

Source: Applicants figure 11-11 in the study report for study 11569 page 63

Study 10850 is a randomized, double-blind, placebo-controlled, group comparison study in healthy young and elderly subjects of both genders to investigate the safety, tolerability, PK and PD of rivaroxaban after a single 10 mg dose (as 2 x 5 mg tablets), given under fasting condition. Elderly subjects exhibited higher exposure than young subjects (Table 8), with mean AUC values being approximately 52% greater in elderly male subjects, and 39% higher in elderly female subjects, compared to the young subjects of the same gender. The respective changes in Cmax were 35% for both male and female subjects. No changes in terminal half-life due to age and/or gender were apparent. The difference pharmacodynamic effect (Factor Xa & PT) Emax and AUC showed a similar trend to that reported for the pharmacokinetic exposure differences reported in Table 8.

Table 8: Ratios of geometric LS means (90% confidence interval) for selected pharmacokinetic parameters

Comparison	AUC	AUC_{norm}	C_{max}	$C_{max,norm}$
Elderly vs Young	1.45 (1.21-1.74)	1.42 (1.14-1.76)	1.35 (1.12-1.64)	1.32 (1.07-1.62)
Male vs Female	1.05 (0.87-1.26)	0.94 (0.76-1.17)	1.42 (1.17-1.72)	1.28 (1.04-1.57)

Source: Applicants figure 11-3 in the study report for study 10850 page 27

Safety information from the Phase 3 studies suggest a trend toward a higher incidence of any bleeding and major and non-major clinically relevant bleeding events in patients greater than 65 years of age receiving rivaroxaban compared to patients less than 65

years of age. Enoxaparin treated patents showed a similar trend which is consistent with its labeling information.

Table 9: Major and Non-major Clinically Relevant Bleeding Events and Corresponding Hazard Ratios (95% CI) by Age

	MNCRBE		Any Bleeding Event	
Age (yr)	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	Rivaroxaban n/N (%)	Enoxaparin n/N (%)
<65	78/2915 (2.7)	54/2905 (1.9)	185/2915 (6.3)	176/2905 (6.1)
65-75	89/2354 (3.8)	66/2381 (2.8)	172/2354 (7.3)	155/2381 (6.5)
>75	30/914 (3.3)	38/914 (4.2)	77/914 (8.4)	70/914 (7.7)

MNCRBE =Major and Non-major Clinically Relevant Bleeding Events

Source: Applicant's Figures 1-5 and 1-6 in "5.3.5.3.8 Integrated Summary of Safety" pages 50-51

The applicant is not proposing any adjustment to the dosing or monitoring of this special population beyond stating "greater sensitivity can not be ruled out." Given the potential for an almost 1.5 fold increase in exposure, the reviewer recommends communicating in the labeling that 1) all patients greater than 65 years of age should have an assessment of renal function prior to starting therapy with rivaroxaban and 2) all patients greater than 65 years of age should be observed closely for signs and symptoms of bleeding while being treated. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

2.3.2.2 Pediatric patients

The safety and effectiveness of rivaroxaban in pediatric patients has not been studied. Phase 1-3 protocols excluded subjects under the age of 18 years from clinical trials.

The applicant is requesting a waiver for the conduct of a clinical program with rivaroxaban for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in pediatric patients (<18 years of age) undergoing total hip or knee replacement surgery. The rationale for the waiver for the conduct of such a clinical program in this indication is the rarity of joint replacement surgery in the pediatric population and the lower risk of DVT and PE, which does not necessarily require routine prophylaxis.

The reviewer agrees with the applicants proposal that the safety and effectiveness of using rivaroxaban in children or adolescents <18 years of age have not been established and, therefore, use of rivaroxaban in this population is not recommended.

2.3.2.3 Gender

The influence of gender on rivaroxaban PK and PD was an objective of three phase 1 studies (11529, 11569, and 10850). None of these studies indicated any relevant differences between men and women within the respective treatment groups, especially when correcting exposure parameters for body weight. For example, a randomized, single-blind, placebo-controlled trial (11569) of the safety, tolerability, PD, and PK of a single oral dose of 10 mg rivaroxaban in male and female subjects older than 75 years compared to young (18 - 43 years) subjects of both genders reported a LS mean [CI_{90}] difference between women/men of 0.99 [0.86 - 1.15] and 0.93 [0.79 - 1.09] for Cmax and AUC, respectively. In addition, differences between men and women did not appear to impact on the potential of rivaroxaban to inhibit FXa or prolongation of PT.

An exploratory across-study pooled analysis on all Phase 1 trials (PH34982)) reported a moderate effect of gender, mainly driven by differences in body weight, on rivaroxaban plasma exposure as well as on PT prolongation (females had higher plasma concentrations and higher PT values than males by approximately 30%). In

addition, an exploratory pop-PK analysis (PK000131) of data from two phase 2 studies (11527 and 10944) suggests a similar trend regarding the relationship between gender, body weight and the C_{max} of rivaroxaban (Figure 23).

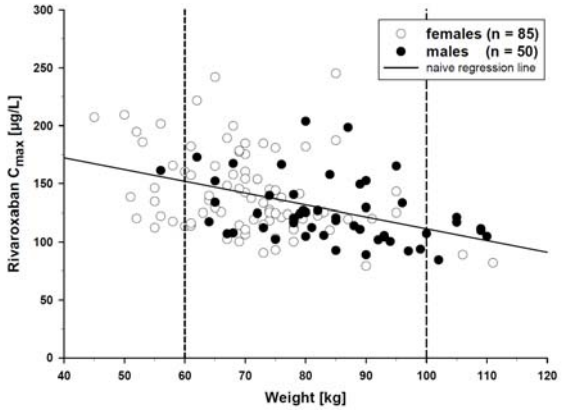


Figure 23: Exploratory Relationships between rivaroxaban Cmax and patient body weight in Phase 2 dose-finding study ODIXa-HIP OD for rivaroxaban 10 mg od [individual data; n=135; regression line is model approximate] (Study PK000131)

Source: Applicants Figure 3-19 in "2.7.2 Summary of Clinical Pharmacology Studies" page 209

Safety information from the Phase 3 studies suggest higher incidence of any bleeding and major and non-major clinically relevant bleeding events in male patients compared to female patients (Table 10). This find is inconsistent with trends from the phase 1 and 2 studies and its relevance is unclear.

Table 10: Major and Non-major Clinically Relevant Bleeding Events and Corresponding Hazard Ratios (95% CI) by Sex

	MNCRBE		Any Bleeding Event	
Sex	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	Rivaroxaban n/N (%)	Enoxaparin n/N (%)
Male	109/2432 (4.5)	86/2519 (1.9)	213/2432 (8.6)	196/2519 (7.8)
Female	88/3751 (2.3)	72/2381 (2)	221/3751 (5.9)	205/2381 (8.6)

MNCRBE =Major and Non-major Clinically Relevant Bleeding Events

Source: Applicant's Figures 1-5 and 1-6 in "5.3.5.3.8 Integrated Summary of Safety" pages 50-51

Given the above information, the reviewer agrees with the applicant's proposed labeling (b) (4) .

2.3.2.4 Body weight

Pop-PK approaches to describe rivaroxaban pharmacokinetics suggest that body weight is an important patient covariate affecting volume of distribution.

The influence of extremely low and high body weight was investigated in a specific Phase 1 study (11568), comparing PK and PD behavior in healthy male and female subjects with body weight below 50 kg (females only) and above 120 kg to normal-weight (70 - 80 kg) control subjects.

The results are presented in Table 11 below. The exposure of 10 mg rivaroxaban in terms of AUC did not appear to be influenced by the different weight categories. In the extreme underweight group (< 50 kg) a larger C_{max} (by 24%) was observed as compared to the normal and the overweight groups. Women appeared to show a trend

toward higher exposure compared to males with respect to exposure. In addition, the impact of under- and overweight on the potential of rivaroxaban to inhibit FXa activity or PT differences showed a similar trend to differences observed in exposure.

Table 11: Point estimates (LS-means) and two-sided 90% confidence intervals for the ratios C:B, D:B and D:C of the parameters AUC and C_{max} of BAY 59-7939 (results of ANOVA, all subjects valid for PK, PD and Safety, N=36)

Ratio	Kinetic parameter	Gender	Estimated ratio (%)	90% confidence interval (%)
≤50 kg : 70-80 kg	AUC	Total (N=24)	113.95	(99.78, 130.13)
	C_{max}	Total (N=24)	124.18	(107.21, 143.84)
>120 kg : 70-80 kg	AUC	Total (N=24)	112.29	(98.33, 128.23)
		Female (N=12)	119.56	(100.33, 142.49)
		Male (N=12)	105.45	(88.49, 125.67)
	C_{max}	Total (N=24)	103.88	(89.68, 120.32)
		Female (N=12)	114.48	(91.02, 143.98)
		Male (N=12)	94.26	(74.95, 118.55)
Men : women (70-80 kg)	AUC	N=12	96.63	(81.08, 115.15)
	C_{max}	N=12	98.31	(78.17, 123.64)
Men : women (>120 kg)	AUC	N=12	85.23	(71.51, 101.56)
	C_{max}	N=12	80.94	(64.36, 101.80)

Source: Applicant's Table 11-7 in the report for study 11568 page 63

Further, an exploratory across-study analysis on all Phase 1 trials showed that body weight did not appear to have an effect on AUC of rivaroxaban plasma concentrations or on the AUC of PT prolongation. Cmax and Emax of PT prolongation were approximately 20% higher at body weights less than or equal to 50 kg. Subjects greater than or equal to 120 kg has an approximately 33% higher Tmax compared to 70-80 kg subjects.

Safety information from the Phase 3 studies suggest higher incidence of any bleeding and major and non-major clinically relevant bleeding events in body weight groups less than or equal to 50 kg and greater than or equal to 90 kg. This find is inconsistent with trends from the phase 1 and 2 studies and its relevance is unclear. One possible explanation may be the greater proportion of female patients in these phase 3 studies. In study 11568 females appeared to have an a higher exposure compared to males in groups less than or equal to 50 kg and greater than or equal to 120 kg. The rates of major and non-major clinically relevant bleeding events in body weight groups less than or equal to 50 kg and greater than or equal to 90 kg was greater than enoxaparin.

Table 12: Major and Non-major Clinically Relevant Bleeding Events and Corresponding Hazard Ratios (95% CI) by Sex

	MNCRBE		Any Bleeding Event	
Body Weight	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	Rivaroxaban n/N (%)	Enoxaparin n/N (%)
<=50 KG	7/147 (4.8)	3/162 (1.8)	12/147 (8.2)	8/162 (4.9)
>50-70 KG	50/1946 (2.6)	41/1826 (2.2)	126/1946 (6.5)	104/1826 (5.7)
>70-90 KG	76/2669 (2.8)	74/2732 (2.7)	167/2669 (6.2)	180/2732 (6.6)
>90-110 KG	44/1103(4)	36/1147(3.1)	89/1103(8.1)	80/1147(7)
>110 KG	18/306 (5.9)	4/327 (1.2)	38/306 (12.4)	28/327 (8.6)

MNCRBE =Major and Non-major Clinically Relevant Bleeding Events

Source: Applicant's Figures 1-5 and 1-6 in "5.3.5.3.8 Integrated Summary of Safety" pages 50-51

Given the above information, the reviewer generally agrees with the applicant's proposed labeling that compared to a body weight of 70 to 80 kg, (b) (4) However, the reviewer recommends rewording to "As compared to a body weight of 70 to 80 kg, extremes in body weight (<50 kg or >120 kg)

resulted in increased rivaroxaban exposure by less than 25%. This effect appeared greatest in female subjects studied." The reviewer also recommends adding in to the "Use in Special Populations" section that despite this relatively minor increase in exposure (less than 25%), increased rates of any bleeding and major and non-major clinically relevant bleeding events in body weight groups less than or equal to 50 kg and greater than or equal to 90 kg were observed inn phase three studies. Therefore, patients in these categories should be observed closely for signs and symptoms of bleeding while being treated. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

2.3.2.5 Race

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 Cmax and AUC compared to other ethnic groups. See Section 2.2.4.4.2 for additional information.

Safety information from the Phase 3 studies are inconclusive regarding the effect of ethnicity on the incidence of any bleeding and major and non-major clinically relevant bleeding events. It is important to note that it is not clear from the Integrated Summary of Safety the proportion of Japanese in the Asian category. The rationale for the higher incidence of bleeding events in black subjects can not be explained by available PK/PD findings.

Table 13: Major and Non-major Clinically Relevant Bleeding Events and Corresponding Hazard Ratios (95% CI) by Sex

	MNCRBE		Any Bleeding Event	
Race	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	Rivaroxaban n/N (%)	Enoxaparin n/N (%)
White	165/4848 (1.3)	136/4876 (2.8)	336/4848 (6.9)	131/4876 (2.7)
Black	6/158 (3.8)	7/126 (5.5)	17/158 (10.7)	14/126 (1.1)
Asian	13/617 (2.1)	7/617 (1.1)	47/617 (7.6)	35/617 (5.7)
Hispanic	4/339(1.2)	4/343(1.2)	22/339 (6.5)	31/343(9)
Other	0/30 (0)	0/46 (0)	0/30 (0)	1/46 (2.2)

MNCRBE =Major and Non-major Clinically Relevant Bleeding Events

Source: Applicant's Figures 1-5 and 1-6 in "5.3.5.3.8 Integrated Summary of Safety" pages 50-51

It is also important to note that the applicant itself has required a 25% dose reduction in Japanese subjects in study 12620 (J- ROCKET-AF) compared to 11630 (ROCKET-AF). These large clinical studies are underway by the applicant to study the potential use of rivaroxaban in prevention of thromboembolic events in subjects with non-valvular atrial fibrillation. It is unclear why the applicant finds an apparent ethnicity effect in the atrial fibrillation population and not for this indication.

Given the above information and information from Section 2.2.4.4.2, the reviewer does not agree with the applicant's proposed labeling (b) (4) . The reviewer recommends rewording to healthy Japanese subjects were found to have 50% higher exposure compared to other ethnicities including Chinese.

2.3.2.6 Renal impairment

Approximately 19 million Americans older than 20 years have chronic kidney disease.[7] Moderate to severe renal disease is more prevalent in the population > 60 years of age as outlined in Table 14. The rate of total hip and knee arthroplasties is significantly higher in patients > 65 years of age.[8] Further, Corsonello et al. suggest almost 14% of patients have concealed renal insufficiency.[9] 44.5% of these patients were greater than 80 years old.

Table 14: Chronic Renal Disease Stage by Age using NHANES Data 1999-2006

Age	Stage1 GFR ≥ 90	Stage 2 GFR 60-89	Stage 3 GFR 30-59	Stage 4-5 GFR < 30	All
20-39	43.7	16.9	2.7	9.4	15.1
40-59	40.1	36.9	21.2	15.6	29
60+	16.2	46.3	76.1	75	55.9
National Health and Nutrition Examination Survey (NHANES); GFR = mL/min/1.73m^2					
Source: Reference 7					

Approximately 2/3 of rivaroxaban dosage is excreted via the kidneys, with 30 - 40% being unchanged parent drug. Renal clearance of rivaroxaban thought to be comprised of both passive glomerular filtration and Pgp/Bcrp-mediated active secretion. The applicant approximates this to be a 1:5 ratio based on renal clearance values from health subjects. Therefore understanding the effects of renal impairment on rivaroxaban is important given a significant number of the target population for this drug may have some degree of renal impairment.

A dedicated renal impairment study (11002) investigated the PK, PD, safety and tolerability of 10 mg rivaroxaban in male and female patients with renal impairment and in age-comparable male and female subjects with normal renal function, following single-dose administration in a single-center, nonrandomized, non-controlled, non-blinded, observational study with group stratification. This study enrolled 24 men and women with mild (CLCR 50 to 79 mL/min, n=8), moderate (CLCR 30 to 49 mL/min, n=8), and severe (CLCR < 30 mL/min, n=8) renal impairment. 8 healthy subjects with normal creatinine clearance (CLCR ≥ 80 mL/min) served as a control. All subjects received 10 mg rivaroxaban as a single dose. Creatinine clearance values were calculated as a 24 hour clearance from the creatinine concentrations measured in serum and urine at the screening visit about 1-2 weeks prior to the start of the study.

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 (Cmax 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 (Table 15). 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.

Mean amounts of rivaroxaban excreted into urine decreased from approximately 30% in the healthy subject group to approximately 10% in subjects with creatinine

[7] U.S. Renal Data System, USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008.

[8] Kurtz S, Mowat F, Ong K, Chan N, Lau E, Halpern M. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. J Bone Joint Surg Am. 2005 Jul;87(7):1487-97

[9] Corsonello A, Pedone C, Corica F, Mussi C, Carbonin P, Antonelli Incalzi R; Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA) Investigators. Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. *Arch Intern Med.* 2005;165:790-5.

clearances below 30 mL/min; in parallel, renal clearance decreased from approximately 2.4 L/h to 0.5 L/h.

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.

Table 15: Result summary of rivaroxaban PK and PD data when investigating renal insufficiency as intrinsic factor [presented as mean ratios (Stratum 2 / Stratum 1) and 90% confidence intervals (CI) for AUC and C_{max} for PK, AUC(0-48) and E_{max} for PD; patients valid for PK/PD, n=32], assessed in the specifically designed clinical pharmacology study 11002

ANOVA results (LS mean ratio and confidence intervals)			
	of the PK parameters AUC and C_{max}		
Stratum 1	Stratum 2	AUC	C_{max}
$CL_{CR} \geq 80$ mL/min	CL_{CR} 50 – 79 mL/min	1.44 (1.08; 1.92)	1.28 (1.07; 1.55)
	CL_{CR} 30 – 49 mL/min	1.52 (1.15; 2.01)	1.12 (0.93; 1.34)
	$CL_{CR} < 30$ mL/min	1.64 (1.24; 2.17)	1.26 (1.05; 1.51)
	of percent inhibition of FXa activity		
Stratum 1	Stratum 2	AUC(0-48)	E_{max}
$CL_{CR} \geq 80$ mL/min	CL_{CR} 50 - 79 mL/min	1.50 (1.07; 2.10)	1.09 (0.96; 1.25)
	CL_{CR} 30 – 49 mL/min	1.86 (1.34; 2.59)	1.10 (0.97; 1.26)
	$CL_{CR} < 30$ mL/min	2.00 (1.44; 2.78)	1.12 (0.99; 1.27)
	of relative prolongation of PT		
Stratum 1	Stratum 2	AUC(0-48)	E_{max}
$CL_{CR} \geq 80$ mL/min	CL_{CR} 50 – 79 mL/min	1.33 (0.92; 1.92)	1.04 (0.98; 1.10)
	CL_{CR} 30 – 49 mL/min	2.16 (1.51; 3.10)	1.17 (1.11; 1.24)
	$CL_{CR} < 30$ mL/min	2.44 (1.70; 3.49)	1.20 (1.13; 1.27)

Source: Applicants Figure 1-3 in "2.7.2 Summary of Clinical Pharmacology Studies" page 21

Safety information from the Phase 3 studies failed to show a trend toward an increased incidence of any bleeding and major and non-major clinically relevant bleeding events relative to increasing renal impairment except for the severe group. Also, these differences appeared to be consistent with those observed with enoxaparin which is also affected by renal impairment as outlined in its product information.

Table 16: The Risk of Bleeding With Rivaroxaban Relative to Enoxaparin in Subjects With Varying Degrees of Renal Impairment from pooled data studies RECORD 1, 2, 3, and 4

Study	Group	All subjects %	Calculated Creatinine Clearance mL/min			
			> 80 % [CI95]	50-80 % [CI95]	30-50 % [CI95]	<30 % [CI95]
11354	R	3.17% [2.48%, 3.99%]	2.96% [2.10%,4.04%]	3.21% [2.09%,4.70%]	3.25% [0.89%,8.12%]	18.18% [2.28%, 51.78%]
	E	2.52% [1.91%, 3.26%]	2.19% [1.46%,3.16%]	3.07% [1.97%,4.53%]	2.76% [0.76%,6.91%]	0.00% 0.00%, 40.96%]
11355	R	3.01% [2.22%, 4.00%]	2.98% [2.01%,4.26%]	3.79% [2.23%,6.01%]	0.00% [0.00%,4.40%]	0.00% [0.00%, 60.24%]
	E	2.25% [1.57%, 3.14%]	2.16% [1.32%,3.32%]	2.74% [1.47%,4.63%]	1.18% [0.03%,6.38%]	0.00% [0.00%, 45.93%]
11356	R	3.34% [2.41%, 4.50%]	3.74% [2.41%,5.51%]	2.78% [1.49%,4.70%]	2.17% [0.26%,7.63%]	11.11% [0.28%, 48.25%]
	E	2.74% [1.91%, 3.81%]	2.27% [1.28%,3.72%]	3.31% [1.91%,5.32%]	2.41% [0.29%,8.43%]	33.33% [0.84%, 90.57%]
11357	R	3.34% [2.41%, 4.50%]	3.48% [2.26%,5.09%]	2.76% [1.39%,4.89%]	4.82% [1.33%,11.88%]	0.00% [0.00%, 52.18%]
	E	2.77% [1.92%, 3.84%]	1.90% [1.04%,3.17%]	3.75% [2.07%,6.22%]	6.25% [2.33%,13.11%	0.00% [0.00%, 26.46%]
Pooled	R	3.19% [2.76%, 3.65%]	3.21% [2.66%,3.83%]	3.15% [2.45%,3.99%]	2.63% [1.27%,4.79%]	10.34% [2.19%, 27.35%]
	E	2.55%	2.14%	3.17%	3.18%	3.57%

		[2.17%, 2.97%]	[1.69%,2.67%]	[2.46%,4.01%]	[1.70%,5.37%]	[0.09%, 18.35%]
R= rivaroxaban and E = Enoxaparin						
Source: Applicant's Integrated analysis of rivaroxaban (BAY 59-7939) studies 11354 (RECORD 1), 11355 (RECORD 4), 11356 (RECORD 3) and 11357 (RECORD 2) with regard to efficacy and safety tables 14.3.1/12.1.1, and 14.3.1/15.2.8.1						

The reviewer considers this safety information from these pooled Phase 3 studies relative to renal impairment inconclusive because of the wide confidence intervals, distribution of creatinine clearance values within the renal function groups, and the potential bias introduced by the limitations of the Cockcroft-Gault equation in this study population. A close review of these post hoc data show that the 75% of the Clcr values (calculated) in the moderate RI group had clcr >40 ml/min and the overall distribution is skewed. In contrast, the dedicated renal study 11002 reported only 50% of its subjects had Clcr (24 hour collection) > 40 mL/min in the moderate RI group. This suggests the dedicated renal impairment study had a better representation of patients with Clcr from 30-50 mL/min.

Further, While a significant number of enrolled patients were categorized as having normal, mild or moderate renal impairment based on a calculated Clcr (Cockcroft-Gault equation), the population had approximately 36% meeting the body mass index (BMI) criteria for obesity (i.e., BMI > 30).[10] Cirillo et. al. reported a direct correlation between BMI and relative error associated with the Cockcroft-Gault equation.[11] This resulted in an approximately 20% over-prediction of glomerular filtration rate (GFR), compared to Inulin clearance, in subjects with BMI greater than 30.

A reviewer generated evaluation of the estimated presurgical Clcr (calculated by the Cockcroft-Gault equation) by age suggest a potential over prediction in patients with a BMI greater than or equal to 30 (Figure 24). These patients are primarily older than 50 years and many appear to have GFR's above what is considered the normal range for young adults (e.g., 90-120 mL/min). This may have resulted in subjects being assigned to the "normal" or "mild" renal impairment groups when their actual renal function was moderately reduced. Therefore, these data can not be considered conclusive regarding the risk of bleeding relative to renal impairment and greater reliance should be placed on the findings of the dedicated renal study discussed above.

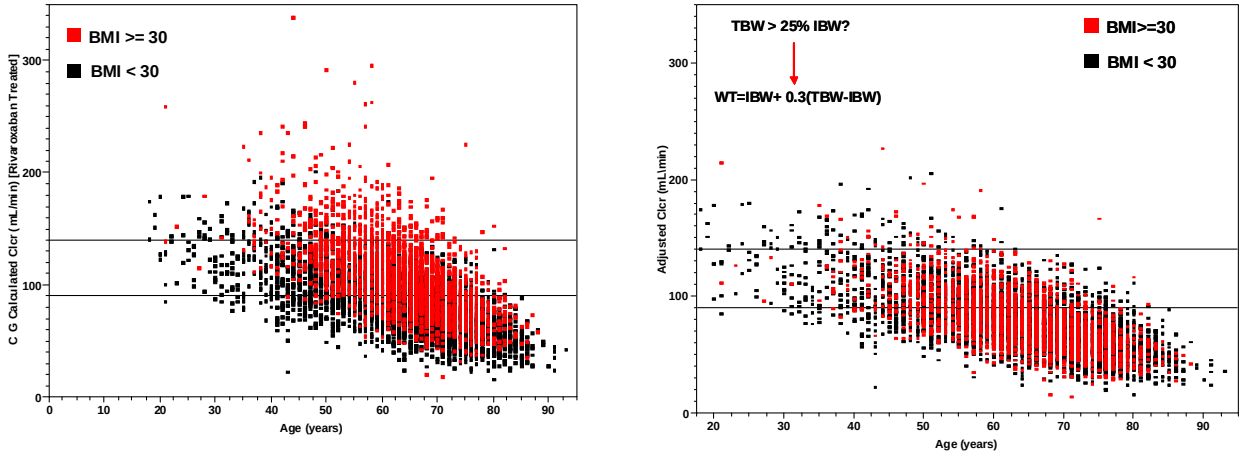


Figure 24: Relationship between age and preoperative Clcr in subjects receiving rivaroxaban from pooled

[10] National Heart, Lung and Blood Institute. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. October 2000.
[11] Cirillo M, Anastasio P, De Santo NG. Relationship of gender, age, and body mass index to errors in predicted kidney function. *Nephrol Dial Transplant*. 2005 Sep;20(9):1791-8.

data of the RECORD studies [left]. Relationship after adjusting for body weight [right]. Red markers signify subjects with a BMI ≥ 30.

Source: Applicants dataset collec.xpt in dataset folder … \NDA022406\0000\m5\datasets\P3-record.

It is also important to note that the applicant itself has required a 25% and 33% dose reduction in subjects with moderate renal impairment at screening (defined as calculated CLCR between 30 and 49 mL/min, inclusive) in studies 11630 (ROCKET-AF) and 12620 (J- ROCKET-AF), respectively. These large clinical studies are underway by the applicant to study the potential use of rivaroxaban in prevention of thromboembolic events in subjects with non-valvular atrial fibrillation. It is unclear why the applicant finds a need to dose adjust in the atrial fibrillation population and not for this indication.

The Applicant proposes the following labeling regarding the use of rivaroxaban in the setting of renal impairment:

(b) (4)

Based on the above analysis and assuming the ability for downward dose titration is not possible due to the availability of a single unscored 10 mg tablet stength the reviewer recommends the following wording:

> *Patients with moderate renal impairment (creatinine clearance 30 to <50 mL/min) should be observed closely by assessing PT and monitoring for signs and symptoms of bleeding while being treated with XARELTO. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.*
>
> *XARELTO is containdicated in patients with severe renal impairment (creatinine clearance <30 mL/min).*
>
> *XARELTO is contraindicated in patients with mild (creatinine clearance 50 to 80 mL/min) or moderate (creatinine clearance 30 to <50 mL/min) renal impairment who are also receiving moderate or strong inhibitors of CYP3A4, P gp, or both CYP3A4 and P gp) because this combination may lead to clinically relevant increased.*

2.3.2.7 Hepatic impairment

Approximately 50% of rivaroxaban dosage is metabolized and approximately 1/3 of the total dosage is excreted via the biliary/fecal route.

The dedicated hepatic impairment study (11003) was conducted by the applicant. This was an investigation of the PK, PD, safety and tolerability of 10 mg rivaroxaban in male and female cirrhotic patients with hepatic impairment (classified as Child Pugh A or B) and in age- and weight-matched male and female healthy subjects following single-dose administration in a single-center, non-randomized, non-controlled, non-blinded,

observational study with group stratification. Cirrhotic patients with severe hepatic impairment (Child Pugh Grade C) were not studied.

The amount of rivaroxaban excreted via urine decreased from 36% of the dose in healthy subjects to 25% of the dose in cirrhotic patients with hepatic impairment of the Child Pugh category A and B, respectively. Renal clearance of rivaroxaban decreased in cirrhotic patients with hepatic impairment, independent of renal function as assessed via creatinine clearance. The latter was comparable between both Child Pugh categories and the healthy control group.

Cirrhotic patients with mild liver impairment (Child Pugh Grade A) exhibited 1.2-fold increase in average rivaroxaban AUC comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (Child Pugh Grade B), rivaroxaban plasma concentrations (AUC) were increased 2.3-fold on average. The increase in exposure appeared to be driven by both reduced hepatic and renal clearance in these subjects. Moderate impairment of hepatic function (Child Pugh category B) also had a 2-fold impact on Inhibition of FXa activity and PT prolongation. The unbound fraction of rivaroxaban was not consistently altered by hepatic impairment and is considered inconclusive.

Table 17: Result summary of rivaroxaban PK and PD data when investigating hepatic insufficiency as intrinsic factor [presented as mean ratios (Stratum 2 / Stratum 1) and 90% confidence intervals (CI) for AUC and C_{max} for PK, AUC(0-tn) and E_{max} for PD; patients valid for PK/PD, n=32], assessed in the specifically designed clinical pharmacology study 11003

ANOVA results (LS mean ratio and confidence intervals)			
of the PK parameters AUC and C_{max}			
Stratum 1	**Stratum 2**	**AUC**	**C_{max}**
healthy subjects	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)
of percent inhibition of FXa activity			
Stratum 1	**Stratum 2**	**AUC(0-tn)**	**E_{max}**
healthy subjects	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)
of relative prolongation of PT			
Stratum 1	**Stratum 2**	**AUC(0-tn)**	**E_{max}**
healthy subjects	Child-Pugh A	1.06 (0.79; 1.42)	1.02 (0.93; 1.12)
	Child-Pugh B	2.14 (1.61; 2.84)	1.41 (1.28; 1.54)

Source: Applicants Figure 1-4 in "2.7.2 Summary of Clinical Pharmacology Studies" page 22

Hepatic impairment: subjects with significant liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis) were to be excluded from enrollment in the Phase 3 RECORD studies.

The Applicant proposes the following labeling regarding the use of rivaroxaban in the setting of hepatic impairment:

(b) (4)

Based on the above analysis and assuming the ability for downward dose titration is not possible due to the availability of a single unscored 10 mg tablet strength the reviewer recommends the following wording:

> *XARELTO is contraindicated in patients with moderate (classified as Child-Pugh B) or severe hepatic disease (classified as Child-Pugh C).*

2.3.2.8 What pregnancy and lactation use information is there in the application?

Pregnancy and lactation was not studied in human clinical trials. Pregnant and breast feeding women were excluded from the RECORD studies. Studies in the rat suggest that penetration of the placental barrier and secretion into breast milk were observed for rivaroxaban.

Whole-body autoradiography study in rats reported the radioactivity distribution in the fetuses appeared homogeneous, except brain which contained low radioactivity concentrations. In none of the fetal organs and tissues the exposure in terms of maximum concentrations or AUC exceeded the maternal blood exposure. With the exception of brain, fetal organ and tissue exposure was also lower than the concentrations in the analogous maternal organs. The average exposure in the fetuses based on AUC(0-24) reached about 20 % of the exposure in maternal blood. The mammary glands had a roughly blood-equivalent AUC which indicates secretion of radioactivity into milk.

[14C]Rivaroxaban was administered orally to lactating Wistar rats (between Day 8 to 10 post partum) as a single oral dose of 3 mg/kg body weight. The compound was dissolved in PEG 400 (60 % of final volume) and demineralized water (40 % of final volume). Milk samples were collected at various time-points after dosing. The radioactivity excretion via milk was calculated on the basis of the radioactivity concentration determined in the milk samples and the respective milk flow.

Radioactivity was secreted into the milk of lactating rats only to a low extent. The estimated amount of radioactivity excreted with milk was 2.1 % of dose within 32 h after administration.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Concomitant use of drugs (e.g., CYP 3A4 and 3A4/PgP inhibitors) with rivaroxaban and the concomitant use of drugs (e.g., CYP 3A4 and 3A4/PgP inhibitors) with rivaroxaban in special populations (i.e., renal impairment) may increase both drug exposure and response. Concomitant use of drugs (e.g., CYP 3A4 and 3A4/PgP inducers) and herbal products (e.g., St Johns Wort) with rivaroxaban may decrease both drug exposure and response. Concomitant use of drugs that affect coagulation (e.g., Enoxaparin, clopidogrel, ASA, etc.) can result in an increased bleeding risk without an increase in rivaroxaban exposure. These will be addressed in detail in Section 2.4.2

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. As described in Section 2.2.5.6, cytochrome P450 3A4/3A5 and CYP2J2 are believed to be the main enzymes responsible for oxidative biotransformation of rivaroxaban in humans, using incubations of [14C]rivaroxaban with human liver microsomes in the absence and presence of CYP isoform-selective inhibitors as well as incubations with recombinant CYP isoforms. In addition, CYP-independent processes (i.e., hydrolysis) are involved in rivaroxaban biotransformation.

The inhibitory potency of rivaroxaban towards ten human CYP isoforms was investigated. CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2 and 3A4 activities were not affected in the presence of rivaroxaban, as indicated by Ki estimates higher than 50 µM. Mean rivaroxaban Cmax at steady-state in VTE prevention patients following 10 mg od are 125 µg/L, corresponding to 0.29 µM.

The enzyme-inducing potential of rivaroxaban was investigated in cultured human hepatocytes of 4 different donors. Cells were exposed with 5 µg/L to 10000 µg/L rivaroxaban for five days in comparison to the prototypic inducers omeprazole (CYP1A2) and rifampicin (CYP3A4). No inductive effects of rivaroxaban on human CYP1A2 and CYP3A4 after repeated exposure up to 10000 µg/L rivaroxaban were observed. This concentration is equivalent to more than 1340 times the mean (total) Cmax value observed in VTE prevention patients treated with 10 mg od rivaroxaban.

In vitro CYP interaction studies with the CYP3A4 substrates midazolam, nifedipine, simvastatin, or atorvastatin showed no notable effect on the human microsomal metabolism of rivaroxaban.

With regard to the potential for CYP-mediated drug-drug interactions between rivaroxaban and potential co-medications, ketoconazole (IC50: 0.28 µM) and ritonavir (IC50: 0.4-0.5 µM) were identified as the most potent inhibitors of both oxidative pathways (CYP3A4/3A5, CYP2J2) of rivaroxaban. As literature-known therapeutic plasma levels (Cmax) for ketoconazole and ritonavir are on average approximately 10 µM (400 mg od, p.o.) and 15 µM (600 mg b.i.d., p.o.), an inhibitory effect has to be anticipated in vivo. Inhibitory effects on rivaroxaban turnover rates in vitro by co-administration of the CYP3A4 substrates midazolam, nifedipine, simvastatin, or atorvastatin were only observed at concentrations well above their respective therapeutic plasma levels (IC50 ≥ 50 µM).

These drugs were part of a broad in vitro screening with common comedications (n=82 drugs from various compound classes) on their potential to affect rivaroxaban microsomal (hepatic) oxidative metabolism (CYP3A4/3A5 and/or CYP2J2- catalyzed) which did not reveal any relevant interactions, except for the already expected ones with antifungal azoles (ketoconazole, clotrimazole > miconazole, itraconazole > fluconazole) and with HIV protease inhibitors (ritonavir > indinavir, azatanavir > saquinavir), known as strong CYP3A4 inhibitors.

Rivaroxaban exhibited a polarized transport in the Caco-2 mqdel and showed a directed efflux in Pgp overexpressing LLC-PK1 (L-MDR1) cell monolayers (efflux ratio of 13.1 at 1 µM), which could almost completely be inhibited by addition of the specific Pgp inhibitor ivermectin (5 µM). No significant directed efflux of rivaroxaban was observed in the wild type LLC-PK1 cells. Therefore, rivaroxaban is classified as a moderate Pgp substrate.

The directed efflux of rivaroxaban in the Pgp overexpressing cells could not be inhibited by the addition of the Pgp substrates atorvastatin, clarithromycin or erythromycin in L-MDR1 cells at concentrations of 5 and 10 µM, respectively. A significant inhibition of the directed efflux of rivaroxaban was achieved by addition of the Pgp substrate/inhibitor amiodarone, however, at supra-therapeutic concentrations (IC50: 14.1 µM). Similarly, the IC_{50} values determined for cyclosporine, ivermectin and verapamil were all above their reported maximum therapeutic plasma concentrations. Ketoconazole, quinidine and ritonavir (potent inhibitors of Pgp) showed their anticipated significant inhibitory effects on the efflux ratio of rivaroxaban in L-MDR1 cells (IC50: 8.98 µM, 4.3 µM, and 27.9 µM, respectively).

To study the in vitro interaction potential of rivaroxaban on Pgp substrates, the influence of rivaroxaban on the polarized (B-A/A-B) transport of two known Pgp substrates, digoxin and dipyridamole, was investigated in vitro. Rivaroxaban (1 to 100 µM) did not have any significant effect on the digoxin or dipyridamole efflux ratios, whereas the addition of known Pgp inhibitors, as positive control, almost completely prevented the net transport of these drugs. Therefore, a relevant inhibition potential of rivaroxaban for Pgp is unlikely.

Rivaroxaban (2 µM) exhibited a polarized transport in Bcrp over-expressing MDCKII cells, resulting in efflux ratios ranging from 27.0 to 41.7 which could completely be

inhibited to an efflux ratio of 1.0 by addition of specific Bcrp inhibitors (5 µM Ko143; 500 µM pantoprazole). Therefore, rivaroxaban can be considered as substrate for the multi-drug transport protein Bcrp, too.

Addition of ritonavir and ketoconazole inhibited the Bcrp-mediated rivaroxaban transport in a concentration-dependent manner. Rivaroxaban efflux ratio decreased from 35.3 without ritonavir down to 0.8 in the presence of 100 µM ritonavir (IC_{50}: 11 µM) and from 41.7 without ketoconazole to 1.0 in the presence of 100 µM ketoconazole (IC50: 5.8 µM). None of the other assayed drugs, including atazanavir, clarithromycin, clotrimazole, cyclosporine, erythromycin, indinavir, itraconazole, miconazole, saquinavir, and verapamil, exhibited a relevant inhibitory potential towards Bcrp-mediated rivaroxaban transport in vitro at (supra-) therapeutic plasma concentrations.

Rivaroxaban (1 to 100 µM) did not have any significant effect on the efflux ratios of known Bcrp substrates, ie prazosin, topotecan, or albendazole sulphoxide. Therefore, a relevant inhibition potential of rivaroxaban for Bcrp is unlikely.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes. See Section 2.2.5.6.

The applicant has collected pharmacogenomic samples from multiple clinical studies; however, it does not appear they were actually analyzed. Genetic differences in metabolism are unlikely because it is not dependent on one single route of elimination being both renally excreted and metabolized via multiple metabolic pathways.

(b) (4)

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

No. This is based on pre-clinical *in vitro* data. See Section 2.4.2.1.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Yes. Rivaroxaban is a substrate of the P-glycoprotein transport processes. This is based on pre clinical *in vitro* data. See Sections 2.2.5.4 and 2.4.2.1.

No. Rivaroxaban is not an inhibitor of the P-glycoprotein transport processes. This is based on pre-clinical *in vitro* data. See Section 2.4.2.1.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Yes. Rivaroxaban is a substrate of active transport protein "breast cancer resistance protein" (BCRP). This is based on pre clinical *in vitro* data. See Sections 2.2.5.4 and 2.4.2.1.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

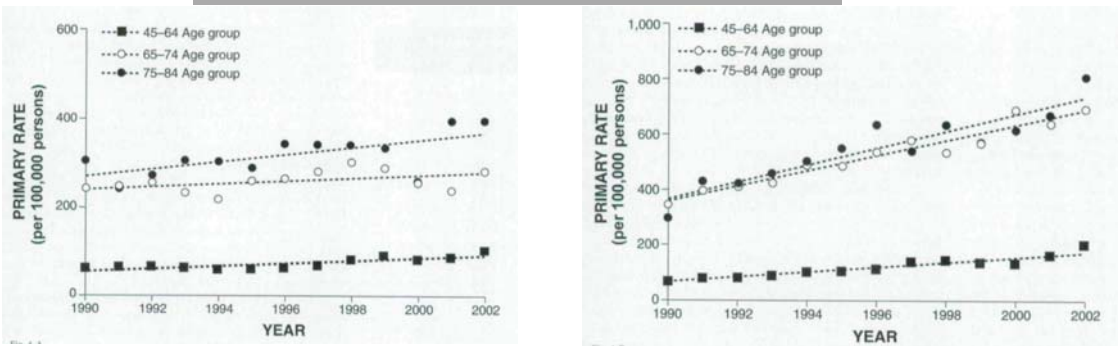
No.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

The rate of total hip and knee arthroplasties is significantly higher in patients > 65 years of age (Figure 25). The prevalence of atrial fibrillation is also greater in this population (Figure 26).[12] The Rotterdam study reports the overall prevalence of atrial fibrillation is

[12] Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial F brillation: a report of the American College of Cardiology/American Heart

6%, the age group 55–59 years and 18% in individuals aged 85 years and older and increasing.[13] Verapamil, diltiazem, quinidine, and amiodarone (CYP 3A4 and/or Pgp Inhibitors) are drugs that may be used in the treatment of atrial fibrillation.[14]



Hip Knee

Figure 25: Rate of Hip and Knee Orthopedic Surgery based on age

Source: Reference 8

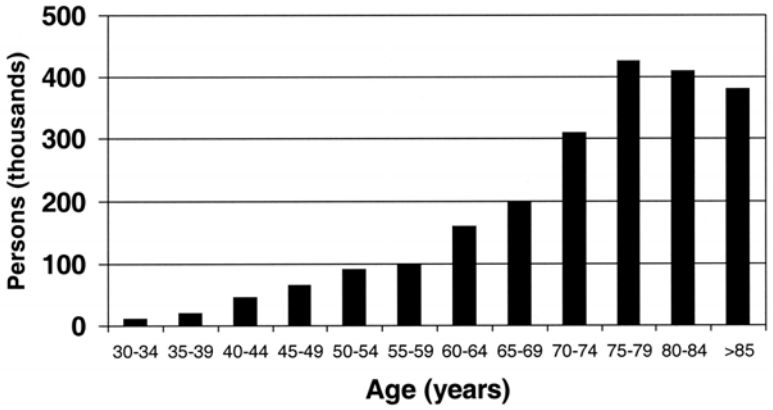


Figure 26: Estimated age-specific prevalence of atrial fibrillation (AF) based on 4 population-based surveys
Source: Reference 12

Bucci et al. reports renal transplant recipients had a cumulative incidence of total hip arthroplasty of 5.1 episodes/1000 person years, which is 5–8 times higher than

Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006; 114: e257–e354.

[13] J Heeringa, DA van der Kuip and A Hofman et al., Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study, *Eur Heart J* 2006; 27: 949–953.

[14] Lip GY, Tse HF. Management of atrial fibrillation. *Lancet*. 2007; 370:604-18.

reported in the general population.[15] Cyclosporine (i.e., Pgp inhibitor) is a drug used ~ 15% of this population.[16]

Thromboprophylaxis for total hip and knee replacement is often multimodal. Agents such as aspirin, warfarin, low molecular weight heparin, and fondaparinux are used alone or sometimes in combination.[17] Although not approved for this use, a recent survey also suggests that clopidogrel therapy may be continued post surgery in the approximately 14% of the 85% patients that were already being treated with this drug prior to surgery.[18]

In addition, post-operative analgesia usually includes general anaesthesia combined with a peripheral nerve block that is continued after surgery or an intrathecal (spinal) injection of local anaesthetic and opioid. Analgesia is then administered using a step-down approach using paracetamol plus conventional non-steroidal anti-inflammatory drugs, with strong or weak opioids as required.[19]

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes. Seventeen drug-drug interaction studies were conducted. The results of those studies relative to exposure are listed in Table 18. In general, the difference pharmacodynamic effect (Factor Xa & PT) E_{max} and AUC showed a similar trend to that reported for the pharmacokinetic exposure differences.

Table 18: Result summary of rivaroxaban exposure data when investigating extrinsic factors potentially affecting its plasma concentrations [presented as mean ratios and 90% confidence intervals (CI) for AUC and Cmax assessed in specifically designed clinical-pharmacology studies]

Influence of	Rivaroxaban AUC ratio [CI]	Rivaroxaban C_{max} ratio [CI]
High-fat, high-calorie meal		
10-mg IR tablet	0.99 [0.93 - 1.05]	1.03 [0.94 - 1.14]
Change in gastric pH		
Ranitidine	1.01 [0.85 - 1.20]	1.08 [0.77 - 1.50]
Adsorption/change in gastric pH		
Antacid	0.95 [0.83 - 1.08]	0.87 [0.73 - 1.03]
CYP 3A4 substrate		
Midazolam	1.01 [0.92 - 1.12]	0.88 [0.72 - 1.07]
CYP 3A4 / P-gp substrate		
Atorvastatin	0.99 [0.91 - 1.08]	0.98 [0.89 - 1.07]
P-gp substrate		
Digoxin	0.90 [0.83 - 0.97]	1.00 [0.85 - 1.14]
CYP 3A4 / P-gp inhibitor (weak-to-moderate)		
Erythromycin	1.34 [1.23 - 1.46]	1.34 [1.21 - 1.48]
CYP 3A4 / P-gp inhibitor (strong / weak-to-moderate)	1.54 [1.44 - 1.64]	1.40 [1.30 - 1.52]
Clarithromycin		
CYP 3A4 / P-gp inhibitor (strong)		
Ketoconazole 200 mg	1.82 [1.59 - 2.08]	1.53 [1.27 - 1.85]
Ketoconazole 400 mg	2.58 [2.36 - 2.82]	1.72 [1.61 - 1.83]
Ritonavir	2.53 [2.34 - 2.74]	1.55 [1.41 - 1.69]
CYP 3A4 / P-gp inducer (strong)		
Rifampicin	0.51 (0.48 - 0.55)	0.78 (0.70 - 0.87)

[15] Bucci JR, Oglesby RJ, Agodoa LY, Abbott KC. Hospitalizations for total hip arthroplasty after renal transplantation in the United States. *Am J Transplant*. 2002; 2:999-1004.
[16] Knoll G. Trends in kidney transplantation over the past decade. *Drugs.* 2008;68 Suppl 1:3-10.
[17] L. D. Dorr, V. Gendelman, A. V. Maheshwari, M. Boutary, Z. Wan, and W. T. Long. Multimodal Thromboprophylaxis for Total Hip and Knee Arthroplasty Based on Risk Assessment. *JBJS* 2007; 89:2648-2657.
[18] Joseph JJ, Pillai A, and Bramley D. Clopidogrel in Orthopaedic patients: a review of current practice in Scotland. *Thrombosis Journal* 2007, 5:6.
[19] Fischer H.B.J. and Simanski C.J.P. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement, *Anaesthesia* 2005;60:1189–1202.

Source: Applicants Table 1-5 in "2.7.2 Summary of Clinical Pharmacology Studies" page 24

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 (Table 18). It is important to note; however, that these studies were conducted using the 30 mg strength in the fasted state. 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. However, the reviewer agrees that a clinically relevant interaction is unlikely.

Clinically relevant drug-drug interactions with substrates of CYP isozymes due to rivaroxaban were evaluated in four in vivo clinical studies using the probe substrates midazolam (CYP3A4 substrate), digoxin (Pgp substrate), atorvastatin (CYP3A4 and Pgp substrate), and warfarin (CYP2C9 substrate). Co-medication of rivaroxaban with these probe substrates at clinically relevant doses did not appear to result in a clinically relevant change in rivaroxaban exposure or pharmacodynamic effect with the exception of warfarin. While an exposure difference was not noted, the combined administration of 5 mg rivaroxaban and 15 mg warfarin resulted in a clinically relevant increase in pharmacodynamic effect (Factor Xa & PT).

Clinically relevant drug-drug interactions with ketoconazole 200 and 400 mg (strong CYP3A4 and Pgp inhibitor), ritonavir (strong CYP3A4 and Pgp inhibitor + theoretical BCRP inhibitor), clarithromycin (strong CYP3A4 and moderate Pgp inhibitor), and erythromycin (weak/moderate CYP3A4 and Pgp inhibitor) were evaluated in five studies at clinically relevant doses (Table 18). These five studies suggest that the use of strong inhibitors of CYP3A4 and/or Pgp may result in a clinically relevant increase exposure and pharmacodynamic effect.

The additional effect of renal impairment to these interactions was not evaluated in vivo by the applicant. However, theoretical simulations by both the applicant and FDA were conducted. FDA simulations differ from the applicant because the applicant failed to consider the contribution of ketoconazole to the renal elimination of rivaroxaban and the effect of renal dysfunction on liver metabolism. However both simulations reflect clinically relevant exposure differences when a moderate/strong CYP3A4 inhibitor is used concurrently with rivaroxaban in a patient with even mild renal impairment and therefore should not be recommended. If downward dose titration is possible then the concurrent use of these drugs in mild renal impairment would likely be possible.

Table 19: Simulated effect of combined strong CYP3A4 Inhibitor plus renal impairment on rivaroxaban exposure (AUC).

GFR (mL/min)		AUCR vs normal			
		Normal	Mild RI	Moderate RI	Severe RI
		(>80)	(50-79)	(30-49)	(<30)
Applicant's estimation	No CYP3A inhibition	1.00	1.49	1.66	1.79
	90% CYP3A inhibition	1.48	2.33	2.74	3.02
FDA's simulation [1]					
	No KTZ	1	1.6		
	+KTZ (SD 400 mg) [2]	2.1-2.7	2.9-3.5	3.4-3.8	3.6-4.0
Observed	No KTZ		1.44	1.52	1.62
	+KTZ (SD 400 mg)	2.58			

[1] simulated from combined scenario: KTZ inhibits CLr and Hepatic P450 decreases by renal impairment

[2] assumes KTZ Ki is between 15nM to 2 µM to CLr

KTZ= Ketoconazole; RI= Renal Impairment

Source: Applicants reports for studies 11936, 11002 and 2/5/2009

regulatory response letter

A clinically relevant drug-drug interaction with antibiotic rifampicin (strong CYP3A4 and Pgp inducer) was evaluated at clinically relevant doses. Co-medication of rifampicin 600 mg qd led to an approximate doubling in rivaroxaban total body clearance, and clinically relevant approximately 50% reduction in rivaroxaban AUC and elimination half-life. While amount of rivaroxaban excreted unchanged into urine was markedly decreased, rivaroxaban renal clearance did not appear to be affected. Given the results from the phase 2 dose ranging study (11527) suggest that a 50% reduction in drug exposure may result in an increase in total venous thromboembolism (10.6% to 14.9%) and major venous thromboembolism (2.7% to 8.5%) this interaction is clinically relevant. Other strong CYP 3A4 inducers such as phenytoin, carbamazepine, phenobarbitone or St. John's wort will likely have similar effects on exposure.

No information on the potential effect of inducers of the transporter proteins Pgp or Bcrp on rivaroxaban PK can be provided due to lack of known selective inducers.

Safety information from the Phase 3 studies failed to show a trend toward an increased incidence of any bleeding and major and non-major clinically relevant bleeding events relative to the concurrent medications discussed above (Table 20).

Table 20: Number and Proportion (%) of Subjects Using Co-medication[a] from RECORD 1, 2, 3, and 4 Pool

Concomitant Drug(s)	Rivaroxaban 10 mg qd (N=6093)	Enoxaparin (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 Pgp inhibitors	467 (8%)	465 (8%)
a Time under concomitant drug use or up to 2 days after last intake of concomitant drug considered time of co-medication use		

Source: Applicant's Integrated analysis of rivaroxaban (BAY 59-7939) studies 11354 (RECORD 1), 11355 (RECORD 4), 11356 (RECORD 3) and 11357 (RECORD 2) with regard to efficacy and safety tables 14.3.1/12.1.1, and 14.3.1/15.2.8.1

Given the interactions were shown to be clinically relevant with moderate to strong inhibitors of CYP3A4 and/or Pgp, a reviewer generated analysis evaluated the risk of bleeding on the drugs individually (Table 21 and Table 22). When displayed in this fashion a pattern consistent with the above information is apparent.

Table 21: Number and Proportion (%) of Subjects Using specific CYP3A4 Inhibitors and proportion reporting any bleeding event a from RECORD 1, 2, 3, and 4 Pool

DRUG/INGREDIENT	Class	RIVAROXABAN			ENOXAPARIN		
		N (Pat.)	N (events	Event rate (%)	N (Pat.)	N (events	Event rate (%)
Any Cyp3a4 Inhibitors		458	10	2.2	453	2	0.4
Amiodarone	N	28	2	7.1	33	0	0.0
Amiodarone Hydrochloride	N	24	1	4.2	18	0	0.0
Aprepitant	M	6	0	0.0	4	1	25.0
Cimetidine	N	118	0	0.0	121	0	0.0
Clarithromycin	S	12	1	8.3	6	0	0.0
Diltiazem	M	53	1	1.9	50	0	0.0
Diltiazem Hydrochloride	M	50	1	2.0	35	0	0.0
Erythromycin	M	9	0	0.0	10	0	0.0
Erythromycin Propionate	M	0	0	0.0	1	0	0.0
Erythromycin Stearate	M	0	0	0.0	2	0	0.0
Fluconazole	M	9	0	0.0	10	0	0.0
Fluoxetine	N	18	0	0.0	17	0	0.0
Fluoxetine Hydrochloride	N	33	1	3.0	46	1	2.2
Fluvoxamine	N	2	0	0.0	0	0	0.0
Fluvoxamine Maleate	N	6	0	0.0	4	0	0.0
Itraconazole	S	1	0	0.0	1	0	0.0

Ketoconazole	S	3	0	0.0	9	0	0.0
Telithromycin	N	0	0	0.0	1	0	0.0
Udramil	N	5	0	0.0	6	0	0.0
Verapamil	M	46	0	0.0	48	1	2.1
Verapamil Hydrochloride	M	55	3	5.5	56	0	0.0
N= Not Classified, S= Strong, M=Moderate, and W=Weak							
Source: Applicant's Integrated analysis of rivaroxaban (BAY 59-7939) studies 11354 (RECORD 1), 11355 (RECORD 4), 11356 (RECORD 3) and 11357 (RECORD 2) with regard to efficacy and safety table 14.3.5/9.6.1							

Table 22: Number and Proportion (%) of Subjects Using specific Pgp Inhibitors and proportion reporting any bleeding event a from RECORD 1, 2, 3, and 4 Pool

Drug /Ingredient	Class	Rivaroxaban			Enoxaparin		
		N (Pat.)	N (events)	Event rate (%)	N (Pat.)	N (events)	Event rate (%)
Any Pgp Inhibitors		128	5	3.9	142	1	0.7
Cyclosporine	S	8	1	12.5	11	0	0.0
Erythromycin	N	9	0	0.0	10	0	0.0
Erythromycin Propionate	N	0	0	0.0	1	0	0.0
Erythromycin Stearate	N	0	0	0.0	2	0	0.0
Itraconazole	N	1	0	0.0	1	0	0.0
Ketoconazole	S	3	0	0.0	9	0	0.0
Quinidine	S	0	0	0.0	1	0	0.0
Quinidine Bisulfate	S	0	0	0.0	1	0	0.0
Quinidine sulfate	S	1	1	100.0	0	0	0.0
Udramil	N	5	0	0.0	6	0	0.0
Verapamil	S	46	0	0.0	48	1	2.1
Verapamil Hydrochloride	S	55	3	5.5	56	0	0.0
N= Not Classified, S= Strong, M=Moderate, and W=Weak							
Source: Applicant's Integrated analysis of rivaroxaban (BAY 59-7939) studies 11354 (RECORD 1), 11355 (RECORD 4), 11356 (RECORD 3) and 11357 (RECORD 2) with regard to efficacy and safety table 14.3.5/9.7.1							

The Applicant proposes the following labeling regarding the use of rivaroxaban the setting of co-administration with the drugs discussed above.

(b) (4)

Based on the above analysis and assuming the ability for downward dose titration is not possible due to the availability of a single unscored 10 mg tablet stength the reviewer recommends the following wording:

> *XARELTO is contrindicated in patients receiving concomitant systemic treatment with strong inhibitors of, CYP3A4 and/or Pgp (eg, amiodarone, quinidine, verapamil, diltiazem, omeprazole, cyclosporin A, colchicine, ketoconazole, itraconazole, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). The concurrent use of these drugs with XARELTO may increase rivaroxaban plasma concentrations to a clinically relevant degree, which may lead to an increased bleeding risk. Grapefruit juice may also increase plasma concentrations of XARELTO and should be avoided.*
>
> *The use of concomitant strong inducers of CYP3A4, Pgp, or both (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, Phenobarbital, St. John's Wort) may decrease rivaroxaban plasma concentrations to a clinically relevant degree, which may lead to an increased incidence of VTE risk and should be avoided.*
>
> *If patients must be coadministered inducers of CYP3A4, Pgp, or both, a XARELTO a dose increase (20 mg) should be considered. If the dose of XARELTO is increased, patients should be observed closely by*

assessing PT and monitoring for signs and symptoms of bleeding while being treated with XARELTO. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Yes. As an anticoagulant, rivaroxaban has the potential to interact with other drugs that influence the coagulation system. 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 pre-clinical rat tail transsection model.

Six confirmatory clinical studies were conducted in humans to assess these potential phymacodynamic interactions.

Both low-molecular weight heparins [LMWHs] and rivaroxaban inhibit Factor Xa. Therefore clarification about potential interferences (e.g. sterical hinderance) as well as additive effects is important. A Phase 1 study in healthy subjects was performed following a single center, non-blinded, randomized, non-placebo-controlled, three-way cross-over design. The investigational drug rivaroxaban was given (fasted) as a single administration in a dose of 10 mg tablets alone or together with Enoxaparin SC. in a dose of 40 mg or Enoxaparin was given alone.

Plasma concentration time profiles for rivaroxaban after oral application of 10 mg rivaroxaban either alone or together with 40 mg enoxaparin s.c. were similar. An analysis of pharmacodynamic effect (Table 23) showed what appears to be an additive effect with regard to anti-Factor Xa activity and PT. This approximately 50% increase in anti-Factor Xa assay is clinically relevant.

Table 23: Treatment effects in different test systems based on maximum observations (ratio; 90% CI)

Test System	Treatment	Enoxaparin	Both
Factor Xa[a]	BAY 59-7939	1.43 (1.31-1.56)	0.98 (0.90-1.07)
	Enoxaparin	1	0.69 (0.63-0.75)
Anti-Factor Xa activity	BAY 59-7939	1.04 (0.91-1.18)	1.48 (1.30-1.69)
	Enoxaparin	1	1.43 (1.25-1.63)
Factor IIa[a]	BAY 59-7939	0.86 (0.67-1.11)	0.94 (0.73-1.20)
	Enoxaparin	1	1.09 (0.84-1.41)
Antithrombin III	BAY 59-7939	0.98 (0.94-1.01)	1.00 (0.97-1.04)
	Enoxaparin	1	1.03 (0.99-1.06)
PT	BAY 59-7939	0.73 (0.70-0.76)	1.01 (0.97-1.05)
	Enoxaparin	1	1.38 (1.33-1.44)
PTT	BAY 59-7939	0.83 (0.71-0.96)	0.97 (0.84-1.13)
	Enoxaparin	1	1.18 (1.01-1.37)
HepTest	BAY 59-7939	2.54 (2.05-3.16)	1.18 (0.95-1.47)
	Enoxaparin	1	0.46 (0.37-0.58)

a Minimum observations

Source: Applicants table 11-9 in the report for study 10848 page 63

Antithrombotic drugs may display an enhanced PD effect when co-administered with drugs that inhibit platelet function. Therefore, a randomized, non-blinded, two-way cross-over study with an aspirin run-in period to investigate the influence of two doses of Aspirin 500 mg once daily on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 15 mg rivaroxaban in 14 healthy male subjects and vice versa was conducted.

Plasma concentration time profiles for rivaroxaban after oral application of 10 mg rivaroxaban either alone or together with aspirin were similar. Increased bleeding time (approximately double) following concomitant administration of rivaroxaban and aspirin was observed (Table 24), but this does not appear to be clinically relevant.

Table 24: Bleeding Time – Relative change from baseline in the course of time – all subjects valid for pharmacodynamics, N=13

Time	N	Aspirin®	N	BAY 59-7939	N	BAY 59-7939 + Aspirin®
0D 04H 00M	13	1.36 1.46/0.287 (0.913 – 1.99)	13	1.00 1.05/0.164 (0.836 – 1.38)	13	2.00 1.96/0.361 (1.38 – 2.48)
1D 00H 00M	13	1.59 1.62/0.551 (0.937 – 2.95)				
2D 00H 00M			13	0.99 0.994/0.200 (0.630 – 1.25)		
3D 00H 00M					13	1.00 1.08/0.230 (0.794 – 1.49)

Data are presented as median, mean/SD, and (range)

Source: Applicants table 11-3 in the report for study 11123 page 49

A randomized, non-blinded, two-way cross-over study with an naproxen run-in period to investigate the influence of two doses of naproxen 500 mg once daily on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 15 mg rivaroxaban in 14 healthy male subjects and vice versa was conducted.

Plasma concentration time profiles for rivaroxaban after oral application of 10 mg rivaroxaban either alone or together with naproxen were similar. Increased bleeding time (approximately double) following concomitant administration of rivaroxaban and naproxen was observed (Table 25), but this does not appear to be clinically relevant.

Table 25: Bleeding Time – Relative change from baseline in the course of time – all subjects valid for pharmacodynamics, N=11

Time	N	Naproxen	N	BAY 59-7939	N	BAY 59-7939+Naproxen
0D 04H 00M[a]	11	1.21 1.46/0.583 (0.844 – 2.60)	11	1.01 1.20/0.613 (0.711 – 2.99)	11	2.09 2.17/0.576 (1.43 – 3.27)
1D 00H 00M[a]	11	1.19 1.22/0.345 (0.811 – 1.86)				
2D 00H 00M[a]			11	0.991 0.982/0.176 (0.764 – 1.27)		
3D 00H 00M[a]					11	1.07 1.15/0.317 (0.794 – 1.75)

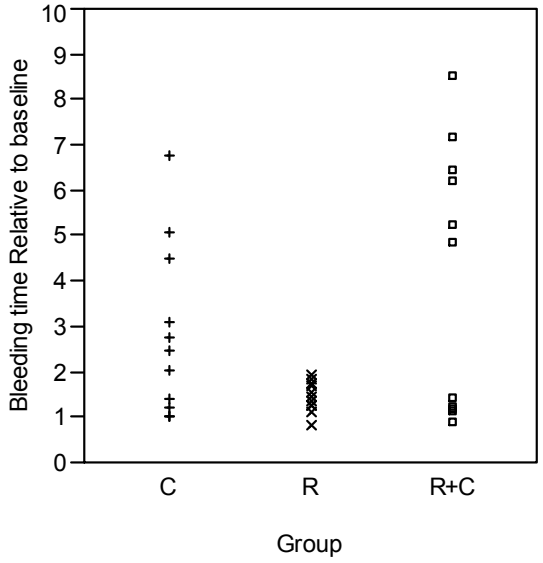
a Data are presented as median, mean/SD, and (range).

Source: Applicants table 11-6 in the report for study 11124 page 43

The applicant performed two clinical studies to evaluate the potential interaction between rivaroxaban in combination with clopidogrel. Plasma concentration time profiles for rivaroxaban after oral application of 10 mg rivaroxaban either alone or together with clopidogrel were similar in both studies. clopidogrel concentrations were not obtained by the applicant in either study.

Rivaroxaban in combination with clopidogrel did not appear to have relevant effects on Factor Xa, PT, aPTT, and HepTest® as compared to rivaroxaban alone based on the reports from these studies. However, a clinically relevant increase in bleeding time was noted in both of these studies. One study reported a clinically relevant increase (Figure 27) 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.

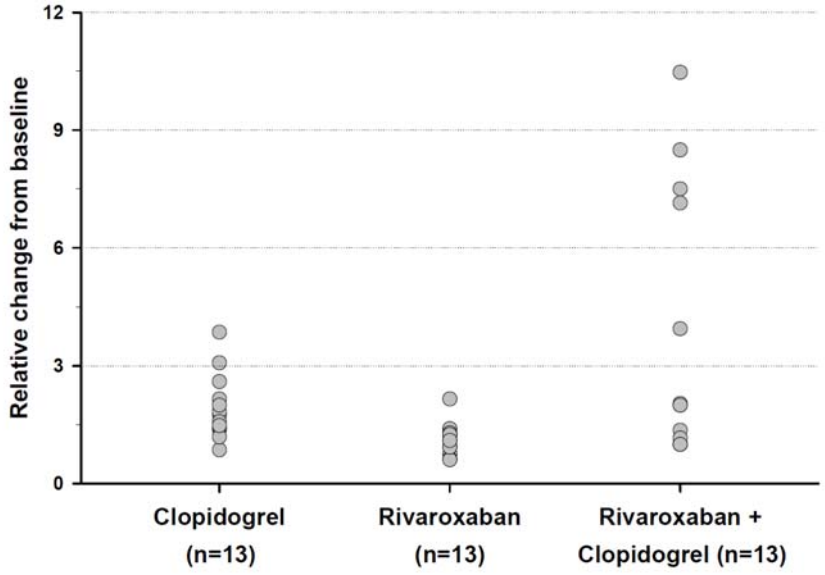


C= Clopidogrel, R= Rivaroxaban, and C+R = Combined therapy

Figure 27: Bleeding time - Individual data for relative change from baseline at 4 h post-dosing (Study 11279)

Source: Adapted from Applicant Table 11-7 in report for study11279 pages 43-44.

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 (Figure 28). 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.



C= Clopidogrel, R= Rivaroxaban, and C+R = Combined therapy

Figure 28: Bleeding time - Individual data for relative change from baseline at 4 h post-dosing (Study 11864)

Source: Applicant's Figure 2-38 in in "2.7.2 Summary of Clinical Pharmacology Studies" page 125

The change in bleeding time in this subpopulation is clinically relevant; however, identification of characteristic to define this subpopulation is not obvious from either study. This is further complicated by not having clopidogrel plama concentration data to evaluate. The applicant did not address potential pharmacogenomic causes which warrant further investigation.

Individual response to clopidogrel is known to be variable and subjects can be characterized as ultrarapid, extensive, intermediate or poor metabolizers. The mechanisms underlying the variability in response are not fully elucidated and are likely multifactorial. Differences in individual absorption of clopidogrel as well as levels of its active metabolite may also lead to clopidogrel response variability.[20] Clopidogrel is a prodrug that requires activation by specific hepatic cytochrome P450 enzymes (CYP2C19, CYP2B6, CYP1A2, and CYP3A4/5.) (b) (4), and previous studies have shown that carriers of the specific alleles of CYP2C19 have an altered response to the antiplatelet effects of clopidogrel compared to the wild-type allele. [21]

In the absence of clopidogrel pharmacokinetics samples, FDA suggested the applicant may consider genotyping patients for variants known to be determinants of clopidogrel response. These include, but are not limited to CYP2C19 variants (e.g., *2, *3, *4, *5, *6, *8, *9, *10, *17). There are marked inter-ethnic differences in the frequency of these allelic variants. CYP2C19*2 and CYP2C19*3 reduced function alleles account for most of the poor metabolizer alleles. The *2 reduced function allele is expected to be most common in the Caucasian population.

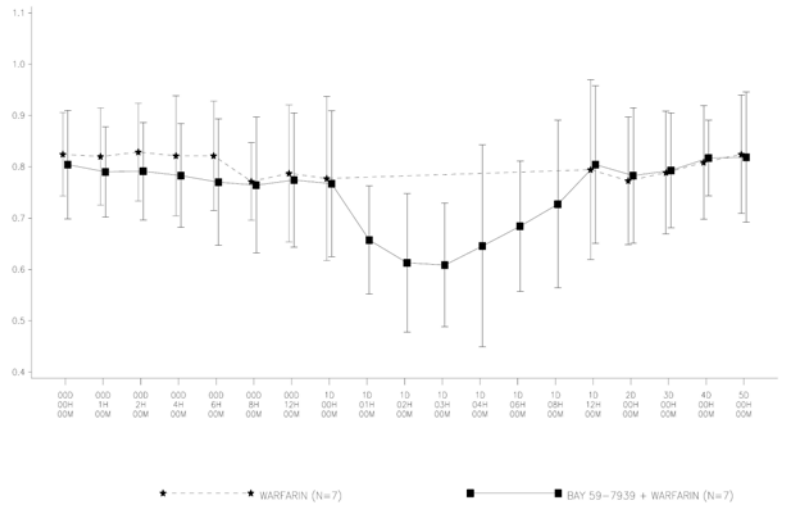
[20] Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, Costa MA. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol.* 2007 Apr 10;49(14):1505-16.

(b) (4)

In response the applicant indicated that the pharmacogenomic samples collected in the clopidogrel interaction studies would be analyzed for CYP2C19*2 and CYP2C19*3 alleles. The result of the CYP2C19*2 and CYP2C19*3 genotyping was submitted to the Agency on March 11. The pharmacogenomics reviewer reports (Section 4.4.2) that based on the submitted pharmacogenetic sub-study report, the clinically relevant increase in bleeding time observed during rivaroxaban/clopidogrel co-treatment cannot be linked to the CYP2C19*2 genotype. Since the mechanism leading to a bleeding time prolongation in some subjects is unclear, the concomitant use of rivaroxaban and clopidogrel is not recommended.

As stated above the sponsor also conducted an exploratory study (12089) of the co-medication of rivaroxaban with warfarin. While an exposure difference was not noted, the combined administration of 5 mg rivaroxaban and 15 mg warfarin resulted in a clinically relevant increase (Figure 29) in pharmacodynamic effect (Factor Xa & PT). The one subject with the highest PT INR value after combined drug administration of rivaroxaban and warfarin had a wild type with 2 active alleles of CYP2D6. The CYP2C9 was a wild type with 2 active alleles in all 7 subjects.

FXa Activity



PT

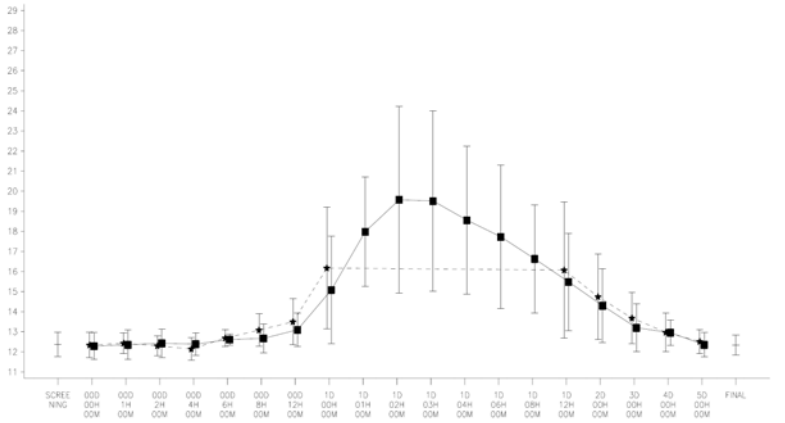


Figure 29: The Effect of Co medication of warfarin and rivaroxaban on Faxtor Xa Activity and PT.

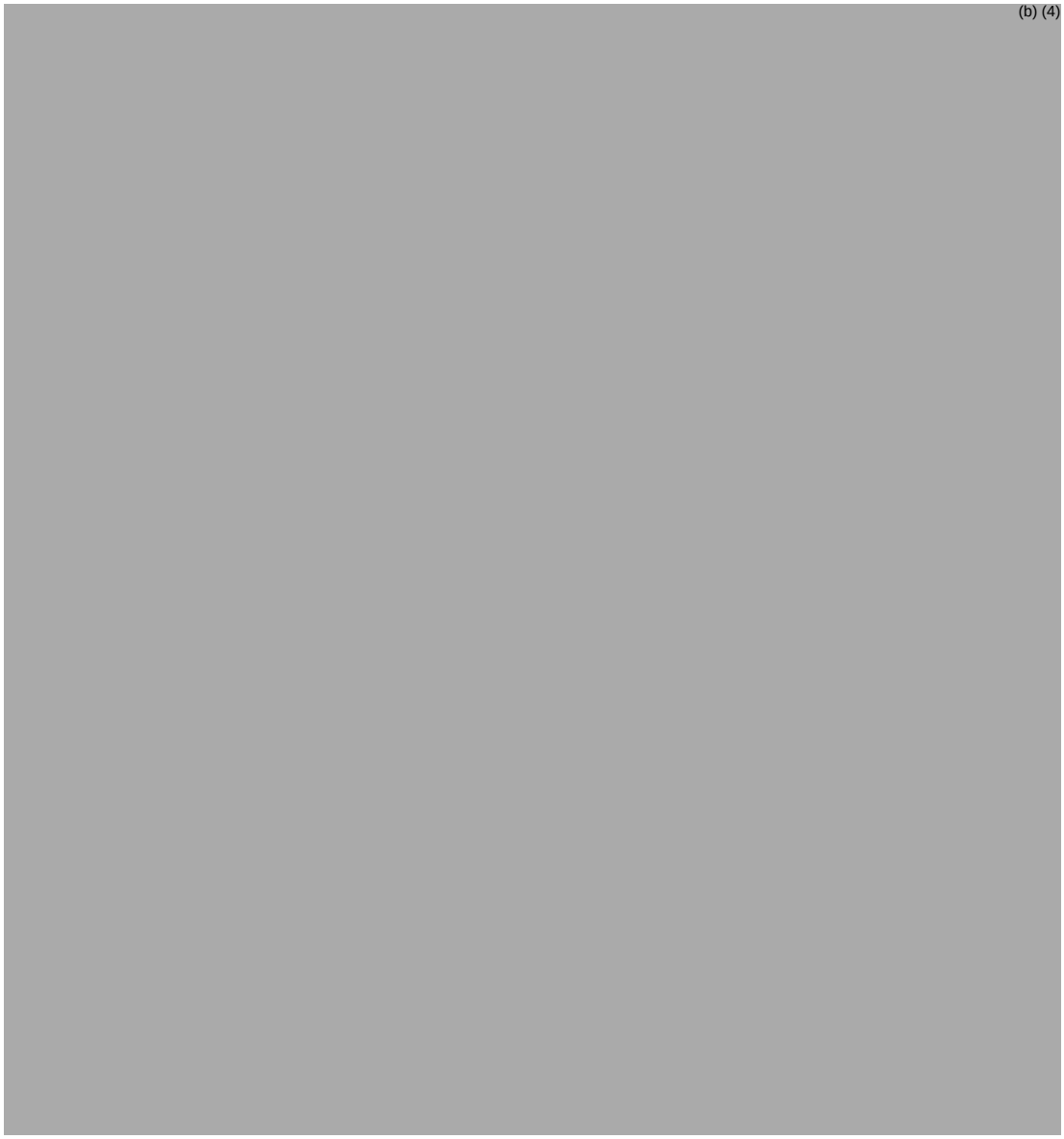
Source: Applicant's Figures 14.2/1.1.1 and 14.2/1.2.1 in report for study 12089 pages 90 and 93.

Safety information from the Phase 3 studies failed to show a trend toward an increased incidence of any bleeding and major and non-major clinically relevant bleeding events

relative to many of the concurrent medications discussed above (Table 20). However, it is important to note that clopidogrel was only used in 26 subjects receiving rivaroxaban.

The Applicant proposes the following labeling regarding the use of rivaroxaban the setting of co-administration with the drugs discussed above.

(b) (4)



Based on the above analysis the reviewer recommends the following wording:

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with XARELTO (10 mg single dose), a clinically relevant additive effect on anti-factor Xa activity was observed without additive effects on clotting tests [prothrombin time (PT), activated partial thromboplastin time (aPTT)]. Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

After combined administration of warfarin 15 mg with XARELTO (5 mg single dose), a clinically relevant additive effect on anti-factor Xa activity

and prothrombin time (PT) was observed. Warfarin did not affect the pharmacokinetics of rivaroxaban in this small study.

Other than for required transitions in therapy, it is not recommended to concurrently use XARELTO with any other anticoagulant due to the increased bleeding risk. During this transition period these patients should be observed closely for signs and symptoms of bleeding while being treated with XARELTO. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

NSAIDs/Aspirin

No clinically relevant pharmacokinetic interaction or prolongation of bleeding time was observed after concomitant administration of XARELTO (15 mg single dose) and 500 mg naproxen (two consecutive days). Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when XARELTO (15 mg single dose) was co-administered with acetylsalicylic acid (500 mg on the first day and 100 mg on the next day).

XARELTO should be used with caution if patients are treated concomitantly with non steroidal anti-inflammatory drugs (NSAIDs/acetylsalicylic acid) and platelet aggregation inhibitors because these drugs typically increase the bleeding risk.

Clopidogrel

Clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) did not show a pharmacokinetic interaction with XARELTO (15 mg single dose), but a clinically relevant increase in bleeding time was observed in a subset of patients, which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels. These findings were confirmed in an earlier exploratory study.

Since characteristics that would identify patients at risk for the clinically relevant increased bleeding time were not obvious and therefore may not be anticipated, concurrent administration is not recommended.

Other Concomitant Therapies

The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH. Coadministration of XARELTO (30 mg single dose) with the H2-receptor antagonist ranitidine (150 mg twice daily) or the antacid aluminum hydroxide/magnesium hydroxide (10 mL) did not show a clinically relevant affect rivaroxaban bioavailability and drug exposure.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Yes. The magnitude of the increase in exposure and pharmacodynamic effect is with the combination of inhibitors of, CYP3A4, Pgp, or both CYP3A4 and Pgp and renal impairment are not known.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

During this review cycle, FDA noted the potential for clinically relevant exposure changes in special populations result from the intrinsic and extrinsic factors noted above. The FDA requested the sponsor develop a lower dose 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. To date, the sponsor has regarded this modification as unnecessary. Thus rivaroxaban therapy is not recommended in these populations at this time.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

According to the criteria of the Biopharmaceutical Classification System(3), rivaroxaban has to be considered as a low solubility, high permeability compound (ie, Class 2).

Rivaroxaban is practically insoluble in water ([redacted] (b) (4)

[redacted] (b) (4)

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The composition of the 10-mg tablet formulation used in the Phase 3 program for VTE prevention in patients undergoing hip or knee replacement surgery is identical to the intended commercial 10-mg formulation manufactured at the Bayer HealthCare AG Leverkusen facility, and remained unchanged when compared to the Phase 1/2 formulation with only one exception [redacted] (b) (4) . In addition, the composition of the commercial supply for the US market from the Janssen Ortho LLC Gurabo facility is identical to the one manufactured at the Bayer Healthcare AG Leverkusen facility.

Rivaroxaban tablets contain micronized rivaroxaban drug substance and standard excipients cellulose microcrystalline, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate and sodium lauril sulfate [redacted] (b) (4) Tablets of all dose strengths have been developed to be of same size [redacted] (b) (4), same tablet weight [redacted] (b) (4) and for clinical Phase 1 and Phase 2 trials also of same appearance (white film coating consisting of hypromellose, macrogol and titanium dioxide).

Although the absolute 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 that 15 mg.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

Not applicable. The applicant is developing a single strength formulation and the applicant states the Phase 1-3 formulations are identical to the commercial formulation with the exception (b) (4)).

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

None

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

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. The applicant conducted two food effect studies using the proposed 10 mg tablet strength.

The pilot study (10846) for the 10-mg dosing regimen, conducted early in the clinical development, employing 2 x 5-mg tablets and a limited number of subjects (n=8 evaluable subjects), indicated a moderate food effect after administration of a high-fat, high-calorie ('American breakfast') meal for rivaroxaban: AUC was increased by about 28% and Cmax was about 41% higher under fed condition. Point estimates (90% confidence interval) for the ratio of fed/fasted showed to be 1.28 (1.15-1.43) for AUC and 1.41 (1.20-1.66) for Cmax. This fails to meet the 80-125% criteria for absence of a food effect. While absorption was also delayed in the fed state showing a lagtime of approximately 1.5 h and a delay in median tmax of about 1.25 h, the elimination phase of the plasma concentration vs time curve appeared unchanged. The pharmacodynamic marker, maximal Factor Xa inhibition, was increased by 27% in the fed group (Figure 30). The changes in Factor Xa inhibition were also reflected by the increased prolongations of PT and HepTest.

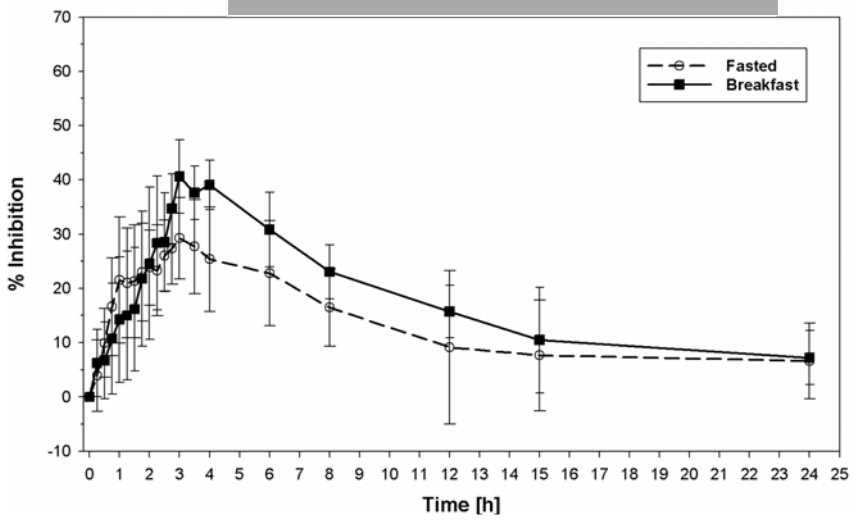


Figure 30: Factor Xa inhibition vs time profiles following administration with or without a high fat high calorie meal [arithmetic mean/ standard deviation] (N=10)

Source: Figure 11-1 in the applicants report for study 10846 page 40

The confirmatory food effect Study 11937 for the 10-mg tablet dose was a single-center, randomized, open-label, two-fold cross-over design investigating the effect of a high-fat, high-calorie meal on the bioavailability of the 10-mg rivaroxaban IR-tablet given orally in the morning to 24 healthy male subjects (Study 11937).

The estimated mean ratios (with food/fasted) were contained in the range 0.80-1.25 which suggests the absence of a food effect (Table 26). Time to reach maximum concentrations (tmax) for rivaroxaban administered with food was prolonged by 0.5 h in comparison to tmax in the fasted state. Changes in Factor Xa inhibition, PT, HepTest, and PTT were not obvious; however a delay reflecting the differences in Tmax was apparent (Figure 31). This difference is not likely to be clinically relevant.

Table 26: Point estimators (LS-means) and two-sided 90% confidence intervals for the ratios rivaroxaban with food/rivaroxaban fasted of the primary parameters AUC and Cmax of rivaroxaban (results of ANOVA, all subjects valid for PK, n = 24)

Test	Reference	Parameter	Estimate (90%CI)
With food	Fasted	AUC	0.9883
			(0.9285 – 1.052)
		C_{max}	1.034
			(0.9378 – 1.140)

Source: Table 11-9 in the applicants report for study 11937 page 47

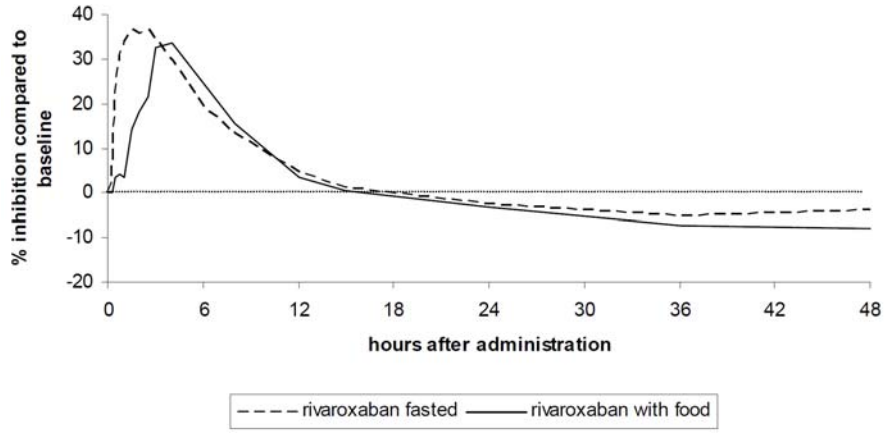


Figure 31: Factor Xa activity: Median inhibition (%) compared to baseline after single oral doses of 10 mg rivaroxaban under fasted conditions and 10 mg rivaroxaban with food, all subjects valid for pharmacodynamics, n=24

Source: Figure 11-1 in the applicants report for study 11937 page 37

Comparing both the pilot and confirmatory studies it appears the content of the test meals and the timing of the dose in relation to the meals were identical. The major difference identified appears to be that two 5 mg tablets were used in the pilot study where the absence of a food effect could not be concluded. Given the proposed formulation was used in the confirmatory study that suggests the absence of a food effect, the reviewer agrees with the applicant's conclusion that there is evidence to support the absence of a food with the proposed 10 mg strength tablet. If the applicant develops a lower strength formulation the food effect issue may need to be revisited.

A relevant food effect (increase in rivaroxaban mean AUC by 39%, in mean Cmax by 76%), was demonstrated for the 20-mg rivaroxaban immediate-release tablet formulation. In studies of higher strength formulations following multiple once- and twice-daily doses administered with food, more complete absorption of these higher strength tablet formulations (e.g., 20 mg or greater) was observed. While the 20 mg tablet is not

planned to be marketed, this food effect may be relevant if a 20 mg dose (i.e., two 10 mg tablets) is used in patient coadministered strong inducers of CYP3A4, Pgp, or both.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable. These studies were conducted (Section 2.5.3).

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Not applicable. This will be addressed in CMC review per MOU between our two divisions.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable. At this time the applicant is developing one tablet strength.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable. The applicant is developing an immediate release formulation.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable. The applicant did not use unapproved products or altered approved products were used as active controls.

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

The absolute bioavailability of the 5-mg tablet, which is not being developed commercially at this time, 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 Cmax was only 50% and related pharmacodynamic effects were more pronounced after administration of the solution (Section 2.2.5.1).

The bioavailability for the 20 mg strength tablet, which is not being developed commercially at this time, 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.

See Section 2.2.5.3 regarding concerns about administering rivaroxaban via a nasogastric tube.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

In all clinical pharmacology studies a data rich sampling scheme was implemented to collect plasma and, when appropriate, urine samples. On the PK profile days as defined in the studies, venous blood samples for the determination of rivaroxaban plasma

concentrations (and for PD assays, respectively) were taken frequently (e.g., every 15 - 30 minutes) for the first 2 - 3 h after administration of study medication, and at regular intervals (every 1 - 4 h) thereafter up to 48 – 72 h post-dosing. Urine collection, to determine rivaroxaban urinary excretion, usually included sampling intervals of 0 - 4, 4 - 8, 8 - 12, 12 - 24, 24 - 48 and 48 - 72 h, respectively.

Plasma rivaroxaban concentrations were measured using a fully validated high-performance liquid chromatography assay with tandem mass spectrometric detection (HPLC-MS/MS), after either solid-phase extraction of rivaroxaban and the internal standard from the matrix using reversed-phase (C18) cartridges or after protein precipitation with methanol. This validation appears consistent with the guidance "Bioanalytical Method Validation." A close chemical analogue of rivaroxaban (BAY 60-4678, dimethyl-derivative of rivaroxaban) was used as internal standard (ISTD). Monitored ion transitions (m/z) were 436 → 145 (rivaroxaban) and 464 → 145 (ISTD). The normally applied calibration range of the procedure was from the lower limit of quantification (LLOQ; for most studies 0.5 µg/L, if not indicated otherwise) to 500 (1000) µg/L. The concentrations were validated by assaying quality control samples of blank plasma spiked with known concentrations of rivaroxaban. Concentrations above LLOQ were determined with a precision of better than 15% and accuracy within 85 - 115%.

Rivaroxaban concentrations in urine were measured using a fully validated HPLC assay with ultra-violet spectrometric (UV) detection at a wavelength of 250 nm, again after solid-phase extraction as sample preparation technique. This validation appears consistent with the guidance "Bioanalytical Method Validation." The normally applied calibration range of the procedure was from 0.01 mg/L (LLOQ) to 5.0 mg/L. The concentrations were validated by assaying quality control samples of blank urine spiked with known concentrations of rivaroxaban. Concentrations above LLOQ were determined with a precision of better than 15% and an accuracy within 85 - 115%.

2.6.2 Which metabolites have been selected for analysis and why?

None. See Section 2.2.3.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

For most studies total concentrations were measured. The reviewer believes this is acceptable given studies evaluating the effect of concurrent drug administration at commonly used doses does not suggest displacement of rivaroxaban from protein binding sights likely or will result in a clinically relevant effect on exposure (Section 2.2.5.4).

Free, bound, and total rivaroxaban concentrations were measured in studies evaluating the effect of disease states that can result in significant changes in drug binding (i.e., renal or hepatic Impairment). See Sections 2.3.2.6 and 2.3.2.7 for additional information about these studies.

2.6.4 What bioanalytical methods are used to assess concentrations?

See Section 2.6.1

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The working range of the assays used in the clinical studies for rivaroxaban are listed in Table 27. This appears reasonable given the expected concentrations from the Phase 1 dose ranging studies.

Table 27: Rivaroxaban working-range of assays

Method-No.	Working Range
BAY 59-7939/RGA/P/version 1.0	2.0-2000 µg/L
BAY 59-7939/RGA/P/1.1	0.5-1000 µg/L
BAY 59-7939/P/01.01	0.5-1000 µg/L
BAY 59-7939/P/01.02	0.5-1000 µg/L
BAY 59-7939/D/02.01	0.5-500 µg/L
M1208 Version 01	0.5-500 µg/L
M1208 Version 2	0.5-500 µg/L
M1208 Version 3	0.5-500 µg/L
BAY 59-7939/P/03.02	2.0-1000 µg/L
BAY 59-7939/P/04.01	0.1-50 µg/L
BAY 59-7939/U/01.01	10-5000 µg/L
BAY 59-7939/U/01.02	10-5000 µg/L
BAY 59-7939/U/01.03	100-20000 µg/L
M1301 Version 1	100-20000 µg/L
M1231 Version 1	99.7-19900 µg/L
M1287 Version 1	n.a.*
SBA_S_04017	0.5 – 750 µg/L
SBA_S_04031	10 – 5000 µg/L

*n.a.= not applicable, relative comparison of peak areas for calculation of enantiomeric ratios

Source: Applicant's table 6.6-1 in the report "Bioanalytical methods and validation data for the determination of rivaroxaban in human plasma, urine and dialysate." Page 23.

Calibration curves were obtained by plotting analyte concentrations vs. relative peak height or area (analyte signal divided by the internal standard signal) and fitting the linear equation y = a + bx to the data. The quality of the calibration curve was proven by back-calculating the concentrations of the calibration samples and evaluating the respective residuals for each calibration curve. Acceptable deviation of back-calculated results from nominal concentrations for calibration samples was defined to be < ± 15 % (< ± 20 % at LLOQ). Moreover, the residual plot was evaluated for any kind of systematic trends.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Table 27.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Precision and accuracy of all the assays at the lower limit of quantitation are given in Table 28 and appears reasonable. Recovery from all the assays is presented in Table 29 and appears reasonable.

Table 28: Rivaroxaban: Limit of quantitation in plasma, urine and dialysate; inter-day precision and accuracy

Method-No	BAY 59-7939 LLOQ	Precision (P) Accuracy (A)
BAY 59-7939/RGA/P/version 1.0	2.0 µg/L	P: 11.8 % (citrate plasma) A: 96.2 % (citrate plasma) P: 14.1 % (NH_4heparin plasma) A: 104.0 % (NH_4heparin plasma)
BAY 59-7939/RGA/P/1.1	0.5 µg/L	P: 6.0 % A: 105.0 %
BAY 59-7939/P/01.01	0.5 µg/L	see BAY 59-7939/RGA/P/1.1
BAY 59-7939/P/01.02	0.5 µg/L	P: 2.6 % * A: 101.1 % * manual sample preparation see BAY 59-7939/RGA/P/1.1
BAY 59-7939/D/02.01	0.5 µg/L	P: 6.7 % A: 97.2 %
M1208 Version 01	0.5 µg/L	P: 7.5 % A: 96.3 %
M1208 Version 2	0.5 µg/L	P: 2.4 % A: 96.6 %
M1208 Version 3	0.5 µg/L	P: 9.9 % A: 96.2 %
BAY 59-7939/P/03.02	2.0 µg/L	P: 9.4 % A: 101.6 %
BAY 59-7939/P/04.01	0.1 µg/L	P: 5.3 % A: 101.0 %
BAY 59-7939/U/01.01	10 µg/L	P: 6.0 % A: 105.8 %
BAY 59-7939/U/01.02	10 µg/L	P: 6.0 % A: 107.3 %
BAY 59-7939/U/01.03	100 µg/L	see M1301 Version1
M1301 Version 1	100 µg/L	P: 3.2 % A: 98.3 %
M1231 Version 1	99.7 µg/L	P: 4.4 % ** A: 97.2 % **
M1287 Version 1	n.a.	n.a.
SBA_S_04017	0.5 µg/L	P: 7.4 % A: 90.5 %
SBA_S_04031	10 µg/L	P: 5.0 % A: 102.0 %

n.a. = not applicable

* with automatic sample preparation ** current method for infectious samples

Source: Applicant's table 6.5-1 in the report "Bioanalytical methods and validation data for the determination of rivaroxaban in human plasma, urine and dialysate." Page 22.

Table 29: Rivaroxaban: Recovery in plasma and urine

Method-No.	Recovery in plasma	Recovery in urine
BAY 59-7939/RGA/P/1.0	82 % (citrate plasma) 87 % (NH_4 heparin plasma)	n.a.
BAY 59-7939/RGA/P/1.1	87-92 %	n.a.
BAY 59-7939/P/01.01	87-92 %	n.a.
BAY 59-7939/P/01.02	see BAY 59-7939/P/01.01	n.a.
BAY 59-7939/D/02.01	88-97 %*	n.a.
M1208 Version 01	103-110 %	n.a.
M1208 Version 2	see M1208 Version 01	n.a.
M1208 Version 3	see M1208 Version 01	n.a.
BAY 59-7939/P/03.02	100-107 %	n.a.
BAY 59-7939/P/04.01	see BAY 59-7939/P/01.01	n.a.
BAY 59-7939/U/01.01	n.a.	81-84 %
BAY 59-7939/U/01.02	n.a.	see BAY 59-7939/U/01.01
BAY 59-7939/U/01.03	n.a.	81 %
M1301 Version 1	n.a.	see BAY 59-7939/U/01.03
M1231 Version 1	n.a.	n.d.
M1287 Version 1	n.a.	n.a.
SBA_S_04017	see BAY 59-7939/P/01.01	n.a.
SBA_S_04031	n.a.	see BAY 59-5939/U/01.01

n.a. = not applicable
n.d. = not determined
* in PBS-buffer or Dialysate

Source: Applicant's table 6.2-1 in the report "Bioanalytical methods and validation data for the determination of rivaroxaban in human plasma, urine and dialysate." Page 19.

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Stability information from all assays is given in Table 30 and appears reasonable.

Table 30: Rivaroxaban stability in spiked samples

Matrix	Storage conditions Temperature		Period	Tube	Result
Plasma supernatant protein precipit.	approx. 9°C	in autosampler	7 days	Glass	Stable
Plasma eluate	Ambient	in autosampler	72 hours	Polypropylene	Stable
Stocksolution in acetonitrile	<=+8°C		5 months	Glass	Stable
Working solution in acetonitrile	<=+8°C		5 months	Glass	Stable
Whole blood (citrate plasma)	Ambient	daylight (window sill)	24 hours	Polypropylene	Stable
	<=+8°C		24 hours	Polypropylene	Stable
Whole blood (heparin plasma)	Ambient	daylight (window sill)	24 hours	Polypropylene	Stable
	<=+8°C		24 hours	Polypropylene	Stable
Plasma (citrate plasma)	Ambient	daylight (window sill)	24 hours	Polypropylene	Stable
	Ambient	yellow light	24 hours	Polypropylene	Stable
	<=+8°C		24 hours	Polypropylene	Stable
	<=-15°C		12 months	Polypropylene	Stable
	+37°C	yellow light	2 hours	Polypropylene	Stable
Plasma (heparin plasma)	Ambient	daylight (window sill)	24 hours	Polypropylene	Stable
	Ambient	yellow light	24 hours	Polypropylene	Stable
	<=+8°C		24 hours	Polypropylene	Stable
	<=-15°C		39 months	Polypropylene	Stable
	+37°C	yellow light	2 hours	Polypropylene	Stable
Plasma (citrate plasma)	Freeze / thaw		3 cycles	Polypropylene	Stable
Plasma (heparin plasma)	Freeze / thaw		3 cycles	Polypropylene	Stable
Urine eluate	approx. 15°C	in autosampler	6 days	Glass	Stable
Urine	Ambient	daylight	72 hours	Polypropylene	Stable
	<=+8°C		72 hours	Polypropylene	Stable
	<=-15°C		19 months	Polypropylene	Stable
Urine	Freeze / thaw		3 cycles	Polypropylene	Stable

Source: Applicant's table 7.1-1 in the report "Bioanalytical methods and validation data for the determination of rivaroxaban in human plasma, urine and dialysate." Page 25

2.6.4.5 What is the QC sample plan?

Quality control samples (QC´s) were analyzed concurrently. For each sequence a set of at least 6 QC samples with concentrations covering the whole working range (3 concentration-levels, 2 replicates each) was analyzed. Acceptance of analytical sequences with study samples was based on the relative residuals of the QC samples, with at least 4 of the 6 QC samples being within ± 15 % of nominal concentration including at least one QC of each concentration level. Concentrations above the ULOQ in study samples were diluted in the working range of the method. The dilution step was validated by a corresponding dilutional QC. Certified reference compounds were used for preparation of calibration and QC samples. This plan appears reasonable.

3 Detailed Labeling Recommendations

59 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 Overview of Study Designs

Biopharmaceutic Studies

Study Identifier (status)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Subjects	Duration of Treatment
011273 (Completed)	Absolute BA IV vs tablet; relative bioavailability	PK, Safety, PD; CO, OL; Fasting	1 mg IV solution, 5-mg tablet, 20-mg tablet; 1 mg, 5 mg, 20 mg; IV respective oral	12	Healthy subjects	Single dose
010924 (Completed)	Intestinal absorption site	PK, Safety; CO, OL; fasting	5-mg tablet, tablet granulate, solution; 5 and 10 mg; oral	9	Healthy subjects	Single dose
010846 (Completed)	Food effect study	PK, Safety, PD; CO, OL; high-fat, high-calorie breakfast	5 mg tablet; 10 mg; oral	10	Healthy subjects	Single dose
010989 (Completed)	Influence of food; dose strength equivalence	PK, Safety, PD; CO, OL; high- fat, high-calorie breakfast	5-mg and 20-mg tablets; 20 mg; oral	11	Healthy subjects	Single dose
011937 (Completed)	Food Effect Study, Phase 3 10-mg tablet formulation	PK, Safety, PD; CO, OL; high-fat, high-calorie breakfast	10-mg tablet; 10 mg; oral	24	Healthy subjects	Single dose
011125 (Completed)	Extended-Release Development	PK, Safety, PD; CO, OL; fasting and fed	25-mg ER prototype; 5-mg tablet; 25 mg; oral	11	Healthy subjects	Single dose
011197 (Completed)	Extended-Release Development	PK, Safety, PD; CO, OL; fasting and fed	25-mg ER prototype; 5-mg tablet; 25 mg; oral	11	Healthy subjects	Single dose
010990 (Completed)	Extended-Release Development	PK, Safety, PD; CO, OL; fasting and fed	25-mg ER prototype; 5-mg tablet; 25 mg; oral	12	Healthy subjects	Single dose
010998 (Completed)	Extended-Release Development	PK, Safety, PD; CO, OL; fasting and fed	30-mg ER prototype, 10-mg tablet; 30 mg; oral	11	Healthy subjects	Single dose
010996 (Completed)	Extended-Release Development	PK, Safety, PD; CO, OL; fasting and fed	30-mg ER prototype, 10-mg tablet; 30 mg; oral	12	Healthy subjects	Single dose
010997 (Completed)	Extended-Release Development	PK, Safety, PD; CO, OL; fasting and fed	30-mg ER prototype, 10-mg tablet; 30 mg; oral	12	Healthy subjects	Single dose
011032 (Completed)	Extended-Release Development	PK, Safety, PD; CO, OL; fasting and fed	10-mg ER prototype, 10-mg tablet; 10 mg; oral	9	Healthy subjects	Single dose
011321 (Completed)	Extended-Release Development	PK, Safety, PD; CO, OL; fasting and fed	10-mg ER prototype, 10-mg tablet; 10 mg; oral	12	Healthy subjects	Single dose
011322 (Completed)	Extended-Release Development	PK, Safety, PD; CO, OL; fasting and fed	20-mg ER prototype, 10-mg tablet; 20 mg; oral	12	Healthy subjects	Single dose
011938 (Completed)	Food Effect Study, Phase 3 20-mg tablet formulation	PK, Safety, PD; CO, OL; fasting and fed	20-mg tablet; 20 mg; oral	24	Healthy subjects	Single dose

Key: BA = bioavailability CO = crossover; DB = double blind; ER = extended release; IV = intravenous; PC = placebo controlled; PD = pharmacodynamic; PG = parallel group design; PK = pharmacokinetic; OL = open label; SB = single blind; ST = sequential treatment;

In Vitro **PK Studies**

Study Identifier (status)	Objective(s) of the Study	Human Biomaterial Used	Study Design and Type of Control	Test Product(s)
PH-32966 (Completed)	Plasma protein binding	Plasma Blood	PK	[^{14}C]Rivaroxaban
PH-33395 (Completed)	Plasma protein binding	Plasma	PK	[^{14}C]Rivaroxaban
PH-34783 (Completed)	Biotransformation in vitro	Hepatocytes Microsomes	DMPK	[^{14}C]Rivaroxaban
PH-34610 (Completed)	Isolation and Structure elucidation	Microsomes Urine	DMPK	[^{14}C]Rivaroxaban
PH-34935 (Completed)	Oxamine metabolism	Microsomes, Hepatocytes, Plasma, Urine	DMPK	[^{14}C]Rivaroxaban / (S)-Oxamine = M-15 of Rivaroxaban
PH-32627 (Completed)	Oxamine metabolism	Recombinant CYP isoforms Microsomes	DMPK	Rivaroxaban/ [^{14}C]Rivaroxaban
PH-34973 (Completed)	Oxidative Metabolism	Liver Microsomes	DMPK	Rivaroxaban
PH-31634 (Completed)	Inhibition	Recombinant CYP isoforms	DMPK	Rivaroxaban
PH-34858 (Completed)	Inhibition	Recombinant CYP isoforms Microsomes	DMPK	Rivaroxaban
PH-33718 (Completed)	Induction	Hepatocytes	DMPK	Rivaroxaban
PH-34936 (Completed)	BCS classification	Caco-2 cells	PK	Rivaroxaban
PH-34986 (Completed)	PgP – Substrate characteristics	recombinant cell line	PK	Rivaroxaban
PH-34937 (Completed)	PgP – Inhibition	recombinant cell line	PK	Rivaroxaban
PH-34987 (Completed)	Bcrp – Substrate characteristics	recombinant cell line	PK	Rivaroxaban

Key: BCS = biopharmaceutical classification system; CYP = Cytochrome P450; DMPK = drug metabolism and pharmacokinetics; PgP = P-glycoprotein; PK = pharmacokinetics

PK Studies

Study Identifier (status)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Subjects	Duration of Treatment
010842 (Completed)	Single dose escalation	Safety, PD, PK; PG, PC, SB; fasting	1.25-mg and 5-mg tablets, oral solution; 1.25, 5, 10, 15, 20, 30, 40, 60, 80 mg; oral	103	Healthy subjects	Single dose
010847 (Completed)	Multiple dose escalation	Safety, PD, PK; PG, PC, SB; fed	5-mg tablet; 5 mg od/bid/tid, 10 mg bid, 20 mg bid, 30 mg bid; oral	64	Healthy subjects	Multiple Dose (5 days)
010991 (Completed)	^{14}C mass balance; metabolism & excretion pattern	Safety, PK; fasting	solution; 10 mg; oral	4	Healthy subjects	Single dose
011529 (Completed)	Single dose escalation in the elderly	Safety, PD, PK; PG, PC, SB; fed	10-mg tablet; 30, 40, 50 mg; oral	48	Male and female healthy subjects > 60 years	Single dose
011569 (Completed)	Comparison young < 45 y vs. subjects > 75 y	Safety, PD, PK; PG, PC, SB; fed	10-mg tablet; 10 mg; oral	34	Male and female healthy subjects > 75 y compared with < 45 y	Single dose
010850 (Completed)	Age and gender study	PK, Safety, PD; PG, PC; SB; fasting	5-mg tablet; 10 mg; oral	48	Young and elderly healthy male and female subjects	Single dose
011568 (Completed)	Subjects of different weight categories (≤50 kg; 70-80 kg; ≥120 kg)	Safety, PD, PK; PG, PC, SB; fed	10-mg tablet; 10 mg; oral	48	Male and female healthy subjects of different body weigh	Single dose
011002 (Completed)	Renal Impairment	Safety, PK, PD; PG, OL; fasting	5-mg tablet; 10 mg; oral	32	Healthy and renally impaired subjects	Single dose
011003 (Completed)	Hepatic Impairment	Safety, PK, PD; PG, OL; fasting	5-mg tablet; 10 mg; oral	32	Healthy and hepatically impaired subjects	Single dose
011126 (Completed)	Single dose escalation, Japan	Safety, PD, PK; PG, PC, SB; fasting	5-mg tablets; 5, 10, 20, 40 mg; oral	40	Healthy Japanese subjects	Single dose
011127 (Completed)	Multiple dose escalation, Japan	Safety, PD, PK; PG, PC, SB; fed	5-mg tablets; 10 mg bid, 20 mg bid, 30 mg bid; oral	30	Healthy Japanese subjects	Multiple dose (6 days)
011325 (Completed)	Single dose escalation in the elderly, Japan	Safety, PD, PK; PG, PC, SB; fed	10-mg tablet; 10, 20, 30, 40 mg; oral	64	Healthy male and female Japanese subjects >60 years	Single dose
012026 (Completed)	Multiple dose escalation in the elderly, Japan	Safety, PD, PK; PG, PC, SB; fed	5-mg tablet; 10, 15, 20 mg od; oral	36	Healthy Japanese subjects >60 years	Multiple dose (7 days)
011608 (Completed)	Single dose escalation,	Safety, PD, PK; PG,	1.25-mg and 5-mg tablets; 2.5, 5, 10,	50	Healthy Chinese	Single dose

	China	PC, SB; fasting	20, 40 mg; oral		subjects	
011609 (Completed)	Multiple dose escalation, China	Safety, PD, PK; PG, PC, SB; fed	5-mg and 10-mg tablets; 5 mg bid, 10 mg bid, 20 mg bid, 30 mg bid; oral	41	Healthy Chinese subjects	Multiple dose (6 days)
011708 (Completed)	Single dose escalation in the elderly, China	Safety, PD, PK; PG, PC, SB; fed	5-mg and 10-mg tablets; 5, 10, 20, 30, 40 mg; oral	76	Healthy male and female Chinese subjects >60 years	Single dose
012090 (Completed)	Ethnic and racial differences	Safety, PD, PK; PG, PC, SB; fed	10-mg tablet; 10 mg; oral	47	Healthy male and female African-American, White, and Hispanic subjects	Single dose
011000 (Completed)	Interaction with Ranitidine	PK, Safety, PD; CO, OL; fasting	5-mg tablet; 30 mg; 150 mg bid Ranitidine; oral	12	Healthy subjects	Single dose Rivaroxaban; multiple dose (4 days) Ranitidine
011001 (Completed)	Interaction with aluminum hydroxide/ magnesium hydroxide	PK, Safety, PD; CO, OL; fasting	5-mg tablet; 30 mg; 10 mL Maalox®; oral	11	Healthy subjects	Single dose
010993 (Completed)	Interaction with Midazolam	PK, Safety, PD; CO, OL; fasting	20-mg tablet; 20 mg; 7.5 mg Dormicum®; oral	12	Healthy subjects	Single dose
010999 (Completed)	Interaction with digoxin	PK, Safety, PD; CO, OL; fed	20-mg tablet; 20 mg bid; 0.375 mg od Lenoxin® mite; oral	19	Healthy subjects	Single & multiple dose (9 days) Rivaroxaban; multiple dose (28 days) digoxin
012359 (Completed)	Interaction with Atorvastatin	PK, Safety, PD; CO, OL; fed	20-mg tablet; 20 mg; 10 mg (Day 1-3) and 20 mg (Day 4-6) od Lipitor®; oral	26	Healthy subjects	Single dose Rivaroxaban; multiple dose (6 days) Atorvastatin
010992 (Completed)	Interaction with Ketoconazole 200 mg od	PK, Safety, PD; CO, OL; fed	10-mg tablet; 10 mg; 200 mg od Nizoral®; oral	12	Healthy subjects	Single dose Rivaroxaban; multiple dose (4 days) Ketoconazole
011936 (Completed)	Interaction with Ketoconazole 400 mg od	PK, Safety, PD; ST, OL; fed	10-mg tablet; 10 mg od; 400 mg od Nizoral®; oral	20	Healthy subjects	Multiple dose (5 days) Rivaroxaban; multiple dose (10 days) Ketoconazole
011935 (Completed)	Interaction with Ritonavir	PK, Safety, PD; ST, OL; fed	10-mg tablet; 10 mg; 600 mg bid Norvir®; oral	16	Healthy subjects	Single dose Rivaroxaban; multiple dose (6 days) Ritonavir
011865 (Completed)	Interaction with Erythromycin	PK, Safety, PD; CO, OL; fed	10-mg tablet; 10 mg; 500 mg tid Erythrocin®; oral	16	Healthy subjects	Single dose Rivaroxaban; multiple dose (5 days) Erythromycin
012680 (Completed)	Interaction with Rifampicin	PK, Safety, PD; ST, OL; fed	20-mg tablet; 20 mg; 150-450 (days 1-3) and 600 (days 4-7)	20	Healthy subjects	Single dose Rivaroxaban; multiple dose (7 days)

			mg od Rifa®; oral			Rifampicin
010848 (Completed)	Interaction with Enoxaparin	Evaluation of several PD parameters, Safety, PK; OL, CO; fasting	10-mg tablet; 10 mg; oral 40 mg Clexane®; subcutaneous	11	Healthy subjects	Single dose
011123 (Completed)	Interaction with Aspirin®	Evaluation of several PD parameters, Safety, PK, CO, OL; fasting	5-mg tablet; 15 mg; 500 mg (Day 1) and 100 mg (Day 2) Aspirin®; oral	14	Healthy subjects	Single dose Rivaroxaban; two doses (500 and 100 mg) of Aspirin®
011124 (Completed)	Interaction with Naproxen	Evaluation of several PD parameters, Safety, PK, CO, OL; fasting	5-mg tablet; 15 mg; 500 mg Proxen®; oral	13	Healthy subjects	Single dose Rivaroxaban; two doses (500 mg each) of Naproxen
011279 (Completed)	Interaction with Clopidogrel	Evaluation of several PD parameters, Safety, PK; CO, OL; fasting	5-mg tablet; 15 mg; 300 mg (Day 1) and 75 mg (Day 2) Plavix®; oral	12	Healthy subjects	Single dose Rivaroxaban; two doses (300 and 75 mg) of Clopidogrel
011864 (Completed)	Interaction with Clopidogrel	of several PD parameters, Safety, PK; CO, OL; fasting	5-mg tablet; 15 mg; 300 mg (Day 1) and 75 mg (Day 2) Plavix®; oral	14	Healthy subjects	Single dose Rivaroxaban; two doses (300 and 75 mg) of Clopidogrel
012089 (Completed)	Pilot interaction with Warfarin	Evaluation of several PD parameters, Safety, PK; OL, ST; fasting	5-mg tablet; 5 mg; 15 mg Coumadin®; 10 mg Konakion® prior to discharge; oral	7	Healthy subjects	Single dose
012612 (Completed)	Interaction with Clarithromycin	PK, Safety, PD; CO, OL, fed	10-mg tablet; 10 mg; 500 mg bid Klacid®; oral	16	Healthy subjects	Single dose Rivaroxaban; multiple dose (5 days) Clarithromycin

Key: bid = twice daily; CO = crossover; DB = double blind; IV = intravenous; od = once daily; OL = open label; PC = placebo controlled; PD = pharmacodynamic; PG = parallel group design; PK = pharmacokinetic; pop = population; SB = single blind; ST = sequential treatment;

PK/PD Studies

Study Identifier (status)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Subjects	Duration of Treatment
PPK03-002 (PH-33730) (Completed)	Exploratory pop PK/PD	N/A	N/A	N/A	N/A	N/A
PK000130 PK000131 (PH-34655) (Completed)	Exploratory pop PK/PD	N/A	N/A	N/A	N/A	N/A
012623 (PH-34928) (Completed)	Exploratory pop PK/PD	N/A	N/A	N/A	N/A	N/A
PPK03-010 (PH-33957)	Exploratory pop PK/PD	N/A	N/A	N/A	N/A	N/A

(Completed)						
PPK04-009 (PH-34169) (Completed)	Exploratory pop PK/PD	N/A	N/A	N/A	N/A	N/A
PK000128 (PH-34168) (Completed)	Pop PK/PD	N/A	N/A	N/A	N/A	N/A
PK000131 (PH-34298 (Completed)	Pop PK/PD	N/A	N/A	N/A	N/A	N/A
012143 (PH-34581) (Completed)	Exploratory pop PK/PD	N/A	N/A	N/A	N/A	N/A

Key: bid = twice daily; CO = crossover; DB = double blind; IV = intravenous; od = once daily; OL = open label; PC = placebo controlled; PD = pharmacodynamic; PG = parallel group design; PK = pharmacokinetic; pop = population; SB = single blind; ST = sequential treatment;

PD Studies

Study Identifier (status)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Subjects	Duration of Treatment
011140 (Completed)	Thrombin Generation Study	Evaluation of several PD parameters, Safety, PK; PG, PC,OL; fasting	5-mg tablet; 5, 30 mg; oral	12	Healthy subjects	Single dose
011275 (Completed)	"Thorough QT Study[a]	QT effects, Safety, PK; DB, CO; positive control; fed	5-mg tablet; 15, 45 mg; 400 mg moxifloxacin; oral	54 (53)[b]	Male and female healthy subjects >50 years	Single dose

a Subject valid for safety
b In Study n=54 valid for safety, n=53 exposed to Rivaroxaban

Key: bid = twice daily; CO = crossover; DB = double blind; IV = intravenous; od = once daily; OL = open label; PC = placebo controlled; PD = pharmacodynamic; PG = parallel group design; PK = pharmacokinetic; pop = population; SB = single blind; ST = sequential treatment;

Efficacy Studies (related to indication)

Study Identifier (status)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Subjects	Duration of Treatment
11354 (MRR-00233) (Completed)	Efficacy and safety (Phase 3)	Randomized, DB, DD, multicenter, multinational, PG, AC		4541 randomized	Total hip replacement	
			Rivaroxaban oral: 10 mg od	2266		Rivaroxaban 10 mg od: 35 ± 4 days
			Enoxaparin 40 mg od SC	2275		Enoxaparin 40 mg od: 36 ± 4 days
11356 (MRR-00218) (Completed)	Efficacy and safety (Phase 3)	Randomized, DB, DD, multicenter, multinational, PG, AC		2531 randomized	Total knee replacement	
			Rivaroxaban oral: 10 mg od	1254		Rivaroxaban 10 mg od: 12 ± 2 days
			Enoxaparin 40 mg od SC	1277		Enoxaparin 40 mg od: 13 ± 2 days
11357 (MRR-00234) (Completed)	Efficacy and safety (Phase 3)	Randomized, DB, DD multicenter, multinational, PG, AC		2509 randomized	Total hip replacement	
			Rivaroxaban oral: 10 mg od	1252		Rivaroxaban 10 mg od: 35 ± 4 days

			Enoxaparin 40 mg od SC	1257		Enoxaparin 40 mg od: 13 ± 2 days
10944 (MRR-00135) (Completed)	Safety, tolerability and efficacy (Phase 2)	Randomized, DB, DD, multicenter, multinational, PG, AC		722 randomized	Total hip replacement	
			Rivaroxaban oral: 2.5 mg bid 5.0 mg bid 10 mg bid 20 mg bid 30 mg bid	135 139 138 137 37		9 ± 2 days
			Enoxaparin 40 mg od SC	136		10 ± 2 days
10945 (MRR-00161) (Completed)	Safety, tolerability and efficacy (Phase 2)	Randomized, DB, DD, multicenter, multinational, PG, AC		621 randomized	Total knee replacement	8 ± 2 days
			Rivaroxaban oral: 2.5 mg bid 5.0 mg bid 10 mg bid 20 mg bid 30 mg bid	100 102 105 102 107		
			Enoxaparin 30 mg bid SC	105		
10942 (MRR-00086) (Completed)	Safety, tolerability and efficacy (Phase 2)	Randomized, (3:1 randomization) OL, multicenter, multinational, PG, AC		641 randomized	Total hip replacement	
			Rivaroxaban oral: 2.5 mg bid 5.0 mg bid 10 mg bid 30 mg od 20 mg bid 30 mg bid	77 84 68 91 79 80		8 ± 2 days
			Enoxaparin 40 mg od SC	162		9 ± 2 days
11527 (MRR-00174) (Completed)	Safety, tolerability and efficacy (Phase 2)	Randomized, DB, DD, multicenter, multinational, PG, AC		873 randomized	Total hip replacement	
			Rivaroxaban oral: 5 mg od 10 mg od 20 mg od 30 mg od 40 mg od	133 147 142 145 146		9 ± 2 days
			Enoxaparin 40 mg od SC	160		10 ± 2 days
11355 (A41857) (Completed)	Efficacy and safety (Phase 3)	Randomized, DB, DD, multicenter, multinational, PG, AC		3148 randomized	Total knee replacement	
			Rivaroxaban oral: 10 mg od	1584		Rivaroxaban 10 mg od: 12 ± 2 days
			Enoxaparin 30 mg bid SC	1564		Enoxaparin 30 mg od: 12 ± 2 days

Key: AC = active control; bid = bis in die, twice daily DB = double blind; DD = double dummy; NA = not applicable; od = once daily; OL = open label; PC = placebo controlled; PD = pharmacodynamic; PG = parallel group; PK = pharmacokinetic; SAEs = serious adverse events; SC = subcutaneous(ly)

Efficacy Studies (NOT related to indication)

Study Identifier (status)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Subjects	Duration of Treatment
11223 (MRR-00150) (Completed)	Safety, tolerability and efficacy (Phase 2)	Randomized, OL (partially blinded), multi-center,		613 randomized	Acute symptomatic DVT	84 days
			Rivaroxaban oral:	120 120		

		multinational, PG, AC	10 mg bid 20 mg bid 40mg od 30 mg bid	123 124		
			VKA/Enoxaparin	126		
11528 (MRR-00223) (Completed)	Safety, tolerability and efficacy (Phase 2)	Randomized, OL (partially blinded), multi-center, multinational, PG, ACI		543 randomized	Acute symptomatic DVT	12 weeks
			Rivaroxaban oral: 20 mg od 30 mg od 40mg od	136 134 136		
			VKA/Enoxaparin	137		
12024 (MRR-00267) (Completed)	Safety, tolerability and efficacy (Phase 2)	Randomized, OL, active comparator, PG		100 Treated	Subjects with atrial fibrillation	28 days
			Rivaroxaban oral: 2.5 mg bid 5 mg bid 10 mg bid	24 26 24		
			Warfarin	26		
11390 (MRR-00199) (Completed)	Safety, tolerability and efficacy (Phase 2)	Uncontrolled, OL, group sequential		36 Treated	Subjects with atrial fibrillation	28 days
			Rivaroxaban oral: 10 mg bid 20 mg bid 30 mg bid	25 11 0		
11866 (MRR-00297) (Completed)	Safety, tolerability and efficacy (Phase 2)	Randomized, OL, active comparator, PG		102 Treated	Subjects with atrial fibrillation	28 days
			Rivaroxaban oral: 10 mg od 15 mg od 20 mg od	26 25 24		
			Warfarin	27		

Key: AC = active control; bid = *bis in die*, twice daily DB = double blind; DD = double dummy; NA = not applicable; od = once daily; OL = open label; PC = placebo controlled; PD = pharmacodynamic; PG = parallel group; PK = pharmacokinetic; SAEs = serious adverse events; SC = subcutaneous(ly)

Reports

Study Identifier (status)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Subjects	Duration of Treatment
PH-34980 (Completed)	Meta-analysis of safety of Phase 1 studies	Meta-analysis	N/A	N/A	N/A	N/A
PH-34982 (Completed)	Meta-analysis of PK and PD of Phase 1 studies	Meta-analysis	N/A	N/A	N/A	N/A
MRR-00300 (Completed)	Meta-analysis of safety of Phase 2 studies	Meta-analysis	N/A	N/A	N/A	N/A
PH-35415 (Completed)	Meta-analysis of safety and efficacy of Phase 3 studies	Meta-analysis	N/A	N/A	N/A	N/A
PH-35408 (Completed)	Meta-analysis of PK of Phase 3 studies	Meta-analysis	N/A	N/A	N/A	N/A
PH-35450 (Completed)	Assessment of SAEs related to liver	N/A	N/A	N/A	N/A	N/A

	function from Phase 3 studies					
PH-35310 (Completed)	Integrated analysis of liver safety in Phase 2	N/A	N/A	N/A	N/A	N/A
PH-35454 (Completed)	Supplemental validity Analysis	N/A	N/A	N/A	N/A	N/A
PH-34787 (Completed)	Pooled analysis of Phase 2	N/A	N/A	N/A	N/A	N/A

Key: AC = active control; bid = *bis in die*, twice daily DB = double blind; DD = double dummy; NA = not applicable; od = once daily; OL = open label; PC = placebo controlled; PD = pharmacodynamic; PG = parallel group; PK = pharmacokinetic; SAEs = serious adverse events; SC = subcutaneous(ly)

4.3 Individual Study Reviews

4.3.1 Study BAY 59-7939/10842 Phase 1 Healthy PK/Dose escalation

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, single-blind, placebo-controlled, group-comparison (with one cross-over dose step) dose-escalation study in healthy male subjects to investigate the safety, tolerability and pharmacodynamic effect as well as the pharmacokinetics of BAY 59-7939 after single oral doses starting with 10 mg of BAY 59-7939 as oral solution or tablet

Study period: 30 Jan 2002 - 10 Feb 2003

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male Caucasian population*
- *Evaluation of solution vs. tablet suggests PD parameters sensitive to changes in Cmax when AUC remains similar. This strengthens the need for a lower strength rather than extended interval in special populations.*
- *Insufficient evidence to conclude "flip-flop" PK as the cause less than dose proportional increases seen in the higher tablet strengths but it is possible.*
- *Higher incidence of GI AE in Tablet cohorts. This may be related to the slower absorption*

Table 5-1: Study 10842

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
10842 Germany 5.3.3.1.1 5.3.3.1.1-1	103 (103/0)	cross-over design 31.1 (21-38) n=10	83.1 (59-100)	5 mg solution n=6	119 (18%)	461 (17%)	0.63 (0.5-0.75)	3.24 (8%)	Less than dose-proportional increases in C_{max} and AUC were observed with higher tablet doses. Due to solubility-limited absorption the apparent half-life increases with dose (flip-flop pharmacokinetics). 41.8% of the dose (arithmetic mean) is excreted into urine as unchanged drug (Ae_{ur}) at 1.25 mg. At the highest investigated doses (40, 60 and 80 mg) the Ae_{ur} is reduced to 19.8, 12.6 and 10.9% of the dose, respectively, as a result of incomplete absorption
				5 mg (1 x 5 mg tablet) n=6	72.0 (20%)	446 (23%)	1.88 (0.5-4.0)	4.27 (25%)	
Randomized, single-blind, placebo-controlled, group-comparison (one cross over dose step) dose escalation study in healthy male subjects, n=8 verum and n=4 placebo planned per step		parallel-design 32.2 (19-45) n=93	81.0 (52-106)	1.25 mg (1 x 1.25 mg tablet) n=8	23.2 (22%)	119 (24%)	3.0 (2.5-4.0)	3.93 (36%)	
				10 mg solution n=8	266 (25%)	997 (25%)	0.5 (0.25-1.0)	4.15 (21%)	
				10 mg (2 x 5 mg tablet) n=8	141 (16%)	1020 (15%)	2.0 (0.5-2.5)	9.07 (62%)	
				15 mg (3 x 5 mg tablet) n=7	176 (39%)	1408 (28%)	1.25 (0.75-4.0)	11.5 (43%)	
				20 mg (4 x 5 mg tablet) n=7	173 (36%)	1612 (36%)	1.5 (0.5-4.0)	7.60 (35%)	
				30 mg (6 x 5 mg tablet) n=6	226 (19%)	1994 (18%)	1.25 (0.75-4.0)	10.8 (89%)	

Table 5-1: Study 10842

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
				40 mg (8 x 5 mg tablet) n=8	234 (37%)	2412 (20%)	1.5 (1.0-4.0)	8.88 (52%)	
				60 mg (12 x 5 mg tablet) n=6-7	350 (9%) n=7	3151 (11%) n=6	2.0 (1.0-4.0) n=7	10.9 (36%) n=6	
				80 mg (16 x 5 mg tablet) n=6	316 (41%)	3298 (31%)	2.0 (0.5-4.0)	17.4 (69%)	

Table 5-37: Study 10842

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PD profile day Treatment Rivaroxaban	PD results Median percentage change from baseline Inhibition of Factor Xa activity [%] (min / max) E_{max}	E (24h)	PT (min / max) E_{max}	E (24h)	Comments / Conclusions
10842 Germany 5.3.3.1.1 5.3.3.1.1-1 Randomized, single-blind, placebo-controlled, group-comparison (one cross over dose step) dose escalation study in healthy male subjects, n=8 verum and n=4 placebo planned per step	103 (103/0)	cross-over design 31.1 (21-38) n=10 parallel design 32.2 (19-45) n=93	83.1 (59-100) 81.0 (52-106)	5 mg solution n=6	31.6 (24 / 38)	0.00 (-4.7 / 8.3)	1.51 (1.4 / 1.6)	1.02 (1.0 / 1.1)	E_{max} of inhibition of Factor Xa activity was dose dependant with some overlap at doses of 30 mg and above. Trough values of inhibition of Factor Xa activity at 24 h were also increasing with dose again with some overlap which as these values are in the range of the physiological baseline of this assay. E_{max} of the prolongation of PT was dose dependant with overlaps at the 20 mg dose. Trough values of prolongation of PT displayed a wide overlap at the total dose range indicating the low propensity for discrimination of this assay at trough.
				5 mg (1 x 5 mg tablet) n=6	20.4 (12 / 30)	0.00 (-3.1 / 5.6)	1.21 (1.1 / 1.3)	0.98 (1.0 / 1.0)	
				1.25 mg (1 x 1.25 mg tablet) n=8	7.17 (5.7 / 16)	3.79 (-9.1 / 8.4)	1.09 (1.1 / 1.1)	1.02 (1.0 / 1.0)	
				10 mg solution n=8	51.2 (48 / 59)	5.19 (-7.0 / 17)	1.91 (1.3 / 2.5)	1.01 (1.0 / 1.1)	
				10 mg (2 x 5 mg tablet) n=8	33.5 (11 / 41)	5.66 (-3.2 / 12)	1.37 (1.1 / 1.5)	1.03 (1.0 / 1.1)	
				15 mg (3 x 5 mg tablet) n=7	43.1 (25 / 54)	3.30 (0.0 / 15)	1.50 (1.2 / 1.8)	1.02 (1.0 / 1.1)	
				20 mg (4 x 5 mg tablet) n=7	40.7 (21 / 50)	3.30 (1.1 / 10)	1.46 (1.3 / 1.7)	1.06 (1.0 / 1.1)	
				30 mg (6 x 5 mg tablet) n=6	40.3 (14 / 47)	8.33 (4.7 / 10)	1.75 (1.5 / 2.0)	1.15 (1.1 / 1.3)	

Table 5-37: Study 10842

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PD profile day Treatment Rivaroxaban	PD results Median percentage change from baseline Inhibition of Factor Xa activity [%] (min / max) E_{max}	E (24h)	PT (min / max) E_{max}	E (24h)	Comments / Conclusions
				40 mg (8 x 5 mg tablet) n=8	48.7 (23 / 60)	10.7 (-4.8 / 24)	1.81 (1.4 / 2.5)	1.03 (1.0 / 1.1)	
				60 mg (12 x 5 mg tablet) n=7	60.2 (45 / 63)	17.1 (9.5 / 21)	2.16 (1.7 / 2.4)	1.11 (1.1 / 1.2)	
				80 mg (16 x 5 mg tablet) n=5-6	61.0 (44 / 75)	16.9 (2.6 / 32)	2.03 (1.6 / 2.8)	1.09 (1.1 / 1.2)	

4.3.2 Study BAY 59-7939/10847 Phase 1 Healthy PK/Dose escalation

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Single-centre, randomised, placebo-controlled, single-blind, parallel-group investigation of the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939 after multiple dose applications of BAY 59-7939 as conventional BAY 59-7939 tablets in healthy male volunteers (BAY 59-7939/010847)

Study period: 15 Jul 2002 to 02 Dec 2002

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male Caucasian population.*
- *One discontinuation due to tinnitus*
- *Agree that dose dependent PD changes noted; however, only dose proportional for PT.*
- Agree minimal accumulation after steady state.
- Agree 5 mg TID does not appear to offer a PD advantage over 5 mg BID dosing.

Table 5-2: Study 10847

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
10847 Germany 5.3.3.1.2 5.3.3.1.2-1 Randomized, single-blind, placebo-controlled, parallel-group, multiple dose application in healthy male subjects; n=8 verum and n=4 placebo planned per step. Study drug administered with food on Day 1 and on days 4-8; no administration on days 2-3. PK profiles collected following first administration on Day 1 and Day 8, respectively	64 (64/0)	32.8 (20-45)	81.6 (59-104)	5 mg od (1 x 5 mg tablet) Day 1 n=7	74.3 (21%)	512 (22%)	4.0 (2.5-6.0)	5.36 (18%)	Exploratory assessment showed a dose-proportional increase of AUC after first dose and in steady state condition, respectively. No undue accumulation was observed in the six treatments as indicated by similar AUCtau,ss (Day 8) and AUC (Day 1). ANOVA results (ratio (90% CI)); first dose (Day 1): 5 mg od vs. 10 mg bid AUCnorm 0.80 (0.65-0.97) $C_{max,norm}$ 0.76 (0.65-0.90) 5 mg od vs. 20 mg bid AUC_{norm} 1.02 (0.83-1.24) $C_{max,norm}$ 0.97 (0.82-1.15) 5 mg od vs. 30 mg bid AUC_{norm} 0.82 (0.67-1.00) $C_{max,norm}$ 0.83 (0.71-0.99)
				5 mg bid (1 x 5 mg tablet) Day 1 n=7	74.5 (25%)	537 (16%)	2.5 (1.0-4.0)	4.91 (16%)	
				5 mg tid (1 x 5 mg tablet) Day 1 n=6	84.8 (11%)	491 (15%)	2.51 (0.5-4.0)	4.54 (30%)	
				10 mg bid (2 x 5 mg tablet) Day 1 n=7	114 (16%)	816 (22%)	4.0 (1.0-4.0)	5.83 (13%)	
				20 mg bid (4 x 5 mg tablet) Day 1 n=7	278 (25%)	1994 (25%)	3.0 (2.5-4.0)	5.59 (13%)	
				30 mg bid (6 x 5 mg tablet) Day 1 n=7	367 (14%)	2472 (16%)	3.0 (2.5-4.0)	5.83 (20%)	

Table 5-2: Study 10847

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
10847 Germany 5.3.3.1.2 5.3.3.1.2-1	64 (64/0)	32.8 (20-45)	81.6 (59-104)	5 mg bid (1 x 5 mg tablet) Day 8 n=7	85.3 (18%)	459 (13%)	3.0 (1.5-4.0)	7.02 (28%)	
Randomized, single-blind, placebo-controlled, parallel-group, multiple dose application in healthy male subjects; n=8 verum and n=4 placebo planned per step. Study drug administered with food on Day 1 and on days 4-8; no administration on days 2-3. PK profiles collected following first administration on Day 1 and Day 8, respectively				5 mg tid (1 x 5 mg tablet) Day 8 n=6	124 (20%)	557 (20%)	2.0 (0.5-4.0)	5.75 (36%)	
				10 mg bid (2 x 5 mg tablet) Day 8 n=7	158 (19%)	864 (19%)	2.98 (1.5-4.0)	7.63 (27%)	
				20 mg bid (4 x 5 mg tablet) Day 8 n=7	318 (19%)	1903 (24%)	2.50 (0.5-4.0)	7.97 (41%)	
				30 mg bid (6 x 5 mg tablet) Day 8 n=7	452 (11%)	2728 (15%)	3.02 (1.5-4.0)	9.15 (64%)	

Table 5-38: Study 10847

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PD results Median percentage change from baseline Inhibition of Factor Xa activity [%] (min / max) E_{max}	E (12h)	PT (min / max) E_{max}	E (12h)	Comments / Conclusions
10847 Germany 5.3.3.1.2 5.3.3.1.2-1 Randomized, single-blind, placebo-controlled, parallel-group multiple dose application in healthy male subjects; planned n=8 verum and n=4 placebo per step. Study drug administered with food on Day 1 and on days 4-8; no administration on days 2-3. PD profiles collected following first administration on Day 1 and Day 8, respectively	68 (68/0)	32.8 (20-45)	81.6 (59-104)	5 mg od (1 x 5 mg tablet) Day 1 n=7	22.8 (4.5 / 28)	1.18[a] (-3.4 / 5.9)	1.25 (1.0 / 1.4)	1.02[a] (1.0 / 1.1)	E_{max} displayed comparable results after the first dose of 5 mg in the first three treatments demonstrating that the assays for inhibition of Factor Xa activity and prolongation of PT provide reproducible results. A dose dependant increase in E_{max} was observed for both parameters. Trough values after the first dose also increased with dose for inhibition of factor Xa acitivity and prolongation of PT. Trough values both for inhibition of Factor Xa and prolongation of PT under active treatment re comparable to placebo data
				5 mg bid (1 x 5 mg tablet) Day 1 n=7	21.8 (8.8 / 33)	0 (-11 / 10)	1.22 (1.1 / 1.3)	1.0 (0.9 / 1.1)	
				5 mg tid (1 x 5 mg tablet) Day 1 n=6	21.7 (13 / 28)	5.0[b] (1 / 12)	1.25 (1.2 / 1.3)	1.04[b] (1.0 / 1.1)	
				10 mg bid (2 x 5 mg tablet) Day 1 n=7	32.6 (26 / 43)	5.3 (0 / 22)	1.39 (1.0 / 1.6)	1.03 (1.0 / 1.2)	
				20 mg bid (4 x 5 mg tablet) Day 1 n=7	56.2 (44 / 67)	10.9 (-7 / 19)	1.92 (1.7 / 2.6)	1.11 (1.0 / 1.3)	
				30 mg bid (6 x 5 mg tablet) Day 1 n=7	68.4 (61 / 75)	15.5 (7 / 29)	2.42 (2.0 / 2.7)	1.22 (1.1 / 1.3)	
				Placebo Day 1 n=21	3.3 (-9 / 46)	-1.3 (-13 / 8)	1.02 (1.0 / 1.1)	0.98 (0.9 / 1.1)	

Table 5-38: Study 10847

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PD results Median percentage change from baseline Inhibition of Factor Xa activity [%] (min / max) E_{max}	Inhibition of Factor Xa activity [%] (min / max) E (12h)	PT (min / max)	PT (min / max) E (12h)	Comments / Conclusions
10847 Germany 5.3.3.1.2 5.3.3.1.2-1 Randomized, single-blind, placebo-controlled, parallel-group multiple dose application in healthy male subjects; planned n=8 verum and n=4 placebo per step. Study drug administered with food on Day 1 and on days 4-8; no administration on days 2-3. PD profiles collected following first administration on Day 1 and Day 8, respectively	68 (68/0)	32.8 (20-45)	81.6 (59-104)	5 mg od (1 x 5 mg tablet) Day 8 n=7	19.8 (4.4 / 26)	-5.11 (-14 / 7.6)	1.30 (1.2 / 1.3)	0.98 (1.0 / 1.1)	E_{max} of Inhibition of Factor Xa activity and prolongation of PT are increasing with dose. As the baseline for inhibition of Factor Xa activity is variable which is especially affecting the trough values. PT is not sensitive enough to detect trough values. Trough values both for inhibition of Factor Xa and prolongation of PT under active treatment are comparable to placebo data
				5 mg bid (1x 5 mg tablet) Day 8 n=7	25.3 (2.3 / 32)	-8.99 (-21 / 1.3)	1.20 (1.1 / 1.4)	0.96 (0.9 / 1.0)	
				5 mg tid (1 x 5 mg tablet) Day 8 n=6	29.1 (13 / 35)	-10.8 (-20 / -2.5)	1.41 (1.2 / 1.5)	0.98 (0.9 / 1.0)	
				10 mg bid (2 x 5 mg tablet) Day 8 n=7	42.7 (29 / 47)	4.29 (-7.8 / 14)	1.52 (1.3 / 1.7)	1.00 (1.0 / 1.1)	
				20 mg bid (4 x 5 mg tablet) Day 8 n=7	53.7 (32 / 63)	-4.47 (-12 / 14)	2.13 (1.6 / 2.7)	1.00 (1.0 / 1.2)	
				30 mg bid (2 x 5 mg tablet) Day 8 n=7	70.8 (68 / 77)	12.1 (1.4 / 23)	2.62 (2.3 / 3.1)	1.03 (1.0 / 1.1)	
				Placebo Day 8 n=21	4.9 (-8 / 23)	-0.1 (-20 / 22)	1.06 (1.0 / 1.1)	0.98 (0.9 / 1.1)	

a: E (24h) b: E (8h)

4.3.3 Study 10991: Mass Balance Study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Single centre, open, non-randomized, non-placebo-controlled study to investigate the metabolism, excretion pattern, mass balance, safety, tolerability and pharmacokinetics after single dose oral administration of 10 mg [14C] BAY 59-7939 in healthy, male subjects balance, safety, tolerability and pharmacokinetics after single dose oral administration of 10 mg [14C] BAY 59-7939 in healthy, male subjects

Study period: 10 Mar 2003 to 25 Mar 2003

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male Caucasian population.*
- *One subject experienced nausea, vomiting and diarrhea starting on Day 3 after drug administration and lasting for about 4 days. The laboratory assessment on Day 7 revealed increased values of lipase, amylase, ALT and gamma GT for him.*
- *Metabolites identified in Report: PH-34935*
- *Overall the applicant's conclusions appear reasonable.*

Table 5-3: Study 10991

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
10991 United Kingdom 5.3.3.1.3 5.3.3.1.3-1	4 (4/0)	41.0 (30-54)	70.5 (66-78)	10 mg solution					Total radioactivity was measured in plasma, urine and feces. More than 80% of total radioactivity exposure in plasma was covered by the parent drug. 94 (90-97) % (arithmetic mean (range)) of the dose were recovered in the excreta. 66 (63-68) % of the dose were found in urine with ca 23-33 % contributed by unchanged drug. Excretion via feces accounted for 28 (24-33) % of the dose.
Single-center, non-randomized, non-placebo-controlled study to investigate metabolism and mass-balance with ^{14}C labeled drug in healthy male subjects				Rivaroxaban/ specific determination n=4	348 (28%)	1163 (37%)	0.5 (0.5-0.5)	5.52 (34%)	
				14C Rivaroxaban associated radioactivity n=4	405 (23%)	1448 (34%)	0.5 (0.5-0.5)	4.47 (37%)	

4.3.4 Study 11529: Dose Escalation Elderly

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, single-blind, placebo-controlled dose escalation study in elderly male and female healthy subjects to investigate the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939 given after a standard breakfast

Study period: 02 Apr 2004 to 15 Jun 2004

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *52% Male & 100% Caucasian population.*
- *~ 20% increased exposure and PD in females. Applicant's conclusion that this is a weight based effect alone is inconclusive.*
- *3 of 12 subjects in the 50 mg dose group reported minor bleeding episodes*
- *Overall the applicant's conclusions appear reasonable.*

Table 5-4: Study 11529

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11529 Germany 5.3.3.3.1 5.3.3.3.1-1 Randomized, single-blind, placebo-controlled, single dose escalation study in elderly (above 60 years) male and female subjects after standard breakfast	52 (27/25)	65.6 (60-76)	77.3 (57-97)	30 mg (3 x 10 mg tablet) n=12 male: n=6 female: n=6	392 (23%)	3531 (20%)	4.0 (2.0-4.0)	11.7 (64%)	Less than dose-proportional increase in systemic exposure from 30 mg to 40 mg but no further increase at 50 mg (ceiling effect). No relevant gender effect on systemic exposure. Small increases in C_{max} and AUC in females at 30 mg and 40 mg likely to be effects of body-weight. 30% (30 mg), 28% (40 mg) and 22% (50 mg) (arithmetic mean) of the dose were excreted into urine as unchanged drug. ANOVA results (Ratio (90% CI)) 40 mg vs. 30 mg tablet: AUC_{norm} 0.91 (0.75-1.12) $C_{max,norm}$ 0.87 (0.72-1.04) 50 mg vs. 30 mg tablet: AUC_{norm} 0.80 (0.65-0.97) $C_{max,norm}$ 0.70 (0.58-0.84)
				40 mg (4 x 10 mg tablet) n=12 male: n=6 female: n=6	461 (17%)	4385 (24%)	4.0 (3.0-6.0)	13.3 (32%)	
				50 mg (5 x 10 mg tablet) n=12 male: n=6 female: n=6	437 (32%)	4496 (34%)	4.0 (2.0-4.0)	11.9 (48%)	

Table 5-39: Study 11529

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PD profile day Regimen Rivaroxaban	PD results Median percentage change from baseline Inhibition of Factor Xa activity [%] (min / max) E_{max}	E (24h)	PT (min / max) E_{max}	E (24h)	Comments / Conclusions
11529 Germany 5.3.3.3.1 5.3.3.3.1-1 Randomized, single-blind, placebo-controlled, single dose escalation study in elderly (above 60 years) male and female subjects after standard breakfast	52 (27/25)	65.6 (60-76)	77.3 (57-97)	30 mg (3 x 10 mg tablet) n=4-12 male: n=6 female: n=6	68.4 (57 / 74)	10.1 (-4.3 / 18)	2.14 (1.2 / 2.4)	1.08 (1.0 / 1.1)	Both inhibition of E_{max} of Factor Xa activity and prolongation of PT displayed a ceeling effect with no further increase beyond 40 mg.
				40 mg (4 x 10 mg tablet) n=12 male: n=6 female: n=6	74.7 (61 / 80)	13.4 (1.4 / 22)	2.49 (1.2 / 3.1)	not available	
				50 mg (5 x 10 mg tablet) n=5-12 male: n=6 female: n=6	74.5 (64 / 87)	15.8 (7.2 / 32)	2.41 (1.9 / 3.6)	1.12 (1.0 / 1.2)	

4.3.5 Study 11569: Intrinsic Factor Study (Age)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Investigation of safety, tolerability, pharmacodynamics, and pharmacokinetics of a single oral dose of 10 mg BAY 59-7939 in male and female subjects older than 75 years compared to young subjects of both genders in a randomized, single-blind, placebo-controlled trial (BAY 59-7939 / 011569)

Study period: 15 Jun 2004 to 27 Sep 2004

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *50% Male & 100% Caucasian population.*
- *Also reports small increase in exposure, but PD factors are somewhat lower in females. The relevance of this finding is unclear.*
- *Two events that concerned minor bleedings (conjunctival hemorrhage about 8 hours after the administration of BAY 59-7939 and gingival bleeding about 23 hours after the administration of BAY 59-7939) were reported.*
- *Agree that age related decreases in renal function may play an important role in this effect*
- *Overall the applicant's conclusions appear reasonable.*

Table 5-5: Study 11569

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11569 Germany 5.3.3.3.2 5.3.3.3.2-1	34 (17/17)	33.9 (22-43)	70.0 (59-79)	10 mg tablet young female n=6	210 (24%)	1210 (13%)	3.0 (0.5-3.05)	11.7 (81%)	No relevant age or gender effect on C_{max} and no gender effect on AUC. 40% increase in AUC in old compared to young subjects partially explainable by lower renal clearance. Ae_{ur} of unchanged drug was 35% (young female), 27% (old female), 33% (young male) and 31% (old male). ANOVA results (Ratio (90% CI)) women vs. men: AUC 0.93 (0.79-1.09) C_{max} 0.99 (0.86-1.15) AUC_{norm} 0.81 (0.66-1.00) $C_{max,norm}$ 0.87 (0.73-1.03) old vs. young: AUC 1.41 (1.20-1.66) C_{max} 1.08 (0.94-1.25) AUC_{norm} 1.39 (1.13-1.71) $C_{max,norm}$ 1.07 (0.90-1.27)
Randomized, single-blind, placebo-controlled, single-dose study in male and female subjects older than 75 years compared to young (18 - 45 years) subjects		77.8 (75-83)	67.4 (59-79)	10 mg tablet old female n=6	245 (18%)	1941 (16%)	4.0 (2.0-4.0)	12.0 (31%)	
		30.3 (18-43)	81.3 (63-99)	10 mg tablet young male n=6	228 (18%)	1477 (30%)	3.0 (2.0-4.0)	6.89 (40%)	
		76.8 (74-83)	80.1 (67-104)	10 mg tablet old male n=6	229 (24%)	1839 (28%)	4.0 (3.0-4.0)	11.1 (33%)	

4.3.6 Study 10850: Intrinsic Factor Study (Gender and Age)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: The effects of age and gender on the pharmacokinetics and pharmacodynamics of BAY 59-7939

Study period: 17 July 2002 to 05 September 2002

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *50% Male & primarily Hispanic population.*
- *Reports significant 42% increase in exposure (Cmax) and PD in females. The reason for this finding is unclear. The body weight of female was lower than males.*
- *Overall the applicant's conclusions appear reasonable.*

Table 5-6: Study 10850

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
10850 USA 5.3.3.3.3 5.3.3.3.3-1	48 (24/24)	34.1 (23-43)	82.6 (59-108)	10 mg (2 x 5 mg tablet) young male n=9	158 (27%)	1220 (25%)	1.5 (0.5-4.0)	9.91 (42%)	The pharmacokinetics were significantly altered in elderly subjects with mean increases in AUC and C_{max} by 45% and 35% compared to young subjects. Gender had no effect on AUC but C_{max} was increased (+ 42%) in females. This effect was less pronounced after body-weight-normalization. Group comparisons (Ratio (90%CI)) elderly vs. young: AUC 1.45 (1.21-1.74) C_{max} 1.35 (1.12-1.64) AUC_{norm} 1.42 (1.14-1.76) $C_{max,norm}$ 1.32 (1.07-1.62) male vs. female: AUC 1.05 (0.87-1.26) C_{max} 1.42 (1.17-1.72) AUC_{norm} 0.94 (0.76-1.17) $C_{max,norm}$ 1.28 (1.04-1.57)
Randomized, single-dose, placebo-controlled, parallel group study in young (18 - 45 years) and elderly (65 - 80 years) healthy subjects of both genders		38.8 (30-45)	68.3 (59-83)	10 mg (2 x 5 mg tablet) young female n=9	224 (33%)	1338 (45%)	2.0 (0.5-4.0)	10.0 (40%)	
		74.0 (68-80)	74.5 (62-88)	10 mg (2 x 5 mg tablet) elderly male n=9	214 (45%)	1852 (35%)	2.5 (1.0-2.5)	9.42 (29%)	
		68.4 (65-75)	71.7 (65-84)	10 mg (2 x 5 mg tablet) elderly female n=9	304 (27%)	1859 (20%)	2.5 (1.0-3.0)	8.43 (48%)	

4.3.7 Study 11568: Intrinsic Factor Study (Gender and Weight)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Single-blind, randomized investigation of safety, pharmacodynamics and pharmacokinetics of a single oral dose of 10 mg BAY 59-7939 in male and female subjects of different weight categories

Study period: 25 Aug 2004 to 29 Oct 2004

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Primarily female Caucasian population. Therefore, it is difficult to rule out the effect of Hispanic race which may have been a factor in study 10850*
- *No males under 50 kg studied*
- *Overall the applicant's conclusions appear reasonable.*

Table 5-7: Study 11568

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11568 Germany 5.3.3.3.4 5.3.3.3.4-1 Randomized, single-blind, placebo-controlled, single-dose administration with food in male and female subjects of different weight categories	48 (16/32)			10 mg tablet BW ≤ 50 kg					No differences between weight categories with regard to AUC. Subjects with ≤ 50 kg body weight had higher C_{max} (+24%) than subjects of the normal weight category. No gender effect on AUC and C_{max} was seen. ANOVA results (Ratio (90% CI)) ≤ 50 kg vs. 70-80 kg (n=24): AUC 1.14 (1.00-1.30) C_{max} 1.24 (1.07-1.44) >120 kg vs. 70-80 kg (n=24): AUC 1.12 (0.98-1.28) C_{max} 1.04 (0.90-1.20) male vs. female 70-80 kg (n=12): AUC 0.97 (0.81-1.15) C_{max} 0.98 (0.78-1.24) male vs. female > 120 kg (n=12): AUC 0.85 (0.72-1.02) C_{max} 0.81 (0.64-1.02)
		35.3 (22-46)	48.3 (47-50)	female n=12	178 (17%)	1172 (22%)	4.0 (1.0-4.02)	9.58 (37%)	
				10 mg tablet BW 70 to 80 kg					
		36.0 (22-54)	74.7 (72-77)	male n=6	142 (30%)	1011 (27%)	3.0 (1.0-4.0)	6.29 (27%)	
		28.5 (20-53)	73.3 (70-76)	female n=6	145 (26%)	1047 (12%)	4.0 (1.0-4.03)	8.14 (53%)	
				10 mg tablet BW > 120 kg					
		38.0 (22-47)	135.8 (123-145)	male n=6	134 (15%)	1067 (13%)	4.0 (4.0-4.02)	6.85 (19%)	
		36.2 (24-44)	128.5 (120-145)	female n=6	166 (21%)	1251 (14%)	3.5 (2.0-4.02)	7.78 (31%)	

4.3.8 Study 11002: Intrinsic Factor Study (Renal)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Investigation of pharmacokinetics, pharmacodynamics, safety and tolerability of 10 mg BAY 59-7939 in male and female patients with renal impairment and in age comparable male and female subjects with normal renal function following single-dose administration in a multiple-center, non-randomized, noncontrolled, non-blinded, observational study with group stratification

Study period: 09 Jul 2004 to 04 May 2005

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Primarily Male and 100% Caucasian population.*
- *No subjects with creatinine clearance < 15 mL/min studied. Conclusions regarding the "severe" group should be analyzed in this context.*
- *Creatinine clearance (CLCR) values, which were calculated as a 24 hour clearance from the creatinine concentrations measured in serum and urine.*
- *PD effects where more pronounced than expected from the exposure change. The role of increased anticoagulation sensitivity in the setting of renal impairment is suspected. This increased sensitivity must be considered when evaluating exposure differences.*
- *Overall the applicant's conclusions appear reasonable; however, the reviewer does not agree with its opinion regarding the clinical relevance of these findings.*

Table 5-8: Study 11002

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11002 Germany 5.3.3.3.5 5.3.3.3.5-1 Non-randomized, non-controlled, non-blind, single dose administration in male and female patients with renal impairment and in age comparable subjects with normal renal function	32 (18/14)	51.3 (39-69)	76.6 (61-95)	10 mg (2 x 5 mg tablet) CLCR ≥ 80mL/min control group n=8	172 (31%)	1247 (49%)	2.0 (0.5-4.0)	8.28 (38%)	Total body clearance and renal clearance (2.38, 1.18, 0.68 and 0.50 L/h in control subjects and patients with increasing degree of impairment) of rivaroxaban decreased with creatinine clearance. Increased AUC (+ 64%) and C_{max} (+ 26%) in severely impaired subjects vs. controls. Fraction of drug unbound in plasma was unaffected by renal impairment. ANOVA results (Ratio (90% CI)) CLCR 50-79 vs. healthy: AUC 1.44 (1.08-1.92) C_{max} 1.28 (1.07-1.55) CLCR 30-49 vs. healthy: AUC 1.52 (1.15-2.01) C_{max} 1.12 (0.93-1.34) CLCR <30 vs. healthy: AUC 1.64 (1.24-2.17) C_{max} 1.26 (1.05-1.51)
		49.4 (39-61)	80.8 (58-110)	10 mg (2 x 5 mg tablet) CLCR 50-79 mL/min mild impairment n=8	218 (38%)	1864 (31%)	2.0 (1.0-6.0)	8.69 (50%)	
		54.9 (38-69)	75.3 (64-88)	10 mg (2 x 5 mg tablet) CLCR 30-49 mL/min moderate impairment n=8	206 (26%)	2068 (33%)	3.0 (1.0-4.0)	8.99 (39%)	
		51.8 (36-65)	72.5 (56-94)	10 mg (2 x 5 mg tablet) CLCR < 30 mL/min severe impairment n=8	232 (33%)	2228 (37%)	3.0 (2.0-4.0)	9.46 (32%)	

4.3.9 Study 11003: Intrinsic Factor Study (Hepatic)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Investigation of pharmacokinetics, pharmacodynamics, safety and tolerability of 10 mg BAY 59-7939 in male and female patients with hepatic impairment (classified as Child Pugh A or B) and in age- and weight-matched male and female healthy subjects following single-dose administration in a single-center, non-randomized, non-controlled, non-blinded, observational study with group stratification

Study period: 19 Jan 2005 to 10 Aug 2005

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Primarily Male and 100% Caucasian population.*
- *No subjects with CP Grade "C." Conclusions regarding this group can not be made.*
- *Effect of plasma protein binding is inconclusive, but the trend suggests a limited effect.*
- *Overall the applicant's conclusions appear reasonable; however, the reviewer does not agree with its opinion regarding the clinical relevance of these findings.*

Table 5-9: Study 11003

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11003 Germany 5.3.3.3.6 5.3.3.3.6-1 Non-randomized, non-controlled, non-blind, parallel group study with single dose administration in male and female patients with hepatic impairment (Child Pugh A or B; 18-65 years) and age- and weight-matched male and female healthy subjects (18-70 years)	32 (18/14)	58.4 (49-68)	81.1 (58-107)	10 mg (2 x 5 mg tablet) patients Child Pugh A n=8	203 (42%)	1746 (42%)	2.0 (1.0-4.02)	10.4 (82%)	Rivaroxaban AUC (2.27 fold) and to a lesser extent C_{max} (1.27 fold) were significantly increased in subjects with hepatic impairment of the Child Pugh B category compared to healthy control subjects. Hepatic impairment had no effect on the unbound drug fraction in plasma. ANOVA results (Ratio (90% CI)) Child Pugh B vs. A: AUC 1.97 (1.38-2.80) C_{max} 1.31 (0.98-1.76) Child Pugh B vs. healthy: AUC 2.27 (1.68-3.07) C_{max} 1.27 (0.99-1.63) Child Pugh A vs. healthy: AUC 1.15 (0.85-1.57) C_{max} 0.97 (0.75-1.25)
		51.9 (40-66)	73.3 (55-91)	10 mg (2 x 5 mg tablet) patients Child Pugh B n=8	279 (46%)	3510 (59%)	3.0 (1.0-4.0)	10.1 (34%)	
		54.3 (36-67)	76.0 (53-99)	10 mg (2 x 5 mg tablet) healthy subjects n=16	214 (37%)	1516 (33%)	2.0 (1.0-4.0)	8.00 (44%)	

4.3.10 Study 11126: Single Dose Escalation (Japanese)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, single-blind, placebo-controlled, dose-escalation study in healthy Japanese male subjects to investigate the tolerability, safety, pharmacokinetics and pharmacodynamic effects of BAY 59-7939 tablet after single oral doses of 5, 10, 20 and 40 mg under the fasting condition

Study period: 23 Jan 2003 to 10 Apr 2003

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *100% Male. Average BMI < 25*
- 3 events of bleeding time prolonged (2 from 10 mg group and 1 from 20 mg group)
- Overall the applicant's conclusions appear reasonable.

Table 5-10: Study 11126

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11126 Japan 5.3.3.3.7 5.3.3.3.7-1 Randomized, single-blind, placebo-controlled, single dose escalation study in fasting healthy Japanese male subjects; n=8 verum and n=2 placebo per dose step	40 (40/0)	22.7 (20-34)	62.6 (50-87)	5 mg (1 x 5 mg tablet) n=8	141 (14%)	816 (13%)	1.38 (0.5-2.5)	5.75 (20%)	Almost dose-proportional increase in AUC from 5 mg to 10 mg but very little additional systemic exposure when increasing dose from 20 mg to 40 mg; C_{max} increase less than dose-proportional across entire dose range. Ae_{ur} of unchanged drug equal to 23.5, 21.3, 16.5 and 7.9 % of dose (5, 10, 20 and 40 mg). Apparent terminal half-life increases with dose
				10 mg (2 x 5 mg tablet) n=8	227 (19%)	1564 (25%)	1.38 (0.5-4.0)	7.08 (35%)	
				20 mg (4 x 5 mg tablet) n=8	342 (30%)	2777 (27%)	3.25 (0.5-4.0)	8.90 (51%)	
				40 mg (8 x 5 mg tablet) n=8	329 (26%)	3051 (21%)	1.38 (0.5-2.0)	12.6 (40%)	

4.3.11 Study 11127: Multiple Dose Escalation (Japanese)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, single-blind, placebo-controlled, dose-escalation study in healthy Japanese male subjects to investigate the tolerability, safety, pharmacokinetics and pharmacodynamic effects of BAY 59-7939 tablet after multiple oral doses of 10, 20 and 30 mg bid for 6 days

Study period: 27 Jun 2003 to 08 Sep 2003

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *100% Male. Average BMI < 25*
- 3 events of bleeding time prolonged (2 in 10 mg group and 1 in 30 mg group)
- Overall the applicant's conclusions appear reasonable.

Table 5-11: Study 11127

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11127 Japan 5.3.3.3.8 5.3.3.3.8-1 Randomized, single-blind, placebo-controlled, multiple dose-escalation study in healthy Japanese male subjects; bid dosing for 6 days with PK profiles describing respective first dose (0-12 h) on Day 1 and Day 6; n=8 verum and n=2 placebo per step	30 (30/0)	23.5 (20-29)	56.9 (50-81)	10 mg bid (2 x 5 mg tablet) Day 1 n=8	203 (20%)	1365 (17%)	3.50 (2.0-4.0)	4.30 (9%)	Almost dose proportional increase in AUC from 10 mg to 20 mg and slightly less than proportional at 30 mg. C_{max} increase less than dose proportional.
				20 mg bid (4 x 5 mg tablet) Day 1 n=8	340 (13%)	2471 (17%)	3.50 (1.0-4.0)	4.91 (14%)	
				30 mg bid (6 x 5 mg tablet) Day 1 n=8	537 (15%)	3914 (20%)	2.75 (2.0-4.0)	5.21 (17%)	
	30 (30/0)	23.5 (20-29)	56.9 (50-81)	10 mg bid (2 x 5 mg tablet) Day 6 n=8	206 (9%)	1218 (13%)	2.25 (1.0-4.0)	4.86 (25%)	Dose proportional increase in $AUC_{tau,ss}$ and $C_{max,ss}$ from 10 mg to 20 mg and slightly less than proportional at 30 mg. Similar values for AUC (Day 1) and $AUC_{tau,ss}$ (Day 6) indicate the absence of unexpected accumulation upon multiple dosing.
				20 mg bid (4 x 5 mg tablet) Day 6 n=8	401 (15%)	2480 (15%)	2.50 (1.0-4.0)	6.69 (39%)	
				30 mg bid (6 x 5 mg tablet) Day 6 n=8	547 (15%)	3331 (22%)	2.50 (1.0-4.0)	5.23 (39%)	

4.3.12 Study 11325: Single Dose Escalation (Japanese Elderly)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, single-blind, placebo-controlled, dose-escalation study in healthy elderly male and female Japanese subjects to investigate the tolerability, safety, pharmacokinetics and pharmacodynamic effects of BAY 59-7939 tablet after single oral doses of 10, 20, 30, 40 and 50 mg under the fed condition

Study period: 27 Jun 2003 to 08 Sep 2003

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *50% Male. Average BMI < 28*
- 1 event of bleeding (urinary occult blood) in 40 mg group.
- Overall the applicant's conclusions appear reasonable.

Table 5-12: Study 11325

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11325 Japan 5.3.3.3.9 5.3.3.3.9-1 Randomized, single-blind, placebo-controlled, single dose escalation study in healthy elderly (aged 60 years or older) male and female Japanese subjects under fed condition (after breakfast); n=12 verum (n=6 male and 6 female) and n=4 placebo per step	64 (32/32)	66.1 (60-76)	58.1 (50-67)	10 mg (1 x 10 mg tablet) male, n=6	177 (28%)	1261 (15%)	3.0 (2.0-6.0)	6.83 (18%)	Dose-dependent but slightly less than proportional increase in C_{max} up to 40 mg. Almost dose-proportional increase in AUC up to 30 mg but no further increase at 40 mg. Ae_{ur} of 29, 24, 25 and 18% (10, 20, 30 and 40 mg). No gender effect on exposure. ANOVA (Ratio (90% CI)); total population Female / male: AUC_{norm} 0.93 (0.83-1.06) $C_{max,norm}$ 1.00 (0.90-1.10) AUC/D 1.06 (0.95-1.18) C_{max}/D 1.13 (1.03-1.24)
				female, n=6	212 (11%)	1480 (15%)	3.5 (1.5-4.0)	9.39 (13%)	
		64.0 (60-72)	61.1 (48-74)	20 mg (2 x 10 mg tablet) male, n=6	313 (20%)	2434 (19%)	2.5 (2.0-6.0)	8.80 (26%)	
				female, n=6	356 (23%)	2542 (27%)	3.5 (2.5-4.0)	8.68 (18%)	
		68.8 (60-79)	59.2 (41-75)	30 mg (3 x 10 mg tablet) male, n=6	485 (26%)	4520 (30%)	4.0 (3.0-4.0)	9.02 (21%)	
				female, n=6	483 (17%)	4106 (11%)	4.0 (3.0-8.0)	8.66 (40%)	
		65.8 (60-76)	56.2 (46-67)	40 mg (4 x 10 mg tablet) male, n=6	569 (14%)	4312 (33%)	2.75 (2.5-4.0)	13.7 (68%)	
				female, n=6	683 (11%)	4853 (19%)	2.5 (2.0-4.0)	17.3 (109%)	

4.3.13 Study 12026: Multiple Dose Escalation (Japanese Elderly)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Clinical pharmacology study in Japanese healthy elderly subjects to investigate pharmacokinetics, pharmacodynamics, safety and tolerability of BAY 59-7939 multiple doses with 10, 15 and 20 mg once daily under fed condition

Study period: 06 Jul 2006 to 18 Aug 2006

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *50% Male. Average BMI < 30*
- One male subject aged 67 years in the 20 mg group showed an increase in AST and ALT.
- Overall the applicant's conclusions appear reasonable.

Table 5-13: Study 12026

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
12026 Japan 5.3.3.3.10 5.3.3.3.10-1	36 (18/18)	68.9 (65-77)	54.3 (44-73)	10 mg od (2 x 5 mg tablet) Day 1 n=12	233 (19%)	1502 (22%)	3.00 (1.0-4.0)	5.7 (18%)	Dose-dependent increases in C_{max} and AUC_{τ}. No effect of gender on rivaroxaban pharmacokinetics.
Open-label, multiple dose-escalation study with once-daily dosing for 7 days in elderly healthy Japanese male subjects under fed condition (after breakfast)		69.2 (65-78)	57.1 (42-73)	15 mg od (3 x 5 mg tablet) Day 1 n=12	348 (23%)	2217 (28%)	4.00 (1.0-4.0)	6.3 (35%)	Day 1 ANOVA (Ratio (90% CI)); 15 mg vs. 10 mg: $AUC_{\tau,norm}$ 1.01 (0.84-1.22) $C_{max,norm}$ 1.05 (0.89-1.23) 20 mg vs. 10 mg: $AUC_{\tau,norm}$ 0.92 (0.77-1.11) $C_{max,norm}$ 0.92 (0.79-1.09)
		69.3 (66-77)	59.4 (49-72)	20 mg od (4 x 5 mg tablet) Day 1 n=12	391 (21%)	2534 (25%)	2.50 (2.0-4.0)	6.1 (21%)	
	36 (18/18)	68.9 (65-77)	54.3 (44-73)	10 mg od (2 x 5 mg tablet) Day 7 n=12	247 (11%)	1533 (15%)	3.00 (1.5-4.0)	7.7 (41%)	Day 7 ANOVA (Ratio (90% CI)); 15 mg vs. 10 mg: $AUC_{\tau,norm}$ 1.03 (0.88-1.20) $C_{max,norm}$ 0.94 (0.81-1.10) 20 mg vs. 10 mg: $AUC_{\tau,norm}$ 1.02 (0.87-1.19) $C_{max,norm}$ 0.89 (0.76-1.03)
		69.2 (65-78)	57.1 (42-73)	15 mg od (3 x 5 mg tablet) Day 7 n=12	331 (21%)	2243 (21%)	3.50 (0.5-4.0)	8.7 (27%)	
		69.3 (66-77)	59.4 (49-72)	20 mg od (4 x 5 mg tablet) Day 7 n=12	399 (25%)	2839 (21%)	3.00 (1.5-4.0)	7.7 (24%)	

4.3.14 Study 11608: Single Dose Escalation (Chinese)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, single-blind, placebo-controlled, dose-escalation study in healthy Chinese men to investigate the tolerability, safety, pharmacokinetics and pharmacodynamic effects of BAY 59-7939 tablets after single oral doses of 2.5, 5, 10, 20 and 40 mg under fasting conditions.

Study period: 18 May 2005 to 19 Jul 2005

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *100% Male. Average BMI < 23*
- Three bleeding time prolongation in the placebo, 5 & 10 mg dose groups.
- Overall the applicant's conclusions appear reasonable.

Table 5-14: Study 11608

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11608 China 5.3.3.3.11 5.3.3.3.11-1 Randomized, single-blind, placebo-controlled, dose escalation study in healthy Chinese men under fasting conditions; n=8 verum and n=2 placebo per dose step	50 (50/0)	34.7 (30-39)	62.1 (50-79)	2.5 mg (2 x 1.25 mg tablet) n=8	51.3 (60%)	252 (38%)	2.00 (0.5-6.0)	3.38 (47%)	Almost dose proportional increase in C_{max} and AUC up to 10 mg and little further increase at higher doses. Ae_{ur} decreases with dose (26% (2.5-10 mg) to 20 % and 11%, respectively, at higher doses). There is general consistency between this data in Chinese subjects and previous data in Caucasian and Japanese subjects.
				5 mg (1 x 5 mg tablet) n=8	67.2 (25%)	411 (18%)	2.00 (1.0-4.0)	7.92 (37%)	
				10 mg (2 x 5 mg tablet) n=8	143 (27%)	1022 (25%)	2.25 (1.0-4.0)	7.57 (34%)	
				20 mg (4 x 5 mg tablet) n=8	204 (16%)	1354 (31%)	2.00 (0.5-3.0)	5.62 (33%)	
				40 mg (8 x 5 mg tablet) n=8	176 (22%)	1402 (21%)	1.25 (0.5-3.0)	7.03 (64%)	

4.3.15 Study 11609: Multiple Dose Escalation (Chinese)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, single-blind, placebo-controlled, dose-escalation study in healthy Chinese male subjects to investigate the tolerability, safety, pharmacokinetics and pharmacodynamics effects of BAY 59-7939 after multiple oral dose of 5 mg, 10 mg, 20 mg and 30 mg bid. for 6 days.

Study period: 5 Sep 2005 to 27 Dec 2005

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *100% Male. Average BMI < 24.5*
- ALT and AST increases were found in 6 subjects.
- Overall the applicant's conclusions appear reasonable.

Table 5-15: Study 11609

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11609 China 5.3.3.3.12 5.3.3.3.12-1	41 (41/0)	34.7 (30-39)	66.0 (51-79)	5 mg bid (1 x 5 mg tablet) Day 1 n=8	97.4 (13%)	614 (22%)	1.50 (0.5-4.0)	4.12 (12%)	Almost dose-proportional increase in C_{max} and AUC from 5 mg to 30 mg in the fed condition.
Randomized, single-blind, placebo-controlled, multiple dose escalation study in healthy Chinese male Chinese subjects; tablet intake with food od on Day 1 and Day 6 and bid on days 2 to 5; n=8 verum and n=2 placebo				10 mg bid (1 x 10 mg tablet) Day 1 n=8	175 (28%)	1150 (22%)	2.75 (1.0-6.0)	4.12 (12%)	Pharmacokinetics were similar to previous studies in healthy Caucasian and Japanese males. ANOVA results (Ratio (90% CI)) Day 1 30 mg vs. 5 mg: AUC_{norm} 0.86 (0.69-1.09) $C_{max,norm}$ 0.81 (0.65-1.01) 20 mg vs. 5 mg: AUC_{norm} 0.92 (0.73-1.15) $C_{max,norm}$ 0.88 (0.71-1.10) 10 mg vs. 5 mg: AUC_{norm} 0.92 (0.73-1.16) $C_{max,norm}$ 0.88 (0.71-1.10)
				20 mg bid (2 x 10 mg tablet) Day 1 n=8	332 (15%)	2173 (22%)	2.50 (1.0-4.0)	4.91 (21%)	
				30 mg bid (3 x 10 mg tablet) Day 1 n=8	469 (19%)	3167 (19%)	2.75 (1.5-4.0)	5.80 (26%)	

Table 5-15: Study 11609

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
	41 (41/0)	34.7 (30-39)	66.0 (51-79)	5 mg bid (1 x 5 mg tablet) Day 6 n=8	115 (24%)	674 (15%)	2.00 (1.0-3.0)	4.92 (19%)	Accumulation ratios for AUC ($AUC_{tau,ss}$: AUC = 110-116 %) and C_{max} ($C_{max,ss}$: C_{max} = 119-126%) close to unity indicate little unexpected accumulation upon multiple dosing.
				10 mg bid (1 x 10 mg tablet) Day 6 n=8	216 (20%)	1305 (18%)	2.50 (1.5-4.0)	5.12 (25%)	
				20 mg bid (2 x 10 mg tablet) Day 6 n=8	415 (16%)	2527 (21%)	2.50 (1.5-3.0)	4.59 (12%)	Ae_{ur} on Day 6 decreased dose-dependently from 52% (5 mg bid) to 28% (30 mg bid)
				30 mg bid (3 x 10 mg tablet) Day 6 n=8	590 (9%)	3601 (14%)	2.25 (1.0-3.0)	5.84 (31%)	ANOVA results (Ratio (90% CI)) Day 6 30 mg vs. 5 mg: AUC_{norm} 0.90 (0.73-1.10) $C_{max,norm}$ 0.86 (0.70-1.06) 20 mg vs. 5 mg: AUC_{norm} 0.97 (0.79-1.19) $C_{max,norm}$ 0.93 (0.76-1.15) 10 mg vs. 5 mg: AUC_{norm} 0.95 (0.78-1.16) $C_{max,norm}$ 0.92 (0.74-1.13)

4.3.16 Study 11708: Single Dose Escalation (Chinese Elderly)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, single-blind, placebo-controlled dose escalation study in elderly male and female healthy Chinese subjects to investigate the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939 (5 mg, 10 mg, 20 mg, 30 mg and 40 mg) given after a standard breakfast.

Study period: 11 Oct 2005 to 28 Mar 2006

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Primarily Male. Average BMI < 24.5*
- Overall the applicant's conclusions appear reasonable.

Table 5-16: Study 11708

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11708 China 5.3.3.3.13 5.3.3.3.13-1	79 (40/39)	62.8 (59-74)	61.6 (44-81)	5 mg (1 x 5 mg tablet) male, n=5 female, n=7	121 (27%)	610 (37%)	2.00 (0.5-4.0)	4.47 (51%)	Dose-proportionality in rivaroxaban AUC but less than dose-proportional C_{max}
Randomized, single-blind, placebo-controlled, single dose escalation study in elderly male and female healthy Chinese subjects after standard breakfast				10 mg (1 x 10 mg tablet) male, n=6 female, n=5	228 (20%)	1060 (18%)	3.00 (2.0-4.0)	9.03 (56%)	ANOVA results (Ratio (95% CI); all subjects valid for PK)
				20 mg (2 x 10 mg tablet male, n=6 female, n=6	386 (17%)	2167 (17%)	3.00 (1.0-4.0)	8.31 (60%)	40 mg vs. 5 mg: AUC_{norm} 0.90 (0.73-1.11) $C_{max,norm}$ 0.70 (0.58-0.84) 40 mg vs. 10 mg: AUC_{norm} 1.10 (0.89-1.36) $C_{max,norm}$ 0.79 (0.66-0.95) 40 mg vs. 20 mg: AUC_{norm} 1.05 (0.85-1.29) $C_{max,norm}$ 0.91 (0.76-1.09) 40 mg vs. 30 mg: AUC_{norm} 0.99 (0.80-1.21) $C_{max,norm}$ 0.93 (0.78-1.11)
				30 mg (3 x 10 mg tablet male, n=6 female, n=6	550 (19%)	3360 (22%)	2.00 (1.0-4.0)	9.56 (62%)	
				40 mg (4 x 10 mg tablet male, n=5 female, n=5	670 (21%)	4339 (22%)	2.00 (1.0-4.0)	8.75 (64%)	

4.3.17 Study 12090: Single Dose Escalation (Black, Hispanic, Caucasian)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: A Study to Evaluate the Single-Dose Pharmacokinetics of BAY 59-7939 (rivaroxaban) in Black, Hispanic and Caucasian Healthy Subjects

Study period: June 6, 2006 through October 19, 2006

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *50% Male. Average Higher BMI in Black and Hispanic groups*
- Overall the applicant's conclusions appear reasonable.

Table 5-17: Study 12090

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
12090 USA 5.3.3.3.14 5.3.3.3.14-1	47 (24/23)	32.7 (19-45)	80.0 (57-94)	10 mg tablet Black, African-American n=11	179 (28%)	1203 (20%)	3.00 (1.0-4.0)	8.8 (54%)	No statistical differences for AUC and C_{max} between the ethnic groups. Mean between-group-differences of less than 10% would not require any dose modification of rivaroxaban. ANOVA (Ratio (90% CI)); Caucasian vs. Black: AUC 0.97 (0.80-1.19) C_{max} 0.98 (0.82-1.18) Caucasian vs. Hispanic: AUC 0.92 (0.75-1.12) C_{max} 1.00 (0.83-1.20) Black vs. Hispanic: AUC 0.94 (0.77-1.15) C_{max} 1.02 (0.85-1.22)
Randomized, single-blind, placebo-controlled study in young male and female Black, Caucasian and Hispanic subjects		34.5 (22-44)	68.6 (51-83)	10 mg tablet White Caucasian n=11	175 (33%)	1175 (40%)	3.00 (1.0-4.0)	10.3 (60%)	
		32.3 (18-45)	72.3 (60-99)	10 mg tablet Hispanic n=12	177 (15%)	1288 (19%)	3.00 (0.5-6.0)	7.2 (28%)	

4.3.18 Study 11000: Drug Interaction Study (Ranitidine)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blinded, non-placebo-controlled, cross-over study to investigate the influence of a 3 day pretreatment with 300 mg of Ranitidine on the safety, tolerability, pharmacodynamics and pharmacokinetics of 30 mg BAY 59-7939 single oral dose in healthy male subjects

Study period: 25 Sep 2003 to 17 Nov 2003

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- *Doses higher than used clinically*
- Overall the applicant's conclusions appear reasonable.

Table 5-18: Comedication Study 11000 Ranitidine

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11000 Germany 5.3.3.4.1 5.3.3.4.1-1 Randomized, non-blinded, non-placebo-controlled 2-fold cross-over study in healthy male subjects; 3 days pre-treatment with and co-administration of ranitidine 150 mg bid	12 (12/0)	32.1 (25-39)	82.7 (71-91)	30 mg (6 x 5 mg tablet) alone n=12	176 (38%)	1741 (26%)	2.00 (1.0-4.0)	8.39 (27%)	Ranitidine had no effect on rivaroxaban AUC, the treatment ratio and 90% confidence interval complying with bioequivalence criteria. The small change in C_{max} was not relevant. In summary, the pharmacokinetics of rivaroxaban were not affected by concomitant ranitidine. ANOVA results (Ratio (90% CI)) Rivaroxaban+ranitidine vs. rivaroxaban alone: AUC 1.01 (0.85-1.20) C_{max} 1.08 (0.77-1.50)
				30 mg (6 x 5 mg tablet) with ranitidine n=12	190 (44%)	1763 (39%)	2.00 (0.5-6.0)	8.54 (37%)	

4.3.19 Study 11001: Drug Interaction Study (Aluminum hydroxide / magnesium hydroxide)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blinded, non-placebo-controlled, cross-over study to investigate the influence of a co-administration of 10 mL of Maalox on the safety, tolerability, pharmacodynamics and pharmacokinetics of 30 mg BAY 59-7939 single oral dose in healthy male subjects

Study period: 10 Sep 2003 to 16 Oct 2003

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable.

Table 5-19: Comedication Study 11001 Magnesium/Aluminum containing antacid (Maalox®)

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11001 Germany 5.3.3.4.2 5.3.3.4.2-1 Randomized, non-blinded, non-placebo-controlled cross-over study in healthy male subjects; co-administration of Maalox® 10 mL suspension (70 mVal equivalent)	12 (12/0)*	33.1 (20-42)	86.1 (57-113)	30 mg (6 x 5 mg tablet) alone n=11	205 (15%)	1828 (18%)	2.50 (1.0-4.0)	8.56 (42%)	Maalox® had no effect on rivaroxaban AUC as demonstrated by 90% confidence limits of the treatment ratio within 0.80-1.25. A small decrease in rate of absorption (C_{max} slightly decreased, t_{max} increased) is considered to be without clinical relevance. ANOVA results (Ratio (90% CI)) Rivaroxaban+Maalox® vs. rivaroxaban alone: AUC 0.95 (0.83-1.08) C_{max} 0.87 (0.73-1.03)
				30 mg (6 x 5 mg tablet) with 10 mL Maalox® n=11	178 (32%)	1734 (21%)	4.00 (0.5-4.0)	7.26 (37%)	

* total study population; valid for safety and PK: n=11

4.3.20 Study 10993: Drug Interaction Study (midazolam)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blinded, non-placebo-controlled, threefold cross-over study to investigate the influence of a coadministration of 7.5 mg midazolam on the safety, tolerability, pharmacodynamics and pharmacokinetics of 20 mg BAY 59-7939 single oral dose and vice versa in healthy male subjects

Study period: 26 Mar 2003 to 19 May 2003

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable.

Table 5-20: Comedication Study 10993 Midazolam

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
10993 Germany 5.3.3.4.3 5.3.3.4.3-1 Randomized, non-blinded, non-placebo-controlled, 3 fold single-dose cross-over study in healthy male subjects in fasting condition. Treatments: a rivaroxaban 1x20 mg tablet b Midazolam 1x7.5 mg tablet c the combination of a. and b.	12 (12/0)	28.5 (19-37)	82.2 (53-93)	20 mg tablet n=12	119 (39%)	1278 (30%)	1.50 (1.0-4.0)	10.7 (32%)	Midazolam had no effect on the pharmacokinetics of rivaroxaban. On the other hand, rivaroxaban did not affect midazolam and α-hydroxy-midazolam pharmacokinetics. ANOVA results (Ratio (90%CI)) Rivaroxaban: (Rivaroxaban+midazolam vs. rivaroxaban alone): AUC 1.01 (0.92-1.12) C_{max} 0.88 (0.72-1.07) Midazolam: (Midazolam+rivaroxaban vs. midazolam alone): AUC 0.89 (0.75-1.05) C_{max} 1.01 (0.73-1.39) α-hydroxy-midazolam: (Midazolam+rivaroxaban vs. midazolam alone): AUC 0.99 (0.85-1.14) C_{max} 1.11 (0.77-1.59)
				20 mg tablet and 7.5 mg Midazolam n=12	104 (49%)	1295 (34%)	4.00 (1.0-6.0)	9.08 (42%)	

4.3.21 Study 10999: Drug Interaction Study (digoxin)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blind, non-placebo-controlled, 2-fold crossover study to investigate the influence of the simultaneous administration of multiple doses of BAY 59-7939 (20 mg bid) and of digoxin (0.375 mg od) on the pharmacokinetics of both drugs and to investigate the safety and tolerability of the combined treatment in 20 healthy male subjects

Study period: 10 Nov 2003 to 14 Jan 2004

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- *Dose of digoxin Higher than generally used in practice.*
- *Gingival bleeding in 3 subjects receiving both rivaroxaban and digoxin.*
- Overall the applicant's conclusions appear reasonable.

Table 5-21: Comedication Study 10999 Digoxin

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
10999 Germany 5.3.3.4.4 5.3.3.4.4-1	20 (20/0)*	33.9 (22-45)	78.8 (61-101)	20 mg tablet n=17	184 (25%)	1699 (26%)	1.50 (0.67-4.0)	9.38 (36%)	Rivaroxaban exposure was not affected by concomitant digoxin, the ratio and 90% CI of rivaroxaban AUC and C_{max} being within 0.80-1.25. On the other hand rivaroxaban had no effect on digoxin plasma concentrations. ANOVA results (Ratio (90% CI)) Rivaroxaban (Rivaroxaban+digoxin vs. rivaroxaban alone): AUC 0.90 (0.83-0.97) C_{max} 1.00 (0.85-1.14) Digoxin (Rivaroxaban+digoxin vs. digoxin alone): AUC_{tau} 1.08 (0.97-1.20) $C_{trough,ss}$ Day 7 0.95 (0.85-1.06) Day 8 1.03 (0.90-1.17) Day 9 0.95 (0.85-1.06)
Randomized, non-blinded, non-placebo-controlled 2-fold cross-over multiple dose study in healthy male subjects; Rivaroxaban 20 mg tablet od on Day 1 and 7 (Group A) or on Day 21 (Group B) followed by bid administration for 9 days starting on Day 8 (Group A) and on Day 22 (Group B). Digoxin: od for 28 days starting on Day 3 (2d).				20 mg tablet and digoxin 0.375 mg once daily n=17	174 (22%)	1501 (18%)	2.00 (0.67-4.0)	8.09 (33%)	

* total study population; subjects valid for PK: n=17

4.3.22 Study 12359: Drug Interaction Study (atorvastatin)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blinded, non-placebo-controlled, three-way crossover study to investigate the influence of multiple doses of 20 mg atorvastatin once daily on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 20 mg BAY 59-7939 and vice versa in healthy male subjects.

Study period: 19 Jan 2007 to 27 Apr 2007

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable.

Table 5-22: Comedication Study 12359 Atorvastatin

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
12359 Germany 5.3.3.4.5 5.3.3.4.5-1 Randomized, non-blinded, non-placebo-controlled 3-way cross-over study to investigate the mutual interaction between multiple doses of atorvastatin and a single dose of rivaroxaban in healthy male subjects	26 (26/0)	41.9 (24-53)	87.1 (62-105)	20 mg tablet n=19 20 mg tablet and 20 mg atorvastatin once daily n=19	247 (15%) 241 (21%)	1906 (14%) 1884 (23%)	3.00 (0.5-4.0) 3.00 (1.0-4.0)	8.02 (45%) 8.06 (34%)	Atorvastatin had no effect on rivaroxaban pharmacokinetics with bioequivalence shown for the treatment ratios of AUC and C_{max} (Rivaroxaban+atorvastatin vs rivaroxaban alone). ANOVA results (Ratio (90% CI)) Rivaroxaban: Rivaroxaban+atorvastatin vs. rivaroxaban alone AUC 0.99 (0.91-1.08) C_{max} 0.98 (0.89-1.07)

4.3.23 Study 10992: Drug Interaction Study (ketoconazole)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blinded, non-placebo-controlled, twofold cross-over study to investigate the influence of a pre- and coadministration of 200 mg ketoconazole once daily on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 10 mg BAY 59-7939 in comparison to a single oral dose of 10 mg of BAY 59-7939 alone in 12 healthy male subjects

Study period: 21 Feb 2003 to 14 May 2003

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable*; however, the reviewer does not agree with its opinion regarding the clinical relevance of these findings.*

Table 5-23: Comedication Study 10992 Ketoconazole 200 mg

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
10992 Germany 5.3.3.4.6 5.3.3.4.6-1 Randomized, non-blinded, non-placebo-controlled 2-fold cross-over study in healthy male subjects; 3 Day pre-treatment with and co-administration of ketoconazole 200 mg with rivaroxaban 10 mg compared to rivaroxaban 10 mg alone	12 (12/0)	33.0 (24-41)	86.4 (73-100)	10 mg (2 x 5 mg tablet) n=12 10 mg (2 x 5 mg tablet) and 200 mg ketoconazole n=12	149 (28%) 228 (22%)	1088 (17%) 1980 (20%)	2.50 (0.75-6.0) 2.25 (0.75-3.0)	7.28 (50%) 5.68 (22%)	Pre- and concomitant treatment with the azole antimycotic agent ketoconazole increased rivaroxaban C_{max} and AUC by 53% and 82%, respectively. There was no effect on terminal half-life. ANOVA results (Ratio (90% CI)) Rivaroxaban+ketoconazole vs. rivaroxaban alone: AUC_{norm} 1.82 (1.59-2.08) $C_{max,norm}$ 1.53 (1.27-1.85)

4.3.24 Study 10992: Drug Interaction Study (ketoconazole)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Non-randomized, non-blinded, non-placebo-controlled study with intra-individual comparison to investigate the influence of multiple doses of 400 mg ketoconazole once daily on the safety, tolerability, pharmacodynamics and pharmacokinetics of multiple oral doses of 10 mg BAY 59-7939 in comparison to multiple oral doses of 10 mg of BAY 59-7939 alone in healthy male subjects.

Study period: 20 Mar 2006 to 26 Apr 2006

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- *Gingival bleeding in one subject in the rivaroxaban group.*
- Overall the applicant's conclusions appear reasonable*; however, the reviewer does not agree with its opinion regarding the clinical relevance of these findings.*

Table 5-24: Comedication Study 11936 Ketoconazole 400 mg

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC_{tau} [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11936 Germany 5.3.3.4.7 5.3.3.4.7-1 Non-randomized, non-blinded, non-placebo-controlled multiple dose study in healthy male subjects; rivaroxaban 10 mg od from Day 1 to Day 10 and ketoconazole 400 mg od from Day 6 to Day 10; intra-individual comparison of rivaroxaban pharmacokinetics on Day 5 (alone) and Day 10 (combination)	20 (20/0)	34.2 (22-45)	82.9 (67-107)	10 mg tablet od Day 5 n=20	138 (22%)	892 (27%)	3.00 (2.0-4.0)	4.75 (22%)	Co-administration of ketoconazole 400 mg over 5 days resulted in increased AUC (2.6 fold) and C_{max} (1.7 fold) of rivaroxaban. Elimination of rivaroxaban from plasma was reduced as indicated by an increase in terminal half-life from 4.8 h (alone) to 6.5 h (combination). ANOVA results (Ratio (90% CI)) Rivaroxaban+ketoconazole vs. rivaroxaban alone: AUC_{tau} 2.58 (2.36-2.82) C_{max} 1.72 (1.61-1.83)
				10 mg tablet od and 400 mg ketoconazole od Day 10 n=20	237 (21%)	2298 (26%)	4.00 (3.0-8.0)	6.52 (24%)	

4.3.25 Study 11935: Drug Interaction Study (ritonavir)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Non-randomized, non-blinded, non-placebo-controlled study with inter-individual comparison to investigate the influence of multiple doses of 600 mg ritonavir bid on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 10 mg BAY 59-7939 in comparison to a single oral dose of 10 mg of BAY 59-7939 alone in healthy male subjects

Study period: 22 Mar 2006 to 04 May 2006

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable*; however, the reviewer does not agree with its opinion regarding the clinical relevance of these findings.*

Table 5-25: Comedication Study 11935 Ritonavir

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11935 Germany 5.3.3.4.8 5.3.3.4.8-1 Non-randomized, non-blinded, non-placebo-controlled, 2 fold cross over study in healthy male subjects; rivaroxaban 10 mg single dose on Day 1 and 8; ritonavir 600 mg bid from Day 3 to 8. Intra-individual pharmacokinetic comparison for rivaroxaban (Day 8 : Day 1) and ritonavir (Day 8 : Day 7)	18* (18/0)	33.2 (18-44)	84.3 (60-99)	10 mg tablet Day 1 n=12	154 (15%)	1000 (16%)	3.00 (2.0-4.0)	5.73 (31%)	Ritonavir 600 mg increased AUC and C_{max} of rivaroxaban by 2.5 fold and 1.5 fold, resp., and $t_{1/2}$ by about 1 h. Ritonavir decreased renal clearance of rivaroxaban from 3.8 to 1.0 L/h. Rivaroxaban had no effect on ritonavir pharmacokinetics. ANOVA results (Ratio (90% CI)) Rivaroxaban: Rivaroxaban+ritonavir vs. rivaroxaban alone (Day 8 / Day 1): AUC 2.53 (2.34-2.74) C_{max} 1.55 (1.41-1.69) Ritonavir: Ritonavir+rivaroxaban vs. ritonavir alone (Day 8 / Day 7)): AUC 0.99 (0.81-1.20) C_{max} 1.06 (0.86-1.30)
				10 mg tablet and 600 mg ritonavir bid Day 8 n=12	238 (23%)	2529 (17%)	4.00 (0.5-8.0)	6.93 (31%)	

* total study population; valid for PK: n=12

4.3.26 Study 11865: Drug Interaction Study (erythromycin)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blinded, non-placebo-controlled, twofold cross-over study to investigate the influence of multiple doses of 500 mg erythromycin tid on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single dose of 10 mg BAY 59-7939 in comparison to a single dose of 10 mg BAY 59-7939 alone in healthy male subjects

Study period: 16 Mar 2006 to 03 May 2006

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable.

Table 5-26: Comedication Study 11865 Erythromycin

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11865 Germany 5.3.3.4.9 5.3.3.4.9-1 Randomized, non-blinded, non-placebo-controlled, 2-fold cross over multiple dose study in healthy male subjects; Treatment A: 10 mg rivaroxaban single dose Treatment B: Erythromycin 500 mg tid on Day 1-4 and 500 mg erythromycin together with 10 mg rivaroxaban on Day 5	16 (16/0)	32.0 (20-44)	79.3 (66-110)	10 mg tablet Day 1 n=15	171 (30%)	1069 (31%)	3.00 (0.5-4.0)	7.04 (44%)	Co-administration of erythromycin resulted in a 34% increase of rivaroxaban AUC and C_{max}. ANOVA results (Ratio (90% CI) Rivaroxaban with erythromycin vs. rivaroxaban alone: AUC 1.34 (1.23-1.46) C_{max} 1.34 (1.21-1.48)
				10 mg tablet and 500 mg erythromycin Day 5 n=15	229 (24%)	1425 (30%)	3.00 (0.5-4.0)	6.03 (33%)	

4.3.27 Study 12612: Drug Interaction Study (clarithromycin)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blinded, non-placebo-controlled, twofold cross-over study to investigate the influence of multiple doses of 500 mg clarithromycin bid on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single dose of 10 mg Rivaroxaban/BAY 59-7939 in comparison to a single dose of 10 mg Rivaroxaban/BAY 59-7939 alone in healthy male subjects.

Study period: 19 Dec 2007 to 7 Feb 2008

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable*; however, the reviewer does not agree with its opinion regarding the clinical relevance of these findings.*

Table 5-34: Comedication Study 12612 Clarithromycin

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
12612 Germany 5.3.3.4.17 5.3.3.4.17-1 Randomized, non-blinded, non-placebo-controlled, 2-fold cross over study in healthy male subjects; Treatment A: 10 mg rivaroxaban single dose Treatment B: Clarithromycin 500 mg bid on Day 1-4 and 500 mg clarithromycin together with 10 mg rivaroxaban on Day 5	16* (16/0)	37.6 (24-50)	81.1 (64-104)	10 mg tablet Day 1 n=15 10 mg tablet and 500 mg clarithromycin Day 5 n=15	139 (16%) 194 (22%)	964 (22%) 1469 (25%)	4.00 (1.0-6.0) 4.00 (0.5-6.0)	6.70 (39%) 5.67 (17%)	Co-administration of clarithromycin resulted in a 54% increase of rivaroxaban AUC and a 40% increase of rivaroxaban C_{max}. ANOVA results (Ratio (90% CI)) Rivaroxaban with clarithromycin vs. rivaroxaban alone: AUC 1.54 (1.44-1.64) C_{max} 1.40 (1.30-1.52)

* total study population; all subjects valid for PK: n=15

4.3.28 Study 12680: Drug Interaction Study (rifampicin)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Non-randomized, non-blinded, non-placebo-controlled study with intra-individual comparison to investigate the influence of multiple doses of rifampicin qd on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 20 mg BAY 59-7939/rivaroxaban in comparison to a single dose of 20 mg of BAY 59-7939/rivaroxaban alone in healthy male subjects.

Study period: 12 Feb 2007 to 24 Mar 2007

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable*; however, the reviewer does not agree with its opinion regarding the clinical relevance of these findings.*

Table 5-27: Comedication Study 12680 Rifampicin

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
12680 Germany 5.3.3.4.10 5.3.3.4.10-1	20 (20/0)	35.0 (20-47)	81.9 (63-112)	20 mg tablet Day 0 n=18	229 (19%)	1776 (22%)	4.00 (1.0-4.0)	9.07 (48%)	Rifampicin reduced mean AUC and C_{max} of rivaroxaban by 49 % and 22 %, respectively.
Non-randomized, non-blinded, non-placebo-controlled study to investigate the effect of multiple doses of rifampicin once-daily (150-300-450-600-600-600-600 mg from Day 3 to 9) on a single dose of rivaroxaban (20 mg on Day 0 and Day 8) in healthy male subjects				20 mg tablet and rifampicin Day 8 n=18	178 (27%)	906 (20%)	4.00 (2.0-4.0)	4.80 (44%)	ANOVA results (Ratio (90% CI)) Rivaroxaban: Rivaroxaban+rifampicin vs. rivaroxaban alone AUC 0.51 (0.48-0.55) C_{max} 0.78 (0.70-0.87)

4.3.29 Study 10848: Drug Interaction Study (enoxaparin)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Single dose, non-blinded, randomized, non-placebo-controlled crossover study to investigate the potential influence of 40 mg of enoxaparin on the safety, tolerability, pharmacodynamics, and pharmacokinetics of 10 mg BAY 59-7939 and vice versa in healthy, male subjects

Study period: 14 Aug 2002 to 02 Oct 2002

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable.

Table 5-28: Comedication Study 10848 Enoxaparin

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
10848 Germany 5.3.3.4.11 5.3.3.4.11-1 Randomized, non-blinded, non-placebo-controlled, 3 fold cross over single dose study in healthy male subjects to investigate the interaction between 40 mg enoxaparin subcutaneous injection and 10 mg rivaroxaban	12* (12/0)	33.6 (24-42)	76.8 (63-95)	10 mg (2 x 5 mg) tablet n=10 10 mg (2 x 5 mg tablet) and 40 mg enoxaparin n=10	123 (21%) 119 (33%)	995 (27%) 957 (27%)	4.00 (1.5-4.02) 2.75 (0.75-4.08)	11.3 (30%) 11.7 (49%)	AUC_{norm} and $C_{max,norm}$ of rivaroxaban were unaffected by concomitant enoxaparin evidencing lack of interaction. ANOVA results (Ratio (90% CI)) Rivaroxaban alone vs. rivaroxaban+enoxaparin AUC_{norm} 1.06 (0.97-1.16) $C_{max,norm}$ 1.03 (0.87-1.22)

* total study population; valid for PK: n=10

4.3.30 Study 11123: Drug Interaction Study (aspirin)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blinded, two-way cross-over study with an Aspirin run-in period to investigate the influence of two doses of Aspirin once daily on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 15 mg BAY 59-7939 in 14 healthy male subjects and vice versa

Study period: 06 Apr 2004 to 07 Jun 2004

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- *Three hematomas of mild intensity reported with rivaroxaban*
- Overall the applicant's conclusions appear reasonable.

Table 5-29: Comedication Study 11123 Acetylsalicylic acid (Aspirin®)

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11123 Germany 5.3.3.4.12 5.3.3.4.12-1 Randomized (treatment B and C), non-blinded, 2-way crossover study in healthy male subjects; Treatments A: Acetylsalicylic acid (Aspirin®) 500 mg on Day -1 and 100 mg on Day 0 B: Rivaroxaban 15 mg on Day 0 C: Aspirin® 500 mg on Day -1 and Aspirin® 100 mg together with 15 mg rivaroxaban on Day 0	14* (14/0)	34.6 (19-44)	80.4 (56-93)	15 mg (3 x 5 mg tablet) n=13	126 (30%)	1156 (31%)	1.00 (1.0-4.0)	9.31 (36%)	Aspirin® had no effect on the pharmacokinetics of rivaroxaban, evidenced by 90% CI of AUC and C_{max} ratios within the conventional bioequivalence range of 0.80-1.25. The fraction unbound in plasma of rivaroxaban was also comparable in both treatments (10.65 % vs. 9.99 %; combination vs. rivaroxaban alone). ANOVA results (Ratio (90% CI)) Rivaroxaban+Aspirin® vs. rivaroxaban alone: AUC 0.91 (0.82-1.01) C_{max} 1.05 (0.95-1.17)
				15 mg (3 x 5 mg tablet) together with Aspirin® n=13	133 (26%)	1053 (23%)	2.00 (1.0-4.0	8.23 (39%)	

* total study population; valid for PK: n=13

4.3.31 Study 11124: Drug Interaction Study (Naproxen)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blinded, two-way cross-over study with a Naproxen run-in period to investigate the influence of two doses of Naproxen once daily on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 15 mg BAY 59-7939 in 14 healthy male subjects and vice versa

Study period: 26 Apr 2004 to 13 Aug 2004

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable.

Table 5-30: Comedication Study 11124 Naproxen

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11124 Germany 5.3.3.4.13 5.3.3.4.13-1	13* (13/0)	32.5 (25-42)	81.4 (62-97)	15 mg (3 x 5 mg tablet) n=11	153 (32%)	1250 (29%)	1.00 (1.0-3.0)	8.59 (29%)	Concomitant administration of naproxen has no relevant effect on rivaroxaban pharmacokinetics. ANOVA results (Ratio (90% CI)) Rivaroxaban+naproxen vs. rivaroxaban alone: AUC 1.12 (1.00-1.27) C_{max} 1.10 (0.91-1.32)
Randomized, non-blinded, 2-way crossover study in healthy male subjects; Treatments A: Naproxen 500 mg on Day -1 and 500 mg on Day 0 B: Rivaroxaban 15 mg on Day 0 C: Naproxen 500 mg on Day -1 and 500 mg on Day 0 together with rivaroxaban 15 mg				15 mg (3 x 5 mg tablet) together with naproxen n=11	165 (28%)	1396 (26%)	2.00 (0.5-4.0)	7.85 (25%)	

* total study population; valid for PK: n=11

4.3.32 Study 11279: Drug Interaction Study (Clopidogrel)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blinded, two-way cross-over study with a Clopidogrel run-in period to investigate the influence of two doses of Clopidogrel once daily on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 15 mg BAY 59-7939 in 14 healthy male subjects and vice versa

Study period: 28 Jun 2004 to 01 Sep 2004

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- *Clopidogrel PK not assessed*
- *Pharmacogemonics sample collected, but not analyzed*
- *Apparent effect on bleeding time in a subpopulation. Characteristics of this population not obvious from these data.*
- Overall the applicant's conclusions appear reasonable*; however, the reviewer does not agree with its opinion regarding the clinical relevance of these findings.*

Table 5-31: Comedication Study 11279 Clopidogrel

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11279 Germany 5.3.3.4.14 5.3.3.4.14-1	14* (14/0)	31.4 (19-42)	80.3 (62-96)	15 mg (3 x 5 mg tablet) n=11	150 (41%)	1150 (25%)	2.00 (0.5-4.0)	8.13 (27%)	Clopidogrel had no effect on the pharmacokinetics of rivaroxaban, evidenced by 90% CI of AUC and C_{max} ratios within the conventional bioequivalence range of 0.80-1.25. ANOVA results (Ratio (90% CI)) Rivaroxaban+clopidogrel vs. rivaroxaban alone: AUC 1.10 (1.03-1.18) C_{max} 1.01 (0.85-1.20)
Randomized, non-blinded, 2-way crossover study with a clopidogrel run-in period to investigate the influence of two doses (300 mg (1st day) and 75 mg (2nd day)) of clopidogrel once daily on the safety, tolerability, pharmacodynamics and pharmacokinetics of rivaroxaban in healthy male subjects and vice versa				15 mg (3 x 5 mg tablet) together with clopidogrel n=11	150 (25%)	1260 (19%)	2.00 (0.5-4.0)	7.53 (27%)	

* total study population; valid for PK: n=11

4.3.33 Study 11864: Drug Interaction Study (Clopidogrel)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: This study will investigate the platelet aggregation response of healthy male subjects to Clopidogrel and continue "responders" in a randomized, non-blinded, three-way cross-over study part to investigate the influence of two doses of Clopidogrel once daily on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 15 mg BAY 59-7939.

Study period: 02 Sep 2005 to 05 Dec 2005

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- *Only clopidogrel "responders" enrolled in the interaction study*
- *Clopidogrel PK not assessed*
- *Pharmacogenomics sample collected, but not analyzed*
- *Apparent effect on bleeding time in a subpopulation. Characteristics of this population not obvious from these data.*
- Overall the applicant's conclusions appear reasonable*; however, the reviewer does not agree with its opinion regarding the clinical relevance of these findings.*

Table 5-32: Comedication Study 11864 Clopidogrel

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11864 Germany 5.3.3.4.15 5.3.3.4.15-1 Randomized, non-blinded, 3-way crossover study in healthy male subjects identified as clopidogrel responders to investigate the interaction between rivaroxaban and clopidogrel (300 mg (1st day) and 75 mg (2nd day))	27* (27/0)	33.2 (25-44)	80.6 (62-104)	15 mg (3 x 5 mg tablet) n=13	168 (33%)	1477 (29%)	1.00 (0.5-4.0)	9.00 (27%)	Clopidogrel had no effect on the pharmacokinetics of rivaroxaban, evidenced by 90% CI of AUC and C_{max} ratios within the conventional bioequivalence range of 0.80-1.25. ANOVA results (Ratio (90% CI)) Rivaroxaban+clopidogrel vs. rivaroxaban alone: AUC 0.98 (0.85-1.12) C_{max} 0.92 (0.81-1.04)
				15 mg (3 x 5 mg tablet) together with clopidogrel n=13	153 (28%)	1432 (38%)	2.00 (1.0-6.0)	8.81 (24%)	

* total study population; valid for PK: n=13

4.3.34 Study 12089: Drug Interaction Study (Warfarin)

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Non-randomized, open-label study with two treatment periods to investigate the potential interaction between a single dose of 15 mg of warfarin and a single dose of 5 mg BAY 59-7939 in healthy male subjects in terms of safety, tolerability, pharmacodynamics and pharmacokinetics

Study period: 26 Jan 2006 (first screening) to 02 Mar 2006

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- *Small exploratory study*
- Overall the applicant's conclusions appear reasonable*; however, the reviewer does not agree with its opinion regarding the clinical relevance of these findings.*

Table 5-33: Comedication Study 12089 Warfarin

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for tmax C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
12089 Germany 5.3.3.4.16 5.3.3.4.16-1 Non-randomized, non-blinded, non-controlled pilot study with 2 sequential single dose treatments in healthy male subjects to investigate the effect of 5 mg rivaroxaban on 15 mg warfarin	7* (7/0)	31.6 (19-41)	80.3 (64-99)	5 mg (1 x 5 mg tablet) together with warfarin n=7	71.1 (28%)	514 (32%)	3.00 (1.0-3.0)	5.25 (15%)	Rivaroxaban exposure was comparable to previous studies using the same dose of 5 mg.

* total study population; all subjects valid for PK: n=7

4.3.35 Study 11275: Thorough QT study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: A randomized, double-blinded, double-dummy, 4-way crossover, placebo- and active-controlled Phase-I study to investigate the influence of single doses (15 and 45 mg) of BAY 59-7939 on the QTc interval in healthy male and female subjects

Study period: 03 May 2004 to 26 July 2004

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *See IRT review*

Table 5-36: PK/PD Study 11275 Effect on QTc

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Regimen Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	$AUC_{(0-tn)}$** [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments / Conclusions
11275 Germany 5.3.4.1.2 5.3.4.1.2-1 Randomized, double-blinded, double-dummy, placebo- and active controlled, 4-way cross-over, single-dose study in healthy male and female subjects to investigate the influence on QTc interval Treatments: Active control (Moxifloxacin 400 mg), placebo and rivaroxaban 15 mg and 45 mg	54* (27/27)	62.4 (51-74)	74.9 (53-102)	15 mg (3 x 5 mg tablet) n=50	222 (29%)	1692 (23%)	4.10 (2.1-5.0)	--	$AUC_{(0-tn)norm}$ (8361 and 6511 g*h/L; 15 mg and 45 mg) and $C_{max,norm}$ (1095 and 790 g/L) indicate a less than dose-proportional increase in rivaroxaban exposure. Systemic rivaroxaban exposure was in the range expected on the basis of previous studies.
				45 mg (9 x 5 mg tablet) n=50	480 (31%)	3953 (26%)	4.10 (0.6-5.1)	--	

* total study population; valid for safety and PK: n=50
** AUC(0-tn) instead of AUC

4.3.36 Study 11273: Absolute Bioavailability

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, non-blind, non-placebo-controlled, 3-way crossover study to assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of BAY 59-7939 following single-dose administrations of either 5-mg or 20-mg immediate-release tablet doses in comparison to 1-mg BAY 59-7939 intravenous infusion for 30 minutes in healthy male subjects.

Study period: 21 Aug 2006 to 10 Oct 2006

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable.

Table 5-1: Summary of Bioavailability Studies

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments/Conclusions
11273 Germany 5.3.1.1.1 5.3.1.1.1-1 Randomized, non blind, 3-fold cross-over, absolute bioavailability study in healthy male subjects	12 (12/0)	31.5 (21-46)	78.5 (61-94)	A: 1 x 5 mg tablet	80.2 (38%)	520 (40%)	2.5 (1.0-4.0)	4.85 (26%)	Absolute bioavailability (fabs) of the 5 mg tablet was complete, while fabs of the 20 mg dose was 66%. Less than dose-proportional increases in AUC were observed from 5 mg to 20 mg paralleled by apparently lower amounts excreted into urine at 20 mg (35%) compared to 5 mg (52%). Both are likely to result from solubility-limited absorption. ANOVA results (ratio (95%CI)) 5 mg tablet vs. 1 mg iv: AUC/D 1.12 (0.97-1.29) Cmax/D 0.51 (0.43-0.60) 20 mg tablet vs. 1 mg iv: AUC/D 0.66 (0.57-0.76) Cmax/D 0.22 (0.18-0.26) CLsys = 10.7 L/h range (5.31-16.0) Vss = 48.2 L range (31.7-76.8)
				B: 1 x 20 mg tablet	136 (32%)	1223 (39%)	1.5 (1.0-3.0)	8.46 (59%)	
				C: 1 mg intravenous infusion over 30 minutes (actual dose 0.934 mg)	29.5 (26%)	87.2 (34%)	0.5 (0.5-0.5)	4.46 (27%)	

4.3.37 Study 10924: Intestinal absorption site study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Single-center, non-randomized, non-placebo-controlled, nonblinded, cross-over investigation of the pharmacokinetics of BAY 59-7939 after single dose application of BAY 59-7939 either as conventional BAY 59-7939 tablets or as topical release of BAY 59-7939 drug substance or drug solution (both via the Enterion capsule) in healthy male volunteers.

Study period: 05 Aug 2002 to 26 Feb 2003

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable.
- *The results of this study foster concerns about exposure following administration of this formulation via a feeding tube which may be placed in the proximal small intestine (i.e., "J-tube")*

Table 5-1: Summary of Bioavailability Studies

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments/Conclusions
10924 United Kingdom 5.3.1.2.1 5.3.1.2.1-1 Single center, non-randomized, non-placebo-controlled, non blinded, 5-fold cross-over single dose bioavailability study with topical release (EnterionTM capsule) in healthy male subjects	9 (9/0)	32.0 (24-46)	77.0 (67-89)	A: 2 x 5 mg tablet n=9	161 (21%)	1383 (20%)	3.0 (1.0-4.0)	10.9 (18%)	Good absorption in proximal small bowel but markedly reduced bioavailability in ascending colon likely due to solubility issues. ANOVA results (ratio (min-max)) 10 mg proximal small bowel vs. tablet: AUCnorm 0.71 (0.51-1.10) Cmax,norm 0.44 (0.11-0.95) 10 mg distal small bowel vs. tablet: AUCnorm 0.55 (0.34-0.97) Cmax,norm 0.29 (0.20-0.54) 10 mg ascending colon vs. tablet: AUCnorm 0.25 (0.13-0.44) Cmax,norm 0.08 (0.04-0.16) 5 mg solution ascending colon vs. tablet: AUCnorm 0.60 (0.52-0.71) Cmax,norm 0.42 (0.23-0.78)
				B: 10 mg crushed tablets to proximal small bowel n=8	72.3 (83%)	972 (31%)	2.5 (1.5-24)	10.4 (36%)	
				C: 10 mg crushed tablets to distal small bowel n=9	46.2 (46%)	768 (27%)	3.0 (1.0-15)	11.9 (40%)	
				D: 10 mg crushed tablets to ascending colon n=9	13.7 (52%)	352 (49%)	15.0 (0.67-24)	11.4 (51%)	
				E: 5 mg solution to ascending colon n=6	32.9 (66%)	379 (24%)	1.5 (0.67-6.0)	10.3 (31%)	

4.3.38 Study 10846: Food Effect study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, open-label, two-fold cross-over study to investigate the effect of a high fat, high calorie meal on safety, tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 given oral as 2 x 5 mg tablets in 12 healthy male subjects

Study period: 17 May 2002 to 27 Jun 2002

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- Overall the applicant's conclusions appear reasonable.

Table 5-1: Summary of Bioavailability Studies

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments/Conclusions
10846 Germany 5.3.1.2.2 5.3.1.2.2-1	10 (10/0)	32.4 (26-38)	84.4 (74-89)	A: 2 x 5 mg tablet fasted n=8	113 (27%)	888 (24%)	2.75 (0.75-4.0)	6.64 (24%)	A relevant food effect has to be considered when Rivaroxaban is administered with a high fat, high calorie meal
Randomized , open label, 2-fold cross-over to investigate the effect of a high fat, high calorie meal in healthy male subjects				B: 2 x 5 mg tablet with food n=8	158 (23%)	1107 (27%)	4.0 (3.0-4.0)	6.15 (38%)	ANOVA results (ratio (90% CI) fed vs. fasted): AUC 1.28 (1.15-1.43) Cmax 1.41 (1.20-1.66)

4.3.39 Study 10989: Food Effect study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Single dose, non-blinded, randomized, non-placebo-controlled crossover study to compare safety, tolerability, pharmacodynamics and pharmacokinetics of 20 mg BAY 59-7939 given either as four 5 mg tablets or one 20 mg tablet and to investigate the effect of a high fat, high calorie or high carbohydrate meal on safety, tolerability and pharmacokinetics of one 20 mg tablet BAY 59- 7939 in healthy, male subjects

Study period: 14 Aug 2002 to19 Sep 2002

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- *One hematoma in the 20 mg fed group*
- Overall the applicant's conclusions appear reasonable.

Table 5-1: Summary of Bioavailability Studies

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments/Conclusions
10989 Germany 5.3.1.2.3 5.3.1.2.3-1 Randomized, non-blinded, non-placebo-controlled cross-over to investigate the effect of a high fat, high calorie meal on 20 mg tablet and to compare 4 x 5 mg and 1 x 20 mg tablet in the fasted state in healthy male subjects	11 (11/0)	33.6 (19-41)	89.2 (76-115)	A: 4 x 5 mg tablet fasted n=10	153 (31%)	1678 (43%)	1.25 (0.75-4.0)	9.29 (60%)	The 2 different formulations are well comparable in the fasted state. Food results in an increase in Cmax and time needed to reach Cmax. Exploratory analysis demonstrates similar effects of Continental and American breakfast.
				B: 1 x 20 mg tablet fasted n=10	158 (33%)	1629 (41%)	2.25 (0.75-4.0)	9.12 (55%)	
				C: 1 x 20 mg tablet with food n=10 (American breakfast n=6; Continental breakfast n=4)	273 (26%)	2021 (34%)	3.5 (1.25-6.0)	7.02 (30%)	ANOVA results (ratio (90% CI)) 4x5 mg vs. 20 mg tablet: AUCnorm 0.98 (0.88-1.08) Cmax,norm 1.04 (0.92-1.17) 20 mg fed vs. 20 mg fasted: AUCnorm 1.24 (1.11-1.37) Cmax,norm 1.74 (1.54-1.96)

4.3.40 Study 11937: Food Effect study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, open-label, two-fold cross-over study to investigate the effect of a high fat, high calorie meal on safety, tolerability and pharmacokinetics of 10 mg BAY 59-7939 tablet given to healthy male subjects

Study period: 18 Oct 2006 to 28 Nov 2006

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- *Injection site hemorrhage, hematoma, epistaxis reported. Higher incidence of hematoma in the fed group.*
- Overall the applicant's conclusions appear reasonable.
- *The difference between the pilot and confirmatory studies appear to be either the dosage strength used (i.e., 2 x 5 mg vs. 1 x 10 mg) and sample size.*

Table 5-1: Summary of Bioavailability Studies

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments/Conclusions
11937 Germany 5.3.1.2.4 5.3.1.2.4-1	24 (24/0)	43.0 (28-54)	81.3 (60-101)	A: 1 x 10 mg tablet fasted n=24	184 (26%)	1234 (23%)	2.50 (1.0-4.0)	7.44 (38%)	Study demonstrates lack of food effect
Randomized, open label, 2-fold cross-over to investigate the effect of a high fat, high calorie meal in healthy male subjects				B: 1 x 10 mg tablet with food n=24	190 (26%)	1219 (24%)	3.02 (0.5-6.0)	6.67 (25%)	ANOVA results (ratio (90% CI) fed vs fasted): AUC 0.99 (0.93-1.05) Cmax 1.03 (0.94-1.14)

4.3.41 Study 11938: Food Effect study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Randomized, open-label, two-fold cross-over study to investigate the effect of a high fat, high calorie meal on safety, tolerability and pharmacokinetics of 20 mg BAY 59-7939 / rivaroxaban tablet given to healthy male subjects.

Study period: 27 Mar 2007 to 14 May 2007

Reviewer Comment:

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*
- *Male & Caucasian population*
- *One report of hematoma in the fed group*
- Overall the applicant's conclusions appear reasonable.

Table 5-1: Summary of Bioavailability Studies

Study #/ Country/ Report Module#/ Study Design	n Total (M/F)	Age Mean (range) [years]	Weight Mean (range) [kg]	Treatments PK profile day Treatment Rivaroxaban	PK Parameters Geometric Mean (%CV) median (range) for t_{max} C_{max} [µg/L]	AUC [µg*h/L]	t_{max} [h]	$t_{1/2}$ [h]	Comments/Conclusions
11938 Germany 5.3.1.2.14 5.3.1.2.14-1	24 (24/0)	33.0 (20-45)	80.8 (62-98)	A: 1 x 20 mg tablet fasted n=22	160 (34%)	1477 (23%)	2.50 (0.75-6.0)	8.00 (31%)	Study demonstrates relevant food effect ANOVA results (ratio (90% CI) fed vs fasted): AUC 1.39 (1..29-1.49) Cmax 1.76 (1.55-2.00)
Randomized, open label, 2-fold cross-over to investigate the effect of a high fat, high calorie meal in healthy male subjects				B: 1 x 20 mg tablet with food n=22	281 (27%)	2031 (23%)	4.00 (2.5-6.0)	7.48 (46%)	

The summary of in vitro dissolution studies can be found in Module 2.3.P.5.4 (DMF #21580)

4.4 Consult Review (including Pharmacometric Review)

4.4.1 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	22406
Submission Number (Date)	July 22, 2008
Clinical Division	DMIHP
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1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this pharmacometrics review is to address the following key questions.

1.1.1 Is there evidence of exposure-response for effectiveness and safety?

A shallow dose/exposure-response relationship was observed for effectiveness (composite endpoint consisting of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), or death from all causes) in the dose-ranging study 11527 for prevention of VTE in patients undergoing elective total hip replacement where doses from 5 to 40 mg qd were administered (see Figure 1). No increase in effectiveness was observed beyond 10 mg qd.

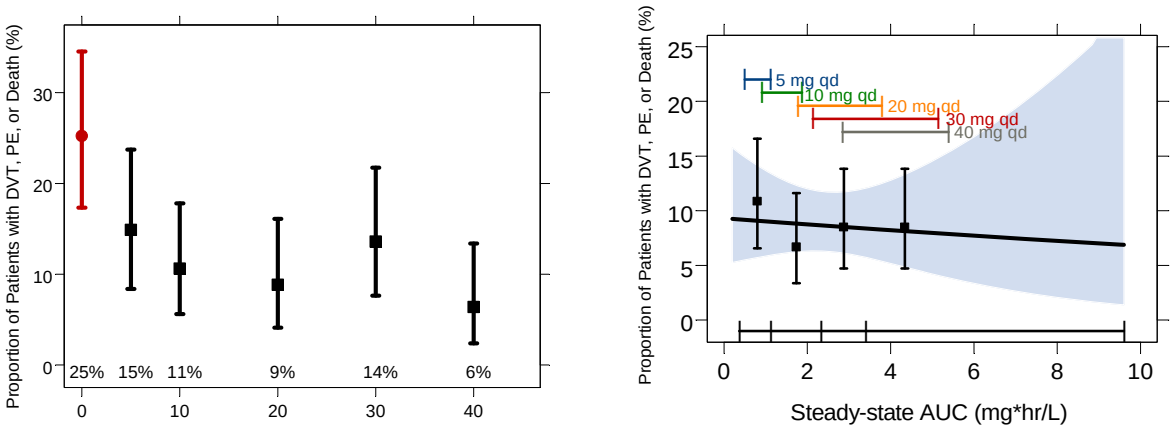


Figure 1: Proportion of patients with DVT, PE, or death vs. (Left) dose and (Right) steady-state AUC_{0-24} quartiles and associated 95% CI in dose-ranging study 11527 receiving 5-40 mg qd (per protocol population). The horizontal black bar shows the steady-state AUC_{0-24} quartiles and the colored bars illustrate the predicted 10-90th AUC and C_{max} percentiles following different dose regimens.

A steep increase in the risk of major bleeding from 0.7% for 10 mg qd (proposed therapeutic dose) to 6.1% for 40 mg qd was observed in the dose-ranging study 11527 whereas only 1.9% receiving the active comparator enoxaparin 40 mg experienced major bleeding event. The proposed therapeutic dose of 10 mg qd is adequate from a safety point of view with similar risk of major bleeding as the comparator.

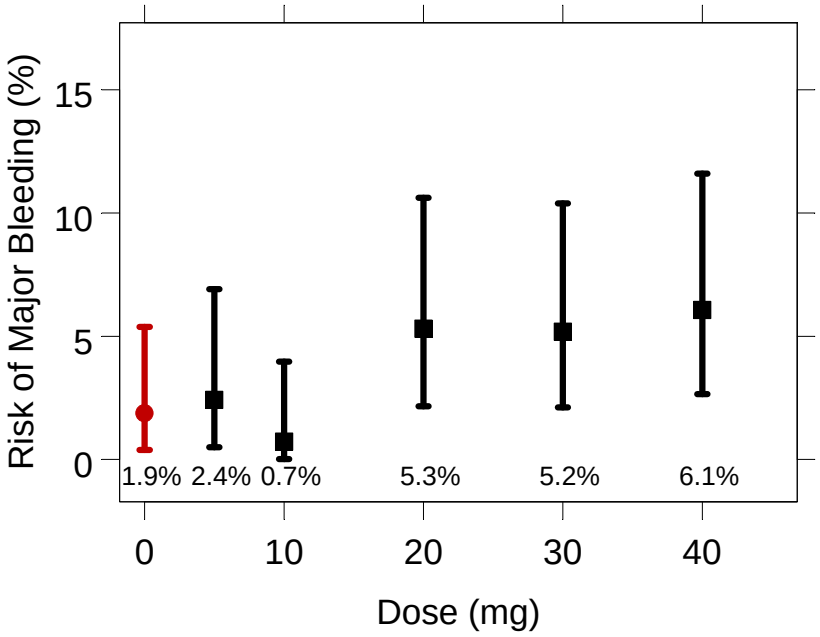


Figure 2: Risk of major bleeding and associated 95% CI vs. dose in dose-ranging study 11527 receiving 5-40 mg qd rivaroxaban (black) and enoxaparin 40 mg (red) (safety population).

The risk of major bleeding was found to increase with increasing exposure ($AUC_{ss,0-24}$ or $C_{max,ss}$) (see Figure 3). The mean exposure percentile following 10 mg qd is associated with a 2.5% risk of major bleeding while a 2-fold increase in exposure due to intrinsic and extrinsic factors (see Table 1) will increase the risk of major bleeding by 50%.

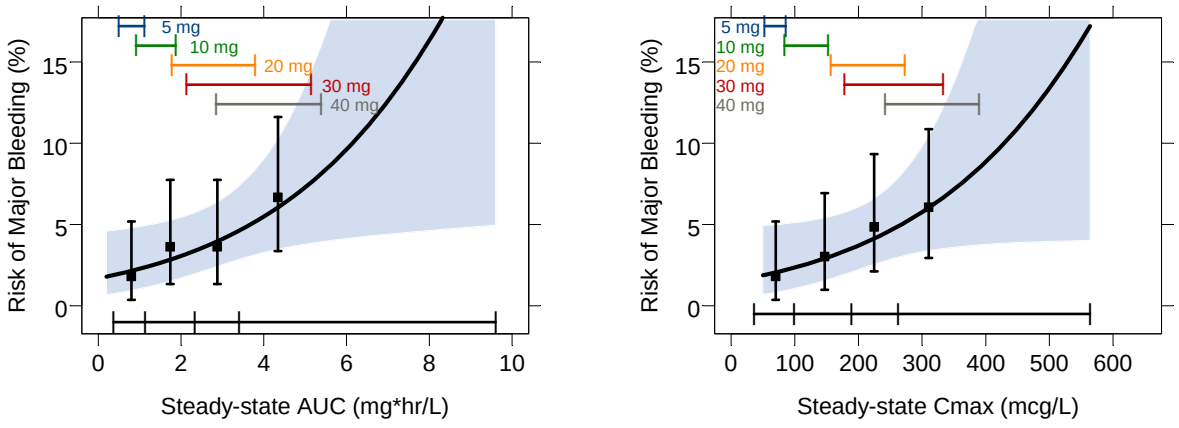


Figure 3: Risk of major bleeding vs. median quartile steady-state (Left) AUC_{0-24} and (Right) C_{max}. The horizontal black bar shows the steady-state AUC_{0-24} quartiles and the colored bars illustrate the predicted 10-90th AUC and C_{max} percentiles following different dose regimens.

1.1.2 Is 10 mg rivaroxaban qd appropriate for all patients?

The identified intrinsic and extrinsic factors affecting rivaroxaban PK/PD are summarized in Table 1.

Table 1: 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-tn)	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		
strong inhibitors of both CYP3A4 and P-gp			
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)
strong inhibitor of CYP3A4 and weak-to-moderate inhibitor of P-gp			
RIVA 10 mg alone	RIVA + clarithromycin 500mg bid	1.54 (1.44 – 1.64)	1.40 (1.30 – 1.52)
weak-to-moderate inhibitor of CYP3A4 and P-gp			
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: Sponsor's Table 2 in fda-response-05-dec-2008.pdf

Several special populations (i.e., patients with severe renal impairment, moderate-severe hepatic impairment, and strong CYP3A4 or P-gp inhibitors) have greater than 2-fold increases in drug exposure (see Table 1).

Since there is very little accumulation with 10 mg qd dosing of rivaroxaban, it is not possible to lower the daily exposure (which was found to increase the risk of major bleeding) in these patients by shifting from once daily to every other day dosing (see Figure 4).

It is therefore recommended that the sponsor develops a 5 mg or scored 10 mg tablet to make dose adjustments in patients with clinically relevant increases in exposure due to intrinsic and extrinsic factors.

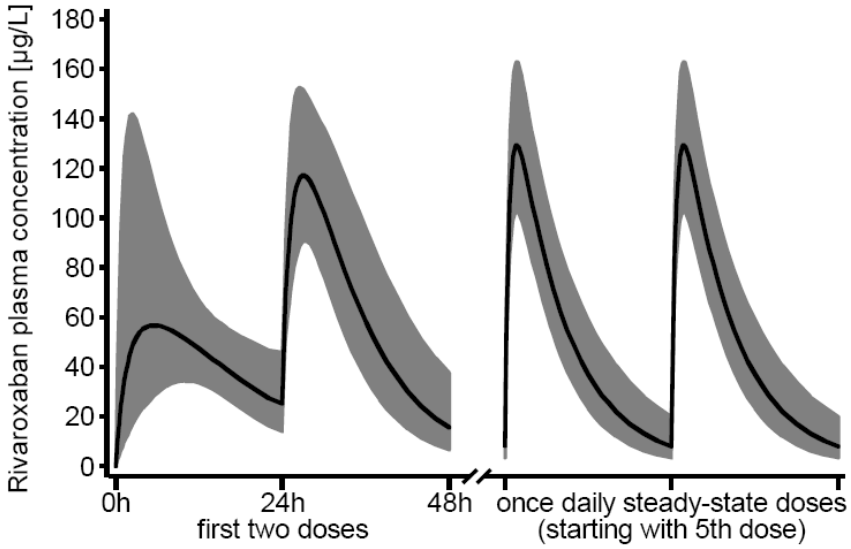


Figure 4: Rivaroxaban plasma-concentration vs time profile for the 10 mg od dosing regimen used in OdIXa-HIP OD trial [geometric mean/SD of individually posthoc estimated plasma concentration/time curves; n=131-140] (Study PK000131).

Source: Sponsor's Figure 3.7 in clinical pharmacology summary on pages 187.

1.1.3 Is there evidence of inter-ethnicity differences in rivaroxaban PK/PD?

Yes, Japanese subjects were found to have an apparent higher dose-normalized rivaroxaban C_{max} and AUC compared to other ethnic groups (i.e., Caucasian, African-American, Hispanic, Japanese, and Chinese, were evaluated) (see Figure 5).

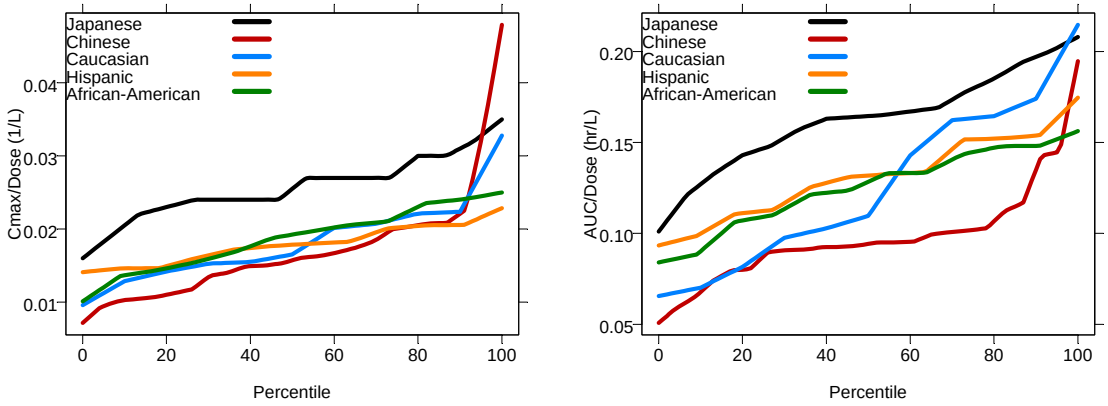


Figure 5: C_{max}/Dose and AUC/Dose vs. percentiles for different ethnicities following single dose 2.5-10 mg rivaroxaban (studies 11126, 11608, and 12090).

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. In conclusion, the observed differences in exposure between Japanese and other ethnicities are unlikely due to demographic differences but rather inter-ethnicity differences.

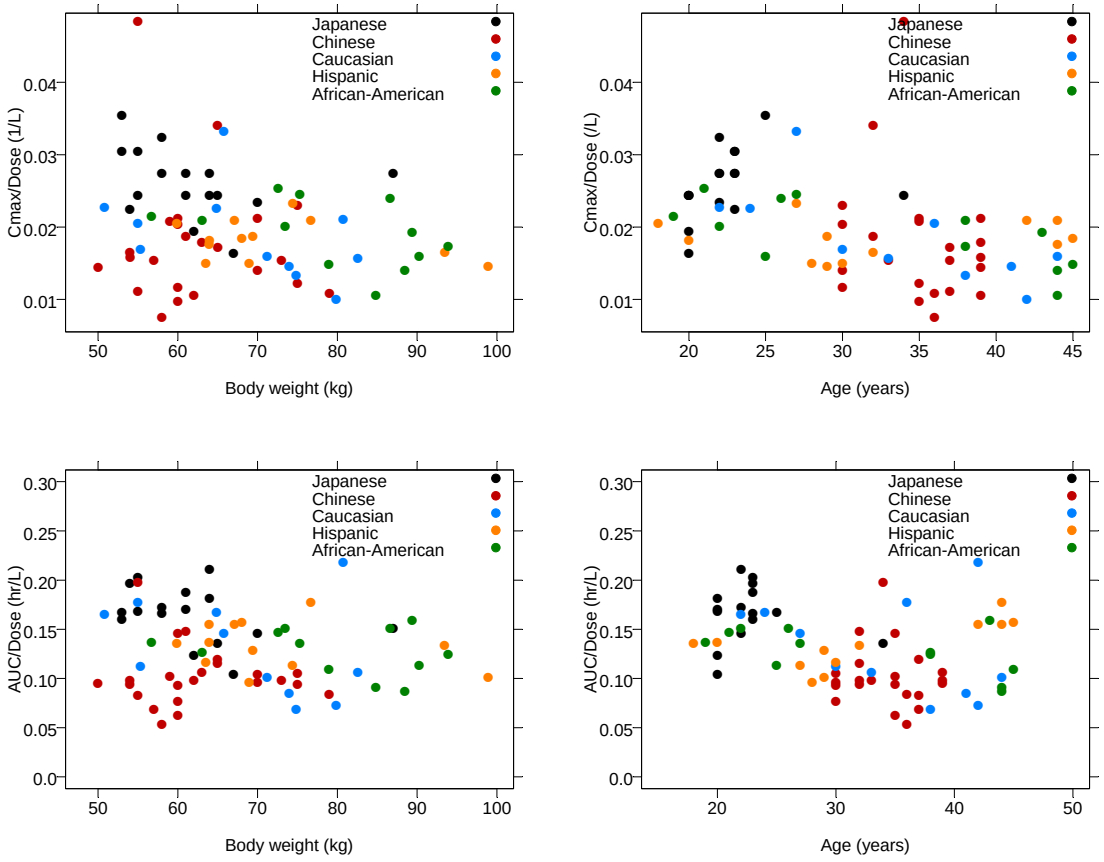


Figure 6: C_{max}/Dose (Top) and AUC/Dose (Bottom) vs. body weight (Left) and age (Right) following single dose 2.5-10 mg rivaroxaban from studies 11126 (Japanese), 11608 (Chinese), and 12090 (Caucasian, African-American, and Hispanic).

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 PK differences are not due to assay or study differences since the same PK/PD relationship is observed in Japanese and Chinese subjects.

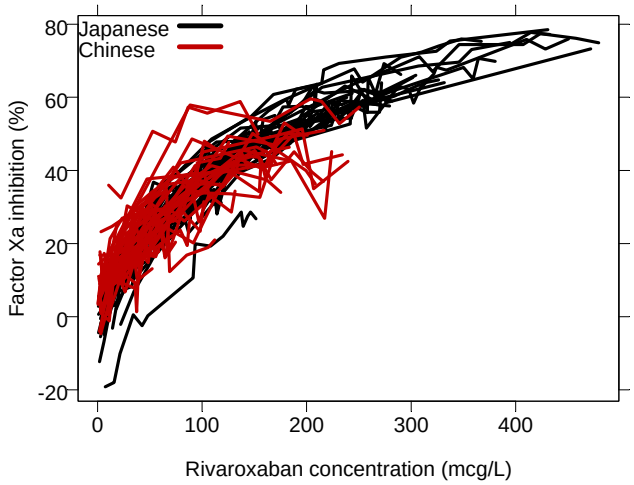


Figure 7: Factor Xa inhibition vs. rivaroxaban concentration in Japanese (black lines) and Chinese (red lines) subjects following 2.5-40 mg single dose rivaroxaban.

1.2 Recommendations

The Division of Pharmacometrics in Office of Clinical Pharmacology finds the NDA acceptable. The sponsor is recommended to produce a 5 mg or a scored 10 mg tablet for patients with clinically relevant increases in exposure due to intrinsic or extrinsic factors, i.e. severe renal impairment, moderate-severe hepatic impairment, concomitant administration of strong CYP3A4/P-gp inhibitors. Combinations of renal impairment and moderate/strong CYP3A4/P-gp inhibitors have not been tested but are expected to have clinically relevant increases in exposure leading to increased risk of major bleeding.

1.3 Label Statements

The following are the labeling recommendations relevant to clinical pharmacology for NDA 22406. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

12.3 Pharmacokinetics
Special Populations

(b) (4)

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population Pharmacokinetics

The PK of rivaroxaban was best described by a two-compartment disposition model with first-order absorption and elimination. However, a one-compartment disposition model was used for the dose-ranging studies due to the sparse PK sampling.

Renal function and age were consistently found to be covariates for rivaroxaban clearance and body weight (lean body mass or body surface area) was found to be a covariate for rivaroxaban volume of distribution. The effects of covariates on the PK of rivaroxaban were generally small, and predictions of 'extreme' covariate scenarios suggest that fixed dosing of rivaroxaban is acceptable. The key covariate findings from sponsor's 8 population PK analyses are summarized in Appendix (see Table 3).

The predicted rivaroxaban plasma concentration-time profile following the proposed dose of 10 mg qd is shown in Figure 4. Inter-individual variability in PK was high for all doses on the first post-operative day, especially within the drug absorption phase. Adding a mixture model, ie to fit two sets of absorption constants and to estimate which patient belongs to which group (slow/fast absorption, both restricted to the first post-operative day), was the most successful approach with respect to improvement in the goodness of fit measures and plots. Drug clearance was both lower and more variable on the first post-operative study day 3 when compared to steady-state conditions on study days 6/7, leading to the inclusion of a time-dependency on clearance in the structural PK model.

2.2 Ethnicity Differences

The sponsor found an apparent higher C_{max} and AUC in Japanese vs. other ethnicities following a single oral dose of 10 mg rivaroxaban under fasting condition (see Figure 8). The sponsor concluded that the minor-to-moderately increased rivaroxaban plasma exposure seen in Japanese subjects (20 to 40% on average) could partially be attributed to the known differences in body weight between ethnic groups.

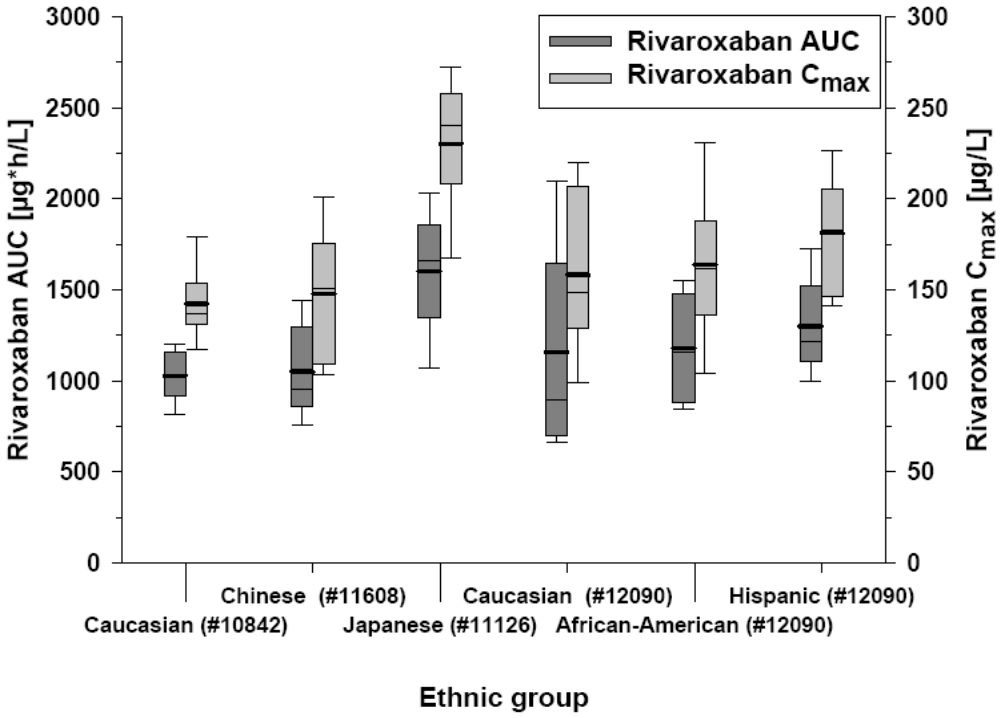


Figure 8: Inter-ethnic comparison of AUC and Cmax data of rivaroxaban in African- American, Caucasian, Chinese, Hispanic and Japanese healthy young male subjects following a single oral dose of 10 mg rivaroxaban [Box-Whisker plot with 10-25-50-75- 90 percentiles, including arithmetic mean; n=6-8 or 11-12 per group] (Studies 10842, 11126, 11608, 12090).

Source: Sponsor's Figure 3.22 in clinical pharmacology summary on pages 217.

2.3 Population Pharmacokinetic/Pharmacodynamic Analysis

The sponsor used an E_{max} model to describe the relationship between plasma rivaroxaban concentration and Factor Xa inhibition and a linear model for the relationship with prothrombin time using data from study 10847 in healthy volunteers (see Figure 9).

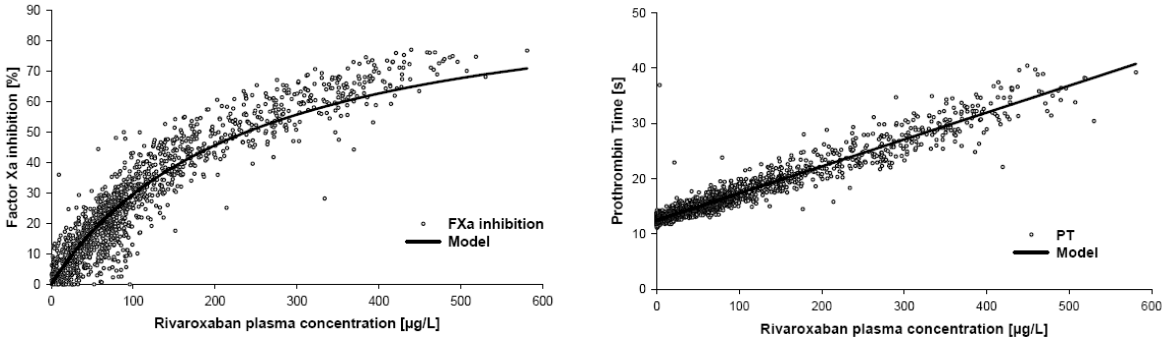


Figure 9: Concentration–effect relationships for (Left) Factor Xa inhibition and (Right) prothrombin time in healthy, young male subjects receiving rivaroxaban in study 10847. The solid lines are the population predictions and the dots are the observed data.
Source: Sponsor's Figure 3-8 and 3-9 in clinical pharmacology summary on pages 190-191.

2.4 Exposure-Response Analysis

The sponsor investigated the relationship between total daily dose and total and major venous thrombotic events as well as post-operative major bleeding events in the dose-ranging studies 10942, 10944, and 10945 receiving 2.5-30 mg bid rivaroxaban.

The entire dose range was found to be efficacious compared to enoxaparin, and as a consequence, analyses of the incidence of total and major VTE failed to show a statistically significant trend with total daily dose of rivaroxaban within the studied dose range (see Figure 10 Left). In contrast, there is a clear trend with increasing total daily dose of rivaroxaban for post-operative major bleeding events (see Figure 10 Right).

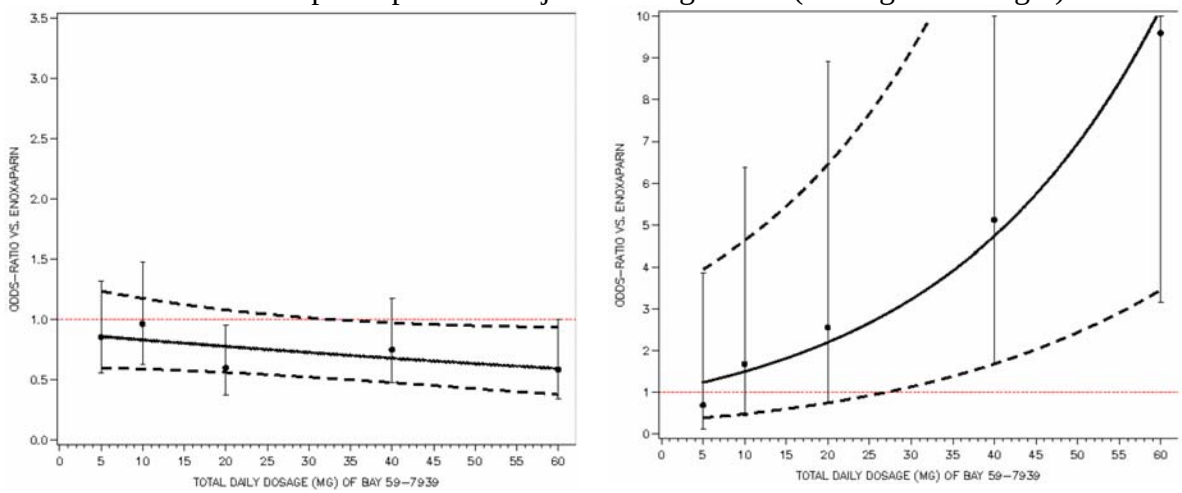


Figure 10: (Left) Total venous thrombotic events odds ratio curve vs enoxaparin and (Right) post-operative major bleeding odds ratio curve vs enoxaparin with total daily dose (2.5-30 mg bid) for studies 10942, 10944, and 10945-safety population.

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

<u>Reviewer's comments on sponsor's analyses:</u>
Sponsor's population PK, PK/PD, and exposure-response analyses are generally acceptable and the significant demographic covariates identified by the sponsor were reproduced. The sponsor should preferably have combined all PK data and performed one combined population PK/PD analysis to identify key demographic covariates.

The following limitations of sponsor's analysis were identified and will be addressed in reviewer's analysis:

- *Lower body weight in Japanese subjects was cited as a reason for observing higher exposure compared to other ethnicities. However, Japanese and Chinese subjects were found to have similar body weight but Japanese subjects had markedly higher exposure compared to Chinese subjects.*
- *The sponsor does not propose dose adjustments for patients with moderate renal impairment or patients receiving strong CYP3A4 or PgP inhibitors even though they were shown to have greater than 50% increased exposure and more than 2-fold increased Factor Xa activity (see* Table 1*).*
- *The exposure-response analysis was only done relative to enoxaparin with total daily dose as the exposure variable.*

3 REVIEWER'S ANALYSIS

3.1 Introduction

3.2 Objectives

The objectives for reviewer's analysis are described below:

1. To explore demographic differences that can explain the observed higher exposure in Japanese subjects
2. To verify the PK covariates identified in sponsor's population PK analyses.
3. To explore the exposure-response relationship for effectiveness and safety for rivaroxaban.

3.3 Methods

Steady-state AUC and C_{max} were calculated using the individual PK parameter estimates from NONMEM by the following formulas:

$$AUC_{ss} = \frac{Dose \cdot F}{CL}$$

$$C_{\max,ss} = \frac{Dose \cdot F \cdot ka}{V(k_a - k_e)}\left(\frac{e^{-k_e t}}{(1-e^{-k_e \tau})} - \frac{e^{-k_a t}}{(1-e^{-k_a \tau})}\right) where\ t = \frac{\ln\left(\frac{k_a}{k_e}\right)}{(k_a - k_e)}\ at\ C_{\max}$$

3.3.1 Data Sets

Data sets used for reviewer's analyses are summarized in Table 2.

Table 2: Analysis Data Sets.

Study Number	Name	Link to EDR
11126	pkvaluc.xpt vitalsv.xpt patinfo.xpt lab.xpt	//Cdsesub1/evsprod/NDA022406/0002/m5/datasets/11126/analysis/
11608	pkvaluc.xpt vitalsv.xpt patinfo.xpt lab.xpt	//Cdsesub1/evsprod/NDA022406/0002/m5/datasets/11608/analysis/
12090	pkvaluc.xpt vitalsv.xpt patinfo.xpt lab.xpt	//Cdsesub1/evsprod/NDA022406/0002/m5/datasets/12090/analysis/
10944	pk000131o1-002.xpt	//Cdsesub1/evsprod/NDA022406/0000/m5/datasets/ppk04-009/analyses/programs
10945	ppk04-009o2-002.xpt	//Cdsesub1/evsprod/NDA022406/0000/m5/datasets/ppk04-009/analyses/programs

3.3.2 Software

S-PLUS and NONMEM were used for the reviewer's analyses.

3.4 Results

3.4.1 Pharmacokinetic Analysis

There is an apparent higher dose-normalized C_{max} and AUC in Japanese compared to other ethnic groups (i.e., Caucasian, African-American, Hispanic, Japanese, and Chinese, were evaluated) (see Figure 11).

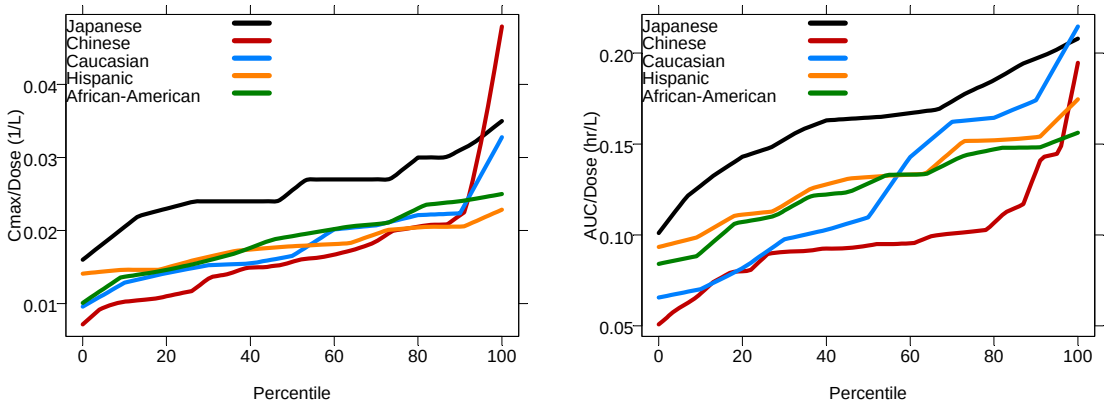


Figure 11: C_{max}/Dose and AUC/Dose vs. percentiles for different ethnicities following single dose 2.5-10 mg rivaroxaban (studies 11126, 11608, and 12090).

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 12).

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. In conclusion, the observed differences in exposure between Japanese and other ethnicities are unlikely due to demographic differences but rather inter-ethnicity differences.

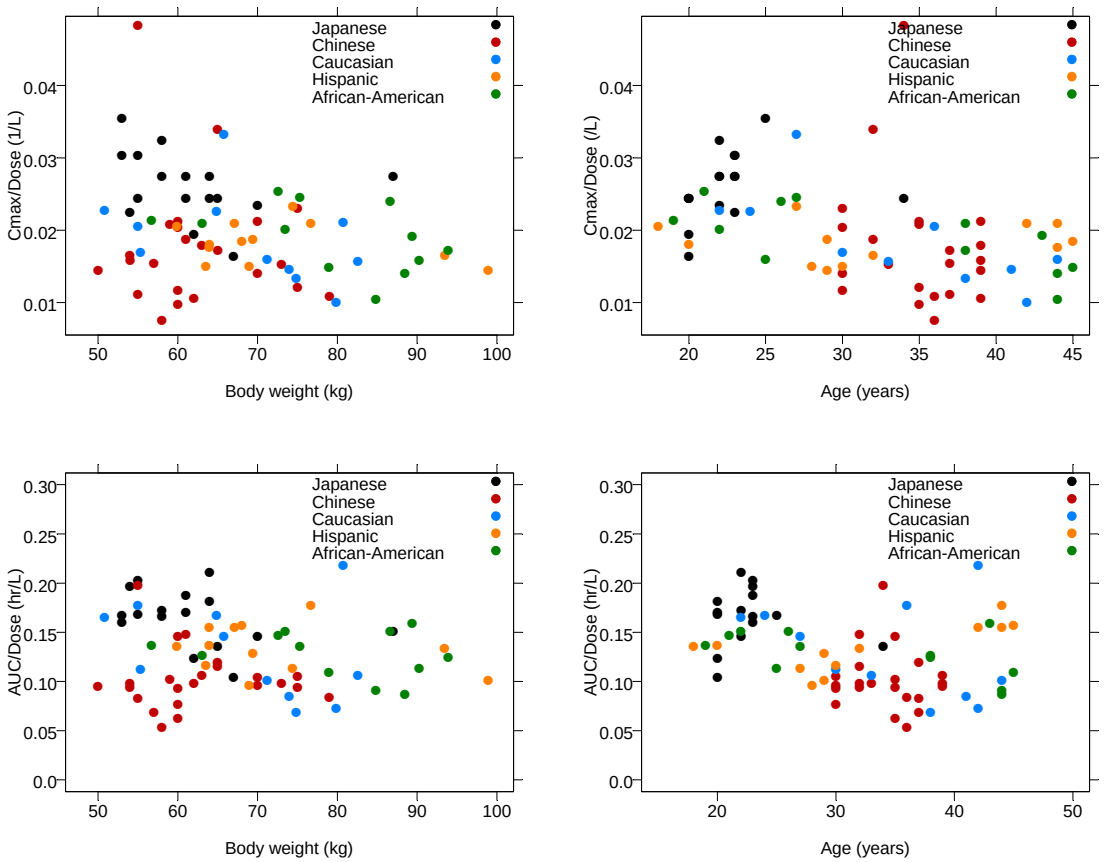


Figure 12: C_{max}/Dose (Top) and AUC/Dose (Bottom) vs. body weight (Left) and age (Right) following single dose 2.5-15 mg rivaroxaban from studies 11126 (Japanese), 11608 (Chinese), and 12090 (Caucasian, African-American, and Hispanic).

There are no apparent differences in Factor Xa inhibition between Japanese (study 11126) and Chinese (study 11608) after adjusting for exposure differences (see Figure 13).

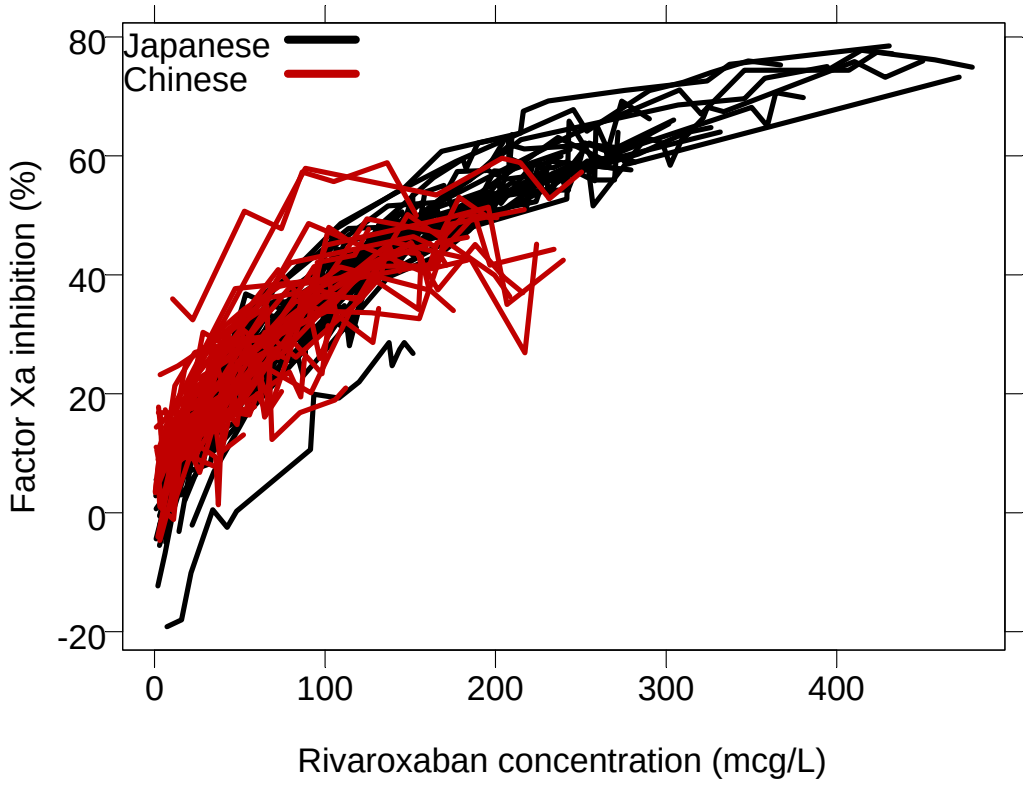


Figure 13: Factor Xa inhibition vs. rivaroxaban concentration in Japanese (black lines) and Chinese (red lines) subjects following 10 mg single dose rivaroxaban.

3.4.2 Population Pharmacokinetic Analysis

Ethnicity was not found to be a covariate for rivaroxaban clearance in sponsor's population PK analyses (see Figure 14). However, Japanese were pooled with other ethnicities under the name "Asian" and there were only 7 Asian patients in studies 10944 and 10945. Inter-ethnicity differences can therefore not be ruled out based on the population PK analysis.

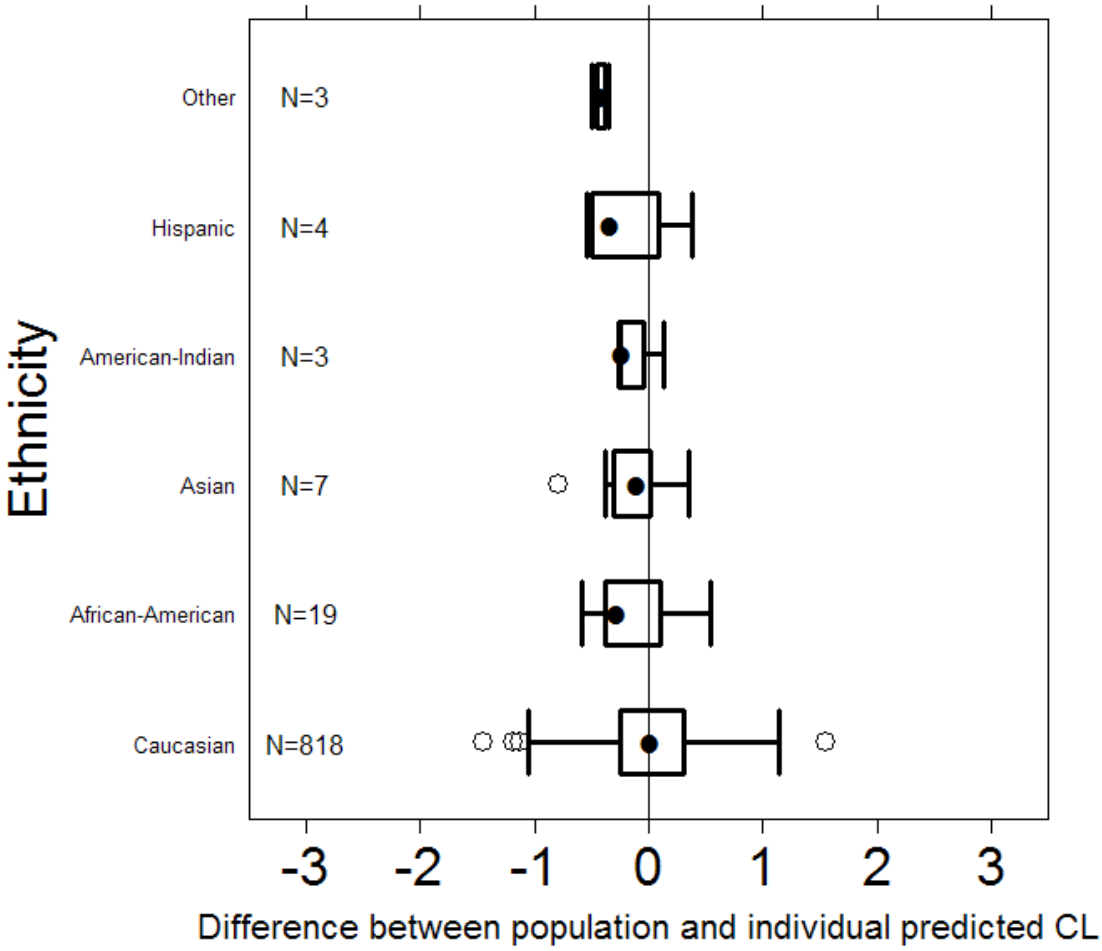


Figure 14: Difference between population and individual predicted clearance vs. ethnicities in studies 10944 and 10945.

3.4.3 Exposure-Response Analysis

Data from study 10944 and 10945 receiving rivaroxaban doses from 2.5 – 30 mg bid and study 11527 receiving 5 - 40 mg qd were used for reviewer's exposure-response analysis.

Similar to sponsor's exposure-response findings relative to enoxaparin, a shallow dose-response relationship was observed for effectiveness (composite endpoint consisting of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), or death from all causes) (see Figure 15 Left).

A steep increase in the risk of major bleeding from 1.8% for 2.5 mg bid to 8.7% for 30 mg bid (see Figure 15 Right).

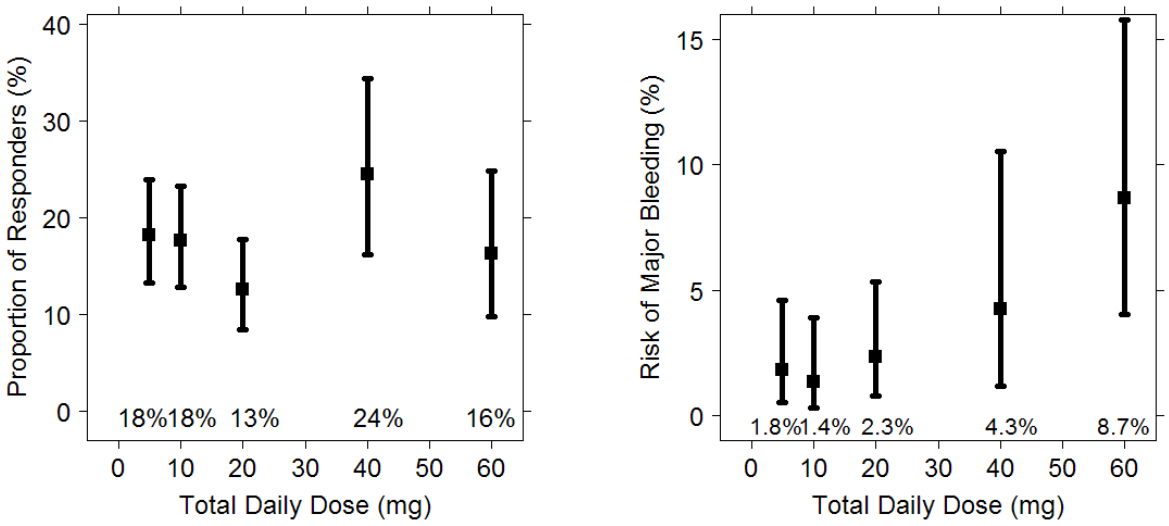


Figure 15: Proportion of (Left) responders and (Right) risk of major bleeding and associated 95% CI vs. total daily dose in dose-ranging studies 10944 and 10945 receiving 2.5-30 mg bid.

Similar to the dose-response for effectiveness in Figure 15, a flat exposure-response relationship is seen when plotting the median quartile steady-state AUC_{0-24} or C_{max} vs. the proportion of responders within each exposure quartile (see Figure 16).

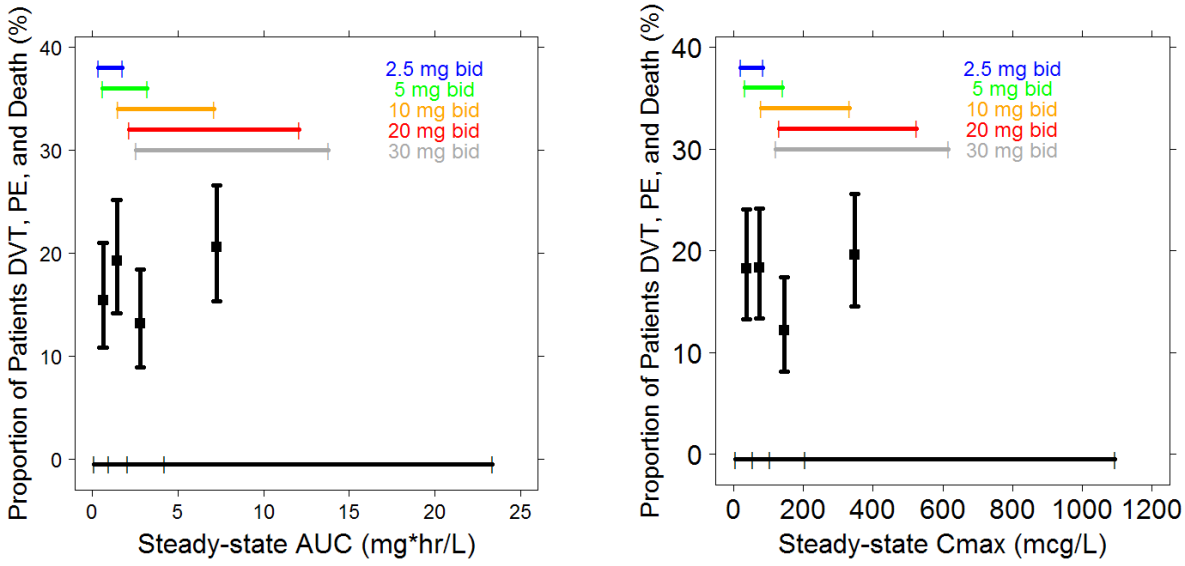


Figure 16: Proportion of responders vs. median quartile steady-state (Left) AUC_{0-24} and (Right) C_{max}. The horizontal black bar shows the steady-state AUC quartiles and the horizontal colored bars illustrate the predicted 10-90th AUC and C_{max} percentiles following different dose regimens.

The risk of major bleeding was found to be correlated with exposure. The risk of major bleeding was around 2% for the three lowest exposure quartiles (AUC or C_{max}) and increases to around 6% for the highest exposure quartile (i.e. AUC_{0-24} above 4 mg*hr/L and C_{max}>200 mcg/L) (see Figure 17). The 80th exposure percentile following 5 mg bid (i.e. equivalent to the proposed dose of 10 mg) is below exposures associated with higher risk of major bleeding while 2-fold increases due to intrinsic and extrinsic factors (see Table 1) will result in a substantial number of patients having exposures similar to 10 mg bid which are associated with higher risk of major bleeding.

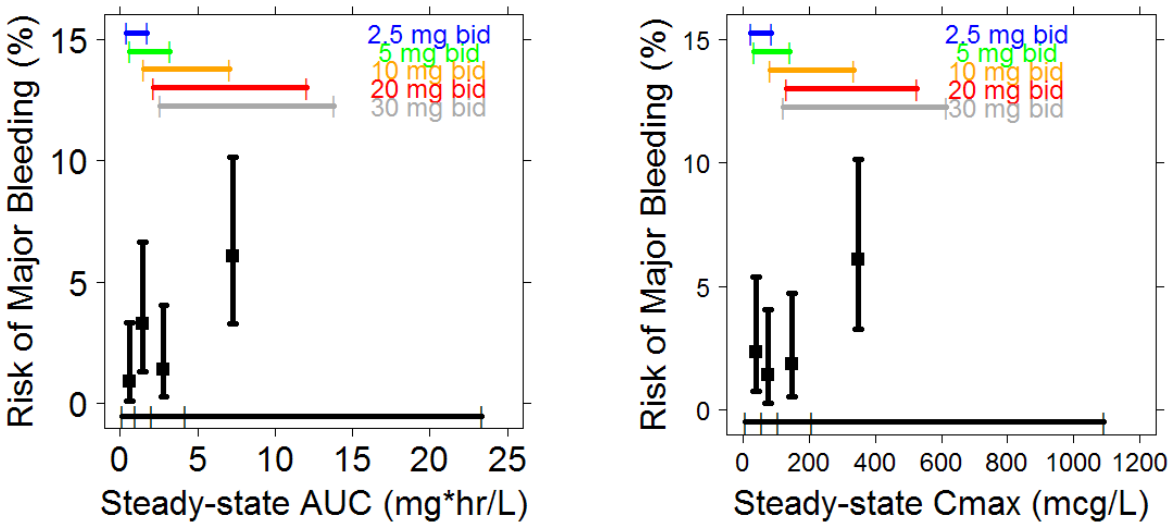


Figure 17: Risk of major bleeding vs. median quartile steady-state (Left) AUC_{0-24} and (Right) C_{max}. The horizontal black bar shows the steady-state AUC_{0-24} quartiles and the horizontal colored bars illustrate the predicted 10-90th steady-state AUC_{0-24} and C_{max} percentiles following different dose regimens.

The daily dosing data from study 11527 exploring doses from 5-40 mg qd shows a similar dose- and exposure-response relationship for risk of major bleeding as the bid dosing (see Figure 18) and a shallow dose- and exposure-response for the composite endpoint (see Figure 19).

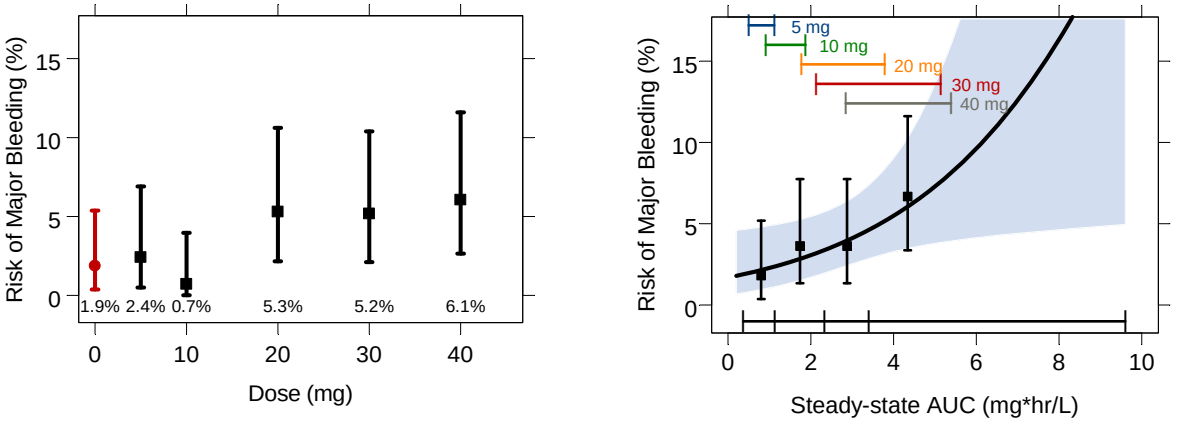


Figure 18: Risk of major bleeding vs. (left) dose in dose-ranging studies 11527 receiving 5-40 mg qd and (right) median quartile steady-state AUC_{0-24}. The horizontal black bar shows the steady-state AUC_{0-24} quartiles and the colored bars illustrate the predicted 10-90th steady-state AUC_{0-24} and C_{max} percentiles following different dose regimens.

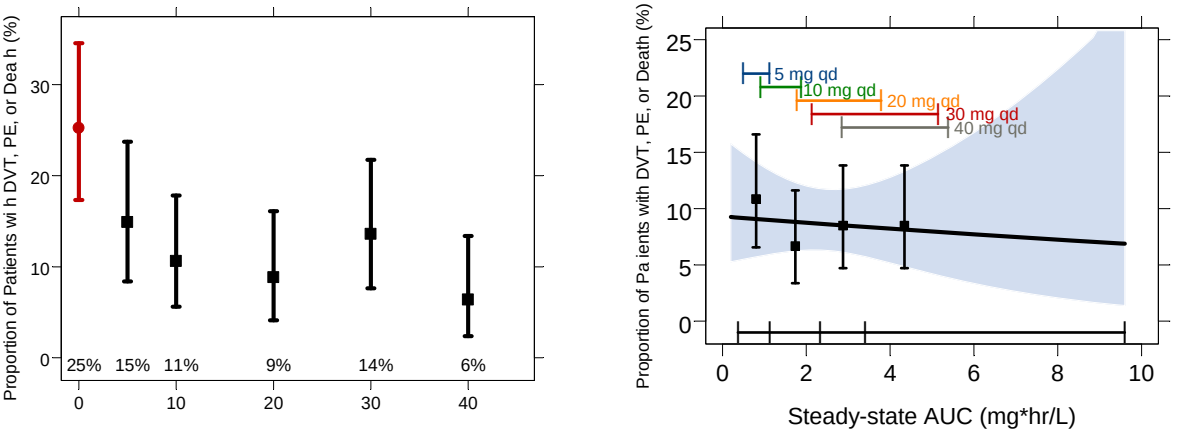


Figure 19: Proportion of patients with DVT, PE, or death vs. (Left) dose and (Right) steady-state AUC_{0-24} quartiles and associated 95% CI in dose-ranging study 11527 receiving 5-40 mg qd. The horizontal black bar shows the steady-state AUC_{0-24} quartiles and the colored bars illustrate the predicted 10-90th AUC and C_{max} percentiles following different dose regimens.

4 APPENDIX

Table 3: Summary of Sponsor's Population PK Analyses Findings.

Pop PK Report	Studies	Objective	Conclusion
PPK03-002	10842 (fasted, 10 mg) 10847 (fed, 5-30 mg bid)	PK of rivaroxaban in healthy volunteers in fed or fasted condition	30 mg dose group have larger V
PK000130-133	11002 (renal) 11003 (hepatic)	Hepatic and renal function	CrCL and Child-Pugh are CL covariates, Height and Sex are V covariates
12623	11865 (erythromycin) 11935 (ritonavir) 11936 (ketoconazole) 10992 (ketoconazole)	Impact of CYP3A4 / Pgp inhibition on rivaroxaban	Explored DDI influence on renal and non-renal clearance. Confirmed NCA results (see Table 1)
PPK03-010	10944 (2.5-30 mg bid)	Characterize variability and identify covariates in VTE prevention patients	Age and CrCL are covariates for CL (patients). LBM/BSA is a covariate for V
PPK04-009	10945 (2.5-30 mg bid)	Characterize variability and identify covariates	CrCL, hematocrit, and sex are CL covariates, BSA is a covariate for V
PK000128	10944 (2.5-10 mg bid) 10945 (2.5-10 mg bid)	Characterize variability and identify covariates	CrCL, Age. Sex, Day are CL covariates, BSA is a covariate for V
PK000131	11527 (5-40 mg qd) 10944 (2.5-30 mg bid)	Characterize variability and identify covariates	CrCL, Age, Sex, Day, albumin, and hematocrit are CL covariates, BSA is a covariate for V
12143	11223 (10-30 mg bid, 40 mg qd) 11528 (20-40 mg qd)	Characterize variability and identify covariates	SCr and Age are CL covariates, LBM and age are V covariates

CrCL=Creatinine clearance, CL=clearance, LBM=lean body mass, SCr=Serum creatinine, V=volume of distribution.

4.4.2 Pharmacogenomics Review

OFFICE OF CLINICAL PHARMACOLOGY:
GENOMICS REVIEW

NDA: 22406
Brand Name: XARELTO™ immediate release tablets
Generic Name: rivaroxaban
Proposed formulation; strength: 10 mg immediate release tablets
Clinical Division: OND/OODP/DMIHP
OCPB division: 5
Primary Genomics Reviewer: Rosane Charlab Orbach, Ph.D.
Associate Director for Genomics & Team Leader: Issam Zineh, Pharm.D., MPH

Rivaroxaban (Bay 59–7939) is an orally bioavailable, small molecule that directly inhibits factor Xa. It is being proposed for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement or knee replacement surgery. Coagulation factor X (FX) is a vitamin-K-dependent plasma protein that plays a key role in the regulation of blood coagulation by converting prothrombin into thrombin. Activated FX (FXa) occupies a central position in the coagulation cascade as it is positioned at the crossroad between intrinsic and extrinsic pathways. In addition to its hemostatic role, FXa is believed to exert pleiotropic cellular effects through complex signaling events (Trends Mol Med. 2008 Oct; 14(10):429-40, PMID: 18774340).

Inter-ethnicity differences were found to influence rivaroxaban pharmacokinetics or pharmacodynamics outcomes as reported by the Clinical Pharmacology and Pharmacometrics reviewers of this submission. This Genomics review addresses the potential for a pharmacogenetic basis underlying these differences.

Key Review Questions:

From our perspective there are two issues at hand where pharmacogenomics information employed in an exploratory fashion could be useful in elucidating the observed differences in pharmacokinetics or pharmacodynamic endpoints in sub-populations. These correspond to questions 1 and 2. Question 3 reviews (functional) variations in drug target or accessory pathway.

1- Is there evidence of inter-ethnicity differences in rivaroxaban PK/PD?

Ethnicity effects on pharmacokinetics or pharmacodynamics outcomes:

Pharmacokinetics analyses revealed that Japanese individuals have significantly higher exposure to rivaroxaban (AUC, Cmax) than other tested groups including Caucasians, Hispanic, African-Americans and Chinese following a single oral dose of rivaroxaban. These pharmacokinetics differences did not correct after taking into account potential

differences in several anthropometric variables, as for example body weight differences (see Pharmacometrics review for studies 11126, 11608, and 12090).

Assessment: Unmeasured, unreported or unknown environmental or demographic factors may still contribute to the observed differences in pharmacokinetics parameters. Furthermore, differences in genetic background in the disposition pathway of rivaroxaban may also play a role.

Rivaroxaban is metabolized via cytochromes P450 CYP3A4/5, CYP2J2, and by hydrolytic cleavage. It is also a P-gp and BRCP substrate. Although the contribution of each CYP450 enzyme to rivaroxaban metabolism is potentially small based on submitted data, the genes involved in rivaroxaban pharmacokinetics (CYP3A4, CYP3A5, CYP2J2, ABCG2, and ABCB1) (b) (4) may contribute to the observed inter-ethnic variability. In addition, linkage disequilibrium and haplotype structure differ for these genes across populations.

(b) (4)

It is therefore plausible that the pharmacokinetics differences seen in the Japanese population may be explained, at least in part, by genetic differences in any or all of the genes involved in rivaroxaban pharmacokinetics. The applicant may consider analysis of candidate SNPs or haplotypes in order to rule out this cause of variability.

Of note, the applicant indicated on a response letter to a FDA Information Request Letter of 19 February 2009 that pharmacogenomic samples were not collected in the ethnic Phase 1 studies, or in the Phase 3 RECORD program, but pharmacogenomic samples are being collected in the other large rivaroxaban Phase 3 programs.

The reviewer recommends including in Xarelto's label that healthy Japanese subjects were found to have higher exposure compared to Caucasians, African-Americans, Chinese and Hispanics.

2 – Is there a pharmacogenetic basis for a pharmacodynamic clopidogrel-rivaroxaban interaction?

In two clinical studies to examine the potential for drug-drug interaction between rivaroxaban and clopidogrel (studies 11864 and 11279), there appeared to be a greater than an additive response to clopidogrel-rivaroxaban co-treatment on the bleeding time endpoint. Clopidogrel pharmacokinetics samples were not obtained, but DNA samples were banked. It is unclear whether there is a synergistic pharmacodynamic effect of

clopidogrel-rivaroxaban which would be expected by their mechanisms of action. In addition, a pharmacokinetics drug-drug interaction cannot be ruled out since clopidogrel active metabolite concentrations were not measured.

Individual response to clopidogrel is known to be variable and subjects can be characterized as ultrarapid, extensive, intermediate or poor metabolizers. The mechanisms underlying the variability in response are not fully elucidated and are likely multifactorial. Differences in individual absorption of clopidogrel as well as levels of its active metabolite may also lead to clopidogrel response variability (J Am Coll Cardiol. 2007 Apr 10; 49(14):1505-16; PMID: 17418288). Clopidogrel is a prodrug that requires activation by specific hepatic CYP450 enzymes (CYP2C19, CYP2B6, CYP2C9, CYP1A2, and CYP3A4/5.) These genes (b) (4) and previous studies have shown that carriers of the specific alleles of CYP2C19 have an altered response to the antiplatelet effects of clopidogrel compared to the wild-type allele (b) (4)

Assessment: In the absence of clopidogrel pharmacokinetics samples, the applicant may consider genotyping patients for variants known to be determinants of clopidogrel response. These include, but are not limited to CYP2C19 variants (e.g., *2, *3, *4, *5, *6, *8, *9, *10, *17). There are marked inter-ethnic differences in the frequency of these allelic variants. CYP2C19*2 and CYP2C19*3 reduced function alleles account for most of the poor metabolizer alleles. The CYP2C19 *2 reduced function allele is expected to be the most common in the Caucasian population. CYP2C19*17 is associated with an increased CYP2C19 activity (Clin Pharmacol Ther. 2006 Jan; 79(1):103-13; PMID: 16413245).

Although the sample population size was small in both clinical studies and the clopidogrel metabolic pathway is complex, genotyping may offer pharmacokinetics-centric mechanistic hypotheses to the observed effect of co-treatment on bleeding time.

A suggestion to perform CYP2C19 genotyping was sent to the applicant through a FDA Information Request Letter of 19 February 2009.

- In response to the FDA Information Request Letter of 19 February 2009, the applicant indicated that the pharmacogenomic samples collected in the clopidogrel interaction studies would be analyzed for CYP2C19*2 and CYP2C19*3 alleles. The result of the CYP2C19*2 and CYP2C19*3 genotyping was submitted to the Agency on March 11 (**Biomarker Report** No. A45974) and is summarized below.

The exploratory pharmacogenetic sub-study involved studies 11279 and 11864. In study 11279, subjects received rivaroxaban and combined rivaroxaban/clopidogrel treatment after a clopidogrel run-in period in a two-way cross-over design. In study 11864, responders to clopidogrel (defined as > 40% inhibition of platelet aggregation) received rivaroxaban, clopidogrel and combined rivaroxaban/clopidogrel treatment in a three-way cross-over design.

Genomic DNA was isolated from white blood cells of consenting subjects. DNA samples were available from 10/14 volunteers and from 16/27 volunteers in studies 11279 and 11864 respectively. Genotypes were performed using by TaqMan® Pre-Developed Assay Reagents for Allelic Discrimination and were correlated with bleeding time. The objective was to explore whether CYP2C19 reduced function alleles *2 and *3 correlate with the relative change in bleeding time observed after rivaroxaban /clopidogrel co-treatment.

The CYP2C19*2 and CYP2C19*3 allele frequencies observed in the studies 11279 and 11864 are indicated below (**Biomarker Report** No.A45974, page 9).

TT 1: Allele frequencies of *CYP2C19*2* and *CYP2C19*3*

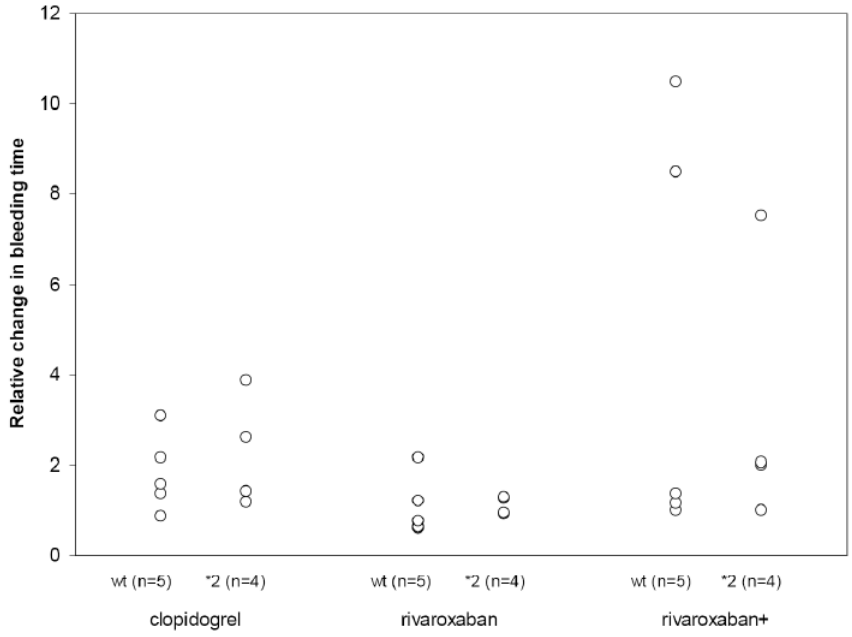
Study	N alleles	n *2 alleles	n *3 alleles	frequency *2 allele	frequency *3 allele
11279	20	1	1	5%	5%
11864	32	5	0	16%	0%

Despite the small sample size, CYP2C19*2 and CYP2C19*3 observed allele frequencies in study 11864 are within the reported frequencies for Caucasians (Clin Pharmacokinet. 2002; 41(12):913-58; PMID: 12222994), while *2 allele frequencies are under-represented in study 11279. The applicant reports that homozygotes for *2 or *3 alleles were not observed.

In study 11279, the CYP2C19*2 carrier did not display a relative prolongation in bleeding time. However, the *CYP2C19*3* allele carrier showed an elevated relative change in bleeding time after clopidogrel treatment, pointing to the complexity of the clopidogrel response.

In study 11864, the CYP2C19*2 allele was associated with a reduced relative change in bleeding time during the evaluation of the clopidogrel response, but had no conclusive effect during the cross-over design phase. The lack of an over-additive prolongation in bleeding time was observed among *2 carriers. In contrast, an over-additive relative change in bleeding time under rivaroxaban/clopidogrel co-treatment was also observed for one CYP2C19*2 carrier. The data is represented in the figure 3 of the applicant's **Biomarker Report** No. A45974, page 12:

TF 3: Effect of *CYP2C19*2* and **3* on relative change in bleeding time in study 11864



In conclusion, based on the submitted pharmacogenetic sub-study report, the clinically relevant increase in bleeding time observed during rivaroxaban/clopidogrel co-treatment cannot be linked to the CYP2C19*2 genotype. Since the mechanism leading to a bleeding time prolongation in some subjects is unclear, the concomitant use of rivaroxaban and clopidogrel is not recommended.

3 – Are there known (functional) variations in drug target or accessory pathway?

Concerning the Applicant statement (Clinical Overview, section 3.2.5 - Possible genetic differences in metabolism and response, page 20)

"In addition, genetically determined deficiencies of factor X that might affect the response to rivaroxaban are one of the most uncommon inherited coagulation disorders".

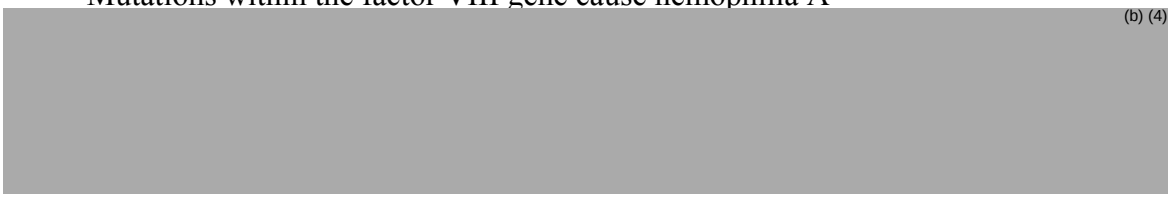
The reviewer agrees with the statement at this time. Given the complexity of coagulation and fibrinolysis, multiple genetic variants may influence the phenotype of an individual, and the potential clinical implication is unknown.

However, it is conceivable that additional (b) (4) mutations in coagulation factors other than *genetically determined deficiencies of factor X* could potentially affect the response to rivaroxaban. (b) (4)

Additional examples extracted from the literature include but are not limited to:

- G/A substitution at position 1691 of the factor V gene, resulting in an arginine to glutamine exchange in codon 506, commonly referred to as Arg506Gln, factor V Leiden, or R506Q
- G/A exchange at position 10976 in the factor VII gene, which results in an arginine to glutamine exchange in codon 353 (also known as Arg353Gln or R353Q)
- G/A exchange at position 20210 in the 3′ untranslated region of the prothrombin gene

- Mutations in the factor IX gene result in FIX deficiency and hemophilia B, a severe bleeding disorder, requiring a lifelong substitution of FIX.
- Mutations within the factor VIII gene cause hemophilia A



- About 10% of the Caucasian population exhibits high FXI levels. A correlation with genotype is unclear. Mutations associated with FXI deficiency have been reported

- Fibrinogen ß-chain -455 G/A - Elevated plasma fibrinogen levels
- Fibrinogen ß-chain -854 G/A - Elevated plasma fibrinogen levels
- Fibrinogen α -chain Thr312Ala - Influences α -chain cross-linking and clot stability
- 4G/5G insertion/deletion in the PAI-1 gene (plasminogen activator inhibitor-1) at a position −675 of the promoter region -Elevated plasma PAI-1 levels
- C/T substitution in the t-PA (tissue-type plasminogen activator) gene at a position -7351 of the promoter region - Increases t-PA release

Platelet glycoprotein (GP) receptor function:

- C/T substitution at position 807 in the GPIa gene
- C/T substitution at position 1565 in exon 2 of the GPIIIa gene, which results in a leucine to proline exchange
- T/C substitution at position −5 upstream of the ATG initiation codon in the GPIbα gene (the von Willebrand factor-binding subunit of the complex)

References:

1. Blood. 2000 Mar 1; 95(5):1517-32; PMID: 10688804
2. Thromb Haemost. 2002 Aug; 88(2):195-9; PMID: 12195688
3. Clin Chim Acta. 2003 Apr; 330(1-2):31-55; PMID: 12636925
4. Arterioscler Thromb Vasc Biol. 2004 Feb; 24(2):216-29; PMID: 14615395
5. Arterioscler Thromb Vasc Biol. 2005 Dec;25(12):2667-72, PMID: 16239598
6. Lancet. 2006 Feb 25; 367(9511):651-8; PMID: 16503463

4.4.3 IRT Review

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22, 406
Brand Name	Xarelto™
Generic Name	Rivaroxaban (BAY 59-7939)
Sponsor	Johnson & Johnson
Indication	Prophylaxes of Deep Vein Thrombosis and Pulmonary Embolism in Patients undergoing Hip & Knee Replacement Surgery
Dosage Form	Tablets
Drug Class	Direct Factor Xa (FXa) Inhibitor
Therapeutic Dosing Regimen	10 mg once daily
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	50 mg
Submission Number and Date	N000, 28 July 2008
Review Division	DMIHP / HFD 160

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of BAY 59-7939 (15 mg and 45 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between BAY 59-7939 (15 mg and 45 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that the assay sensitivity of the study was established.

In this randomized, double-blinded, four-way crossover study with 27 male and 27 female subjects single oral doses of 15 and 45 mg BAY 59-7939, placebo, and 400 mg of moxifloxacin. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for BAY 59-7939 (15 mg and 45 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
BAY 59-7939 15 mg	24	1.5	(-0.9, 4.0)
BAY 59-7939 45 mg	24	1.6	(-0.9, 4.0)
Moxifloxacin 400 mg*	4	12.1	(10.2, 14.1)

*Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 9 time points is 9.1 ms.

The supratherapeutic dose (45 mg) produces mean C_{max} values of 2-fold higher than the mean C_{max} for the therapeutic dose (10 mg once daily). These concentrations are above those for the predicted worst case scenario (drug interaction with strong inhibitor of CYP3A4 and P-gp) and show that at these concentrations there are no detectable prolongations of the QT-interval. It is expected from drug interaction studies that co-administration of rivaroxaban with ketoconazole can elevate rivaroxaban's mean C_{max} as much as 1.7-fold higher than the C_{max} of the 10 - mg dose. The proposed label warns that use of rivaroxaban is not recommended in patients receiving concomitant strong inhibitors of both CYP3A4 and P-gp. Also, hepatic or renal impairment have been shown to increase C_{max} by as much as 1.3-fold. Rivaroxaban is contraindicated in patients with hepatic disease and not recommended in patients with kidney failure.

2 PROPOSED LABEL

"In a thorough QT study in healthy men and women aged 50 years and older, no QTc prolonging effects were observed for XARELTO™ (15 mg and 45 mg, single dose)."

Reviewer's Comment: The proposed label statement is acceptable.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Rivaroxaban is a competitive inhibitor of FXa, it inhibits human FXa with >10,000-fold greater selectivity than for other serine proteases. Activated serine protease FXa plays a central role in blood coagulation. It is activated by both the intrinsic and extrinsic coagulation pathways. In human plasma, submicromolar concentrations of rivaroxaban prolonged the clotting assays HepTest, PT, and aPTT.

3.2 MARKET APPROVAL STATUS

Rivaroxaban is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From the Investigator Brochure (version 12, 2006):

> "Preclinical investigations have identified no QTc prolonging propensity of Rivaroxaban in hERG channel or Purkinje fiber experiments or in anesthetized dogs."

From the NDA submission, nonclinical overview:

> "The effects of Rivaroxaban have been extensively investigated on vital organ systems (cardiovascular system including ECG, respiratory system and central nervous system) as well as on supplemental organ systems (hematology and blood coagulation, gastrointestinal function, renal function, and metabolism (glucose, lipids)) in several in vitro and in vivo studies. The studies were conducted according to the ICH S7A and the ICH S7B guidelines. The core battery as well as most of the supplemental studies was performed under the Principles of Good Laboratory Practice (GLP). Doses administered were chosen to cover sufficient safety margins and expressed in terms of x-fold-difference from therapeutic human plasma concentration (125 mg/L total or 6.3 mg/L unbound), here termed C_{max}. The highest C_{max} achieved in rats is 38-fold (10-fold unbound) and in dogs 31-fold (64-fold unbound) greater than the therapeutic human plasma levels.
>
> "The overall results of the safety pharmacology studies with Rivaroxaban showed no biologically relevant adverse effects on the central nervous system (CNS), cardiovascular and respiratory system, renal function and metabolism, and gastrointestinal tract. In studies addressing the risk for QT-prolongation in humans, no biologically relevant findings were observed in cardiovascular in vitro (hERG potassium channel, action potential assay) and in vivo studies (recordings of anesthetized dogs). Thus, it is concluded that Rivaroxaban is devoid of a proarrhythmic risk."

Reviewer's Comments: Rivaroxaban was negative in the Purkinje fiber assay and hERG assay. In vivo safety pharmacology studies in dogs were negative at equivalent human therapeutic concentrations and showed wide safety margins.

3.4 PREVIOUS CLINICAL EXPERIENCE

From the NDA submission (clinical overview and module 5 Integrated Summary of Safety):

> "Safety data provided are from 4 pivotal Phase 3 studies (RECORD 1 through 4), 9 Phase 2 studies, and 51 Phase 1 studies. These completed studies were primarily short- term (i.e., <35 days) exposure studies. In addition, safety data from subjects in 8 ongoing randomized, controlled studies are included in this submission, some of which contributed information on longer exposure durations.
>
> "Routine electrocardiographic safety monitoring was not done in the Phase 3 RECORD program. A pooled analysis of electrocardiographic data from the Phase 2 orthopedic VTE prophylaxis studies did not reveal any clinically meaningful differences among treatment groups with respect to newly-emerging ECG findings."
>
> "RECORD Studies. The total number of cardiovascular events (centrally adjudicated myocardial infarction, stroke and death) during treatment and follow-up was 30 events (0.49%) in the rivaroxaban group and 39 events (0.63%) in the enoxaparin group. The incidence of on-active treatment events appeared lower in the rivaroxaban group (13 [0.2%]) compared with enoxaparin (25 [0.4%]), while

off-active treatment events were balanced in the 2 groups; 16 (0.3%) and 14 (0.2%) in the rivaroxaban and enoxaparin groups, respectively.

"Death was considered to be cardiovascular when there was an obvious cardiovascular cause (e.g. myocardial infarction, pulmonary embolism, terminal heart failure, or multiorgan failure including heart failure). Death was also considered to be cardiovascular in origin in case of sudden, unexplained death. In all other situations, death was considered to be non-cardiovascular.

"The total number of cardiovascular events (centrally adjudicated myocardial infarction, stroke and death) during treatment and follow-up was 30 events (0.49%) in the rivaroxaban group and 39 events (0.63%) in the enoxaparin group.

Table 2: Incidence of cardiovascular events (retrospective central adjudication) (Pooled RECORD1-4 studies)

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

From the sponsor's table 1-22, module 5, Integrated Summary of Safety, page 58

"Cardiovascular events were not formally assessed in the Phase 2 studies and there were no events in the Phase 1 studies.

"A central core laboratory analyzed ECG data for Study 11223. There were no differences between rivaroxaban and the comparator with respect to changes in the PR interval, QRS interval, or QT interval. Generally, critical cardiac events were rare in Study 11223, and serious ventricular dysrhythmias were not reported."

Reviewer's comments: in the RECORD studies the number of cardiovascular events in the rivaroxaban arm was lower than that reported in the active control arm.

No seizures or ventricular arrhythmias were reported. No clinical relevant ECG findings were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of rivaroxaban's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted a thorough QT study (study report # 011275) for rivaroxaban, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A randomized, double-blinded, double-dummy, 4-way crossover, placebo- and active-controlled Phase-I study to investigate the influence of single doses (15 and 45 mg) of BAY 59-7939 on the QTc interval in healthy male and female subjects

4.2.2 Protocol Number

011275

4.2.3 Study Dates

03 May 2004 to 26 July 2004

4.2.4 Objectives

Primary Objective

- To rule out an effect (i.e. to demonstrate a lack of effect) of a single 45 - mg oral dose of BAY 59-7939 on manually read QTc interval as compared to placebo.

Secondary Objectives

- To assess/validate the sensitivity of QTc interval assessment, to characterize the effect of a single oral dose of 400 mg of moxifloxacin on QTc interval relative to placebo.
- To characterize the effect on QTc relative to placebo of a single oral dose of 15 mg of BAY 59-7939.
- To characterize the effect on QTc and HR relative to placebo of single oral doses of 400 mg of moxifloxacin, 15 mg and 45 mg of BAY 59-7939.
- To characterize the plasma exposure behavior of BAY 59-7939 and moxifloxacin, respectively.
- To explore the relationship between BAY 59-7939 and moxifloxacin exposure versus ECG parameters (QTc and HR).

4.2.5 Study Description

4.2.5.1 Design

This was a single-center, randomized, double-blinded, double-dummy, 4-way crossover, placebo- and active-controlled Phase-I study.

Single doses of placebo- and active- (400 mg moxifloxacin) control and two single doses of BAY 59-7939 (15 and 45 mg) were studied. The study comprised 4 treatment periods with one dosing day and two follow-up days, each (0d to 2d). Treatments were separated with washout periods of at least 7 days.

The sponsor applied a 4-fold crossover design with complete blocks of orthogonal-latin-squares, 60 subjects were envisaged and 54 subjects were included. Subjects were assigned to one of the 12 possible sequences as listed in Table 2.

Table 2: Crossover design using 12 treatment sequences

Study Sequence
A-B-D-C
A-C-B-D
A-D-C-B
B-A-C-D
B-C-D-A
B-D-A-C
C-A-D-B
C-B-A-D
C-D-B-A
D-A-B-C
D-B-C-A
D-C-A-B

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The study was performed in a double-blind design with double-dummy placebo.

All ECGs were reviewed and interpreted by one board-certified cardiologist for possible drug effects, in particular for drug-induced T- and/or U-wave changes. The reader was blinded to subject, time, sequence and treatment.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

The following 4 different treatments (A, B, C and D) were applied to each of the sequences:

A: 15 mg BAY 59-7939 were given as 3 tablets containing 5 mg BAY 59-7939, plus 6 tablets of placebo-BAY 59-7939, plus 1 capsule of placebo-moxifloxacin.

B: 45 mg BAY 59-7939 were given as 9 tablets containing 5 mg BAY 59-7939, plus 1 capsule of placebo-moxifloxacin.

C: Placebo-BAY 59-7939 was given as 9 tablets placebo-BAY 59-7939, plus 1 capsule of placebo-moxifloxacin.

D: 400 mg moxifloxacin were given as 1 capsule moxifloxacin, plus 9 tablets of placebo-BAY 59-7939.

4.2.6.2 Sponsor's Justification for Doses

"In the preceding Phase-I studies doses of BAY 59-7939 up to 80 mg single dose and 30 mg bid multiple dose revealed to be safe and well tolerated. In addition, doses of up to 30 mg bid were tested in clinical trials in orthopedic patients directly after hip surgery. This

dose was also still considered to be safe, although incidences of bleeding events tended to be higher after this dose group compared to lower doses. Despite this tendency the dose of 30 mg bid was not stopped prematurely as predefined stopping rules were not met, which were in place to safeguard the patients. As 15 mg BAY 59-7939 was anticipated to be an appropriate dose in further clinical trials, this dose was chosen in this study.

"Guidance documents request that the safety range of an investigational drug should be explored. Previous studies have demonstrated that there is no further increase in exposure when the dose of BAY 59-7939 is increased from 40 to 50 mg (administered with food). Furthermore, the dose of 50 mg was identified as the maximal tolerated dose in humans(2). Therefore, a single dose of 45 mg BAY 59-7939 was considered appropriate in this trial. Additionally, guidance documents recommend the inclusion of a positive control in the trial, which was able to produce a mean QTc prolongation of 5 ms on the one hand and considered to be safe on the other hand. Moxifloxacin served these purposes at the approved dose of 400 mg. Since no active or major metabolites were identified for BAY 59-7939, a single dose design was considered to be adequate for this "through QT study" according to the ICH E 14 Guidance document."

Reviewer's Comment: The sponsor's proposed dose of rivaroxaban (45 mg) is expected to give the same exposures as the maximum tolerated dose (50 mg) due to limited absorption at does greater than 40 mg. The proposed dose is expected to cover the extent of exposure under the expected high clinical exposure scenarios of co-administration of a strong inhibitor of both CYP3A4 and P-gp (1.7-fold increase in C_{max}), and renal or hepatic impairment (1.3-fold increase in C_{max}).

4.2.6.3 Instructions with Regard to Meals

After an overnight fast, study medication was administered on day 0 at about 8:00 am (0d00h) with 240 mL of water within 5 minutes after completion of a standardized breakfast. Breakfast was to be eaten within 30 minutes while subjects stay in bed in semi-supine position.

Subjects rested for 45 minutes in supine position before performance of an ECG; except for the 0.5- and 5-hour post-dose ECGs where a supine resting time of 30 minutes was acceptable due to intake of breakfast and lunch. The study medication was administered in sitting position in the morning together with approximately 240 mL of non-sparkling water within 5 minutes after completion of a standardized breakfast, which had to be eaten within 30 minutes.

Reviewer's Comment: Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 - mg dose. Therefore, dose administration after a standardized breakfast is acceptable.

4.2.6.4 ECG and PK Assessments

ECG measurements for assessment of QTc were obtained post-dose at 0.5, 1, 2, 3, 4, 5, 6, 24 and 48 hours. Blood samples for measurement of rivaroxaban were obtained post-dose at 0.5, 1, 2, 3, 4, 5, 6 and 24 hours.

Reviewer's Comment: ECG and PK assessments are adequate to capture the QT effect at peak concentration of rivaroxaban (T_{max} = 2 – 4 hours).

4.2.6.5 Baseline

Baseline was the average of all pre-dose measurements.

4.2.7 ECG Collection

12-lead ECGs were recorded (3 recordings at each time point about 1 minute apart) after the subject was resting at least for 45 minutes in supine position except for the 0.5- and 5 hour post-dose ECGs where a supine resting time of 30 minutes was acceptable due to intake of breakfast and lunch.

For each time point, manual on-screen interval measurements were made from 3 consecutive QRST complexes primary lead was lead-II, if measurements were not possible in lead-II, V2 or, if lead-II and V2 were not possible, lead V5 was used for measurements.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 27 female and 27 male subjects participated in this study, 50 subjects completed the study as planned. Female (non-childbearing potential) and male Caucasian subjects ≥50 years of age (average age was 60 years), normal body weight as calculated by body mass index between 20 and 32 kg/m^2.

Reviewer's Comments: The sponsor does not explain why the study enrolled subjects over 50 years of age.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary parameter of the study was the difference in QTcF change at 3 hours between 45 mg BAY 59-7939 and placebo, i.e., 45 mg BAY 59-7939 minus placebo. Secondary parameters were the differences in the variable change between (i) 15 mg BAY 59-7939 and placebo, (ii) 400 mg moxifloxacin and placebo, and (iii) 45 mg BAY 59-7939 and 400 mg moxifloxacin.

To compare the effect of treatments, the absolute QTc change at 3 hour post-dose was analyzed using analysis of covariance (ANCOVA) including sequence, subject (sequence), period and treatment effects as well as corresponding baseline values as covariate. Based on this analysis, point estimates (LS-means) and a confirmatory one-sided 95% CI for the primary parameter was calculated.

The sponsor's results are presented in Table 3. The results showed no treatment effect on QTcF (upper bounds of the 95% CI were below 5 ms). The lower bounds of the 95% CI for the 400 mg moxifloxacin exceeded 5 ms, confirming the responsiveness of the study participants towards an increase in QTcF induced by moxifloxacin.

Table 3: ANCOVA Treatment Comparisons Based on LS-mean Changes in QTcF According to Primary and Secondary Analysis

(Source: Sponsor's CSR Table 2-2)

Fridericia-corrected QT (QTcF)	BAY 59–7939 moxifloxacin	Minus comparator incl. active/negative control	Difference (Upper – lower 95% CI)
Primary analysis			
QTcF after 3 hours	15 mg BAY 59–7939	Placebo	- 1.83 (- 4.19 – 0.54)
	45 mg BAY 59–7939	Placebo	- 0.91 (- 3.33 – 1.52)
Secondary analyses			
QTcF after 3 hours (all treatments)	15 mg BAY 59–7939	Moxifloxacin	-11.3 (-13.6 – -8.88)
		Placebo	- 1.49 (- 3.88 – 0.90)
	45 mg BAY 59–7939	Moxifloxacin	-10.8 (-13.3 – -8.34)
		Placebo	- 1.03 (- 3.47 – 1.42)
	Moxifloxacin	Placebo	9.77 (7.39 –12.15)
QTcF at time of t_{max}	15 mg BAY 59–7939	Moxifloxacin	-10.6 (-13.2 – -8.05)
		Placebo	- 0.49 (- 3.05 – 2.07)
	45 mg BAY 59–7939	Moxifloxacin	- 8.04 (-10.7 – -5.43)
		Placebo	2.08 (- 0.51 – 4.67)
	Moxifloxacin	Placebo	10.12 (7.56 –12.68)
QTcF post-dose mean	15 mg BAY 59–7939	Moxifloxacin	- 7.54 (- 8.83 – -6.24)
		Placebo	- 1.19 (- 2.48 – 0.10)
	45 mg BAY 59–7939	Moxifloxacin	- 6.97 (- 8.29 – -5.65)
		Placebo	- 0.62 (- 1.93 – 0.68)
	Moxifloxacin	Placebo	6.35 (5.07 – 7.64)
QTcF post-dose maximum	15 mg BAY 59–7939	Moxifloxacin	- 8.94 (-11.0 – -6.91)
		Placebo	- 1.43 (- 3.45 – 0.59)
	45 mg BAY 59–7939	Moxifloxacin	- 7.94 (-10.0 – -5.87)
		Placebo	- 0.43 (- 2.47 – 1.61)
	Moxifloxacin	Placebo	7.51 (5.50 – 9.52)

Reviewer's Comments: The sponsor's results were based on a single time point (3 hours post-dose). Following ICH-E14 guideline, the reviewer will present results for each time point so that the largest upper (lower) bounds among all time points are evaluated (see Section 5.2.)

4.2.8.2.2 Categorical Analysis

No QT, QTcF or QTcI interval exceeded 500 ms for any treatment. Absolute values of QT, QTcF and QTcI intervals were either comparable for both doses of BAY 59-7939 and placebo or occurred prior to drug administration. Incidences of prolonged QT, QTcF or QTcI intervals for moxifloxacin were clearly higher than for BAY 59-7939 but in the range observed in previous studies (See Table 4). No QT, QTcF or QTcI interval change from baseline exceeded 60 ms for any treatment. Changes of QT, QTcF or QTcI interval to baseline were below 30 ms for both treatments of BAY 59-7939 and placebo (See Table 5).

Table 4: QTcF – Classified Absolute Values [all observations]

(Source: Sponsor's CSR Table 2-3)

Frequency (Percent)	BAY 59–7939 15 mg	BAY 59–7939 45 mg	Placebo	Moxifloxacin
≤430 ms	1456 (93.39%)	1433 (91.80%)	1472 (91.49%)	1316 (83.40%)
>430-450 ms	87 (5.58%)	117 (7.50%)	124 (7.71%)	225 (14.26%)
>450-480 ms	14 (0.90%)[a]	11 (0.70%)[a]	13 (0.81%)[a]	37 (2.34%)[b]
>480-500 ms	2 (0.13%)[a]	0 (0.00%)	0 (0.00%)	0 (0.00%)
>500 ms	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Total	1559	1561	1609	1578

[a], All values were observed in female Subject 011275-0006.
[b], Nine values were observed in female Subject 011275-0006 and 1 each in Subjects 011275-0031 and 011275-0050

Table 5: QTcF – Classified Absolute Changes from Baseline [all observations]

(Source: Sponsor's CSR Table 2-4)

Frequency (Percent)	BAY 59–7939 15 mg	BAY 59–7939 45 mg	Placebo	Moxifloxacin
≤ 30 ms	1404 (100.00%)	1343 (100.00%)	1443 (100.00%)	1386 (100.00%)
>30-60 ms	0 (0.00%)	0 (0.00%)	0 (0.00%)	9 (0.65%)
>60 ms	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Total	1404	1343	1443	1395

Source: Table 14.2 / 1.5.2

4.2.8.3 Safety Analysis

Altogether 56 treatment-emergent adverse events were reported by 25 of the 54 healthy volunteers (46%). Only 4 adverse events (bleeding events) were considered treatment-related, but 2 of them occurred after placebo, 1 after moxifloxacin and 1 after 15 mg BAY 59–7939. Forty-six adverse events were considered to be of mild and 8 of moderate intensity. The most frequently reported adverse event was headache.

The number of subjects with treatment-emergent adverse events was comparable within the 4 different treatments. Two significant adverse events were reported, which led to premature discontinuation of the study drug: abdominal pain, which was diagnosed as appendicitis, and sinusitis. There were 2 SAEs (appendicitis and elbow fracture) of severe intensity, which were assessed as being not related to the study drug and led to premature discontinuation of the study drug.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 6 for rivaroxaban and moxifloxacin. C_{max} and AUC values in the thorough QT study were 2-fold higher following administration of the supratherapeutic dose of rivaroxaban, 45 mg, compared with 15 mg rivaroxaban. The therapeutic dose, 10 mg once daily, was not administered in this study. Since

accumulation at steady state for C_{max} and AUC is 3-39%, a single dose of 15 mg provides reasonable, if conservative, estimates of C_{max} and AUC for the therapeutic dose.

Table 6: Pharmacokinetic Parameters Following Single Oral Doses of 15 and 45 mg Rivaroxaban and 400 mg Moxifloxacin [Geometric Mean/ CV% (range)]

Parameter	Unit	N	15 mg BAY 59-7939	N	45 mg BAY 59-7939	Unit	N	400 mg Moxifloxacin
AUC_{0-6}	µg*h/L	50	821.8/27.41 (498.0 – 1780)	50	1813/31.83 (874.2 – 4890)	mg*h/L	49	11.54/31.90 (5.58 – 22.30)
$AUC_{norm,0-6}$	g*h/L	50	4061/26.25 (2297 – 8935)	50	2986/34.00 (1558 – 8182)	kg*h/L	49	2.14/26.90 (1.08 – 3.24)
AUC_{0-tn}	µg*h/L	50	1692/23.29 (969.8 – 3375)	50	3953/25.55 (2408 – 9567)	mg*h/L	49	32.32/28.19 (11.09–56.87)
$AUC_{norm,0-tn}$	g*h/L	50	8361/25.92 (4442 – 16940)	50	6511/31.00 (3462 – 16010)	kg*h/L	49	5.99/22.94 (2.17 – 8.70)
C_{max}	µg/L	50	221.7/28.67 (125.0 – 543.1)	50	479.7/30.53 (256.3 – 1386)	mg/L	49	3.18/25.89 (1.91 – 6.72)
$C_{max,norm}$	g/L	50	1095/25.38 (572.4 – 2726)	50	790.2/31.59 (451.2 – 2320)	kg/L	49	0.5891/20.54 (0.3700 – 0.9603)
t_{max} [a]	h	50	4.1 (2.1 – 5.0)	50	4.1 (0.6 – 5.1)	h	49	3.1 (0.5 – 5.1)

Source: Clinical Study Report P-79, Table 11-13.

4.2.8.4.2 Exposure-Response Analysis

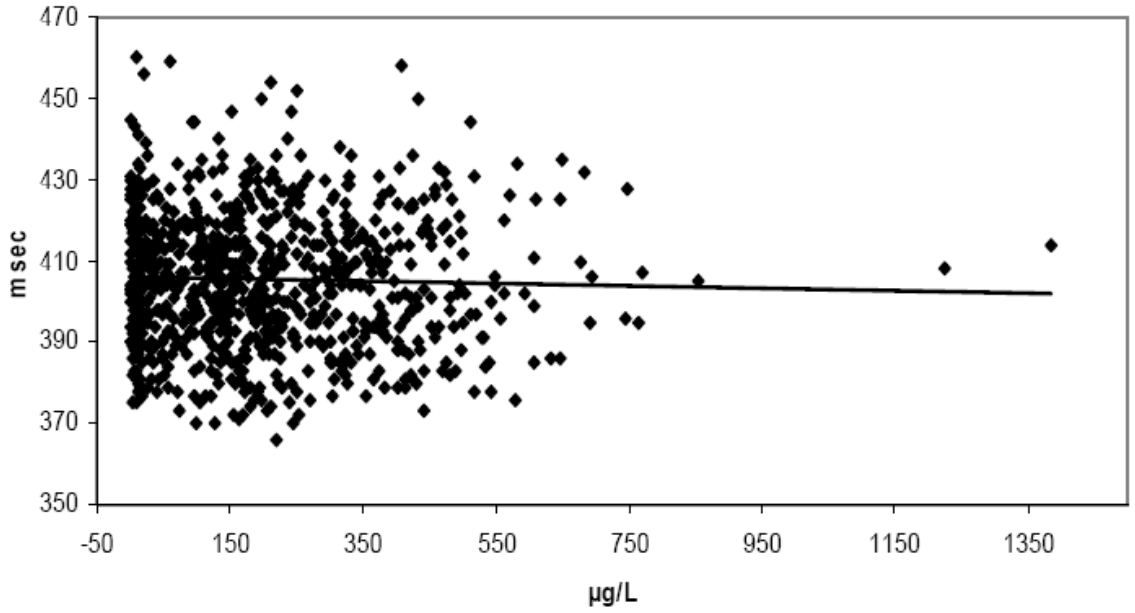
The exposure-response relationship was assessed by linear regression analysis of QTcF vs. rivaroxaban and moxifloxacin concentrations. The relationship between QTcF and rivaroxaban concentrations (Figure 1) was best described by the equation:

QTcF = -0.003*Rivaroxaban Concentration+406.1.

The relationship between QTcF and moxifloxacin concentrations (Figure 2) was best described by the equation:

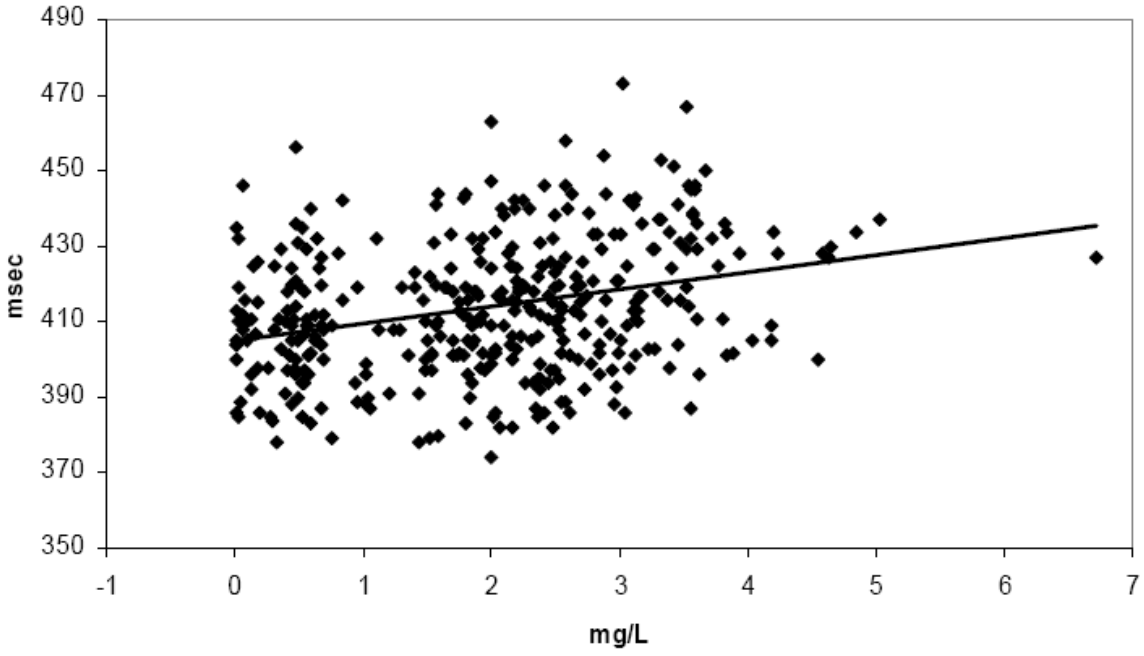
QTcF = 4.5*Moxifloxacin Concentration + 404.8.

Figure 1: QTcF vs. Rivaroxaban Concentrations Following Single Doses of 15 and 45 mg



Source: Clinical Study Report P-73, Figure 11-3.

Figure 2: QTcF vs. Moxifloxacin Concentrations Following a Single Dose of 400 mg



Source: Clinical Study Report P-74, Figure 11-4.

Reviewer's Comments: Plots of ΔΔQTc vs. rivaroxaban and moxifloxacin concentrations are presented in Figure 9 *and* Figure 10*, respectively.*

5 REVIEWERS' ASSESSMENT

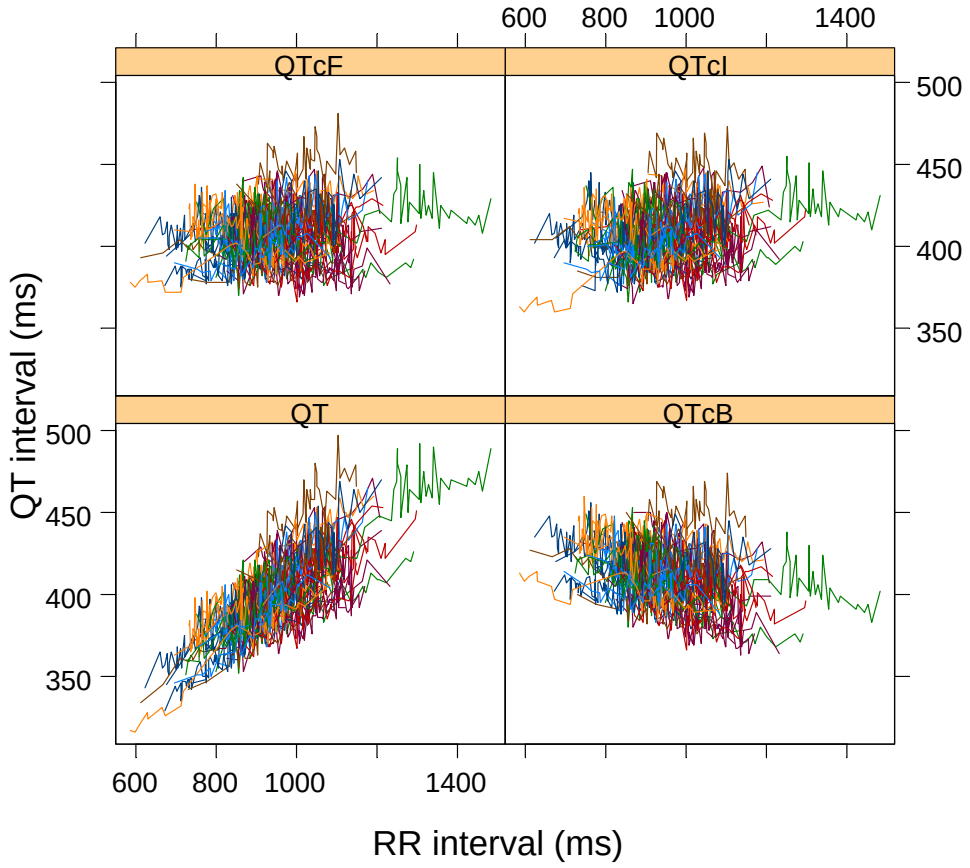
5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We also evaluated the linear relationships between different correction methods (QTcB, QTcF, QTcI) and RR. We used the average sum of squared slopes as the criterion. Baseline values were excluded in our validation. The smaller this value is, the better the correction. Based on the results listed in Table 7 and Figure 3, it appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis.

Table 7: Average of Sum of Squared Slopes for Different QT Correction Methods (Post-dose Only)

Correction Method	Gender	Treatment									
		BAY 59-7939 15 mg		BAY 59-7939 45 mg		Moxifloxacin		Placebo		All	
		N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	Female	25	0.0095	26	0.0110	26	0.0139	27	0.0128	27	0.0079
	Male	27	0.0089	26	0.0084	27	0.0061	27	0.0140	27	0.0058
	All	52	0.0092	52	0.0097	53	0.0099	54	0.0134	54	0.0069
QTcF	Female	25	0.0023	26	0.0037	26	0.0074	27	0.0053	27	0.0024
	Male	27	0.0023	26	0.0023	27	0.0019	27	0.0053	27	0.0010
	All	52	0.0023	52	0.0030	53	0.0046	54	0.0053	54	0.0017
QTcI	Female	25	0.0064	26	0.0049	26	0.0087	27	0.0033	27	0.0046
	Male	27	0.0036	26	0.0037	27	0.0042	27	0.0039	27	0.0013
	All	52	0.0049	52	0.0043	53	0.0064	54	0.0036	54	0.0030

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 Primary Analysis for BAY 59-7939

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes TREATMENT, SEQUENCE, and PERIOD, and baseline values as fixed effects; and SUBJECT as a random effect. The model is repeated for each time point. The analysis results are listed in the following tables.

Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = A: BAY 59-7939 15 mg

	ΔQTcF: BAY 59-7939 15 mg		ΔQTcF: Placebo		ΔΔQTcF	
Time (hr)	LS Mean	Std Err.	LS Mean	Std Err.	LS Mean	90% CI
0.5	-1.4	1.1	-0.6	1.1	-0.8	(-2.8, 1.1)
1	-5.1	1.1	-2.2	1.1	-2.9	(-4.9, -1.0)
2	-7.6	1.1	-5.9	1.1	-1.7	(-3.6, 0.3)
3	-8.2	1.2	-6.8	1.2	-1.4	(-3.5, 0.7)
4	-5.1	1.1	-4.2	1.1	-1.0	(-2.9, 1.0)
5	-4.3	1.1	-3.2	1.1	-1.1	(-3.1, 0.8)
6	-7.2	1.1	-6.3	1.1	-0.9	(-2.9, 1.0)
24	-4.7	1.1	-6.2	1.1	1.5	(-0.9, 4.0)
48	-7.3	1.4	-6.4	1.4	-0.9	(-3.1, 1.3)

Table 9: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = B: BAY 59-7939 45 mg

	ΔQTcF: BAY 59-7939 45 mg		ΔQTcF: Placebo		ΔΔQTcF	
Time (hr)	LS Mean	Std Err.	LS Mean	Std Err.	LS Mean	90% CI
0.5	-1.3	1.1	-0.6	1.1	-0.7	(-2.7, 1.3)
1	-3.2	1.2	-2.2	1.1	-1.0	(-3.0, 1.0)
2	-7.5	1.1	-5.9	1.1	-1.6	(-3.6, 0.4)
3	-7.6	1.3	-6.8	1.2	-0.8	(-2.9, 1.3)
4	-2.6	1.1	-4.2	1.1	1.6	(-0.4, 3.6)
5	-3.3	1.1	-3.2	1.1	-0.1	(-2.1, 1.9)
6	-6.3	1.1	-6.3	1.1	-0.1	(-2.0, 1.9)
24	-4.7	1.1	-6.2	1.1	1.6	(-0.9, 4.0)
48	-8.9	1.4	-6.4	1.4	-2.4	(-4.6, -0.2)

The largest upper bounds of the 2-sided 90% CI for the mean difference between 15 mg BAY 59-7939 and placebo, and between 45 mg BAY 59-7939 and placebo were both 4.0 ms.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 10. The largest lower bound of the unadjusted 90% confidence interval is 10.2 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower bound is 9.1 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 10: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

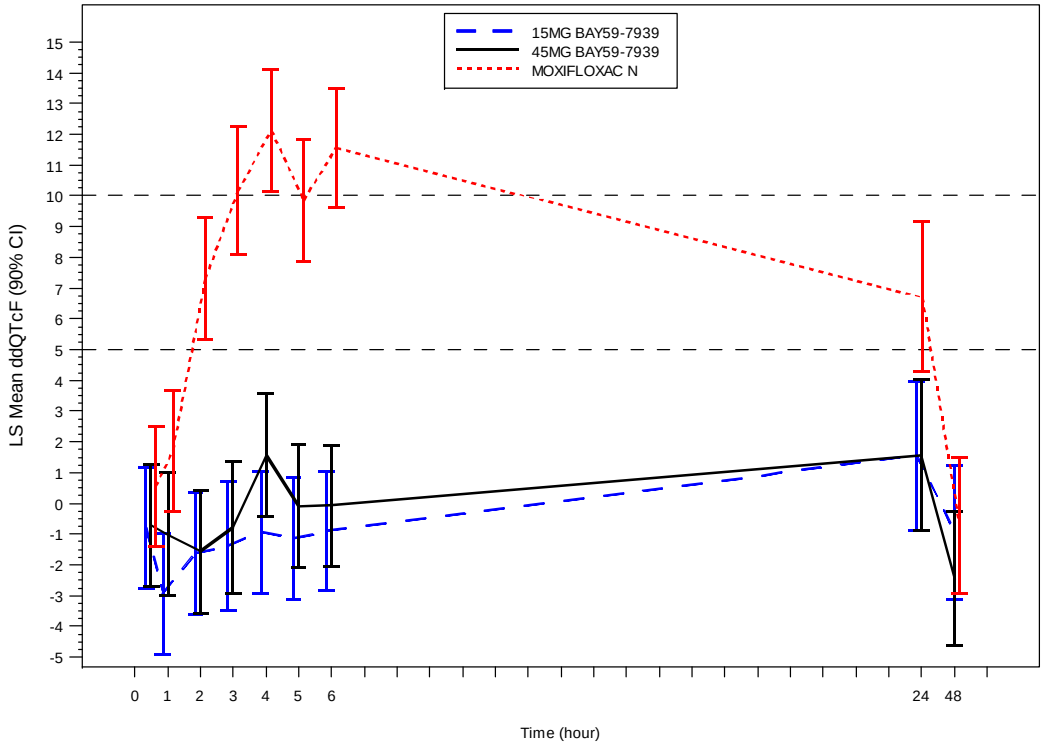
	ΔQTcF: Moxifloxacin		ΔQTcF: Placebo		ΔΔQTcF		
Time (hr)	**LS Mean**	**Std Err.**	**LS Mean**	**Std Err.**	**LS Mean**	**Unadjusted 90% CI**	**Adjusted* 90% CI**
0.5	-0.0	1.1	-0.6	1.1	0.6	(-1.4, 2.5)	(-2.5, 3.6)
1	-0.5	1.1	-2.2	1.1	1.7	(-0.3, 3.7)	(-1.3, 4.8)
2	1.4	1.1	-5.9	1.1	7.3	(5.3, 9.3)	(4.2, 10.4)
3	3.3	1.2	-6.8	1.2	10.2	(8.1, 12.2)	(6.9, 13.4)
4	8.0	1.1	-4.2	1.1	12.1	(10.2, 14.1)	(9.1, 15.2)
5	6.7	1.1	-3.2	1.1	9.9	(7.9, 11.8)	(6.8, 12.9)
6	5.3	1.1	-6.3	1.1	11.6	(9.6, 13.5)	(8.5, 14.6)
24	0.5	1.1	-6.2	1.1	6.7	(4.3, 9.2)	(2.9, 10.5)
48	-7.1	1.4	-6.4	1.4	-0.7	(-2.9, 1.5)	(-4.1, 2.7)

* Bonferroni method was applied for multiple endpoint adjustment for 9 time points.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 4: ΔΔQTcF Time Course



5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose absolute QTcF values are ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. There was one subject whose baseline QTcF was between 480 ms and 500 ms. None of the subjects had a QTcF of above 480 ms at post-dose. No subject's change from baseline was above 30 ms.

Table 11: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms <Value <=480 ms	480 ms < Value <=500 ms
Baseline	54	53 (98.1%)	0 (0.0%)	1 (1.9%)
BAY 59-7939 15 mg	52	51 (98.1%)	1 (1.9%)	0 (0.0%)
BAY 59-7939 45 mg	52	51 (98.1%)	1 (1.9%)	0 (0.0%)
Moxifloxacin	53	50 (94.3%)	3 (5.7%)	0 (0.0%)
Placebo	54	53 (98.1%)	1 (1.9%)	0 (0.0%)

5.2.2 PR Analysis

The same statistical analysis used for QTcF was performed for PR intervals. The point estimates and the 90% confidence intervals are presented in Table 12 and Table 13 and also shown in Figure 5. The largest upper limits of 90% CI for the PR mean differences

between 15 mg BAY 59-7939 and placebo, and 45 mg BAY 59-7939 and placebo are 4.6 ms and 3.7 ms, respectively.

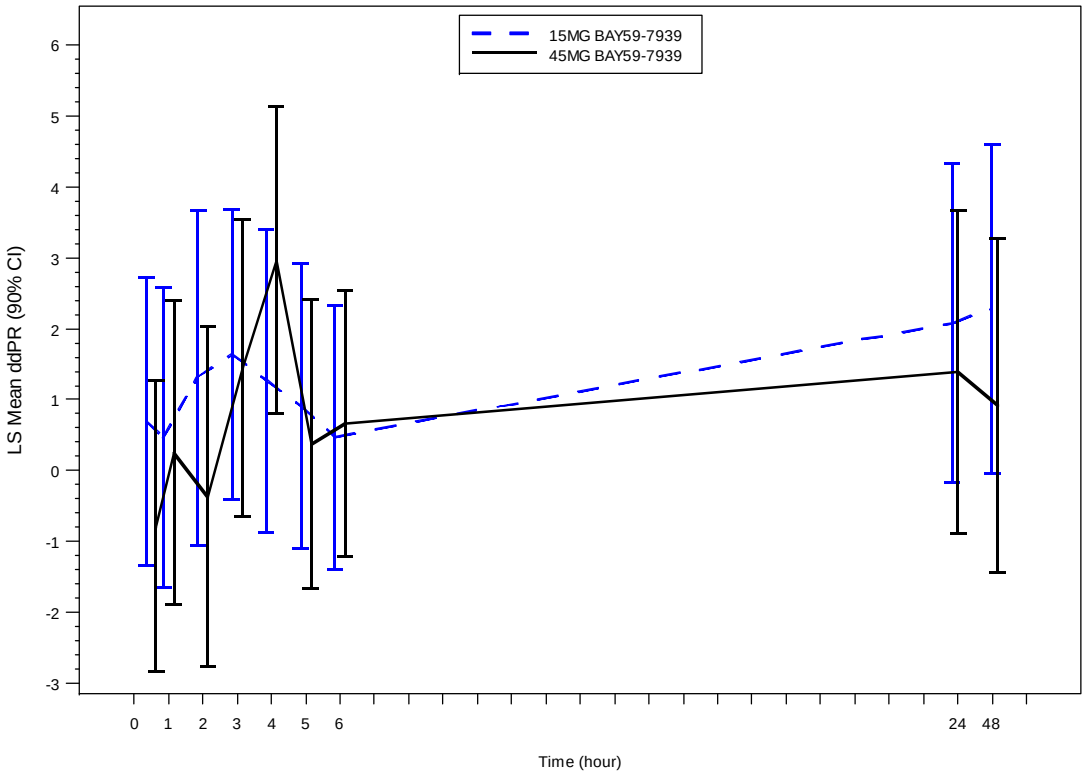
Table 12: Analysis Results of ΔPR and ΔΔPR for Treatment Group = A: BAY 59-7939 15 mg

	ΔPR: BAY 59-7939 15 mg		ΔPR: Placebo		ΔΔPR	
Time (hr)	LS Mean	Std Err.	LS Mean	Std Err.	LS Mean	90% CI
0.5	0.2	1.0	-0.5	1.0	0.7	(-1.3, 2.7)
1	-2.3	1.1	-2.8	1.1	0.5	(-1.7, 2.6)
2	-2.9	1.2	-4.2	1.1	1.3	(-1.1, 3.7)
3	-3.5	1.2	-5.1	1.2	1.6	(-0.4, 3.7)
4	-3.9	1.1	-5.1	1.1	1.3	(-0.9, 3.4)
5	-5.9	1.2	-6.8	1.2	0.9	(-1.1, 2.9)
6	-4.9	1.2	-5.4	1.1	0.5	(-1.4, 2.3)
24	-1.8	1.0	-3.9	1.0	2.1	(-0.2, 4.3)
48	-0.8	1.0	-3.0	1.0	2.3	(-0.1, 4.6)

Table 13: Analysis Results of ΔPR and ΔΔPR for Treatment Group = B: BAY 59-7939 45 mg

	ΔPR: BAY 59-7939 45 mg		ΔPR: Placebo		ΔΔPR	
Time (hr)	LS Mean	Std Err.	LS Mean	Std Err.	LS Mean	90% CI
0.5	-1.3	1.0	-0.5	1.0	-0.8	(-2.8, 1.3)
1	-2.5	1.1	-2.8	1.1	0.3	(-1.9, 2.4)
2	-4.6	1.2	-4.2	1.1	-0.4	(-2.8, 2.0)
3	-3.7	1.2	-5.1	1.2	1.4	(-0.6, 3.5)
4	-2.2	1.1	-5.1	1.1	3.0	(0.8, 5.1)
5	-6.4	1.2	-6.8	1.2	0.4	(-1.7, 2.4)
6	-4.7	1.2	-5.4	1.1	0.7	(-1.2, 2.5)
24	-2.5	1.1	-3.9	1.0	1.4	(-0.9, 3.7)
48	-2.1	1.0	-3.0	1.0	0.9	(-1.4, 3.3)

Figure 5: ΔΔPR Time Course



The categorical analysis results for PR are presented in Table 14. For subjects whose post-dose PR results 200 ms or above, a detailed listing of pre- and post-dose results is presented in Table 15.

Table 14: Categorical Analysis for PR

Treatment Group	N	PR < 200 ms	PR >=200 ms
Baseline	54	47 (87.0%)	7 (13.0%)
BAY59-7939 15 mg	52	47 (90.4%)	5 (9.6%)
BAY59-7939 45 mg	52	46 (88.5%)	6 (11.5%)

Table 15: Detailed Results for Subjects Whose PR were 200 ms and above at Post-dose

Subject ID	Treatment	Period	Time	PR at Baseline	PR at Post-dose	PR Change
11275-DE-00001-000000016						(b) (6)

Table 15: Detailed Results for Subjects Whose PR were 200 ms and above at Post-dose

Subject ID	Treatment	Period	Time	PR at Baseline	PR at Post-dose	PR Change
11275-DE-00001-000000017						
11275-DE-00001-000000040						
11275-DE-00001-000000041						

(b) (6)

Table 15: Detailed Results for Subjects Whose PR were 200 ms and above at Post-dose

Subject ID	Treatment	Period	Time	PR at Baseline	PR at Post-dose	PR Change
	[redacted]					(b) (6)
11275-DE-00001-000000046						
11275-DE-00001-000000052						

5.2.3 QRS Analysis

The same statistical analysis used for QTcF was performed for QRS intervals. The point estimates and the 90% confidence intervals are presented in Table 16 and Table 17 and also shown in Figure 6. The largest upper limits of 90% CI for the QRS mean differences between 15 mg BAY 59-7939 and placebo and 45 mg BAY 59-7939 and placebo are 2.0 ms and 2.4 ms, respectively. There was one subject who had an absolute QRS interval greater than 120 ms under placebo treatment.

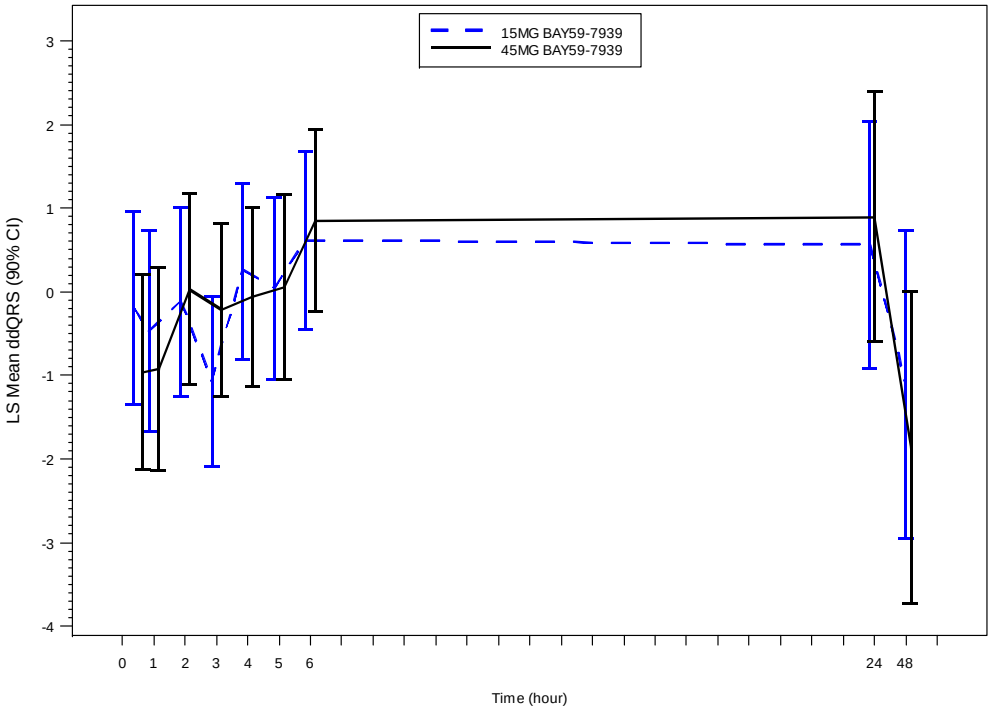
Table 16: Analysis Results of ΔQRS and ΔΔQRS for Treatment Group = A: 15 mg BAY 59-7939

	ΔQRS: BAY 59-7939 15 mg		ΔQRS: Placebo		ΔΔQRS	
Time (hr)	LS Mean	Std Err.	LS Mean	Std Err.	LS Mean	90% CI
0.5	1.2	0.6	1.4	0.6	-0.2	(-1.3, 1.0)
1	0.2	0.6	0.6	0.6	-0.5	(-1.7, 0.7)
2	-1.6	0.5	-1.5	0.5	-0.1	(-1.2, 1.0)
3	-2.6	0.5	-1.5	0.5	-1.1	(-2.1, -0.1)
4	-1.4	0.5	-1.6	0.5	0.2	(-0.8, 1.3)
5	-1.0	0.7	-1.0	0.6	0.0	(-1.1, 1.1)
6	-2.0	0.6	-2.6	0.6	0.6	(-0.5, 1.7)
24	-1.2	0.7	-1.7	0.7	0.6	(-0.9, 2.0)
48	-0.6	0.9	0.5	0.9	-1.1	(-3.0, 0.7)

Table 17: Analysis Results of ΔQRS and ΔΔQRS for Treatment Group = B: 45 mg BAY 59-7939

	ΔQRS: BAY 59-7939 45 mg		ΔQRS: Placebo		ΔΔQRS	
Time (hr)	LS Mean	Std Err.	LS Mean	Std Err.	LS Mean	90% CI
0.5	0.5	0.6	1.4	0.6	-1.0	(-2.1, 0.2)
1	-0.3	0.6	0.6	0.6	-0.9	(-2.1, 0.3)
2	-1.4	0.5	-1.5	0.5	0.0	(-1.1, 1.2)
3	-1.7	0.5	-1.5	0.5	-0.2	(-1.2, 0.8)
4	-1.7	0.5	-1.6	0.5	-0.1	(-1.1, 1.0)
5	-0.9	0.7	-1.0	0.6	0.0	(-1.1, 1.2)
6	-1.7	0.6	-2.6	0.6	0.9	(-0.2, 1.9)
24	-0.9	0.7	-1.7	0.7	0.9	(-0.6, 2.4)
48	-1.4	0.9	0.5	0.9	-1.9	(-3.7, -0.0)

Figure 6: ΔΔQRS Time Course



5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile of rivaroxaban and moxifloxacin are illustrated in Figure 7 and Figure 8, respectively.

Figure 7: Mean BAY59-7939 Concentration-Time Profiles for 15 mg (blue line) and 45 mg rivaroxaban (red line)

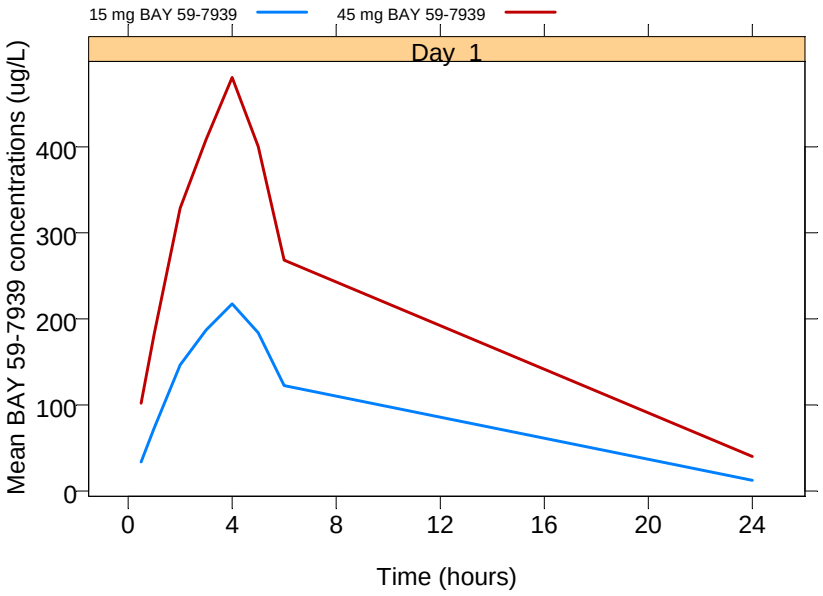
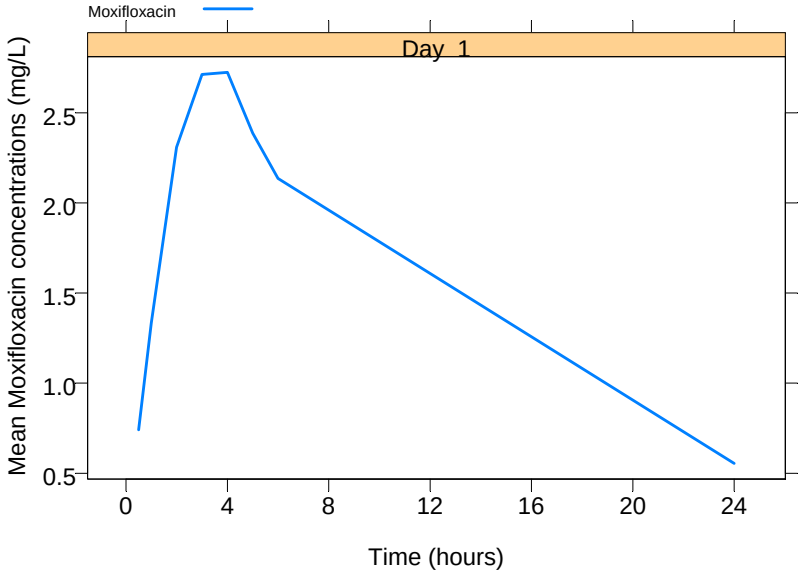


Figure 8: Mean moxifloxacin Concentration-Time Profile for 400 mg Dose



The relationship between ΔΔQTcF and rivaroxaban concentrations is visualized in Figure 9 with no evident exposure-response relationship. The relationship between ΔΔQTcF and moxifloxacin concentrations are illustrated in Figure 10 with an expected increase in ΔΔQTcF with increasing moxifloxacin concentrations.

Figure 9: ΔΔ QTcF vs. Rivaroxaban concentration

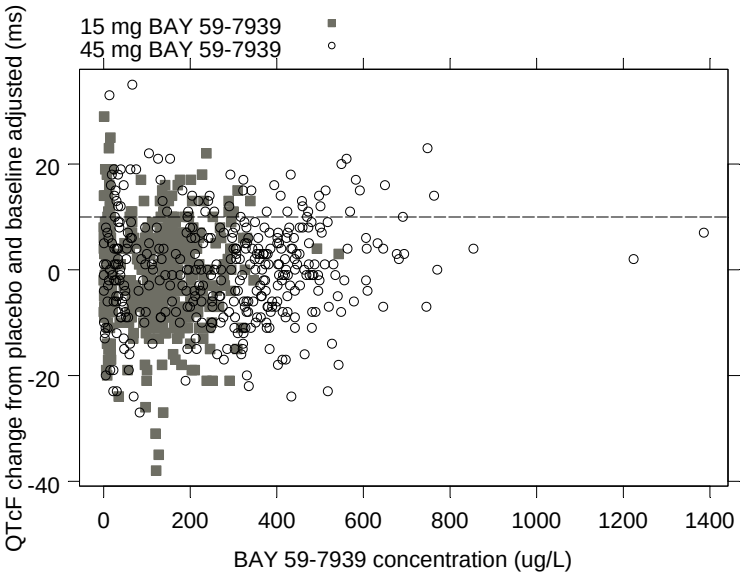
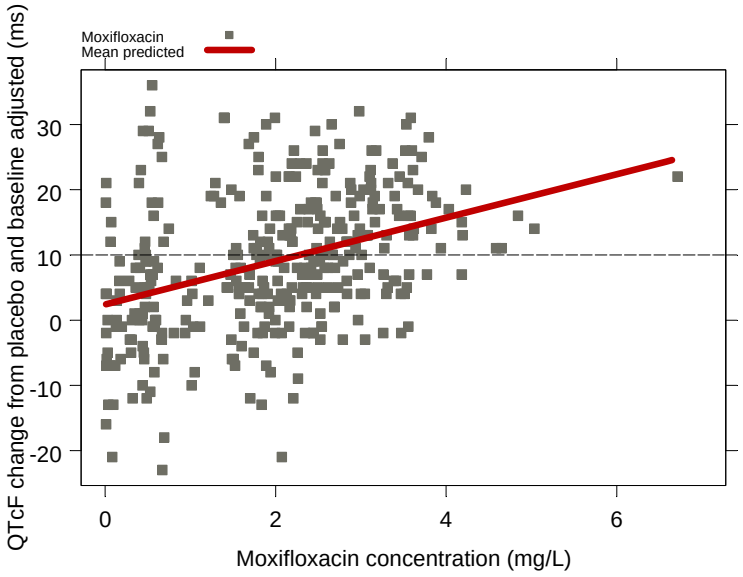


Figure 10: ΔΔ QTcF vs. Moxifloxacin concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. ECG warehouse statistics shows that less than 0.5% of ECGs reported have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

The sponsor reported several minor changes in T-wave morphology (mainly flat T-waves).

5.4.3 PR and QRS Interval

There were no significant changes in PR duration after 15 mg and 45 mg BAY 59-7939 being the largest upper limits of 90% CI for the differences between 15 mg BAY 59-7939 and placebo, and 45 mg BAY 59-7939 and placebo 4.6 ms and 3.7 ms, respectively.

Categorical analysis for PR showed that 7 subjects had PR ≥200ms at baseline. Five subjects had PR ≥200 ms post-dose in the Bay 59-7939 15 - mg period and 6 in the 45-mg period.

In one subject (Bay 59-7939 45mg) there was an increase over baseline in PR interval in all time points (from 0.5 to 6 hours post-treatment). The maximum increase was 20 ms at 4 hours post-dose. Another subject (Bay 59-7939 15 mg, 45 mg) had in the two treatment periods increases of 26 ms (15 mg) and 16 ms (45 mg) at 24 hours post-dose. In both cases the absolute PR baseline value was < 200 ms.

There were no significant changes in QRS interval after 15 mg and 45 mg BAY 59-7939, being the largest upper limits of 90% CI for the QRS mean differences between 15 mg BAY 59-7939 and placebo and 45 mg BAY 59-7939 and placebo 2.0 ms and 2.4 ms, respectively.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	10 mg once daily	
Maximum tolerated dose	Phase I studies did not identify a maximal tolerated dose in humans. There was however a ceiling effect observed for the PK and PD due to limited absorption at a dose of 40 mg single dose administered with food. This effect is due to the limited aqueous solubility of Rivaroxaban. Although a 12-fold dose range was studied in phase II, none of the doses had to be stopped prematurely due to adverse events. No dose limiting toxicity was observed for Rivaroxaban in toxicological investigations. In dogs, doses up to 150 mg/kg were administered without showing any cardiovascular effects. Due to the pharmacological effects of Rivaroxaban bleeding after invasive manipulations and subsequent anemia was observed at doses at 15 mg/kg and above in dogs treated up to 52 weeks. In repeat-dose studies in rats of up to 26-week treatment duration up to the highest dose tested (200 mg/kg) no treatment-related adverse effects were seen. An overview of the multiples of exposure from the toxicological investigations is provided in appended Section 'Maximum tolerated dose'	
Principal adverse events	The most common treatment emergent adverse events in phase I were headache, nasopharyngitis, fatigue, diarrhea, ALT increase, haematoma, erythema. No dose limiting toxicity was observed. Further details, see appended Section 'Principal adverse events'.	
Maximum dose tested	Single Dose	80 mg single dose (fasted); see appended Table 3
	Multiple Dose	30 mg bid for 5 consecutive days (fed); see appended Table 5
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV); see appended Table 3 C_{max}: 316 (40.7) µg/L AUC: 3298 (31.0) µg*h/L
	Multiple Dose	Mean (%CV); see appended Table 5 C_{max}: 452 (10.5) µg/L AUC_{τ}: 2728 (14.6) µg*h/L (dosing interval τ of 12 h for bid)
Range of linear PK	5 mg qd up to 30 mg bid; see appended Table 5	
Accumulation at steady state	3-39% for C_{max}, 4-39% for AUC; see appended Table 5	
Metabolites	See appended Section 'Metabolites'. In total, 89% of the dose administered could be attributed to known structures. Unchanged drug was the main compound in plasma at all investigated time-points and accounted for 89% of the area under the data (AUC(0-tn)) of total radioactivity. No major or active circulating metabolites were detected in plasma.	

Absorption	Absolute/Relative Bioavailability	The absolute bioavailability of the 5 mg oral dose was complete while that of the 20 mg dose was 66% compared to the intravenously administered dose (see appended Section 'Absorption, Absolute/Relative Bioavailability'.
	Tmax	• 2 to 4 hours for parent drug (see appended Table 3, Table 4, Table 5) • No major or active circulating metabolites were detected in plasma.
Distribution	Vd/F or Vd	Vss after intravenous infusion was 48.2 (27.3%) L, respectively 0.62 L/kg (21%)
	% bound	92% to 95%; see appended Section 'Distribution'
Elimination	Route	Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then eliminated renally and the other half eliminated by the fecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion. Rivaroxaban is metabolized via CYP 3A4, CYP 2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on in vitro investigations, rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).
	Terminal t½	Elimination of rivaroxaban from plasma occurred with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly. No major or active circulating metabolites were detected in plasma.
	CL/F or CL	Systemic clearance (CLsys) after intravenous infusion was 10.7 (34%) L/h, respectively, 0.14 (28.7%) L/(h*kg).
Intrinsic Factors	Age (elderly ≥ 65 y vs young ≤ 45 y)	C_{max} ratio (90%CI): 1.11 [0.96 – 1.28] AUC ratio (90%CI): 1.46 [1.26 – 1.71]
	Sex (male versus female)	C_{max} ratio (90%CI): 0.99 [0.85 - 1.14] AUC ratio (90%CI): 0.90 [0.77 - 1.05]
	Race	Ethnicity (investigated groups: Afro-American, Caucasians, Chinese, Hispanics, Japanese) itself could be excluded to be a relevant intrinsic

		factor to alter rivaroxaban pharmacokinetics or pharmacodynamics. The minor-to-moderately increased rivaroxaban plasma exposure seen eg in Japanese subjects (20 to 40%) compared to Caucasians seems at least partially attributable to the known differences in average body weight.
	Hepatic Impairment (according to Child Pugh classification)	Child Pugh A vs Healthy • C_{max} ratio (90%CI): 0.97 [0.75 - 1.25] • AUC ratio (90%CI): 1.15 [0.85 - 1.57 Child Pugh B vs Healthy • $C_{max\,r}$ ratio (90%CI): 1.27 [0.99 - 1.63] • AUC ratio (90%CI): 2.27 [1.69 - 3.07]
	Renal Impairment	Mild (CL_{CR} = 50 –79 mL/min) vs. Healthy • C_{max} ratio (90%CI): 1.28 [1.07 - 1.55] • AUC ratio (90%CI): 1.44 [1.08 - 1.92] Moderate (CL_{CR} = 30 - 49 mL/min) vs. Healthy • C_{max} ratio (90%CI): 1.12 [0.93 - 1.34] • AUC ratio (90%CI): 1.52 [1.15 - 2.01] Severe (CL_{CR} = < 30 mL/min) vs. Healthy • C_{max} ratio (90%CI): 1.26 [1.05 - 1.51] • AUC ratio (90%CI): 1.64 [1.24 - 2.17]
Extrinsic Factors	Drug interactions (combined/alone)	See appended Table 7
	Food Effects (fed/fasted)	C_{max} ratio (90%CI): 1.03 [0.94 - 1.14] AUC ratio (90%CI): 0.99 [0.93 - 1.05] 10 mg Rivaroxaban single dose after a standardized high-fat – high calorie breakfast
Expected High Clinical Exposure Scenario	10 mg Rivaroxaban once daily is the dose to be used in clinical practice for the prevention of VTE after total hip or knee replacement surgery. In the present QT Study doses of 15 and 45 mg Rivaroxaban single dose were administered. Influences that may increase plasma levels of Rivaroxaban are: age, decreased renal function, and strong inhibitors of CYP 3A4 and P-gp. As is demonstrated by the summary of the PK results of the respective Phase I Studies, these plasma levels are covered by the doses used in the QT Study. The accumulation after multiple doses is moderate and also covered by the exposure data of the QT study. No major or pharmacologically active metabolites were observed in plasma.	

	Basic Pharmacokinetics 10 mg Rivaroxaban single dose administered to young healthy male volunteers with food: C_{max} (%CV): 114 (15.7%) µg/L AUC (%CV): 817 (22.0) µg*h/L 10 mg Rivaroxaban multiple dose (5 days of treatment) administered to young healthy male volunteers with food: C_{max} (%CV): 158 (18.8) µg/L AUC (%CV): 864 (18.6) µg*h/L 10 mg Rivaroxaban administered to male volunteers aged > 75 years with food: C_{max} (%CV): 229 (23.8) µg/L AUC (%CV): 1839 (28.3) µg*h/L 10 mg Rivaroxaban administered to female volunteers aged > 75 years with food: C_{max} (%CV): 245 (18.2) µg/L AUC (%CV): 1941 (16.2) µg*h/L **Relevant effects on absorption of Rivaroxaban** A ceiling effect (absorption limit) is observed between 40 and 50 mg single dose (Study 11529, healthy male and female volunteers aged ≥ 60 years, drug administered with food) 40 mg single dose Rivaroxaban • C_{max} (%CV): 461 µg/L (16.8) µg/L • AUC (%CV): 4385 (24.1) µg*h/L 50 mg single dose Rivaroxaban • C_{max} (%CV): 437 (32.0) µg/L • AUC (%CV): 4496 µg*h/L (33.9) µg*h/L **Relevant drug-drug interactions for Rivaroxaban** Co-administration of a strong CYP 3A4 and P-gp Inhibitor (Ritonavir 600 mg bid) with 10 mg Rivaroxaban in healthy young male volunteers • C_{max} (%CV): 238 (23.4) µg/L • AUC (%CV): 2529 (16.8) µg*h/L Co-administration of a strong CYP 3A4 and P-gp Inhibitor (Ketoconazole 400 mg once daily) with 10 mg Rivaroxaban in healthy young male volunteers

	• C_{max} (%CV): 237 (20.9) µg/L • AUC (%CV): 2298 (25.9) µg*h/L **Results of the renal impairment study** Mild renal impairment (CL_{CR} = 50 –79 mL/min) • C_{max} (CV%): 218 (37.9) µg*h/L • AUC (CV%): 1863 (30.9) µg*h/L Moderate renal impairment (CL_{CR} = 30 - 49 mL/min) • C_{max} (CV%): 206 (26.0) µg*h/L • AUC (CV%): 2068 (33.1) µg*h/L Severe renal impairment (CL_{CR} = < 30 mL/min) • C_{max} (CV%): 232 (26.0) µg*h/L • AUC (CV%): 2238 (37.0) µg*h/L **Hepatic impairment study** Child Pugh A (mild hepatic impairment) • C_{max} (CV%): 202 (41.8) µg*h/L • AUC (CV%): 1746 (42.4) µg*h/L Child Pugh B (moderate hepatic impairment) • C_{max} (CV%): 279 (45.8%) µg/L • AUC (CV%): 3510 (59.1) µg*h/L Child Pugh C (severe hepatic impairment) • was not tested in this trial due to the pharmacological effect of rivaroxaban as an anticoagulant **Results of the "QT Study"** Pharmacokinetic results of the "thorough QT" study in male and female subjects aged > 60years 15 mg single dose with food • C_{max} (%CV): 222 (28.7) µg/L • AUC (%CV): 1692 (23.3) µg*h/L 45 mg single dose with food • C_{max} (%CV): 480 (30.5) µg/L • AUC (%CV): 3953 (25.5) µg*h/L In summary, all relevant influences on the pharmacokinetics of Rivaroxaban are covered by the doses used in the "QT study".

6.2 TABLE OF STUDY ASSESSMENTS

	Screening[a]	Periods 1, 2, 3 and 4												EOS[f]
Time (d)		-01	00	00	00	00	00	00	00	00	00	00	01	02	
Time (h)		00	00	00	01	02	03	04	05	06	08	12	00	00	
Time (min)			00	30	00	00	00	00	00	00	00	00	00	00	
Admission		X[b]													
Randomization (Period 1)			X												
Administration of study drug			X												
Supine phase			X[c]	X	X	X	X	X							
Well being	X		X		X	X	X	X		X	X		X	X	X
Blood pressure, pulse rate[d]	X		X			X		X			X		X	X	X
ECG[e]	X		X	X	X	X	X	X	X	X			X	X	X
Physical examination	X														X
Drug screening, HIV-/hepatitis serology	X														
Hematology, clinical chemistry	X		X										X	X	X
Coagulation tests (PT, PTT)	X		X		X	X	X	X		X	X		X	X	X
Urinalysis	X		X												X
Pharmacokinetics			X	X	X	X	X	X	X	X			X		
Discharge														X	

a. Screening was done within 14 days before the first study drug administration.
b. For Period 1, admission on pre-dose day (–1d) was done at 7:00 am. For Periods 2 to 4, subjects were confined to the institute at 4:00 pm.
c. Subjects rested in supine position for 45 minutes pre-dose
d. Measured after 15 minutes in supine position
e. Three standard 12-lead ECGs were recorded at each time point, about 1 minute apart
f. End-of-study (EOS) examination was performed 7 to 14 days after the last dosing (Period 4)

4.5 Cover sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-406**	**Brand Name**	**XARELTO™ immediate release tablets**
OCPB Division (I, II, III)	**5**	**Generic Name**	**rivaroxaban**
Medical Division	**OND/OODP/DMIHP**	**Drug Class**	**Direct factor Xa inhibitor**
OCPB Reviewer	**Joseph A. Grillo, Pharm.D.**	**Indication(s)**	
		• **The prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.**	
OCPB Team Leader	**Young Moon Choi, Ph.D.**	**Dosage Form**	**Immediate release tablets**
		Dosing Regimen	
		• **10 mg tablet taken once daily with or without food.**	
Date of Submission	**7/28/08**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**4/11/09**	**Sponsor**	**Johnson & Johnson Pharmaceutical Research and Development, L.L.C**
PDUFA Due Date	**5/28/09**	**Priority Classification**	**Standard Review**
Division Due Date	**TBD**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**	**1**	
I. Clinical Pharmacology				
Mass balance:	**X**	**1**	**1**	
Isozyme characterization:		**11**	**11**	
Blood/plasma ratio:	**X**			
Plasma protein binding:	**X**	**2**	**2**	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**	**1**	
multiple dose:	**X**	**1**	**1**	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**			
fasting / non-fasting multiple dose:	**X**			
Drug-drug interaction studies -		**17**	**17**	
In-vivo effects on primary drug:	**X**			
In-vivo effects of primary drug:	**X**			
In-vitro:				
Subpopulation studies -				
ethnicity:	**X**	**8**	**8**	

gender:	X	1	1	
pediatrics:				
body weight:	X	1	1	
geriatrics:	X	2	2	
renal impairment:	X	1	1	
hepatic impairment:	X	1	1	
PD:			2	
Phase 2:	X	2	2	
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	4	4	
Phase 3 clinical trial:	X	4	4	
Unrelated to proposed indication	X	5	5	
Population Analyses -				
Data rich:				
Data sparse:	X	8	8	
II. Biopharmaceutics				
Absolute bioavailability:	X	2	2	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	10	10	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	3	3	
Dissolution:				
(IVIVC):				
Bio-wavier				
BCS class	X	1	1	
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
In vitro PD bridge study				
Literature References	X	122	122	
Reports/Meta-analysis	X	9	9	
Total Number of Studies		98 (220 with Refs)	98 (220 with Refs)	

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	
Comments sent to firm ?	**X**	• **Please provide datasets in SAS transfer format for studies 11273, 10924, 10846, 10989, 11937, 11125, 11197, 10990, 10998, 10996, 10997, 11032, 11321, 11322, 11938, 10842, 10847, 10991, 11529, 11569, 10850, 11568, 11002, 11003, 11126, 11127, 11325, 12026, 11608, 11609, 11708, 12090, 11000, 11001, 10993, 10999, 12359, 10992, 11936, 11935, 11865, 12680, 10848, 11123, 11124, 11279, 11864, 12089, 12612, 11140, PH-34980, & PH-34982.** • **Please provide a table of all clinical pharmacology & biopharmaceutics studies containing** Product, Formulation/Formulation Code, Drug Substance Batch Number, Drug Product Batch Number, site of manufacture. • **Please provide a table of all clinical pharmacology & biopharmaceutics studies containing validated analytical method(s) used in each study, cross reference to the validation report, overview of the methodology, LLQ , Validated Range , Within-run Precision, Between-run Precision, Accuracy , Stability in Human Plasma , Processed Extract Stability.**
QBR questions (key issues to be considered)	• **Ethnicity (Japanese)** • **Need for Dose adjustment in moderate/severe RI & HI** • **Need for Dose adjustment for CYP 3A4 & PGP in the absence of RI** • **Pharmacogenomics**	
Other comments or information not included above	**None**	
Primary reviewer Signature and Date	**/s/ Joseph A. Grillo, Pharm.D.**	
Secondary reviewer Signature and Date	**/s/ Young Moon Choi, Ph.D.**	

CC: NDA 22-291, HFD-850(Electronic Entry or Lee), HFD-160(CSO), HFD-860(TL, DD, DDD), CDR (B. Murphy)

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Joseph Grillo
4/2/2009 12:59:25 PM
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Christoffer Tornoe
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Atiqur Rahman
4/6/2009 02:16:14 PM
BIOPHARMACEUTICS

ONDQA (Biopharmaceutics) Review

NDA:	22-406
Submission Date:	07/22/08
Product:	XARELTO^{TM} (Rivaroxaban) tablets, 10 mg
Type of Submission:	Original NDA
Sponsor:	Johnson & Johnson
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: The original New Drug Application (NDA 22-406) is for an immediate release 10-mg oral tablet of Rivaroxaban (XARELTO^{TM}) for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. Rivaroxaban is a Factor Xa inhibitor and is being codeveloped through a joint research program between Bayer Healthcare AG (Bayer) and Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD).
The purpose of this review is to recommend dissolution specifications for the proposed product.

The manufacturing process for rivaroxaban 10-mg tablets was initially developed by Bayer Healthcare AG at the Leverkusen facility in Germany. The manufacturing process used at the proposed commercial manufacturing facility, Gurabo in Puerto Rico, was transferred from the Leverkusen facility. The process used at the Gurabo facility is equivalent to that of the Leverkusen facility with the appropriate adjustment to the equipment and process parameters in order to produce rivaroxaban tablets of the same quality.

Recommendation:

While the sponsor's selection and validation of dissolution methodology is acceptable by the reviewer, the sponsor proposed dissolution specifications, (b) (4) *as mentioned below is not acceptable.*

(b) (4)

(b) (4)

In light of the release data of the pilot and commercial batches, the Agency proposes the following in-vitro dissolution specification:

Q = (b) (4) ***at 15 minutes*** *using the following dissolution methodology:*

Apparatus	USP apparatus 2 (paddle)
Dissolution medium	900 mL acetate buffer pH 4.5 + 0.2 % SDS
Rotation speed	75 rpm
Analytical procedure	HPLC with UV/VIS detection or UV/VIS spectrophotometry Both analytical procedures lead to the same results and may thus be used interchangeably.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

Description and Composition of the Drug Product

The selected dosage form is an immediate release 10-mg tablet for oral administration. Rivaroxaban 10-mg tablets are round, light red, biconvex film coated tablets. The tablets are debossed with a triangle pointing down above a "10" on the top of the tablet and an "Xa" on the bottom of the tablet. Each tablet contains 10 miligrams of micronized Rivaroxaban with the formulation described below:

Table 1: Composition of Rivaroxaban 10-mg Tablets

Component	Reference to Quality Standard[a]	Function	Amount (mg/tablet)	Amount (% wt)
Core Tablet				
Rivaroxaban Micronized	Company Specification	Active ingredient	10.00	(b) (4)
Microcrystalline Cellulose (b) (4), NF	Ph.Eur./NF/Ph.Jap.			
Croscarmellose Sodium, NF	Ph.Eur./NF/Ph.Jap.			
Hypromellose (b) (4) USP	Ph.Eur./USP/Ph.Jap.			
Lactose Monohydrate, NF	Ph.Eur./NF/Ph.Jap.			
Magnesium Stearate (b) (4), NF	Ph.Eur./NF/Ph.Jap.			
Sodium Lauryl Sulfate, NF (b) (4)	Ph.Eur./NF/Ph.Jap.			
Film Coating				
OPADRY® Pink (b) (4)				
Total Tablet Weight			(b) (4)	100.00

Description of Dissolution Method:

In the course of method development the following parameters were evaluated and optimal conditions selected:

***Detection/Quantification*:** (b) (4) analytical procedures (HPLC with UV/VIS detection or UV/VIS spectrophotometry) for the quantification of the drug substance were evaluated and validated.

***Dissolution medium*:** Different media covering a pH-range from 1 to 8 were tested. (b) (4). Stability and sufficient solubility of the drug substance were obtained with acetate buffer pH 4.5 + 0.2 % sodium dodecyl sulfate (SDS).

Dissolution apparatus: the USP-paddle apparatus (2) was selected.

***Time point*:** During development dissolution profiles with sampling time points 15, 30, 45 and 60 minutes were recorded. The specification was finally set (b) (4).

***Rotation speed*:** Methods using 50, 75 and 100 rpm were compared. 75 rpm was found to be most suitable to ensure both discriminatory power and robustness of the dissolution method.

***Robustness*:** The robustness of the dissolution test method has been investigated to assess the impact of small, deliberate changes (e.g. temperature, rotation speed, pH value, surfactant concentration, deaeration) on the dissolution conditions.

As a result of these investigations, the following dissolution test method has been finalized as the optimum and official *in-vitro* dissolution method for Rivaroxaban tablets. This method was used during release testing of clinical phase III study medication and NDA stability studies and is proposed as the test method for the commercial product.

Proposed Dissolution Test Method:

Apparatus	USP apparatus 2 (paddle)
Dissolution medium	900 mL acetate buffer pH 4.5 + 0.2 % SDS
Rotation speed	75 rpm
Analytical procedure	HPLC with UV/VIS detection or UV/VIS spectrophotometry Both analytical procedures lead to the same results and may thus be used interchangeably.

(b) (4)

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(b) (4)

Reviewer's Comment:

While the sponsor's selection and validation of dissolution methodology is acceptable by the reviewer, the sponsor proposed dissolution specifications, (b) (4) *as mentioned below is not acceptable.*

In light of the release data of the pilot and commercial batches, the Agency proposes the following in-vitro dissolution specification:

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/s/

Tapash Ghosh
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Patrick Marroum
4/1/2009 11:31:22 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	22-406
Drug Substance	Xarelto (rivaroxaban) tablets (Factor Xa inhibitor)
Sponsor	Johnson & Johnson
Indication	Prophylaxis of DVT & PE
Type of Submission	Response to FDA Information request
Date of Submission	12/19/2008
Reviewer	Joseph A. Grillo, Pharm.D.

Synopsis

Xarelto (rivaroxaban) is a competitive, selective, and direct oral Factor Xa 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 QD for 14 (knee) or 35 days (THR).

At the midcycle meeting held on 12/2/08, Office of Clinical Pharmacology (OCP) reported review issues related to clinically relevant increases in drug exposure requiring dose adjustment in the patients with renal impairment, hepatic impairment, and/or concurrent use of a moderate or strong CYP3A4 inhibitor. OCP expressed concern that a method for dose adjustment in these populations was not available since the sponsor was proposing a single strength unscored tablet as the marketed formulation. Without downward dose adjustment a significant part of the target population will not be able to utilize this drug and inappropriate use of the current strength in these populations could pose a risk to public health. A preliminary pharmacometric analysis revealed that extending the dosing interval was not a viable option to lower the daily exposure.

OCP also reported that there is an approximately 40% higher exposure of rivaroxaban in Japanese subjects compared to other ethnic groups including Chinese. Although the sponsor suggests this is related to body weight, an OCP pharmacometrics preliminary analysis did not suggest this to be the case since Chinese subjects were found to have 40% lower exposure compared to Japanese but with similar body weight.

FDA contacted the sponsor on 12/5/2008 to inform them of the need for a lower strength tablet or scored 10 mg tablet and to ask for further explanation of the higher exposure noted in the Japanese population.

In its response to FDA regarding the need for a lower strength tablet or scored 10 mg tablet (Question #3) the sponsor stated that based on the totality of the clinical data, 1) a once daily dose of 10 mg rivaroxaban is an effective treatment that is considered safe for use in a wide variety of patients, including those patients with mild or moderate renal impairment, mild hepatic disease and following co-administration of CYP3A4 inhibitors (except for co-administration with strong inhibitors of both CYP3A4 and P-gp), 2) the clinically acceptable limits for exposure increases are proposed as a doubling, and the proposed Product Label addresses the appropriate use of rivaroxaban in each of these

special populations. Based on this rationale the sponsor does not believe dose adjustment or a lower strength tablet was necessary in the populations highlighted by FDA.

In its is response to FDA regarding an approximately 40% higher exposure of rivaroxaban in Japanese subjects compared to other ethnic groups including Chinese (Question #4) the sponsor stated that 1) the increased rivaroxaban plasma exposure in Japanese subjects can be attributed to the known differences in average body weight: when corrected by the dose per body weight ($C_{max, norm}$, $AUC_{(0-12)norm}$) there was no such tendency of increased exposure noted for C_{max} or AUC, 2) uncorrected exposure ratios, i.e. <1.41 are considerably lower than the 2-fold changes that were mentioned as clinically relevant, 3) PT values were comparable across different ethnic groups including Asian subjects who generally may have a lower body weight, (b) (4)

(b) (4)

FDA Response:

Question #3

FDA has reviewed the sponsor's response and supporting data addressing the request to develop a lower strength tablet (in addition to the proposed 10 mg tablet) or a scored 10 mg tablet and is not persuaded by your argument. As outlined in table 1 and figure 1 of your response, there is a steep dose response relationship, relative to enoxiparin, for the risk of major bleeding events. These 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. Table 1 in your response to FDA reports 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. This is an important safety concern.

Without the ability to downward titrate the proposed dose of rivaroxaban the following populations may be potentially at increased risk for major bleeding based on the exposure and PD (i.e., FXa inhibition and PT) data you submitted: 1) moderate to severe renal impairment, 2) mild to severe renal impairment when used with a CYP3A4 inhibitor, 3) moderate to severe hepatic impairment, and 4) concurrent use with a moderate or strong CYP3A4 inhibitor plus a moderate or strong Pgp inhibitor. Further, the potential increase in exposure from renal impairment combined with a CYP3A4 inhibitor is of particular concern given it was not studied and could be significant given both major elimination pathways are blocked.

Therefore, FDA continues to recommend that without downward dose adjustment, a significant part of the target population will not be able to utilize rivaroxaban and inappropriate use of the current strength in these populations could pose an unacceptable

risk (e.g., medication error). We again strongly recommend you to develop a lower strength tablet or a scored 10 mg tablet of rivaroxaban and provide adequate data to support bioequivalence between the current formulation and the lower strength or scored 10 mg tablet. We encourage you to promptly obtain this information and submit it as an amendment to your application. We suggest having a teleconference with you prior to your submitting your next response. This will afford us an opportunity to further clarify our position and discuss any additional questions or comments you may have on this matter.

Question #4

FDA has reviewed your response and supporting data regarding an approximately 40% higher exposure of rivaroxaban in Japanese subjects compared to other ethnic groups including Chinese and is not persuaded by your argument. Based on its preliminary analysis FDA finds that the median C_{max}/Dose and AUC/Dose were found to be approx. 50% higher in Japanese compared to other ethnicities (see Figure 1).

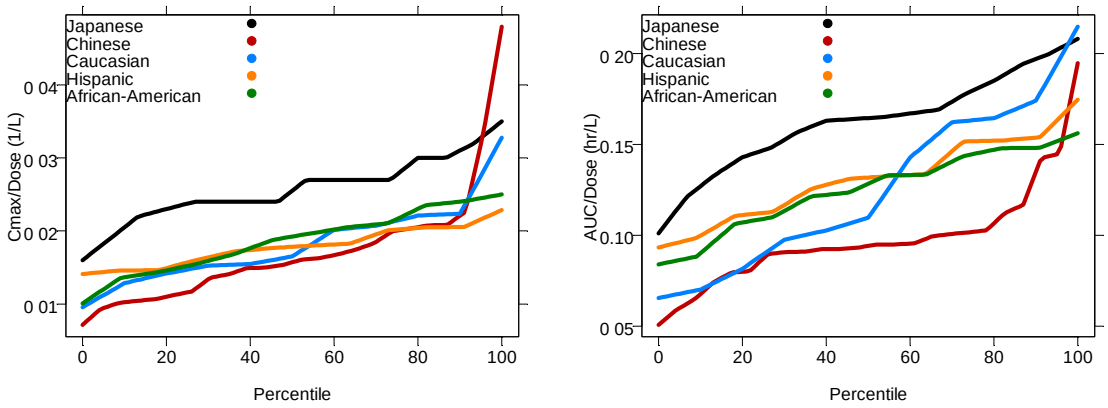

Figure 1: C_{max}/Dose and AUC/Dose vs. percentiles for different ethnicities following single dose 2.5-15 mg rivaroxaban (studies 11126, 11608, and 12090).

The only apparent differences in covariates for Japanese compared to other ethnicities are body weight and age where the Japanese were the youngest and lightest subjects (see Figure 2) potentially explaining the higher exposure.

However, the exposure in Japanese was approx. 50% higher compared to Chinese subjects weighing the same as Japanese. The Japanese were approx. 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 therefore expect the younger Japanese subjects to clear the drug faster (age was found to be a covariate for clearance in population PK) and thus lower exposure (AUC). The opposite was observed in studies 11126 and 11608.

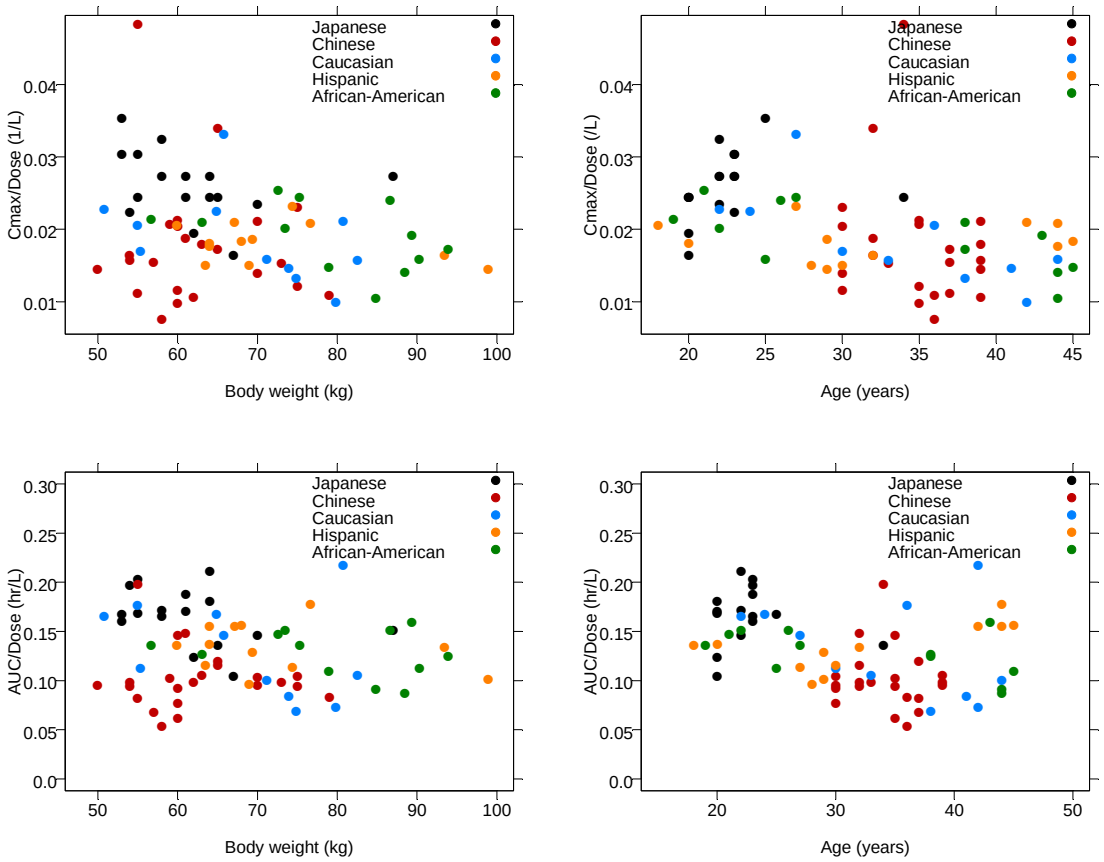

Figure 2: C_{max}/Dose (Top) and AUC/Dose (Bottom) vs. body weight (Left) and age (Right) following single dose 2.5-15 mg rivaroxaban from studies 11126, 11608, and 12090.

No apparent inter-ethnicity differences were found 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 3).

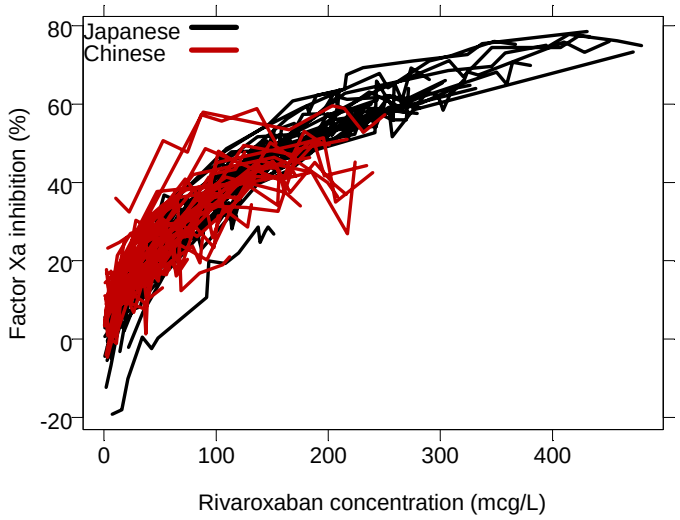

Figure 3: Factor Xa inhibition vs. rivaroxaban concentration in Japanese (black lines) and Chinese (red lines) subjects following 10 mg single dose rivaroxaban.

Based on the PK/PD data from studies 11126 and 11608 in Japanese and Chinese subjects, we conclude that there are significant differences in rivaroxaban pharmacokinetics for Japanese subjects compared to other ethnicities.

Given these preliminary findings and additional clarification we again ask you to provide an additional explanation for the higher exposure in the Japanese population. Pharmacogenetic differences should be considered in detail, in addition to other factors, in your response.

Recommendation:

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 5 reviewed the above submission, and provided two comments from a clinical pharmacology perspective that need to be communicated to the sponsor.

Signatures:

Joseph A. Grillo, Pharm.D. Reviewer Division of Clinical Pharmacology 5	Young Moon Choi, Ph.D. Team Leader Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **M Cato;** MTL - **K Robie-Suh**; MO – **M Lu**
DCP-5: Reviewer - **JA Grillo;** TL - **YM Choi;** PM - **C Tornoe;** PG - **RC Orbach** Deputy DD – **B Booth** DD - **A Rahman**

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/s/

Joseph Grillo
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Young-Moon Choi
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