CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA	202-439
Submission Date	01/05/2011
Generic Name	Rivaroxaban
Brand Name	XARELTO®
Dose & Dosage Form	Once daily, 20 & 15 mg Film Coated Immediate Release Tablets
Indication	To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
Sponsor	Ortho Mcneil Janssen Pharmaceuticals Inc.
Submission Type	Standard
Purpose	Addendum to clinical pharmacology review dated 08/10/2011
Reviewers	Sreedharan Nair Sabarinath, PhD Tzu-Yun McDowell, PhD
Team Leader	Rajanikanth Madabushi, PhD

EXECUTIVE SUMMARY

This review is an addendum to the original clinical pharmacology review submitted to DARRTS on 8/10/2011. The purpose of this document is:

(1) To provide revisions to dosing recommendations for patients with moderate hepatic impairment (Child-Pugh B).

(2) To provide additional information substantiating the dosing recommendations described in the original clinical pharmacology review for patients with severe renal impairment (CrCL 15 to <30 mL/min).

1. Dosing Recommendations in Moderate Hepatic Impairment (Child-Pugh B)

Previously we had recommended a reduced dose of 10 mg once daily with food in patients with moderate hepatic impairment (Child-Pugh B) based on exposure matching.

The revised dosing recommendation is to avoid the use of rivaroxaban in patients with moderate hepatic impairment (Child-Pugh B).

The original recommendation was derived by matching exposure and pharmacodynamics for subjects with moderate hepatic impairment to those with normal hepatic function based on the results from a dedicated hepatic impairment study designed to evaluate the impact of hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (PD) of rivaroxaban. However, during the internal discussions with the medical review team concerns were raised with regard to the lack of clear understanding of the impact of hepatic function on the coagulation cascade and eventually how it translates to efficacy and bleeding outcomes. Given this uncertainty, it was felt that dose adjustment for patients with moderate hepatic impairment cannot be provided.

2. Dosing Recommendations in Severe Renal Impairment

The recommended dose for patients with moderate (Creatinine clearance, CrCL 30 to <50 mL/min) and severe (CrCL 15 to <30 mL/min) renal impairment is 15 mg once daily with food. The dose adjustment for patients with severe renal impairment (CrCL 15 to <30 mL/min) was derived based on the results from a dedicated renal impairment study. As previously described (see Clinical Pharmacology Review, DARRTS date 8/10/2011), the impact of moderate renal impairment and severe renal impairment on the PK and PD of rivaroxaban was similar.

Additional analyses were performed upon further discussion with the Cross Discipline Team Leader (CDTL), Dr. Aliza Thompson to explore the impact of renal function on efficacy and safety based on the data from ROCKET-AF. It can be seen that after adjusting for the exposures based on renal function, the effect of rivaroxaban compared to warfarin was similar across different cut-offs of renal function (described in detail below).

Reference ID: 3031381

In ROCKET-AF study, the pivotal efficacy trial for rivaroxaban, a reduced dose of 15 mg was used in patients with moderate renal impairment to achieve exposures similar to that observed in normal subjects receiving the full 20 mg dose. The event rates (100 pt-yr) for critical organ bleeding, defined as intracranial, intraspinal, intraocular, perichardial, intra-articular, intramuscular with compartment symptom or retroperitoneal bleeding, were comparable (0.76 vs 0.83) between patients with moderate renal impairment (receiving 15 mg dose) and patients with mild renal impairment or patients with normal renal function (receiving 20 mg dose). The efficacy of rivaroxaban compared to warfarin also was similar across the renal function categories (Ref. ROCKET-AF Study report 39039039AFL3001, page 164). The bleeding risk across all three renal function categories was also similar between rivaroxaban and warfarin (Ref. ROCKET-AF Study report for 39039039AFL3001, page 209).

Traditionally, the impact of impaired renal function on efficacy and safety are evaluated based on three categories - mild, moderate and severe. However, these do not provide information with regard to the performance at the lower end of the categories. This is a challenge when continuous data are categorized. In order to have a better understanding, finer bins of creatinine clearance was considered. The baseline creatinine clearance was grouped into seven categories (~1000 patients/group/treatment) and the hazard ratios (95% CI) for primary efficacy endpoint, principal safety endpoint, primary ischemic stroke as well as major bleeding as defined in ROCKET-AF were calculated (See **Table 1** below). This table was not provided in the original clinical pharmacology review.

Table 1. Hazard ratios and 95% confidence intervals for protocol defined (A) primary efficacy endpoint (B) principal safety endpoint (C) primary ischemic stroke and (D) major bleeding with baseline creatinine clearance in ROCKET-AF trial

(A) Primary Efficacy Endpoint[§] (per-protocol set excluding site 042012/last dose plus 2 days)			
Baseline CrCL (mL/min) Median (Range)	Rivaroxaban N 6950 n/N	Warfarin N 6995 n/N	HR (95% CI)
39 (20-44)[†]	33/970	43/972	0.80 (0.51-1.26)
50 (45-54)	35/999	43/1033	0.86 (0.55-1.34)
58 (55-62)	22/951	40/975	0.56 (0.33-0.95)
67 (63-72)	36/1049	28/1065	1.29 (0.79-2.12)
77 (73-83)	15/956	43/990	0.36 (0.20-0.64)
91 (84-101)	28/1029	33/1000	0.85 (0.51-1.40)
119 (≥ 102)	18/996	10/960	1.77 (0.82-3.84)

[§]Composite of Stroke, and Non-CNS SE
[†]Eight patients with CrCL <30 mL/min

(B) Principal Safety Endpoint[‡] (safety set excluding site 042012/last dose plus 2 days)			
Baseline CrCL (mL/min) Median (Range)	Rivaroxaban N 7053 n/N	Warfarin N 7073 n/N	HR (95% CI)
39 (20-44)[†]	231/986	240/986	0.98 (0.82-1.18)
50 (45-54)	227/1012	238/1043	0.99 (0.82-1.18)
58 (55-62)	222/960	210/989	1.10 (0.91-1.33)
67 (63-72)	214/1065	225/1074	0.94 (0.78-1.14)
77 (73-83)	204/976	191/995	1.09 (0.89-1.33)
91 (84-101)	204/1041	190/1013	1.07 (0.88-1.31)
119 (≥ 102)	168/1013	150/973	1.10 (0.88-1.37)

[‡]Composite of Major and NMCR bleeding
[†]Eight patients with CrCL <30 mL/min

(C)Primary Ischemic Stroke (per-protocol set excluding site 042012/last dose plus 2 days)			
Baseline CRCL (mL/min) Median (Range)	Rivaroxaban N 6950 n/N	Warfarin N 6995 n/N	HR (95% CI)
39 (20-44)[†]	28/970	29/972	1.01 (0.60-1.70)
50 (45-54)	28/999	28/1033	1.05 (0.62-1.78)
58 (55-62)	16/951	29/975	0.56 (0.31-1.04)
67 (63-72)	26/1049	17/1065	1.54 (0.84-2.84)
77 (73-83)	14/956	27/990	0.53 (0.28-1.01)
91 (84-101)	21/1029	23/1000	0.91 (0.50-1.65)
119 (≥ 102)	14/996	6/960	2.30 (0.88-5.99)

[†]Eight patients with CrCL <30 mL/min

(D) Major Bleeding[*] (safety set excluding site 042012/last dose plus 2 days)			
Baseline CRCL (mL/min) Median (Range)	Rivaroxaban N 7053 n/N	Warfarin N 7073 n/N	HR (95% CI)
39 (20-44)[†]	71/986	70/986	1.06 (0.76-1.48)
50 (45-54)	63/1012	73/1043	0.89 (0.64-1.25)
58 (55-62)	55/960	52/989	1.09 (0.75-1.60)
67 (63-72)	54/1065	62/1074	0.87 (0.61-1.26)
77 (73-83)	45/976	51/995	0.90 (0.60-1.34)
91 (84-101)	56/1041	47/1013	1.20 (0.81-1.76)
119 (≥ 102)	50/1013	29/973	1.70 (1.08-2.69)

[†]Eight patients with CrCL <30 mL/min
[*]Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥ 2 g/dL, transfusion of ≥ 2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome

The results show that there is no clear trend for hazard ratio across the seven renal function groups for both efficacy and safety endpoints in ROCKET-AF. These findings are in line with the original recommendation for the reduced dose of 15 mg in patients with moderate renal impairment (CrCL 30 to <50 ml/min) as used in ROCKET-AF, and also lend support with regard to the proposed dose of 15 mg in patients with severe renal impairment (CrCL 15 to <30 ml/min).

The proposed language in the package insert for rivaroxaban is as follows:

(b) (4)

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/s/

SREEDHARAN N SABARINATH
10/19/2011

TZU-YUN C MCDOWELL
10/19/2011

RAJANIKANTH MADABUSHI
10/21/2011

ONDQA (Biopharmaceutics) Review

NDA:	202-439
Submission Date:	01/05/11
Product:	XARELTO^{TM} (Rivaroxaban) Tablets, 15 and 20 mg
Type of Submission:	Original NDA
Applicant:	Johnson & Johnson
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: Rivaroxaban is a Factor Xa inhibitor and co-developed through a joint research program between Bayer Healthcare AG (Bayer) and Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD). In 2008, another NDA (22-406) for Rivaroxaban was filed to Division of Hematology (DHP) by Bayer for immediate release 10 mg tablet for propylaxis of deep vein thrombosis and it got approved on 7/1/2011.

Submission: This original New Drug Application (NDA 202-439) is for the immediate release 15 and 20-mg oral tablets of Rivaroxaban (XARELTO^{TM}) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The initial formulation development of the rivaroxaban 15- and 20-mg film-coated tablets was performed by Bayer Schering Pharma AG at the Leverkusen facility in Germany, based on the development conducted for the 10- mg strength tablet (DMF 21580 and DMF 21592). 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.

Biopharmaceutics: This review is been focused on the evaluation of **1)** the dissolution data supporting the proposed acceptance criterion for the proposed product, and **2)** the dissolution data supporting the scale-up and manufacturing site change for the to-be-marketed product.

Reference ID: 3025198

Recommendations:

ONDQA-Biopharmaceutics had evaluated the provided information and has the following comments:

1. *The proposed dissolution method and acceptance criterion described below are acceptable.*

Dissolution Method and Acceptance Criterion for XARELTO™ (Rivaroxaban) Tablets, 15 and 20 mg	
Apparatus	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm
Medium	900 ml Acetate Buffer pH 4.5 = 0.4% SDS at 37oC
Acceptance Criterion	**Q =** (b) (4) **at 15 minutes**

2. *The provided dissolution data support the approval of the scale-up from pilot to commercial scale and manufacturing site to Gurabo, Puerto Rico*

Overall Assessment

From the Biopharmaceutics viewpoint, NDA 202-439 for XARELTO™ (Rivaroxaban) Tablets is recommended for approval.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer

Initialed by Angelica Dorantes, Ph. D. _____

Reference ID: 3025198

Bioparmaceutics Review

Drug Product Formulation: The composition of the formulation for the proposed rivaroxaban 15- and 20-mg film-coated tablets intended for commercial distribution is presented in the following table:

Component	Quality Reference [a]	Function	Quantity (mg/tablet) 15	20
Core Tablet				
Rivaroxaban Micronized	Company Specification	Active substance	15.0	20.0
Microcrystalline Cellulose (b) (4) NF	NF/Ph.Eur./Ph.Jap.			(b) (4)
Croscarmellose Sodium, NF	NF/Ph.Eur./Ph.Jap.			
Hypromellose (b) (4) USP	USP/Ph.Eur./Ph.Jap.			
Lactose Monohydrate, NF	NF/Ph.Eur./Ph.Jap.			
Magnesium Stearate (b) (4) NF	NF/Ph.Eur./Ph.Jap.			
Sodium Lauryl Sulfate, NF (b) (4)	NF/Ph.Eur./Ph.Jap. USP			
Core Tablet Weight:				
Film Coat				
Opadry® Red (b) (4)	DMF (b) (4)			
Opadry® II Dark Red (b) (4)	DMF			
(b) (4)	(b) (4)			
Total Tablet Weight:			87.5	87.5

[a] Where multiple compendia are listed, the compendium applied is specific to the applicable region of the submission.

(b) (4)

Proposed Dissolution Method:

Selection of the dissolution medium: During the selection of the dissolution medium for the 15- and 20 mg tablets, it was considered that the drug substance rivaroxaban is practically insoluble in aqueous media and that the solubility is almost pH independent over a range of pH 1-6.8. The solubility in the tested media at 37^0C is presented in Table 1.

Table 1: Solubility of Rivaroxaban in Different Media

Buffer System	Surfactant Level (SDS) (%)	Quantity[a] Dissolved at 37 °C in 900 mL (mg)
0.1 M HCl pH 1	0	10
0.01 M HCl pH 2	0	10
Acetate Buffer pH 4.5	0	12
Acetate Buffer pH 4.5	0.1	13
Acetate Buffer pH 4.5	0.2	30
Acetate Buffer pH 4.5	0.3	52
Acetate Buffer pH 4.5	0.4	72
Acetate Buffer pH 4.5	0.5	91
Phosphate Buffer pH 6.8	0	9

[a] Approximate

Selection of the Amount of Surfactant: As a standard requirement for dissolution testing, the drug substance should be sufficiently soluble in the dissolution medium to achieve sink conditions (defined as the volume of medium at least greater than 3 times that which is required to form a saturated solution of the drug substance). Different levels of SDS in the aqueous buffer systems were evaluated. The solubility results are shown in Table 1. The presence of 0.4% SDS increases the solubility of rivaroxaban to approximately 72 mg/900 mL and is the minimum concentration required to reach 3-fold sink conditions for both 15- and 20-mg dosages. Therefore, a level of 0.4% SDS is selected.

Discussion on development and optimization of the rest of the of dissolution method parameters are the same as described in the Biopharmaceutics review of NDA 22-406 and as described below. Therefore, it has not been repeated here.

Dissolution Parameters

Apparatus:	USP Apparatus 2 (Paddle)
Rotation Speed:	75 rpm
Volume of Medium:	900 mL
Dissolution Medium:	Acetate Buffer pH 4.5 + 0.4% SDS
Temperature:	37 ± 0.5 °C
Sample Introduction:	Introduce 1 tablet into each of the 6 dissolution vessels.
Sample Pull Time:	30 minutes
Filter:	10 μm Poroplast (Polyethelene)

Reviewer's Comment: Based on the solubility data provided in Table 1 above, the overall dissolution method as outlined in the Table above including the sponsor's justification of increasing the SDS level to 0.4% for 15- and 20 mg rivaroxaban tablets from 0.2% approved for 10 mg tablet is acceptable.

Reference ID: 3025198

Dissolution Acceptance Criterion: In line with the NDA 22-406 for the 10 mg tablet, in this original submission for 15- and 20 mg tablets, the Applicant proposed (b) (4) using little modification of the dissolution medium (0.4% SDS for 15- and 20 mg tablets instead of 0.2% SDS for 10 mg tablets).

However, in the communication dated April 28, 2011, the Applicant agreed to the Agency's proposed dissolution specification of *Q* (b) (4) *in 15 minutes* for the 10 mg tablets (NDA 22-406). The Agency issued an information request (IR) dated 03 May 2011 regarding this NDA for 15- and 20 mg tablets asking the sponsor to change their proposed dissolution specification of **Q** (b) (4) to **Q** (b) (4) **at 15 minutes** as well based on the available dissolution data as listed below:

Table 40: Release Dissolution Test Results for Bulk Rivaroxaban 15-mg Film-Coated Tablet Batches at Commercial Scale – Batch 9LG0433-X

(b) (4)

Table 43: Release Dissolution Test Results for Bulk Rivaroxaban 20 mg Film-Coated Tablet Batches at Commercial Scale – Batch 9MG0637-X

(b) (4)

In the submission dated 17 May, 2011, the Applicant agreed to revise the proposed dissolution specification from (b) (4) to **Q** (b) (4) **at 15 minutes** for Rivaroxaban 15- and 20-mg film-coated tablets.

*Reviewer's Comment: The dissolution Acceptance Criterion for the sponsor's proposed 15- and 20 mg rivaroxaban immediate release tablets will be **Q** (b) (4) **at 15 minutes.***

Scale-Up Change and Manufacturing Site Change

Due to low solubility of the drug substance, rivaroxaban is assigned to BCS class 2. According to the SUPAC IR guidance, the applicant provided multi-point dissolution profile in the proposed medium and four (4) other mediums to support the approval of the rivaroxaban 15- and 20-mg film-coated tablets manufactured at pilot scale at the Leverkusen facility in Germany and commercial scale at Gurabo in Puerto Rico. The physical properties and **dissolution profiles** are compared to demonstrate the equivalence between the tablets manufactured in both scales. The similarity factor (f2) was calculated for the commercial scale tablets with respect to the representative pilot scale clinical batches BX02AHT (15-mg strength) and BX02KET (20-mg strength), which were used in Phase III clinical studies. Table 46 presents the f2 values of 15-mg tablets commercial scale batch 9LG0433-X with respect to the representative Phase III pilot scale batch BX02AHT. Table 47 presents the f2 values of 20-mg tablets commercial scale batch 9MG0637-X with respect to the representative Phase III pilot scale batch BX02KET.

The similarity factors were evaluated for dissolution profiles in the registration dissolution medium (acetate buffer, pH 4.5 with 0.4% sodium lauryl sulfate) and 4 other types of media. Table 46 and Table 47 show that all f2 values in all the dissolution media tested are between 50 and 100, indicating comparability of the dissolution profiles of the commercial scale and Phase III pilot scale tablets. The *in-vitro* dissolution results demonstrated the equivalence of the 15- and 20-mg tablets manufactured at commercial scale and at pilot scale. Dissolution profile comparisons at all these medium are presented below:

Figure 27: Comparison of Dissolution Profile of Rivaroxaban 15-mg Tablets Manufactured at Pilot Scale (Phase III) and at Commercial Scale (Medium: 0.1 N HCl with 0.4% SLS)

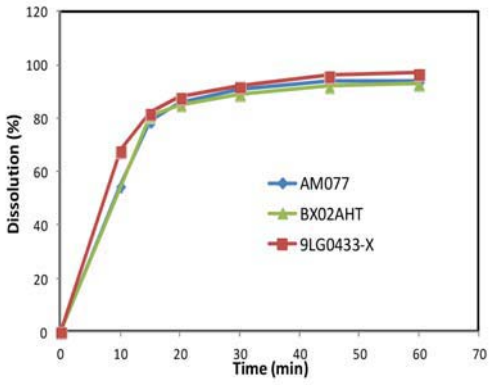


Figure 28: Comparison of Dissolution Profile of Rivaroxaban 15-mg Tablets Manufactured at Pilot Scale (Phase III) and at Commercial Scale (Registration Dissolution Medium: pH 4.5 Acetate Buffer with 0.4% SLS)

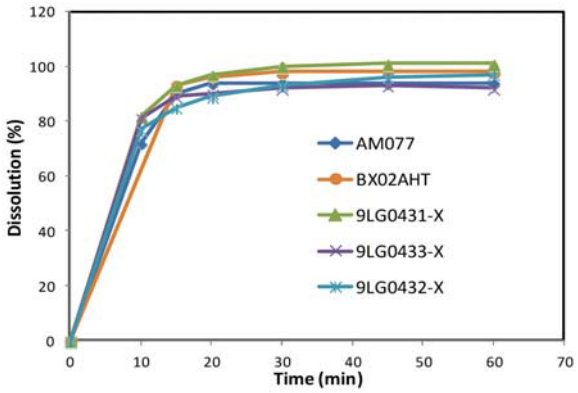


Figure 29: Comparison of Dissolution Profile of Rivaroxaban 15-mg Tablets Manufactured at Pilot Scale (Phase III) and at Commercial Scale (Medium: pH 6.5 with 0.4% SLS)

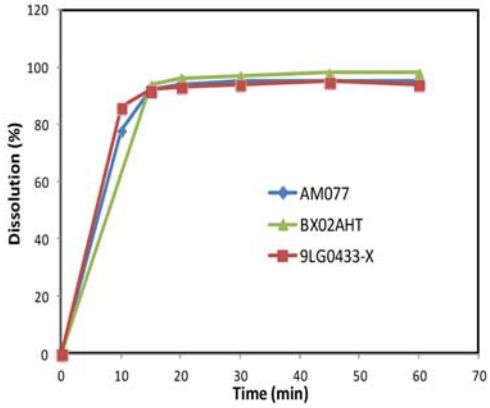


Figure 30: Comparison of Dissolution Profile of Rivaroxaban 15-mg Tablets Manufactured at Pilot Scale (Phase III) and at Commercial Scale (Medium: pH 7.5 with 0.4% SLS)

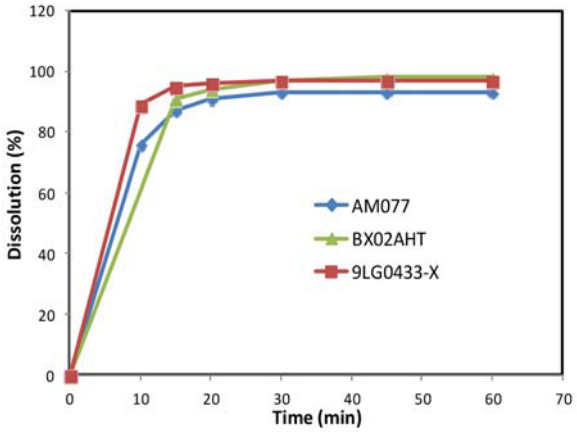


Figure 31: Comparison of Dissolution Profile of Rivaroxaban 15-mg Tablets Manufactured at Pilot Scale (Phase III) and at Commercial Scale (Medium: Water with 0.4% SLS)

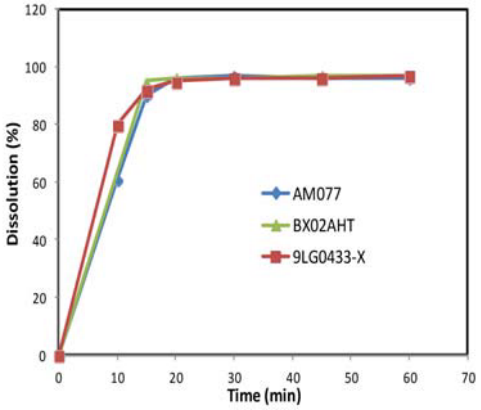


Figure 32: Comparison of Dissolution Profile of Rivaroxaban 20-mg Tablets Manufactured at Pilot Scale (Phase III) and at Commercial Scale (Medium: 0.1 N HCl with 0.4% SLS)

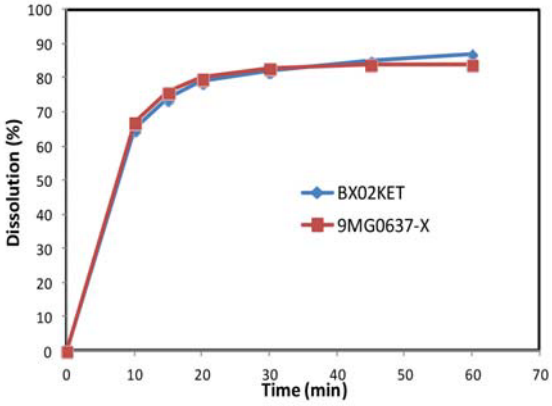


Figure 33: Comparison of Dissolution Profile of Rivaroxaban 20-mg Tablets Manufactured at Pilot Scale (Phase III) and at Commercial Scale (Registration Dissolution Medium: pH 4.5 Acetate Buffer with 0.4% SLS)

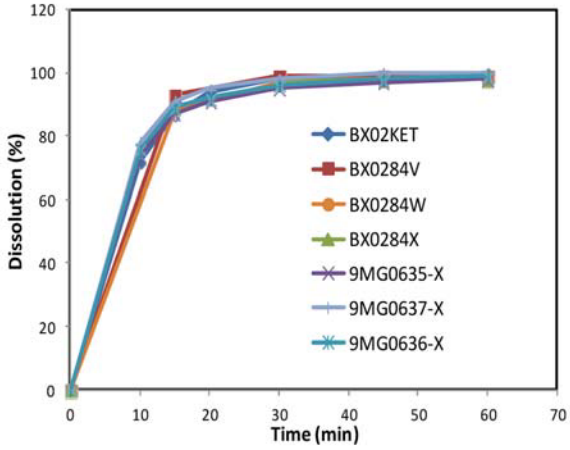
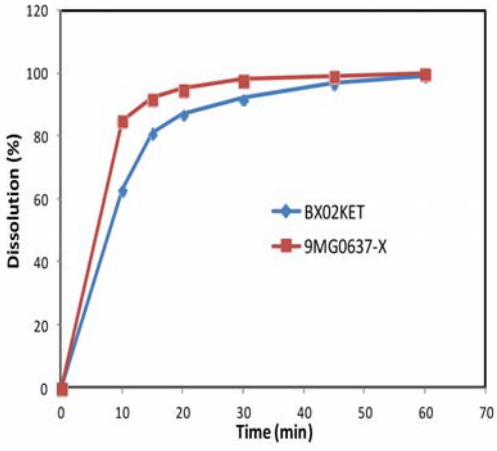


Figure 34: Comparison of Dissolution Profile of Rivaroxaban 20-mg Tablets Manufactured at Pilot Scale (Phase III) and at Commercial Scale (Medium: pH 6.5 with 0.4% SLS)



Reference ID: 3025198

Figure 35: Comparison of Dissolution Profile of Rivaroxaban 20-mg Tablets Manufactured at Pilot Scale (Phase III) and at Commercial Scale (Medium: pH 7.5 with 0.4% SLS)

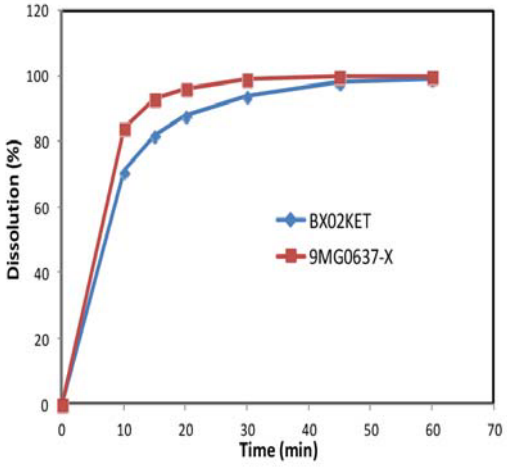


Figure 36: Comparison of Dissolution Profile of Rivaroxaban 20-mg Tablets Manufactured at Pilot Scale (Phase III) and at Commercial Scale (Medium: Water with 0.4% SLS)

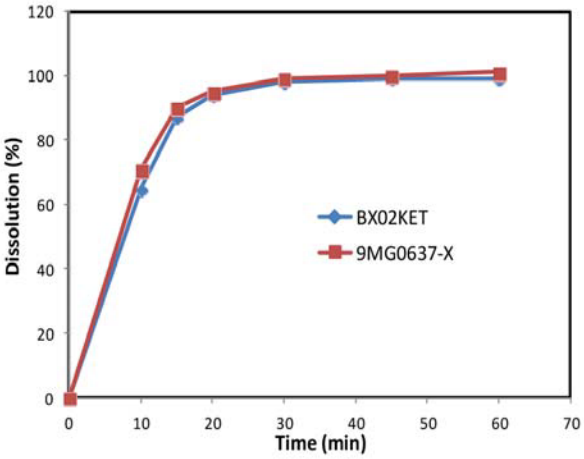


Table 46: Similarity Factor F2 Calculated for Rivaroxaban 15-mg Tablet Commercial Scale Batch 9LG0433-X with Respect to The Representative Pilot Scale Batch BX02AHT

Dissolution Medium (Each with 0.4% Sodium Lauryl Sulfate (SLS))	F2[a] (9LG0433-X vs BX02AHT)
0.1 N HCl	84
pH 4.5	72
pH 6.5	83
pH 7.5	91
Water	93

[a] f2 calculated using all data beginning with 15 minute timepoint

Table 47: Similarity Factor F2 Calculated for Rivaroxaban 20-mg Tablet Commercial Scale Batch 9MG0637-X with Respect to The Representative Pilot Scale Batch BX02KET

Dissolution Medium (Each with 0.4% Sodium Lauryl Sulfate (SLS))	F2[a] (9MG0637-X vs BX02KET)
0.1 N HCl	84
pH 4.5	83
pH 6.5	58
pH 7.5	59
Water	84

[a] f2 calculated using all data beginning with 15 minute time point

Reviewer's Comment: Based on the comparable dissolution profiles characteristics and f2 values of the products manufactured at pilot and commercial scale at Leverkusen facility in Germany and Gurabo facility in Puerto Rico respectively, the approval of the proposed changes (i.e., scale-up from pilot to commercial scale and manufacturing site to Gurabo, Puerto Rico) is supported.

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/s/

TAPASH K GHOSH
10/05/2011

ANGELICA DORANTES
10/05/2011

CLINICAL PHARMACOLOGY REVIEW	
NDA	202-439
Submission Date	01/05/2011
Generic Name	Rivaroxaban
Brand Name	XARELTO®
Dose & Dosage Form	Once daily, 20 & 15 mg Film Coated Immediate Release Tablets
Indication	To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
Sponsor	Ortho Mcneil Janssen Pharmaceuticals Inc.
Submission Type	Standard
Reviewers	Sreedharan Nair Sabarinath, PhD Tzu-Yun McDowell, PhD
Pharmacometrics Team Leader	Pravin Jadhav, PhD
Team Leader	Rajanikanth Madabushi, PhD

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1 EXECUTIVE SUMMARY

Ortho Mcneil Janssen Pharmaceuticals Inc. submitted NDA 202-439 for rivaroxaban immediate release tablets for the primary prevention of stroke and systemic embolism in patients with atrial fibrillation (SPAF) on 5th January 2011. Rivaroxaban is a synthetic, competitive and selective oral, direct factor Xa inhibitor. A 10 mg dose strength of rivaroxaban is approved in the US under NDA 022-406 for the prophylaxis of deep vein thrombosis (DVT) that may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. This report evaluates the clinical studies relevant to the proposed SPAF indication or the clinical pharmacology studies which were not reviewed under NDA 022-406.

A single pivotal efficacy and safety study (ROCKET-AF) forms the basis for seeking approval in SPAF. ROCKET-AF was a randomized, double-blind, double-dummy study for stroke prevention in subjects with non-valvular atrial fibrillation and at least two other risk factors for stroke such as congestive heart failure (CHF), hypertension, age ≥75 years and diabetes or a prior history of stroke, TIA or systemic embolus events. A total of 14,269 patients were randomized to rivaroxaban (20 mg once daily or 15 mg once daily if creatinine clearance was 30-49 ml/min) or to warfarin dose titrated to a target INR of 2 to 3. The primary objective of the study was to demonstrate that the efficacy of rivaroxaban was non-inferior to dose-adjusted warfarin in the studied population. A non-inferiority margin of 1.46 (later changed to 1.38) for the hazard ratio was used to design the study.

The proposed dose strengths for commercial distribution are 20 mg and 15 mg film coated immediate release tablets.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP) has reviewed the studies relevant to the proposed indication submitted to NDA 202-439 and used prior OCP reviews on NDA 022-406 for rivaroxaban (DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo) to derive the following recommendations.

From a clinical pharmacology perspective, the submission is acceptable and can be approved, provided the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

The Office has the following specific recommendations:

- Rivaroxaban should be administered daily at the recommended dose with the evening meal.
- Patients with moderate (creatinine clearance 30-49 ml/min) and severe (creatinine clearance 15-29 ml/min) renal impairment should receive 15 mg rivaroxaban once daily.

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- Patients with moderate hepatic impairment (Child-Pugh B) should receive 10 mg rivaroxaban once daily.
- The concurrent use of aspirin is a major risk factor for bleeding. This increase in bleeding risk is similar between rivaroxaban and warfarin. However, concomitant aspirin use does not seem to provide an additional benefit for the stroke prevention. Patients should be advised about the increased bleeding risk with concomitant aspirin use while on rivaroxaban therapy.
- A transition strategy must be employed for switching patients from rivaroxaban to warfarin. A reasonable transition strategy for switching patients from rivaroxaban to warfarin, considering the time course of their PD effects, is concomitant administration of rivaroxaban and warfarin for 2 days or more. The strategy ensures an INR ≥2 during the transition period. Rivaroxaban should be stopped once the observed pre-dose INR is ≥2 and the INR should be maintained within the target range of 2-3 with warfarin. Since rivaroxaban is recommended to be dosed with the evening meal, for the purpose of monitoring the INR during the transition period, the INR measurement on the next day (ie, after 16 hours post dose) can serve as the pre-dose INR for the decision to stop rivaroxaban. The INR should be measured daily during the transition until the INR ≥ 2.

2 CLINICAL PHARMACOLOGY SUMMARY

2.1 BACKGROUND

Rivaroxaban is an orally active factor Xa inhibitor. Ortho Mcneil Janssen Pharmaceuticals Inc. is seeking approval for rivaroxaban 20 mg and 15 mg tablets for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF). This section summarizes the clinical pharmacology aspects of rivaroxaban (Reference: OCP review of NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo) and major findings from the studies relevant to the SPAF indication.

2.2 CURRENT SUBMISSION

The current submission (NDA 202-439) for rivaroxaban consists of one pivotal efficacy and safety study (ROCKET-AF, See Appendix 1 for details), a smaller add-on phase III study in Japanese patients (J-ROCKET), and interaction studies with fluconazole and omeprazole (Appendix 2). All other clinical pharmacology studies reviewed separately under NDA 022-406 were also referenced for this NDA (NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo). Rivaroxaban 10 mg tablets (NDA 022-406) was approved for the prophylaxis of deep vein thrombosis (DVT) that may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

2.3 PHARMACOKINETICS OF RIVAROXABAN

- Absolute bioavailability of 66% in fasted condition for 20 mg dose
- Maximum plasma concentration attained in 2-4 hours
- Food increases AUC and C_{max} of 20 mg dose by ~39 and 76 % respectively
- Almost 50 % of an oral dose undergoes hepatic metabolism
- Metabolism predominantly by CYP3A4 (18%), 2J2 (14%) and hydrolysis (14%)
- No circulating major or active metabolites
- Approximately 36% of oral dose eliminated renally as unchanged drug
- Renal elimination involves active tubular secretion and glomerular filtration
- Approximately 28% of oral dose is excreted in feces
- Substrate for P-gp and BCRP
- Elimination half-life is 6-8 hrs in healthy and 11-13 hrs in elderly subjects

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2.4 EXPOSURE-PHARMACODYNAMICS-OUTCOME RELATIONSHIPS

- Concentration dependent changes in pharmacodynamic measures such as prothrombin time (PT), factor Xa activity (FXa) and prothrombinase induced clotting time (PiCT) for rivaroxaban were observed. The PT measurements increased linearly with rivaroxaban concentration. The linear relationship observed in SPAF patients was similar to that observed in healthy subjects.
- The probability of ischemic stroke, a major component of the primary efficacy endpoint, was independent of the PT, measured mostly during 12-24 hours post rivaroxaban dose, over the observed range.
- Major bleeding events increased with an increase in PT, measured mostly during 12-24 hours post rivaroxaban dose, over the observed range.
- As expected, ischemic stroke events with warfarin decreased with an increase in the last observed INR while the risk for major bleeding increased with an increase in the last observed INR.
- The concomitant use of aspirin (≥50% of time) during the double-blind phase significantly increased the risk for major bleeding with rivaroxaban. However, the risk for ischemic stroke was not significantly affected with co-administration of aspirin. A similar increase in bleeding risk with aspirin was found in the warfarin treated patients as well. Patients should be advised about the increased bleeding risk when aspirin and rivaroxaban are co-administered.
- Based on the time-course of the pharmacodynamic effect of rivaroxaban and warfarin, a reasonable transition strategy for switching patients from rivaroxaban to warfarin is concomitant administration of rivaroxaban and warfarin for 2 days or more. The strategy ensures an INR≥ 2 during the transition period. Rivaroxaban should be stopped once the observed pre-dose INR is ≥ 2 and the INR should be maintained within the target range of 2-3 for warfarin. Since rivaraxoban is recommended to be dosed with the evening meal, for the purposes of monitoring INR during the transition, the INR measurement on the next day (i.e, after the 16 hrs post-dose) can serve as the pre-dose INR for the decision to stop rivaroxaban. The INR should be measured daily during the transition, until the INR ≥ 2.

2.5 INTRINSIC FACTORS

- **Renal impairment**: Exposure to rivaroxaban increased with the severity of renal function impairment as demonstrated in the dedicated renal impairment study (Study number 11002, OCP review for NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo). The ROCKET-AF study used a 20 mg once daily dose for patients with normal and mild renal impairment. A reduced dose of 15 mg once daily was studied in patients with moderate renal impairment. This dose adjustment provided rivaroxaban exposure in moderate renal impairment comparable to that of normal renal function patients after the 20

mg dose. The efficacy of rivaroxaban compared to warfarin was similar across the renal function categories (Ref. ROCKET-AF Study report 39039039AFL3001, page 164). The bleeding risk across all three renal function categories was also similar between rivaroxaban and warfarin (Ref. ROCKET-AF Study report for 39039039AFL3001, page 209). Since the increases in exposure and PT (as AUC-PT) in moderate and severe renal impairment are comparable, it is reasonable to use the same reduced dose of 15 mg once daily in severe renal impairment.

- **Hepatic impairment**: Rivaroxaban exposure did not change significantly in subjects with mild hepatic impairment (Child-Pugh A). Exposure to rivaroxaban increased by approximately 2-fold in subjects with moderate hepatic impairment (Child-Pugh B) compared to subjects with normal hepatic function (Study number 11003, OCP review for NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo). The PD effects were also increased with the moderate hepatic impairment. No information is available on patients with severe hepatic impairment (Child-Pugh C). No dose adjustments are required for mild (Child-Pugh A) hepatic impairment. A reduced dose of 10 mg should be used in moderate hepatic impairment (Child-Pugh B) so as to have similar exposure as of 20 mg dose in healthy subjects. Avoid the use of rivaroxaban in patients with severe (Child-Pugh C) hepatic impairment and any hepatic disease associated with coagulopathy.

3 QUESTION BASED REVIEW

3.1 BACKGROUND

Ortho Mcneil Janssen Pharmaceuticals Inc. is seeking approval for rivaroxaban for the prevention of stroke and systemic embolism in patients with atrial fibrillation (SPAF). Rivaroxaban as 10 mg immediate release tablets was approved in the US under NDA 022-406 for the prophylaxis of deep vein thrombosis (DVT) that may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. A detailed review of clinical pharmacology aspects of rivaroxaban was conducted under NDA 022-406. This modified question based review (QBR) for the current NDA 202-439 will address the issues relevant to the proposed SPAF indication. Please refer to the OCP reviews under NDA 022-406 (DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo) for clinical pharmacology aspects of rivaroxaban.

Briefly, rivaroxaban is an orally active, competitive and selective, direct factor Xa inhibitor. Activation of factor Xa by intrinsic or extrinsic pathways plays a central role in blood coagulation cascade. The current submission has a single pivotal efficacy and safety study (ROCKET-AF) and an add-on phase III study in Japanese patients (J-ROCKET).

ROCKET-AF was a randomized, multi-center, double-blind, double-dummy, parallel group, active-controlled, event-driven Phase III study with a total of 14,269 patents randomized to rivaroxaban (20 mg once daily or 15 mg once daily if creatinine clearance is 30-49 ml/min) or dose adjusted warfarin for an INR target of 2-3 in patients with non-valvular atrial fibrillation with at least two of the risk factors such as congestive heart failure (CHF), hypertension, age≥75 years and diabetes or a prior history of stroke, TIA or systemic embolus events. Both rivaroxaban and warfarin treatment arms were well balanced in terms of baseline characteristics and had about 37-38% vitamin K antagonist naïve patients in the safety population. Aspirin use during the double blind phase was limited to ≤100 mg. The primary efficacy end point was a composite of stroke or non-CNS systemic embolism and the study was designed to demonstrate that the efficacy of rivaroxaban was non-inferior to adjusted-dose warfarin in the studied population. A non-inferiority margin of 1.46 (later changed to 1.38) for hazard ratio was used in designing the study. The principal safety objective of this study was to demonstrate that rivaroxaban is superior to dose adjusted warfarin as assessed by the composite of major and non-major clinically relevant bleeding events.

The add-on phase III study, J-ROCKET was designed to evaluate the safety of rivaroxaban in Japanese patients with non-valvular atrial fibrillation and used 15 mg once daily dose (10 mg if creatinine clearance was 30-49 mL/min) compared with dose adjusted warfarin (as per Japanese guidelines for INR maintenance). A reduced rivaroxaban dose of 15 mg was selected to match exposures in Japanese patients to that obtained with a 20 mg dose in other populations. A total of 1,280 patients were randomized to either warfarin or rivaroxaban treatment groups. The rate of the primary safety endpoint, composite of adjudicated major and non-major clinically relevant

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bleeding events, was 18.04/100 pt-yrs for rivaroxaban and 16.42/100 pt-yrs for wafarin in the safety, on treatment analysis [HR: 1.11 (0.87-1.42)]. Non-inferiority of rivaroxaban to warfarin was demonstrated for the primary safety endpoint with a pre-specified margin of 2. Rivaroxaban group also had numerically lower event rates for the primary efficacy endpoints, the composite of adjudicated stroke and non-CNS systemic embolism, compared with warfarin in the per-protocol, on treatment population (Event rate: 1.26 vs. 2.61/100 pt-yrs respectively).

The following review questions were identified for the current clinical pharmacology review:

3.2 Is the proposed dose and dosing regimen justified?

The dose selection in ROCKET-AF study was based on the results from two DVT studies (Study Number 11223 ODIXa-DVT and 11528 Einstein-DVT) and the sponsor concluded that a 20 mg once daily dose has desired safety and efficacy profile for studies supporting the SPAF indication. However, the difference between the once daily and twice daily regimens for the same total daily dose was not studied within a single study and the cross-study comparisons were inconclusive. Further, a recently concluded TIMI-ACS 46, a dose selection study conducted in patients with acute coronary syndrome (ACS) covering a total daily dose range of 5 mg to 20 mg, as once or twice daily regimen, showed numerical advantage for safety and efficacy for the twice daily regimen. So the sponsor selected a twice daily regimen for their on-going phase III ACS program based the results from TIMI-ACS 46. The pharmacokinetic and pharmacodynamic characteristics suggest that a twice daily regimen might offer lower peak to trough ratio in PT levels within a dosing interval compared to the once daily regimen (see Figure 1). The clinical benefit of the difference in the peak to trough ratio and higher trough PT levels after twice daily regimen cannot be derived from the existing data.

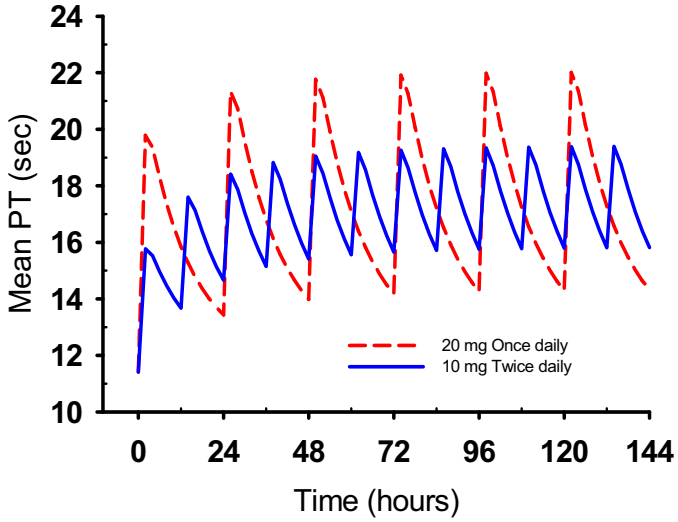

Figure 1 Simulated PT-time course for the PK-PD subset in ROCKET-AF for a total daily dose of 20 mg rivaroxaban, given as once daily (red-dashed line) or as twice daily (blue-solid line). The simulations were based on rivaroxaban PK model and rivaroxaban PK-PT relationship presented in Figure 2.

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There are no meaningful dose-ranging studies in the target population of patients with atrial fibrillation. Hence it is not clear whether the 20 mg once daily dose selected in ROCKET-AF is optimal for the SPAF indication. Nevertheless, the results from the ROCKET-AF study showed rivaroxaban 20 mg once daily to be non-inferior to dose-adjusted warfarin (See
Table 1).

Table 1 Top-line efficacy and safety analysis results from ROCKET-AF

Endpoint	Rivaroxaban		Warfarin		Rivaroxaban Vs. Warfarin	
	n/N	Event rate (100 pt-yr)	n/N	Event rate (100 pt-yr)	HR (95 % CI)	*p* value
Primary efficacy endpoint*	188/6958	1.71	241/7004	2.16	0.79 (0.66-0.96)	<0.001
Principal safety endpoint**	1475/7111	14.91	1449/7125	14.52	1.03 (0.96-1.11)	0.44

*Non-inferiority on primary efficacy endpoint based on treatment data from the per-protocol population
** Superiority on principle safety endpoint on treatment data from the safety population

3.1 Is there a relationship between rivaroxaban concentration and pharmacodynamic (PD) measures such as prothrombin time (PT), factor Xa activity (FXa) and prothrombinase induced clotting time (PiCT)?

In the ROCKET-AF study, matching pharmacokinetic-pharmacodynamic (PK-PD) samples were collected from a subset of about 161 patients (See Appendix 1 for details). The sponsor did not collect PK in all subjects; however, the PD samples were collected during the visits at weeks 12 and 24 from all eligible patients. Most of these PD measurements (~78%) were made during 12-24 hours after the rivaroxaban dose. These PD measures included the PT, FXa and PiCT and were described by the term pre-dose PD in subsequent sections.

Factor Xa activity, PT (Figure 2) and PiCT were found to be dependent on rivaroxaban concentration in the patients with the matching PK-PD samples. This is in agreement with observations from the dedicated rivaroxaban PK and PD studies in healthy volunteers (NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo). Based on this observation, the PD measures (such as, PT) can be used as surrogates for PK measurements in the PD-Outcome analyses.

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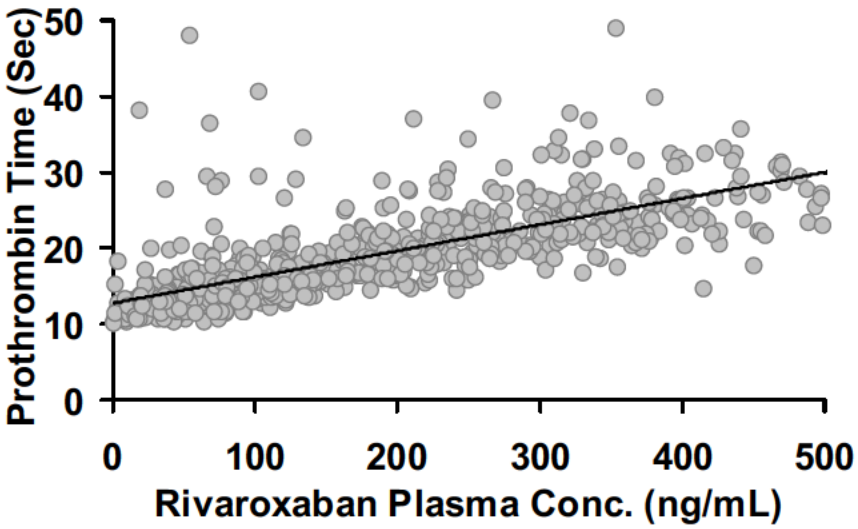

Figure 2 Prothrombin time increases linearly with rivaroxaban concentration. Data from the PK-PD subset of ROCKET-AF is shown. Solid curve is the trend line.

3.2 What are the characteristics of the PD-outcome relationship for efficacy?

The probability of ischemic stroke, a major component of the primary efficacy endpoint, was independent of the pre-dose PT measures over the observed range for rivaroxaban (Figure 3).

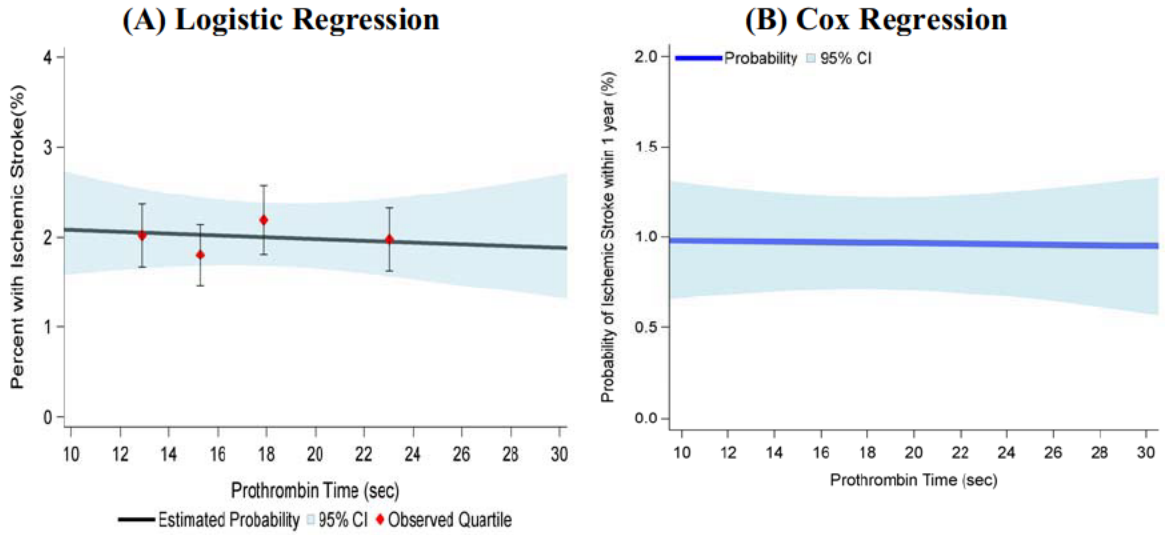

Figure 3 Ischemic stroke events are independent of pre-dose PT over the observed range (per-protocol, on treatment analysis set). Probability of ischemic stroke by pre-dose PT with rivaroxaban shown in (A) linear logistic regression model and (B) Cox regression model with a plot indicating probability of an event within 1 year. The PT measurements made either at week 12 or week 24, whichever was closer to the reported ischemic stroke event was used for the analysis. Majority of the PT measurements were made during 12-24 hours after the previous dose and is referred to as pre-dose PT.

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3.3 What are the characteristics of the PD-outcome relationship for safety?

The probability for major bleeding event, the primary safety endpoint as defined as clinically overt bleeding associated with a decrease in hemoglobin ≥ 2g/dl, or a transfusion of ≥ 2 units of packed red blood cells or whole blood, or bleeding at critical sites, or a fatal outcome, increased with an increase in pre-dose PT as shown in Figure 4. See Appendix 1 for details on PD-Outcome analysis.

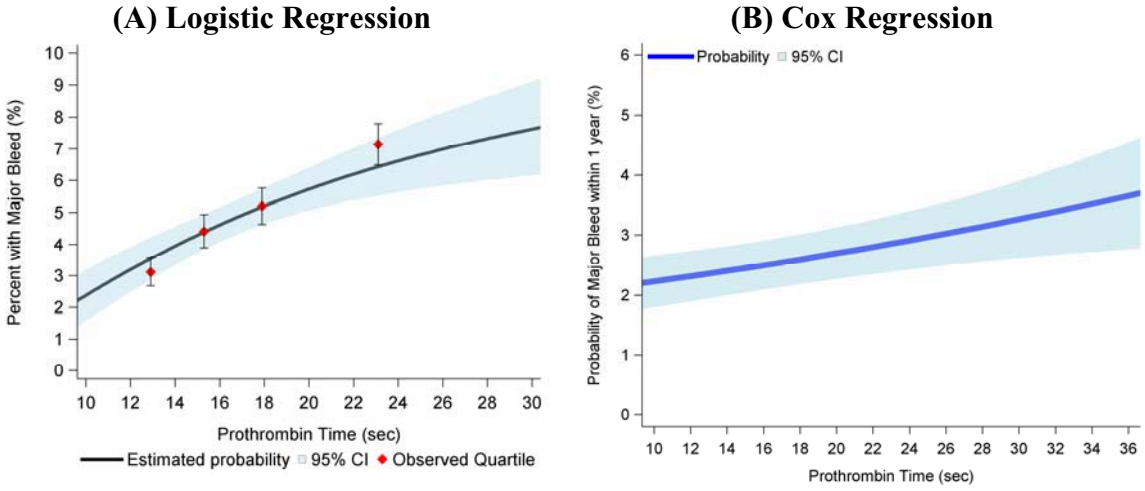

Figure 4 Major bleeding events increased with an increase in pre-dose PT over the observed range (per-protocol, on treatment analysis set). Probability of major bleeding by pre-dose PT with rivaroxaban shown in (A) logistic regression model (E_{max}) and (B) Cox regression model with a plot indicating probability of an event within 1 year. The PT measurements made either at week 12 or week 24, whichever was closer to the reported major bleeding event was used for the analysis. Majority of the PT measurements were made during 12-24 hours after the previous dose and is referred to as pre-dose PT.

3.4 What is the PD-outcome relationship for warfarin in ROCKET-AF study?

The risk for both safety (major bleeding) and efficacy (ischemic stroke) endpoints for warfarin in ROCKET-AF were dependent on the last observed INR (Figure 5), consistent with the expected warfarin INR-Outcome relationship. For patients who had no events on treatment, their last observed INR before or on the censored date was selected for this analysis. See Appendix 1 for details on PD-Outcome analysis.

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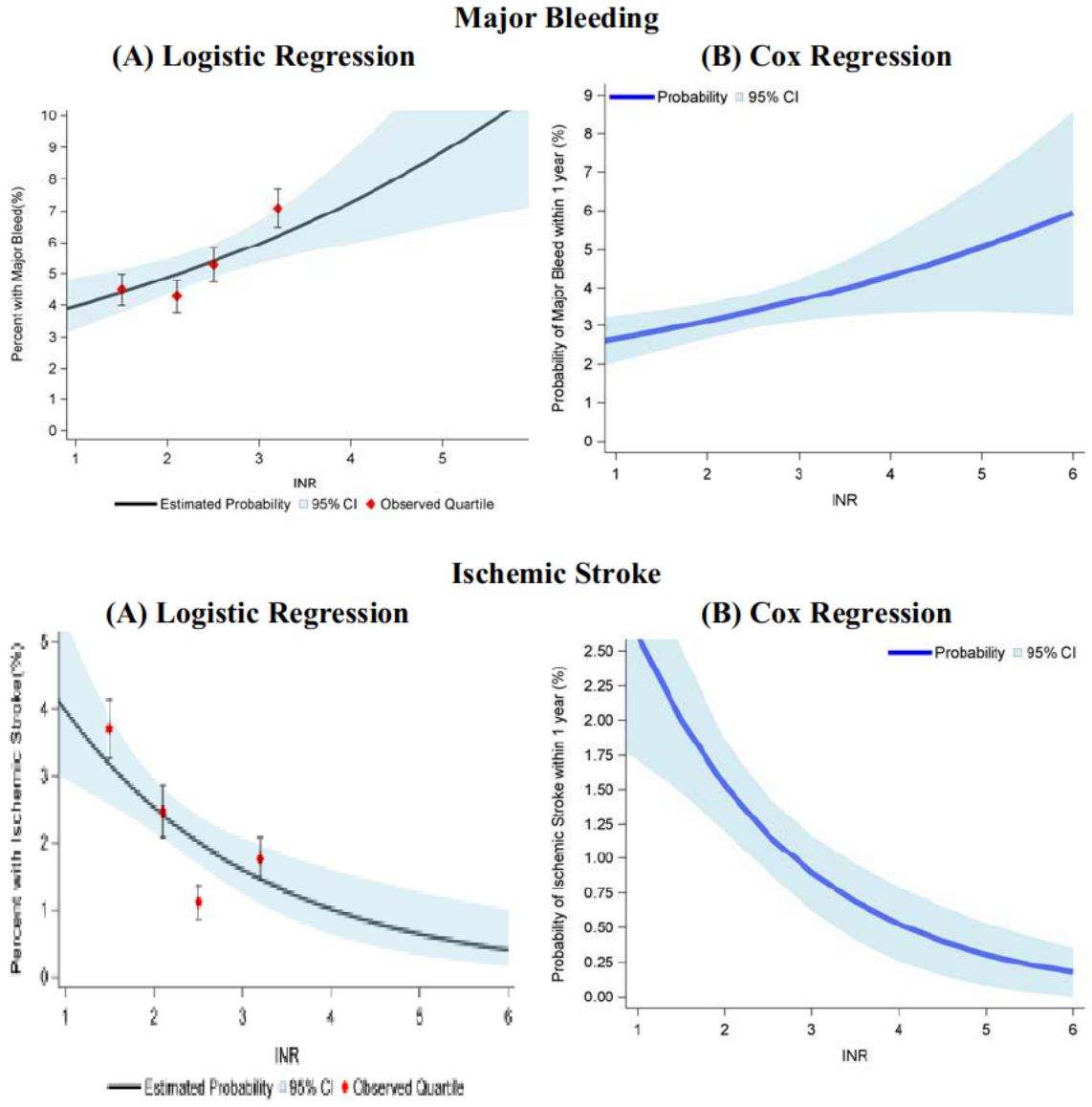

Figure 5 Probability of major bleeding and ischemic stroke by the last observed INR (before or at an event) for warfarin (per-protocol, on treatment analysis set). (A) Linear logistic regression model and (B) Cox regression model with a plot indicating probability of an event within 1 year.

3.5 Does concomitant aspirin use affect the safety and efficacy of rivaroxaban and warfarin?

The concomitant use of aspirin during the double blind phase (≥50% of time) significantly increased the risk for major bleeding with rivaroxaban (Figure 6 & Table 2). The pre-dose PT-major bleeding relationship for rivaroxaban was steeper among the aspirin users. However, concomitant aspirin use seemed not to have a significant effect on the efficacy outcome (ischemic stroke). These observations were consistent with various levels of aspirin use (Yes/No, ≥25%, 50%, 75% or 90% during the double blind

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phase). The concomitant aspirin use with warfarin in ROCKET-AF also had similar results as described in Figure 6 and Table 2 (See Appendix 1 for details). Patients should be made aware that concomitant aspirin use with rivaroxaban will increase the risk for bleeding.

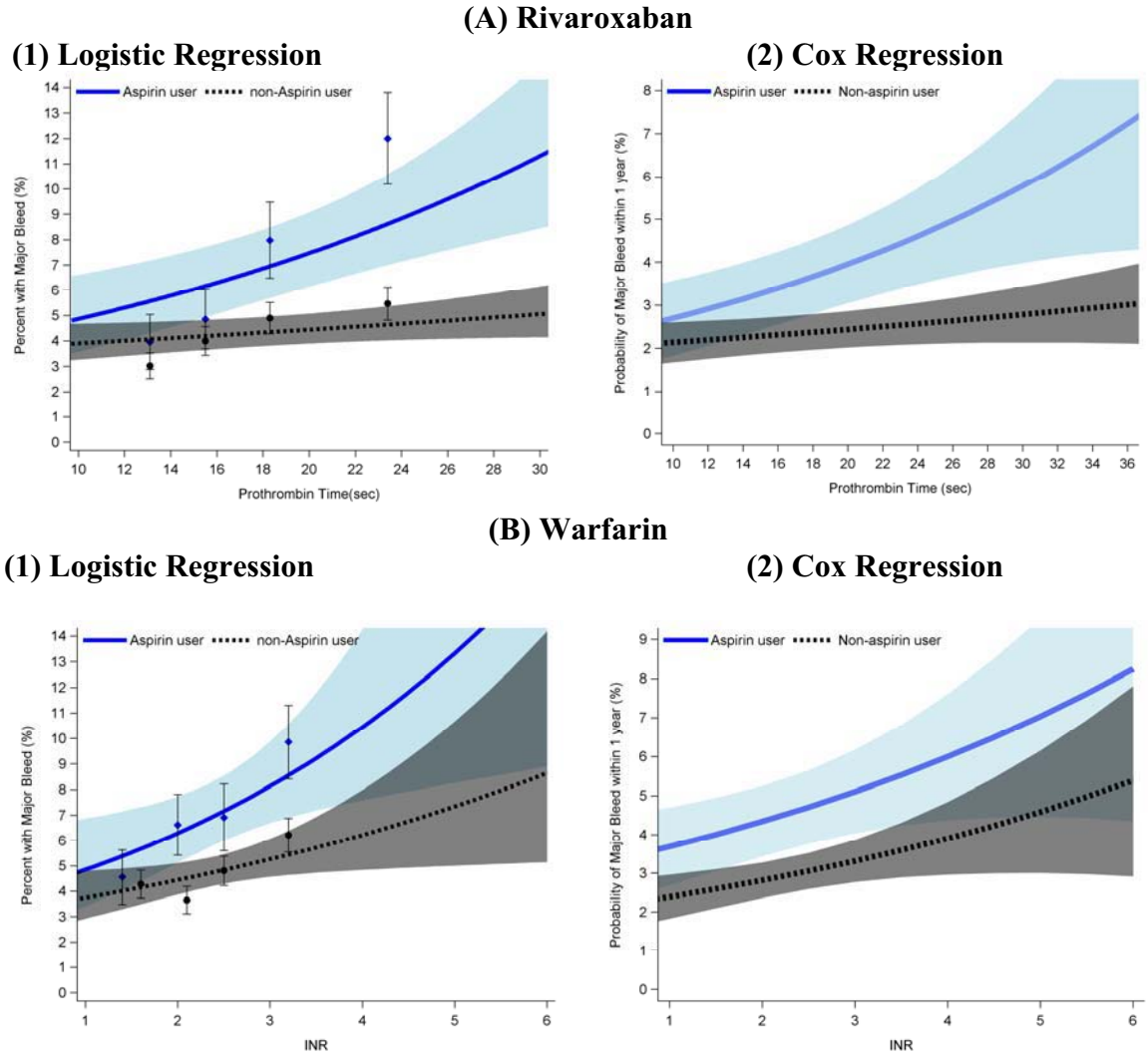

Figure 6 Relationship between probability for major bleeding and PD with or without the concomitant aspirin use during the double blind phase (≥ 50% of time) in ROCKET-AF for (A) rivaroxaban and (B) warfarin. (1) Linear logistic regression model and (2) Cox regression model with a plot indicating probability of an event within 1 year (per-protocol, on treatment analysis set).

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Table 2 Concomitant aspirin use during the double blind phase (≥ 50% of time) increased event rate for bleeding for both (A) rivaroxaban and (B) warfarin, but did not change event rate for ischemic stroke significantly (per-protocol, on treatment analysis set).

(A) Rivaroxaban (N 7008)				
Endpoint	Aspirin user (N 1577)		Non-Aspirin user (N 5431)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Primary efficacy endpoint	40 (2.5)	1.69	150 (2.8)	1.73
Ischemic stroke	31 (2.0)	1.31	119 (2.2)	1.38
Primary safety endpoint	407 (25.8)	19.9	1050 (19.3)	13.6
Major bleeding	135 (8.6)	5.82	257 (4.7)	3.02

(B) Warfarin (N 7046)				
Endpoint	Aspirin user (N 1664)		Non-Aspirin user (N 5382)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Primary efficacy endpoint	57 (3.4)	2.26	185 (3.4)	2.13
Ischemic stroke	37 (2.2)	1.47	124 (2.3)	1.43
Primary safety endpoint	399 (24.0)	18.4	1034 (19.2)	13.4
Major bleeding	118 (7.1)	4.76	260 (68.8)	3.03

3.6 Is there a need for dose adjustments in patients with renal and hepatic impairment?

Renal and hepatic impairment increased the exposures to rivaroxaban relative to normal subjects (Figure 7). The increase in PT (as AUC-PT) in subjects with moderate and severe renal impairment was more than the observed increase in exposures. In subjects with Child-Pugh B hepatic impairment approximately 2-fold increase in exposure and PT were observed (NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo).

In ROCKET-AF study a reduced dose of 15 mg was used in patients with moderate renal impairment to achieve exposures similar to that observed in normal subjects receiving the 20 mg dose. The event rates (100 pt-yr) for critical organ bleeding, defined as intracranial, intraspinal, intraocular, perichardial, intra-articular, intramuscular with compartment symptom or retroperitoneal bleeding, were comparable (0.76 vs 0.83) between patients with moderate renal impairment (receiving 15 mg dose) and patients with mild renal impairment or patients with normal renal function (receiving 20 mg dose). The efficacy of rivaroxaban compared to warfarin also was similar across the renal function categories (Ref. ROCKET-AF Study report 39039039AFL3001, page 164). The bleeding risk across all three renal function categories was also similar between rivaroxaban and warfarin (Ref. ROCKET-AF Study report for 39039039AFL3001, page

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209). Therefore, we recommend a reduced dose of 15 mg once daily in patients with moderate renal impairment, as studied in ROCKET-AF study.

Since the increase in exposure observed in moderate and severe renal impairment are comparable (1.5 vs 1.6 fold increase relative to normal) and have similar effect on PD measurements (AUC-PT), a 15 mg dose should be suitable for severe renal impairment as well.

Moderate hepatic impairment results in 2.3 fold increase in rivaroxaban exposure and a 2.1 fold increase in AUC-PT. Therefore, we recommend a dose of 10 mg once daily in patients with moderate hepatic function (Child-Pugh B) to match rivaroxaban exposures to those observed in normal subjects with the 20 mg dose.

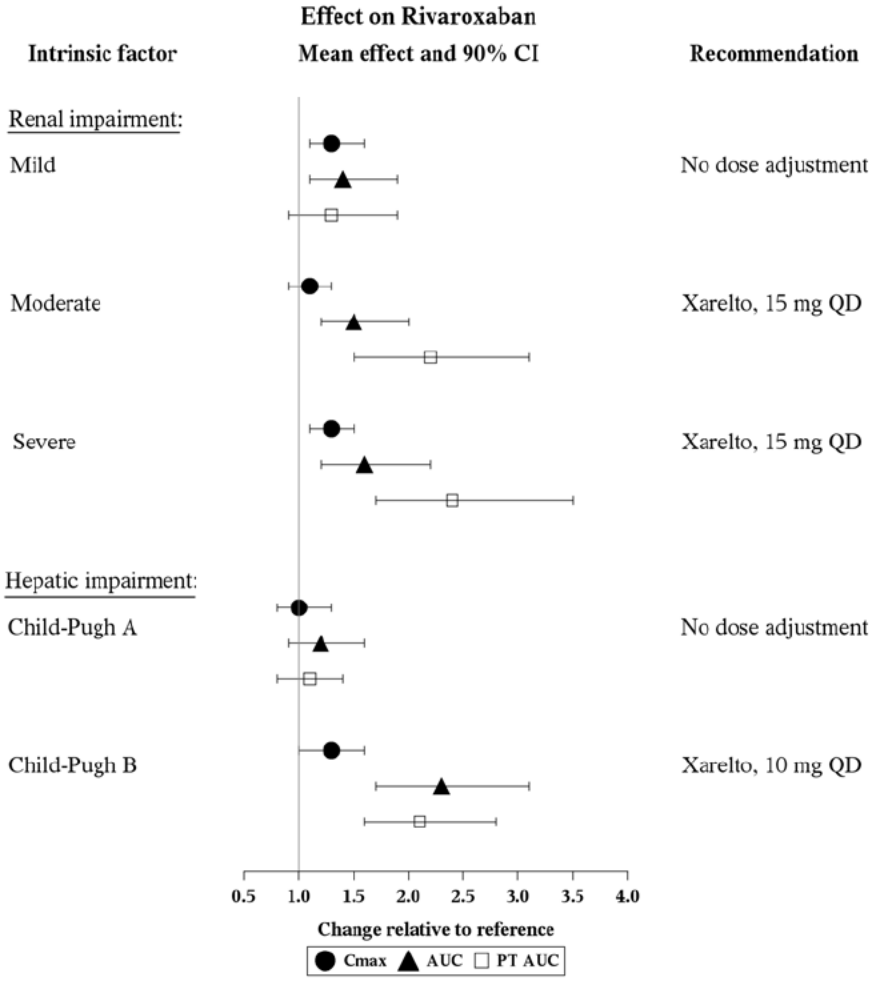

Figure 7 Effect of renal and hepatic impairment on the PK (as AUC and C_{max}) and PD (as AUC-PT) of rivaroxaban. Data from dedicated renal and hepatic impairment study with 10 mg rivaroxaban dose is shown. The X-axis represents changes in PK and PD relative to subjects with normal renal/hepatic function. Creatinine clearance 50-79 ml/min Mild, 30-49 ml/min Moderate, 15-29 ml/min Severe for renal impairment. Dose recommendations made on the basis of exposure matching.

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3.9 What is the impact of food on rivaroxaban exposure?

Rivaroxaban at 20 mg dose has significant food effect (Food increases exposure by ~ 39%). In ROCKET-AF study, patients took rivaroxaban with the evening meal as it minimizes the chance for variability in exposure. Therefore, rivaroxaban should be administered daily with the evening meal for the proposed indication.

3.10 What is a safe strategy to transition patients from rivaroxaban to warfarin?

In the ROCKET-AF, after the pre-specified number of adjudicated clinical events was accrued (N 405), sites were notified to close out ongoing subjects. Subjects then had an End of Study (EOS) visit as soon as possible but within approximately 30 days, and a post-treatment observation period with a follow-up visit approximately 30 days (± 5 days) after the EOS visit. At the EOS visit, subjects were transitioned from study drug to open-label VKA or other appropriate therapy as determined by the investigator. Importantly, the end-of-study transition from blinded study drug to open-label warfarin (or other VKA or antithrombotic therapy) was to be done without breaking the study blind. Hence, investigators were asked not to measure INR values for at least 3 days after last dose to preserve study blinding. After 3 days, VKA dosing was managed at the discretion of the treating physician using local unblinded INR measurements. Most of the patients who completed study drug treatment were transitioned to open-label warfarin within approximately 1-2 days after the last dose of the study drug in the double-blind phase. Exploratory analysis of the data in the post-treatment phase showed a significant rise in ischemic stroke events in patients who were on rivaroxaban compared to those on warfarin. From day 3 to day 30 after the last dose of study medication, 18/4587 (0.39%) ischemic stroke events occurred among completers in rivaroxaban compared to 4/4652 (0.09%) events in warfarin treated patients.

Similar results were seen with the add-on phase III study J-ROCKET as well. From day 3 to day 30 after the J-ROCKET study, there were more primary efficacy endpoint events in rivaroxaban patients than in warfarin treated patients (11 vs. 4 primary efficacy endpoint events in the ITT population) [Ref. Study number 12620, J-ROCKET study report, Pages 97-100].

Two potential hypotheses can be laid out to explain this increased event rates for ischemic stroke: 1) potential hypercoagulability (rebound blood coagulation after the withdrawal of an anticoagulant) due to the cessation of rivaroxaban treatment and 2) shorter half-life of rivaroxaban's effects (approximately 12 hours) in comparison to time required to reach therapeutic effect with warfarin that may lead to longer sub-optimal INR levels during transition. It is likely that there was a potential inadequate anticoagulation during the transition from rivaroxaban to warfarin therapy due to the absence of an appropriate bridging strategy.

To explore which of these hypotheses are more likely, a comparison of the incidence of ischemic strokes in the first 30 days following randomization in warfarin naïve patients treated with warfarin (8/2634, ie 0.30 %) and the last ~30 days following completion of

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study in patients treated with rivaroxaban during the double-blind phase (18/4587, ie 0.39 %) was made. Since the incidence rates were different initially and comparable at the end of the 30 day period for the two groups (0.30 vs. 0.39%) it may be assumed that the hypercoagulability due to the cessation of rivaroxaban treatment is less likely (See Figure 8). It is more likely that an optimal transition strategy was not implemented following the completion of ROCKET-AF study.

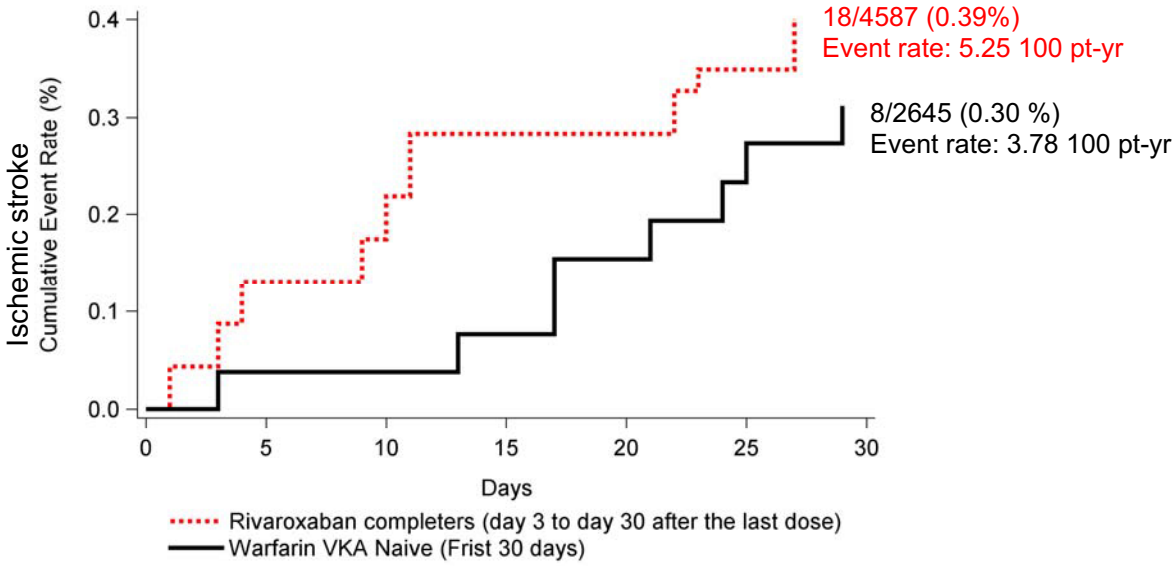

Figure 8 Kaplan-Meier curves for ischemic stroke events for patients who were on rivaroxaban and completed treatment during day 3 to day 30 after the last study medication (red dotted line) and VKA naïve patients on warfarin during the first 30 days of ROCKET-AF study (black solid line).

Given the inadequate strategy in ROCKET studies, a reasonable transition strategy for switching patients from rivaroxaban to warfarin can be derived based on the time-course of the effects of rivaroxaban and warfarin. A concomitant administration of rivaroxaban and warfarin for 2 days or more can be a useful strategy (See Figure 8). The strategy ensures an INR ≥ 2 during the transition period is reached sooner. Rivaroxaban should be stopped once the observed pre-dose INR is ≥ 2 and the INR should be maintained within the target range of 2-3 for warfarin. Since rivaroxaban is recommended to be dosed with the evening meal, for the purpose of monitoring INR during the transition, the INR measurement on the next day (ie, after 16 hours post-dose) can serve as the pre-dose INR for the decision to stop rivaroxaban. The INR should be measured on the daily during transition until the INR ≥ 2.

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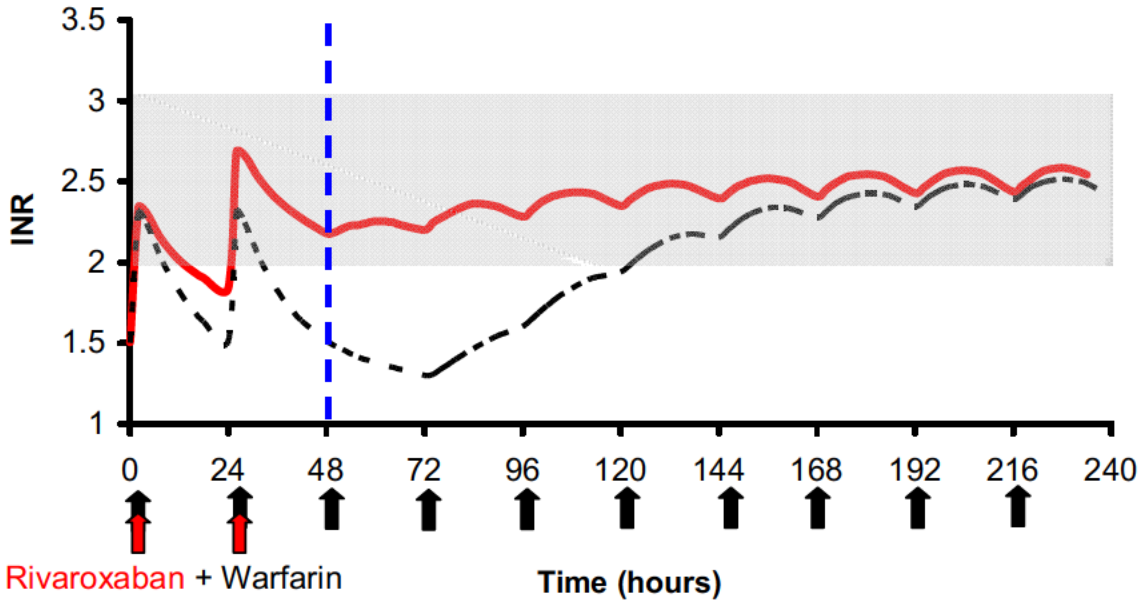

Figure 9 Time-course of INR for two transition strategies. The proposed strategy is represented by red solid-line as INR profile in an average patient after two days of concomitant rivaroxaban and warfarin (rivaroxaban and warfarin dosing indicated as red and black block arrows respectively). The strategy that may have been used in ROCKET-AF study is black dashed-line representing the INR profile in an average patient when open-label warfarin regimen was started with a gap of 24 hours after the last rivaroxaban dosing day (warfarin dose started at 72 hours in the plot). Target INR range of 2 to 3 is marked with the grey-shaded band. The vertical blue dashed line indicates the end of rivaroxaban treatment for both strategies.

APPENDIX 1 – ROCKET-AF ANALYSIS

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4 BACKGROUND

ROCKET-AF was a randomized, multi-center, double-blind, double-dummy, parallel group, active-controlled, event-driven Phase III study with a total of 14,269 subjects randomized to rivaroxaban (20 mg once daily or 15 mg once daily if creatinine clearance was 30-49 ml/min) or dose-adjusted warfarin for an INR target of 2-3 in subjects with non-valvular atrial fibrillation with at least two of the risk factors such as congestive heart failure (CHF), hypertension, age≥75 years and diabetes or a prior history of stroke, TIA or systemic embolus events. Both rivaroxaban and warfarin treatment arms were well balanced in terms of baseline characteristics and had about 37-38% vitamin K antagonist naïve subjects in the safety population. Aspirin use during the double blind phase was limited to ≤ 100 mg. The primary endpoint was a composite of stroke or non-CNS systemic embolism and the study was designed to demonstrate that the efficacy of rivaroxaban was non-inferior to adjusted dose warfarin in the studied population. A non-inferiority margin of 1.46 (later changed to 1.38) for the hazard ratio was used in designing the study. The principal safety objective of this study was to demonstrate that rivaroxaban is superior to dose adjusted warfarin as assessed by the composite of major and non-major clinically relevant bleeding events. A brief schematic of the study design is presented in Figure 1 below:

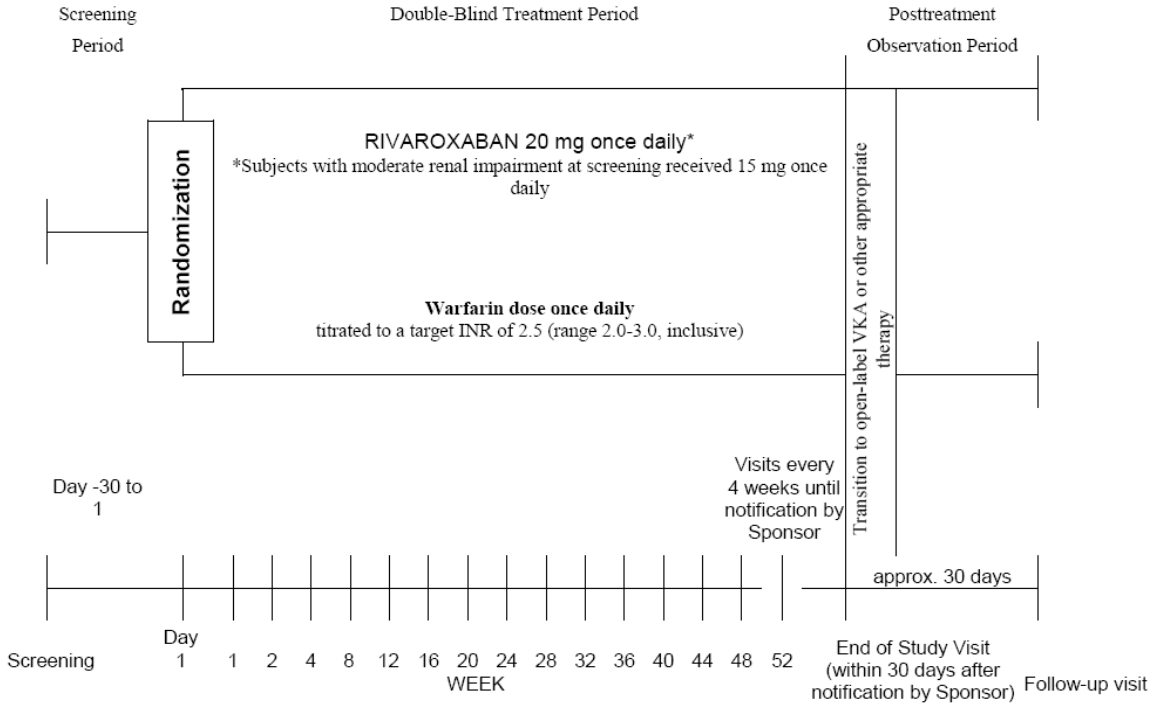

Figure 1 Flow diagram for ROCKET-AF study design. Source: Sponsor's submission Page 40, Figure 1: \\cdsesub1\EVSPROD\NDA202439\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\afib\5351-stud-rep-contr\39039039afl3001

The dose selection in ROCKET-AF was based on the results from two DVT studies (Study Number 11223 ODIXa-DVT and 11528 Einstein-DVT) and the sponsors

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concluded that a 20 mg once daily dose has desired safety and efficacy profile for investigation in subsequent studies. However, the once daily and twice daily regimens were not studied within a single study or in the target population and the dose-response relationships in the DVT studies were shallow over the studied dose-range and not adequately powered to explore the effects of different dosing regimen. Moreover, the recently concluded TIMI-ACS 46 study, a dose selection study conducted in subjects with acute coronary syndrome (ACS) covering a total daily dose range of 5 mg to 20 mg as once or twice daily regimen, showed a numerical advantage for safety and efficacy for the twice daily regimen. (Ref. Clinical study report ATLAS ACS TIMI 46, Page 99 and 137). The sponsor selected a twice daily regimen for their phase III ACS program based on the results from TIMI-ACS 46. The pharmacokinetic and pharmacodynamic characteristics of rivaroxaban suggest that a twice daily regimen might offer lower peak to trough ratio in prothormbin time (PT) within a dosing interval compared to the once daily regimen (See Figure 2). The clinical benefit of the difference in the peak to trough ratio and higher trough PT levels after a twice daily regimen cannot be derived from the existing data.

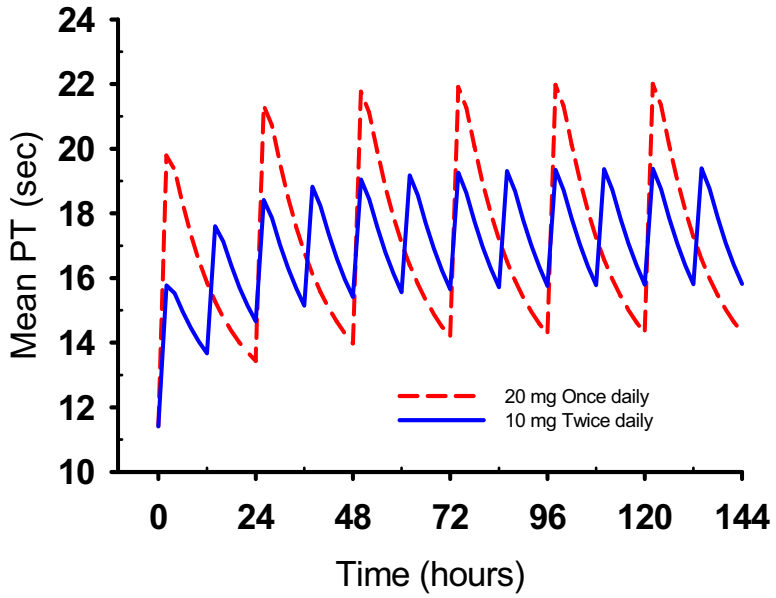

Figure 2 Simulated PT-time course for the PK-PD subset in ROCKET-AF for a total daily dose of 20 mg rivaroxaban, given as once daily (red-broken line) or as twice daily (blue-solid line). The simulations were based on rivaroxaban PK model and rivaroxaban PK-PT relationship presented in Figure 3.

There are no meaningful dose-ranging studies in the target population of subjects with atrial fibrillation. Hence it is not clear whether the 20 mg once daily dose selected in ROCKET-AF is optimal for the proposed indication. Nevertheless, the results from the ROCKET-AF study showed rivaroxaban 20 mg once daily to be non-inferior to dose-adjusted warfarin (Table 1).

Table 1 Top-line efficacy and safety analysis results from ROCKET-AF

Endpoint	Rivaroxaban		Warfarin		Rivaroxaban Vs. Warfarin	
	n/N	Event rate (100 pt-yr)	n/N	Event rate (100 pt-yr)	HR (95 % CI)	*p* value
Primary efficacy endpoint*	188/6958	1.71	241/7004	2.16	0.79 (0.66-0.96)	<0.001
Principal safety endpoint**	1475/7111	14.91	1449/7125	14.52	1.03 (0.96-1.11)	0.44

*Test for non-inferiority on primary efficacy endpoint based on treatment data from the per-protocol population

**Test for superiority on principle safety endpoint on treatment data from the safety population

A total of 786 time-matched pharmacokinetic-pharmacodynamic (PK-PD) samples were collected from a subset of 161 subjects (2% of per-protocol analysis set) and PD samples were collected during week 12 and 24 visits from all eligible subjects. The PD measures included prothrombin time (PT), factor Xa activity (FXa) and prothrombinase induced clotting time (PiCT). INR values from point-of-care Hemosense INRatio® Device and PT-INR derived directly from the measured PT were also provided by the sponsor. See Table 2 for PK-PD sampling schedule followed in ROCKET-AF study.

Table 2 PK-PD sampling schedule in ROCKET-AF. Source: Sponsor's submission Page 61, Table 5: \\cdsesub1\EVSPROD\NDA202439\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\afib\5351-stud-rep-contr\39039039afl3001

	Day 1	Between Week 2 and the End-of-Study Visit			Week 12[a]	Week 24[a]	At Least 1 Month, Preferably at Least 6 to 12 Months, After the First Matched PK/PD Sample[b]	
	Hours Predose	Hours Predose	Hours Postdose[c]				Hours Predose	Hours Postdose 1-3
			1-3	3-16				
PD sampling only (ALL subjects)	X[d]				X	X		
Matched[e] PK & PD blood sampling (select sites and subjects)[f]		X	X	X			X	X[g]

PD=pharmacodynamic; PK=pharmacokinetic; PT= prothrombin time; FXa= factor Xa; PiCT= Prothrombinase-induced clotting time;

[a] PD sampling was to be taken as either a predose or postdose sampling for the Weeks 12 and 24. Predose or postdose sampling had to be documented.

[b] As close to the end-of-study visit as possible.

[c] Postdose samples were taken after supervised study drug administration; study drug was to be administered in the evening.

[d] Only subjects enrolled at sites participating in the matched PK/PD substudy had a baseline PD sample collected. The baseline sample was to be drawn either at screening or on Day 1 (before dosing).

[e] Matched samples = PD blood samples to determine coagulation characteristics (PT, FXa activity, PiCT) taken at the same time points as PK blood samples.

[f] On days of matched PK/PD sample collections, subjects may have been confined to the study site.

[g] If agreed to by the subject.

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All the PD measurements were found to be dependent on rivaroxaban concentration (Figure 3) in subjects with the matching PK and PD samples. This is in agreement with observations from other PK and PD studies for rivaroxaban (Ref. OCP Review, NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo).

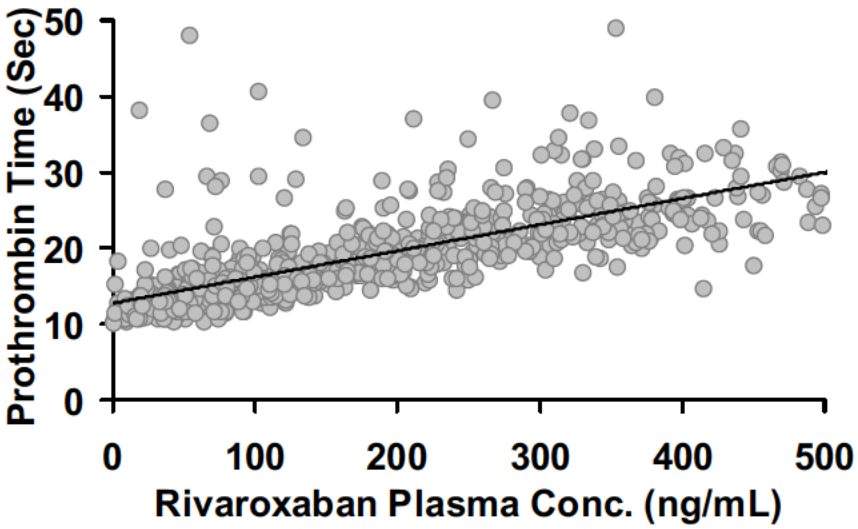

Figure 3 Prothrombin time increases linearly with rivaroxaban concentration. Time matched plasma concentrations of rivaroxaban and PT measures available from the PK-PD subset (161 subjects) of ROCKET-AF are shown. Solid black curve is the trend line.

Therefore, PT measurement, measured at week 12 or week 24 whichever is closer to an event (efficacy/safety), was used as a surrogate for PK. The PD-Outcome analyses were conducted for rivaroxaban using PT as the primary PD measure and the last observed INR value closer to an event was used for similar analyses in the warfarin group.

4.1 PHARMACOMETRIC ANALYSIS

4.1.1 INTRODUCTION

Independent analyses were conducted to explore the relationship between the PD measurements and efficacy as well as safety outcomes in the ROCKET-AF study. All available PD measures (PT, FXa, PiCT, PT-INR and last observed INR) were used in the analyses with a focus on the PT-Outcome relationships. The focus on PT as a surrogate was because PT could be converted to INR for comparison with warfarin. A comparative analysis was performed in the warfarin treatment arm using the last observed INR before or on the date of the endpoint of interest (INR is the most widely used PD marker for warfarin).

These analyses were conducted to address the following review questions:

- What are the characteristics of the PD-Outcome relationship of rivaroxaban for safety?

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- What are the characteristics of the PD-Outcome relationship of rivaroxaban for efficacy?
- What is the PD-Outcome relationship for warfarin in ROCKET-AF study?
- Does concomitant aspirin use affect the safety and efficacy of rivaroxaban and warfarin?

4.1.2 OBJECTIVES

The primary objectives included:

1. Evaluate the relationship between the PT measurements at weeks 12 or 24 (closest to the event) and probability of ischemic stroke for rivaroxaban
2. Evaluate the relationship between the PT measurements at weeks 12 or 24 (closest to the event) and probability of major bleeding for rivaroxaban
3. Evaluate the relationship between the last observed INR and probability of ischemic stroke for warfarin
4. Evaluate the relationship between the last observed INR and probability of major bleeding for warfarin

Other objectives included:

1. Relationship between other PD markers and efficacy outcomes for rivaroxaban
2. Relationship between other PD markers and safety outcomes for rivaroxaban

4.1.3 PD-EFFICACY ANALYSIS

4.1.3.1 Data and Methods

All the analyses presented here were done on the per-protocol dataset provided by the sponsor. The PD samples were collected at week 12 and week 24 in almost all subjects in ROCKET-AF (sponsor's dataset: adpd.xpt). To examine any PD-efficacy relationship, a PD measurement that is collected closer and prior to the event of interest was used (last observed PD before an event). For example, if a subject had an efficacy event after week 24, PD measurement at week 24, if available, was used in the analysis. To approximate an on-treatment analysis, the time period from randomization to the last dose of study medication plus 2 days were chosen. If an outcome event did not occur during this timeframe, time was censored at the last dose of study medication plus 2 days. Only time to the first event was considered in the analysis (sponsor's dataset: adtteef3.xpt).

4.1.3.2 Logistic Regression

To examine the relationship between PD and efficacy outcome, subjects were binned into quartiles based on their PD measurements. The observed probability for an efficacy event in each quartile (number of event/ number of subjects in a quartile) was calculated and plotted against the median value of PD measurements for each quartile.

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A logistic regression was used to predict the probability of an efficacy event as (1) a linear or (2) an E_{max} function of a PD measurement.

Linear logit (pi) ln (pi/1-pi) logit $P_0 + \beta_1 \bullet$ PD (1)

E(max) logit (pi) logit P_0+ logit $P_{max} \bullet$ (PD)/(β_{50}+PD) (2)

where pi is the probability of an event; β_1 is the additive effect on the log of the odds for a unit change in PD; P_0 is the probability of event at PD 0; *logit* P_{max} is the additive effect on the log of the odds related to PD (*i.e.* very high value of PD); β_{50} is the value of PD that produces 50% of logit P_{max}. Equation 2 is a nonlinear function relating probability of an event and PD.

A logistic regression model with a better fit was chosen for plotting. An overlay-plot with observed probability in each quartile of PD as well as a predicted probability from the regression model was used to display the relationship between a PD measurement and an efficacy outcome.

4.1.3.3 Time to Event Analysis

Time to first occurrence of ischemic stroke was modeled with a Cox proportional hazard (PH) model:

$$\lambda(t \mid X) = \lambda_0(t)\exp(\beta' X).$$

This expression gives the hazard at time t for an individual with a linear function of covariates, where β' is coefficient vector for a set of fixed covariates X.

To identify potential covariates in a model, a bivariate analysis of the association between each covariates (dataset: adsl.xpt) and survival time was performed. Potential covariates tested included age, sex, race, body weight, baseline creatinine clearance, prior stroke/TIA/systemic embolism, baseline CHADS2 score, diabetes mellitus, hypertension, myocardial infarction, prior VKA and PPI use and aspirin use during double blind period.

All covariates that were close to be significant in the bivariate analysis ($p < 0.20$) and other covariates that were judged to be of clinical importance (e.g. age) were selected in the final model fitting. The reduced model was then fitted and a covariate was considered to be significant at p value <.05. Once a reasonable "main effect" model was selected, biologically plausible interaction terms were tested and significant interaction terms ($p < .05$) were retained to derive the final model. Further, an alternative method using the stepwise selection, which consists of forward selection ($p < .05$) followed by backward elimination steps ($p > .05$), was employed to verify the covariate selection in the final model. The proportional hazard assumption was checked by plotting the weighted Schoenfeld residuals against the log survival time. All the analyses and plots were conducted and generated in SAS 9.2.

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4.1.3.4 Prothrombin Time-Ischemic Stroke Relationship for Rivaroxaban

A subset of rivaroxaban per-protocol analysis set [n 6193/7008 (88%)], which included all subjects with a PT measurement closer to an ischemic stroke event, was used in this analysis. The majority of PD samples (~78%) were collected during 12-24 hours post-dose representing trough levels of PD (referred to as pre-dose PD in subsequent sections). The distribution of sampling time for PT measurements is presented in Figure 4.

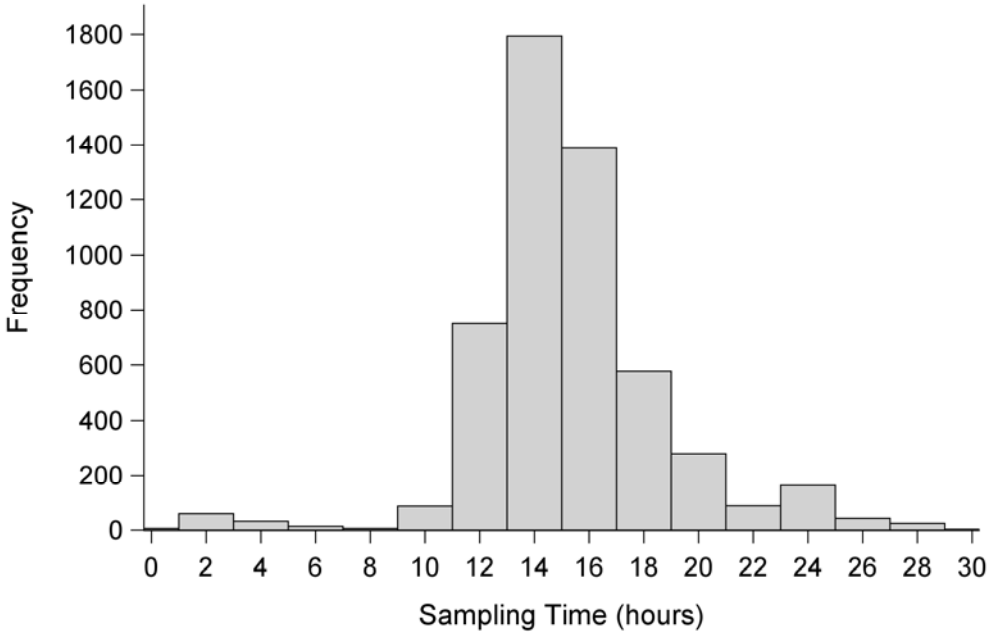

Figure 4 Distribution of PT sampling times in PT-Ischemic stroke subset (n 6193). Majority of the PT samples were collected during the 12-24 hrs post dose window.

A total of 124 ischemic stroke events were included in this subset [83% of ischemic strokes (n 150) in the per-protocol population]. The observed and predicted probability (un-adjusted association) of ischemic stroke by pre-dose PT is shown in Figure 5. This analysis shows that there is no pre-dose PT dependent decrease in ischemic stroke over the range of 10-30 seconds. A sensitivity analyses that included subjects with PT measured between 12-24 hours and 12-15 hours after the dose (limit the subset with trough level of PD) were conducted and showed consistent results as demonstrated in Figure 5.

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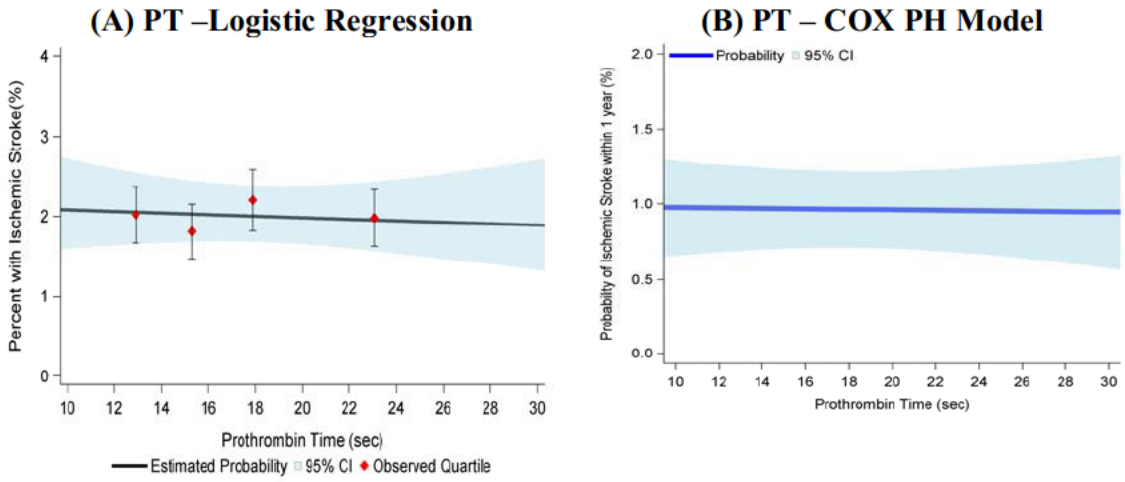

Figure 5 Probability of ischemic stroke as a function of PT and for rivaroxaban. (**A**) Logistic regression. The solid line represents the predicted probability from an unadjusted linear logistic regression. The points represent the observed probability at the median pre-dose PT and the error bar represents standard error for a given quartile. (**B**) Cox PH model. The blue line represents probability of ischemic stroke within 1 year by pre-dose PT for rivaroxaban in ROCKET-AF from the Cox PH model. The shaded regions represent the 95% confidence interval in both plots.

A Cox PH model was used to examine the relationship between pre-dose PT and time to the first ischemic stroke while controlling for potential covariates. Baseline body weight and prior stroke/TIA/embolism were identified as significant risk factors. After adjusting for the covariates, the pre-dose PT remained unassociated with the probability of ischemic stroke but was included in the model for the illustration purpose. Table 3 shows the parameter estimates from the final Cox PH model. The mean predicted probability for ischemic stroke within one year according to PT was calculated from the model and illustrated in Figure 5**.** The results demonstrated the lack of association between PT and ischemic stroke in ROCKET-AF.

Table 3 Parameter estimates of the final pre-dose PT-ischemic stroke model†

Parameter	Estimate (SE)	Hazard Ratio*(95% CI)	P value
Baseline body weight (kg)	-0.01 (0.006)	0.89 (0.80-0.99)	0.04
Prior stroke/TIA/non-CNS Systemic Embolism (Yes vs. No)	0.71 (0.20)	2.11 (1.42-3.14)	0.0005
Pre-dose PT (sec)	-0.001 (0.01)	0.99 (0.77-1.26)	0.92

†The region was used as a stratification variable for model fitting to account for different baseline risk across regions

* Hazard ratio for continuous predictors was calculated for 10 units increase for baseline body weight and PT.

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4.1.3.5 Other PD measures-Ischemic Stroke Relationship for Rivaroxaban

Further analyses with different PD measurements (Pre-dose Factor Xa activity, PiCT, PT-INR and last observed INR from the point-of-care device) and ischemic stroke events were performed for rivaroxaban (Figure 6).

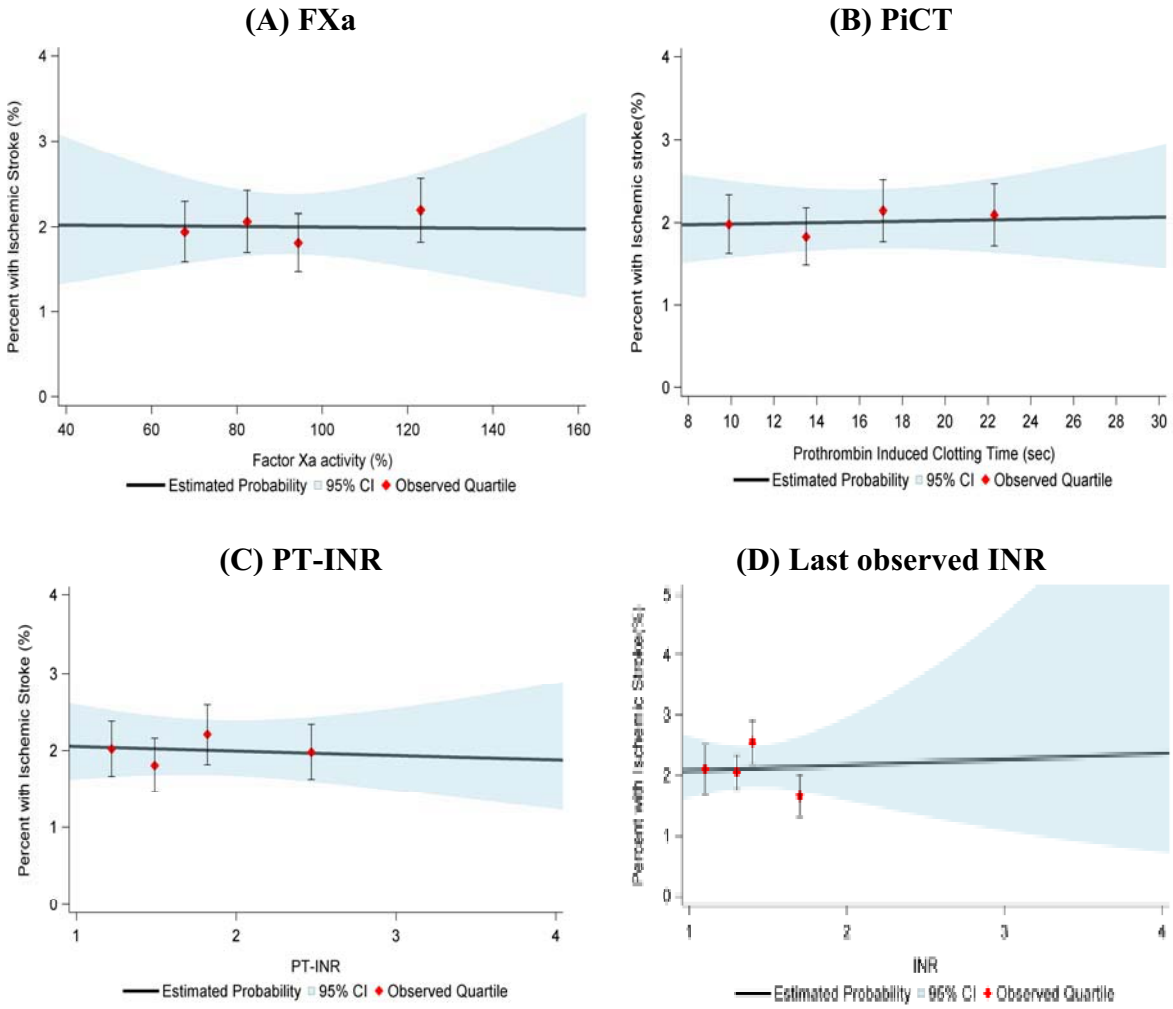

Figure 6 Probability of ischemic stroke as a function of (**A**) pre-dose Factor Xa activity and (**B**) Pre-dose PiCT (**C**) Pre-dose PT-INR and (**D**) Last observed INR from the point-of-care device for rivaroxaban. The solid line represents predicted probability from an unadjusted linear logistic regression and the shaded region represents the 95% confidence interval. The red points represent the observed probability at the median pre-dose PD and the error bars represent standard errors for a given quartile.

In addition to ischemic stroke, primary efficacy endpoint defined as a composite of stroke and non-CNS systemic embolism was also used to examine the PD-Efficacy relationship. In the per-protocol analysis set (N 7008), there were total of 190 primary efficacy endpoint events and the results were in agreement with PD-ischemic stroke relationships.

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Overall, the results demonstrated the lack of association between any PD measurements used and efficacy endpoints for rivaroxaban. These observations were consistent with the findings from the PT-ischemic stroke analysis (see Section above).

4.1.3.6 Last observed INR-Ischemic Stroke Relationship for Warfarin

The dataset used for this analysis included all warfarin treated subjects in the per-protocol analysis set for whom there were available INR and ischemic stroke information. The last observed INR was defined as the last measured INR value prior to or on the date of ischemic stroke event (censored date if no event). In the ROCKET-AF study, the INRs were measured using a point-of-care device at the study centers for warfarin and an INR of greater than 6 were truncated to 6.1. To avoid the bias associated due to truncation of INR, the analysis excluded patients with INR greater than 6.0 (i.e., n 82; 3 ischemic stroke events excluded). A total of 6,878 subjects with 156 ischemic stroke events were included in the final dataset (ischemic stroke events was 161/7046 in per-protocol warfarin analysis set). Figure 7 illustrates the observed and predicted probability with ischemic stroke by the last observed INR. The results showed that the probability of ischemic stroke reduction was dependent on the last observed INR for warfarin with the smallest observed probability for stroke ranged between INR of 2 and 3 (target INR range).

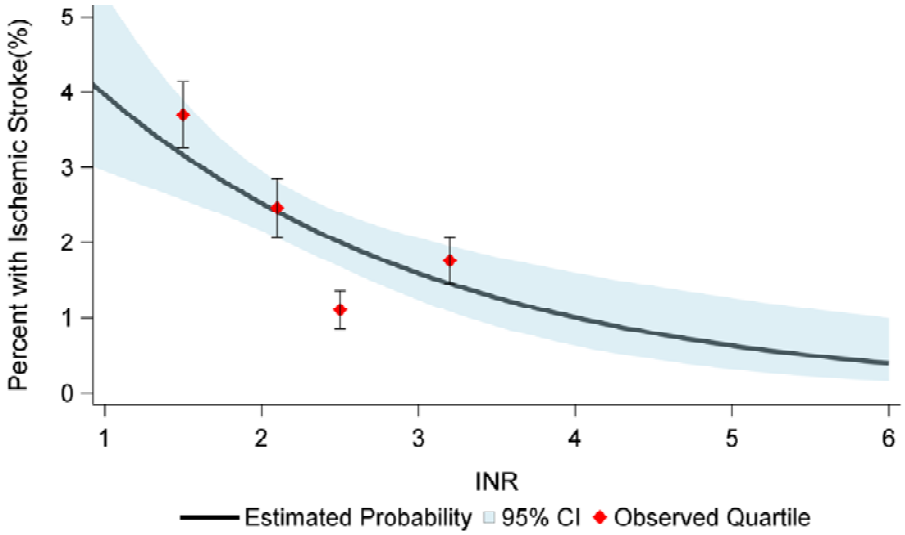

Figure 7 Probability of ischemic stroke as a function of the last observed INR (from point-of-care device) for warfarin. The solid line represents predicted probability from an unadjusted linear logistic regression and the shaded region represents the 95% confidence interval. The red points represent the observed probability at the median INR and the error bars represent standard error for a given quartile.

The Cox PH model was employed to examine the association between the last observed INR and ischemic stroke, while controlling for covariates. The analyses identified baseline body weight, CHADS2 score, and congestive heart failure (CHF) in addition to

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the last observed INR as independent predictors of ischemic stroke. Table 4 shows the parameter estimates from the final Cox PH model.

Table 4 Parameter estimates of the final INR-ischemic stroke model in warfarin†

Parameter	Estimate (SE)	Hazard Ratio* (95% CI)	P value
Last observed INR	-0.54 (0.13)	0.58 (0.46-0.75)	<0.0001
Baseline body weight (kg)	-0.02 (0.005)	0.82 (0.74-0.91)	0.0002
Baseline CHADS2 score	0.33 (0.09)	1.39 (1.06-2.13)	0.0001
Baseline CHF (Yes vs. No)	0.40 (0.18)	0.67 (0.47-0.94)	0.02

† The region was used as a stratification variable for model fitting to account for different baseline risk across regions

* Hazard ratio was calculated for 1 unit increase for last observed INR and baseline CHADS2 score, and 10 units increase in baseline body weight

The mean predicted probability for ischemic stroke within one year as per the last observed INR was calculated from the model (Figure 8). Unlike the findings from pre-dose PT-ischemic stroke analysis for rivaroxaban, the probability of having ischemic stroke within a year for warfarin was dependent on the last observed INR. The results from the logistic regression and Cox PH analyses were consistent.

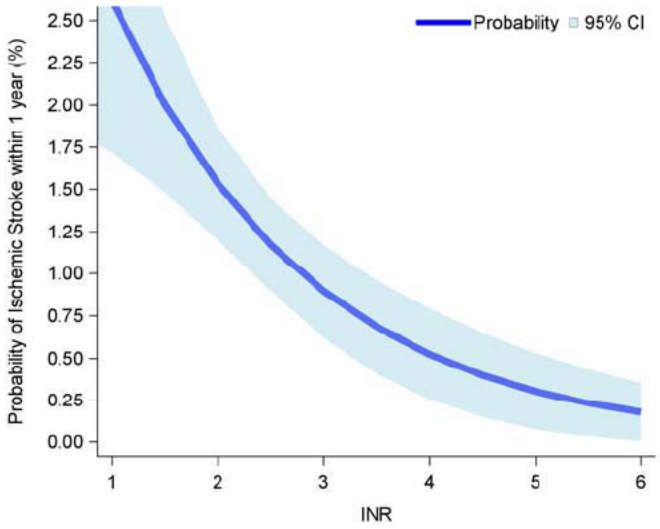

Figure 8 Probability of ischemic stroke within 1 year as a function of the last observed INR for warfarin in ROCKET-AF. The shaded region represents the 95% confidence interval.

4.1.4 PD-SAFETY ANALYSIS

4.1.4.1 Data and methods

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PD samples were collected at weeks 12 and 24 in all subjects in ROCKET-AF (dataset: adpd.xpt). To examine the PD-safety relationship, a PD measurement that was collected closer and prior to the target event (major bleeding, TIMI Major bleeding or PLOT bleeding for respective analyses) was used (i.e. the last observed PD measurement before an event). For example, if a subject had a safety event occurred after week 24, PD measurements at week 24, if available, were used in the analysis. To approximate an on-treatment analysis, the time period from the first dose to the last dose of study medication plus 2 days were chosen. If an outcome event did not occur during this timeframe, time was censored at the last dose of the study medication plus 2 days. Only time to the first event was considered (dataset: adtteepb.xpt).

4.1.4.2 Logistic Regression

To examine the relationship between PD and safety outcome, subjects were binned into quartiles based on their PD measurements. The observed probability for a safety event in each quartile (number of event/ number of subjects in a quartile) was calculated and plotted against the median value of PD measurements for each quartile.

A logistic regression was used to predict the probability of a safety event as (1) a linear or (2) an E_{max} function of a PD measurement.

Linear logit (pi) ln (pi/1-pi) logit $P_0 + \beta_1 \bullet$ PD (1)

E(max) logit (pi) logit P_0+ logit $P_{max} \bullet$ (PD)/(β_{50}+PD) (2)

where pi is the probability of an event; β_1 is the additive effect on the log of the odds for a unit change in PD; P_0 is the probability of event at PD 0; *logit* P_{max} is the additive effect on the log of the odds related to PD (*i.e.* very high value of PD); β_{50} is the value of PD that produces 50% of logit P_{max}. Equation 2 is a nonlinear function relating probability of an event and PD.

A logistic regression model with a better fit was chosen for plotting. An overlay-plot with observed probability in each quartile of PD as well as a predicted probability from the regression model was used to display the relationship between a PD measurement and a safety outcome.

4.1.4.3 Time to Event Analysis

Pre-dose PT and major bleeding were chosen as the primary PD marker and safety endpoint respectively for the model building. Major bleeding was chosen as a primary endpoint because it was defined in the protocol and provided a sufficient number of "serious" bleeding events for the analysis. Major bleeding event was defined as clinically overt bleeding associated with a decrease in hemoglobin ≥ 2g/dl, or a transfusion of ≥ 2 units of packed red blood cells or whole blood, or bleeding at a critical site, or a fatal outcome. Other definitions of serious bleeding events were also explored and documented in the later sections.

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Time to first occurrence of bleeding was modeled with a Cox proportional hazard (PH) model:

$$\lambda(t \mid X) = \lambda_0(t)\exp(\beta' X)$$

This expression gives the hazard at time t for an individual with a linear function of covariates, where β' is coefficient vector for a set of fixed covariates X. To identify the potential covariates in the model, bivariate analysis of the association between covariates (dataset: adsl.xpt) and survival time was performed.

Several potential covariates such as age, sex, race, body weight, baseline creatinine clearance, prior stroke/TIA/Embolism, baseline CHADS2 score, diabetes mellitus, hypertension, myocardial infarction, prior VKA and PPI use and aspirin use during double blind period were tested. Aspirin use was defined as ≥ 50% use during double blind treatment period. Sensitivity analyses using different definitions of aspirin use (any, ≥10, 25, 75, or 90% use) were also tested.

All covariates that were close to be significant in the bivariate analysis ($p < 0.20$) and other covariates that were judged to be of clinical importance (i.e. age) were selected. A reduced model was then fitted and a covariate was considered to be significant at p value <.05. Once a reasonable "main effect" model was selected, biologically plausible interaction terms were tested and significant interaction terms ($p < .05$) were retained to derive the final model. Further, an alternative method using the stepwise selection, which consists of forward selection ($p < .05$) followed by backward elimination steps ($p > .05$), was employed to verify the covariate selection in the final model. PH assumption was checked by plotting the weighted Schoenfeld residuals against log survival time. All the analyses and plots were conducted and generated in SAS 9.2.

Upon the request of the medical reviewers some of the exploratory analyses were stratified by region (US and Rest of the world).

4.1.4.4 Prothrombin Time-Major Bleeding Relationship for Rivaroxaban

A subset of rivaroxaban per-protocol analysis set [n 6172/7008 (88%)], including all subjects with an available PT measurement prior to the first major bleeding event, was used in this analysis. There were 306/392 (78% of total events) major bleeding events included in this subset. Table 5 shows the incidence and event rate (per 100 subject years) for the first major bleeding event according to the quartiles of pre-dose PT.

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Table 5 Incidence and event rate for the first major bleeding (Adjudicated by CEC) while on treatment (up to last dose plus 2 days) according to pre-dose PT

PT Quartiles	Rivaroxaban (PT-Major bleeding subset) N 6172	
	Incidence n (%)	Event Rate (100 pt-yrs)
Q1 (<14.2 sec)	49/1573 (3.12)	1.88
Q2 (14.2-<16.6 sec)	68/1543 (4.41)	2.54
Q3 (16.6-<19.8 sec)	78/1501 (5.20)	2.95
Q3 (≥19.8 sec)	111/1555 (7.14)	4.29

An increasing bleeding rate was observed in U.S. compared to the rest of the world for rivaroxaban. However, the sample size is relatively small in the U.S. to derive any meaningful conclusions (Table 6). Both incidence and event rate (per 100 subject-years) increased with pre-dose PT quartile.

Table 6 Incidence and event rate for the first major bleeding (Adjudicated by CEC) while on treatment (up to last dose plus 2 days) according to PT: US vs. Rest of the world

PT Quartiles	Rivaroxaban (PT-Major bleeding subset) N 6172			
	US (N 819)		Other countries (N 5353)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Q1 (<14.2 sec)	8/108 (7.4)	4.39	41/1465 (2.8)	1.69
Q2 (14.2-<16.6 sec)	15/172 (8.7)	4.38	53/1371 (3.9)	2.27
Q3 (16.6-<19.8 sec)	27/228 (11.8)	6.70	51/1273 (4.0)	2.27
Q4 (≥19.8 sec)	43/311 (13.8)	8.11	68/1244 (5.5)	3.30

Since rivaroxaban showed increased bleeding event rates across PT quartiles in the US compared to rest of the world, we looked into the bleeding event rates for warfarin across the last observed INR values (See Table 7). The major bleeding event rates were higher in the US than rest of the world for both rivaroxaban and warfarin.

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Table 7 Incidence and event rate for the first major bleeding (Adjudicated by CEC) while on treatment (up to last dose plus 2 days) according to last observed INR for Warfarin: US vs. Rest of the world

INR Quartiles	Warfarin (INR-Major bleeding subset) N 6877			
	US (N 946)		Other countries (N 5931)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Q1 (<1.8)	11/162 (6.8)	4.13	70/1646 (4.3)	2.98
Q2 (1.8-<2.2)	17/215 (7.9)	4.56	50/1349 (3.7)	2.24
Q3 (2.2-<2.7)	24/293 (8.2)	4.62	67/1435 (4.7)	2.83
Q3 (≥2.8)	32/276 (11.6)	7.10	94/1501 (6.3)	3.89

The observed and predicted probability with major bleeding by pre-dose PT (unadjusted association) is shown in Figure 9. This analysis showed that risk of major bleeding increased with pre-dose PT. In our dataset, majority of the PD samples (~78%) were collected during 12-24 hours post-dose, which represents through PTs. Sensitivity analyses only including subjects with PT measured between 12-24 hours and 12-15 hours showed consistent results as demonstrated here.

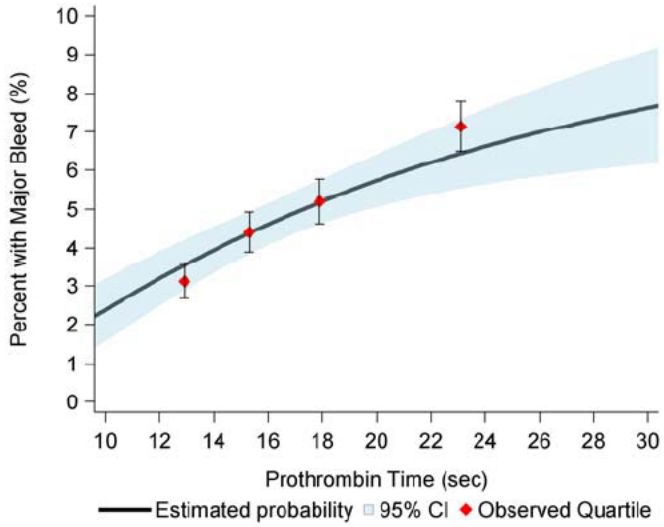

Figure 9 Probability of major bleeding as a function of pre-dose PT for rivaroxaban. The solid line represents the predicted probability from an E_{max} logistic regression and the shaded region represents the 95% confidence interval. The point represents the observed probability at the median value of pre-dose PT for a given quartile and error bars represent standard errors.

Further analysis of the pre-dose PT-major bleeding relationship demonstrated that the effect of PT on the risk for major bleeding was found to be modified by the aspirin use during the double blind phase (Figure 10). There are 1308/6172 (21%) subjects who had

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concomitant use of aspirin with rivaroxaban during treatment period. Aspirin use was defined as ≥ 50% use during double blind treatment period.

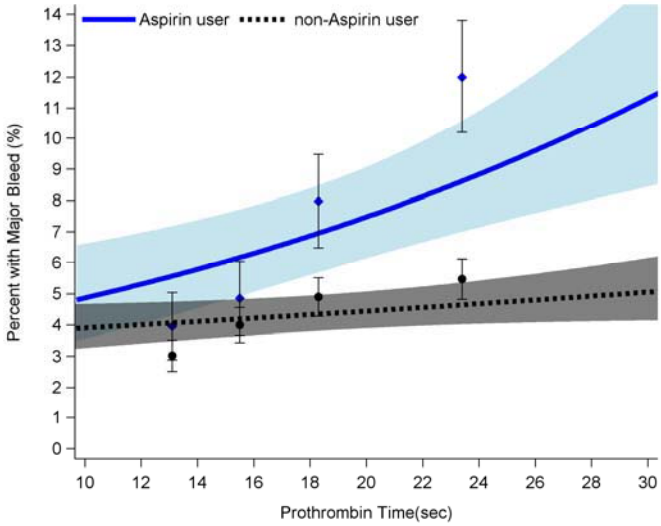

Figure 10 Predicted and observed probability of major bleeding as a function of pre-dose PT and Aspirin use (50 % use during double blind phase) for rivaroxaban in ROCKET-AF. The solid line represents the predicted probability from a linear logistic regression and the shaded region represents the 95% confidence interval. The point represents observed probability at the median PT of a given quartile.

Sensitivity analyses using different definitions of aspirin use (any, ≥10, 25, 75, or 90% use) showed similar results (See Figure 11). Subjects who used aspirin during rivaroxaban treatment had an increased risk of major bleeding compared to those who did not use aspirin. The pre-dose PT-major bleeding relationship was steeper among Aspirin users. These findings were observed in both U.S. and the rest of the world with the bleeding event rates increasing with PT quartiles among aspirin users (Table 8).

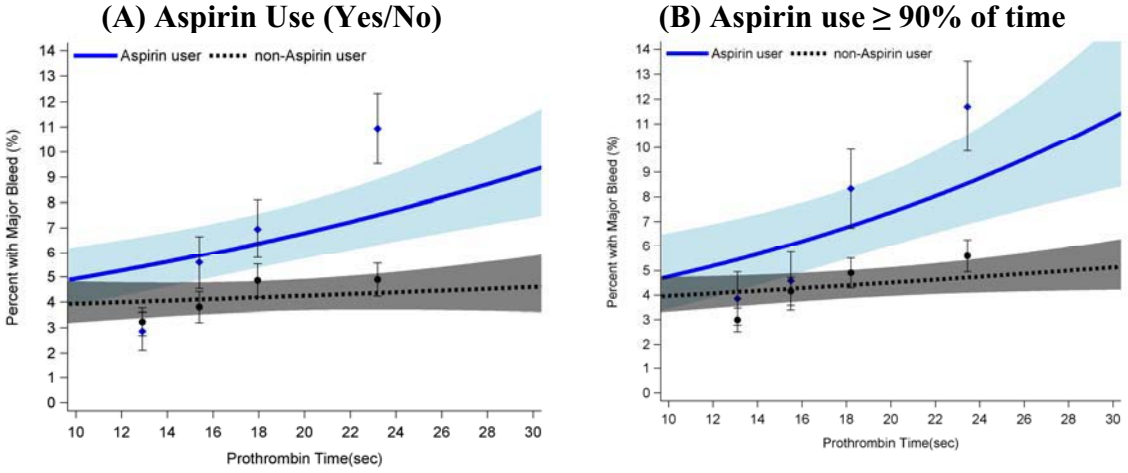

Figure 11 Sensitivity analysis for different levels of aspirin use during double blind phase: Predicted and observed probability of major bleeding as a function of pre-dose PT and Aspirin use (A) defined as Yes/No use and (B) ≥ 90% of time during double blind

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phase for rivaroxaban in ROCKET-AF. The solid line represents the predicted probability from a linear logistic regression and the shaded region represents the 95% confidence interval. The point represents observed probability at the median PT of a given quartile

Table 8 Incidence and event rate for the first major bleeding (Adjudicated by CEC) on treatment (up to last dose plus 2 days) according to PT and aspirin user in (A) US and (B) other countries

PT Quartiles	(A) US (N 819)			
	Aspirin user (N 286)		Non-aspirin user (N 533)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Q1 (<14.2 sec)	5/41 (12.2)	7.22	3/67 (4.5)	2.66
Q2 (14.2-<16.6 sec)	6/61 (9.8)	5.00	9/111 (8.1)	4.05
Q3 (16.6-<19.8 sec)	7/72(9.7)	5.39	20/156 (12.8)	7.32
Q4 (≥19.8 sec)	26/112 (23.2)	14.37	17/199 (8.5)	4.86
PT Quartiles	**(B) Other Countries (N 5353)**			
	Aspirin user (N 1022)		Non-aspirin user (N 4331)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Q1 (<14.2 sec)	7/269 (2.6)	1.60	34/1196 (2.8)	1.71
Q2 (14.2-<16.6 sec)	9/259 (3.5)	2.01	44/1112 (4.0)	2.34
Q3 (16.6-<19.8 sec)	15/242(6.2)	3.52	36/1031 (3.5)	1.98
Q4 (≥19.8 sec)	19/252(7.5)	4.89	49/992 (4.9)	2.93

A Cox PH model was used to examine the relationship between PT and time to the first major bleeding event while controlling for potential covariates. Age, baseline body weight, baseline proton pump inhibitor use, and PT by aspirin use interaction were identified as significant risk factors. Table 9 shows the parameter estimates and hazard ratios from the final Cox PH model. The parameter of PT by aspirin use interaction was of marginal significance (p 0.06) but was included in the final model. Similar results were obtained when sensitivity analyses were conducted for different definition for Aspirin use (any, ≥10, 25, 75, or 90% use). After adjusting the covariates, there is increased risk of major bleeding with increased PT and the magnitude of that is larger among subjects who had concomitant use of aspirin with rivaroxaban (for 10 sec increased in PT, there is 47% increase in the risk of major bleeding among the aspirin users compared to 14% increase in non-aspirin users). The mean predicted probability of major bleeding within one year according to PT and aspirin use was calculated from the model and illustrated in Figure 12.

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Table 9 Parameter Estimates and Hazard Ratio from Cox-Proportional Hazard model for the association between PT and major bleeding†

Parameter	Estimate (SE)	P value
Age (years)	0.04 (0.01)	<0.0001
Baseline body weight (kg)	0.008 (0.003)	0.02
PPI use at baseline	0.36 (0.15)	0.01
PT (sec)	0.04 (0.01)	0.8
Aspirin use(> 50%) during double blind phase	-0.09 (0.30)	0.76
PT*Aspirin use (>50% use)	0.03 (0.01)	0.06
Parameter	**Hazard ratio (95 % CI)**	
Age (10 year increase)	1.50 (1.28-1.75)	
Baseline body weight (10 kg increase)	1.04 (1.02-1.06)	
PPI use at baseline (Yes or No)	1.44 (1.08-1.92)	
Aspirin user (10 sec increase in PT)	1.47 (1.18-1.85)	
Non-Aspirin user (10 sec increase in PT)	1.14 (0.98-1.32)	

† The region was used as a stratification variable for model fitting to account for different baseline risk across regions

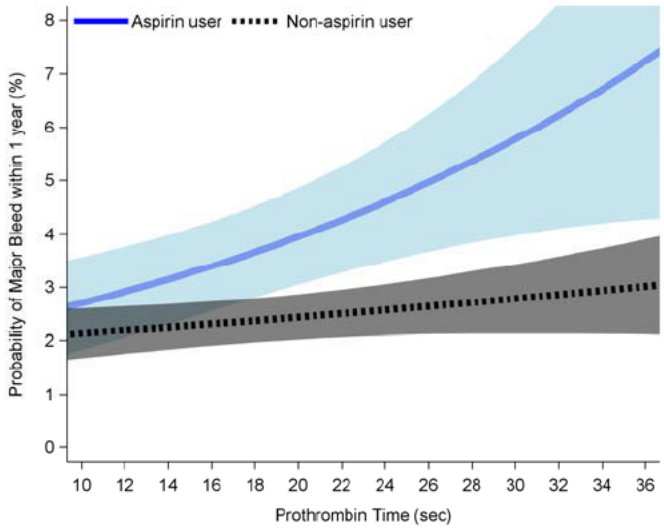

Figure 12 Probability of major bleeding within 1 year as a function of pre-dose PT and aspirin use for rivaroxaban in ROCKET-AF. The shaded region represents the 95% confidence interval.

4.1.3.5 Other PD measures-Bleeding Relationship for Rivaroxaban

Analyses with different pairs of PD measurements (Pre-dose FXa, PiCT, PT-INR and last observed INR from point-of-care device) and safety endpoints were performed for rivaroxaban (Figure 13, Figure 13). In addition to major bleeding event, TIMI major

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bleeding and potential life/organ threatening major bleeding event (PLOT) were also used for the analysis (dataset:adtteepb.xpt).

(A) PT-TIMI Major Bleeding **(B) PT-PLOT Bleeding**

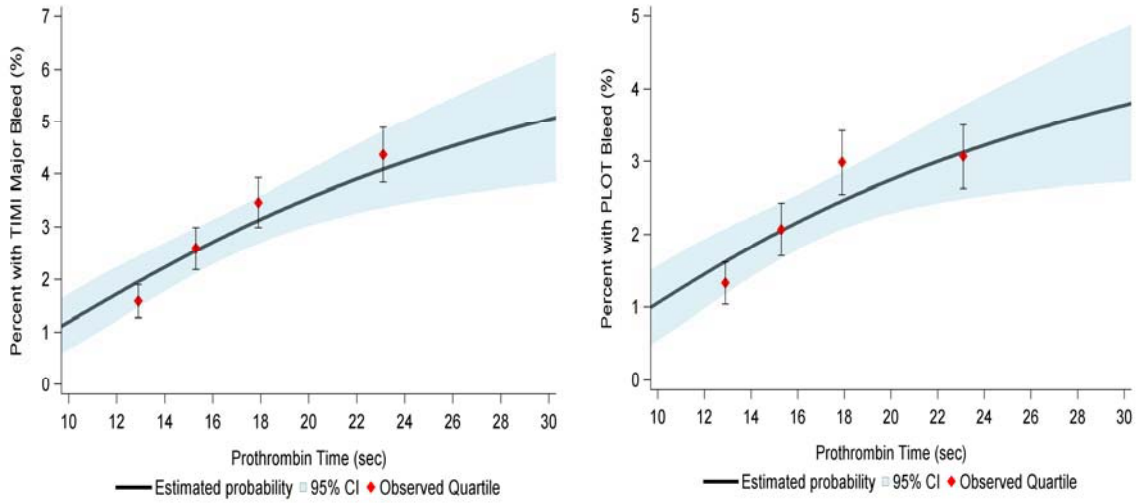
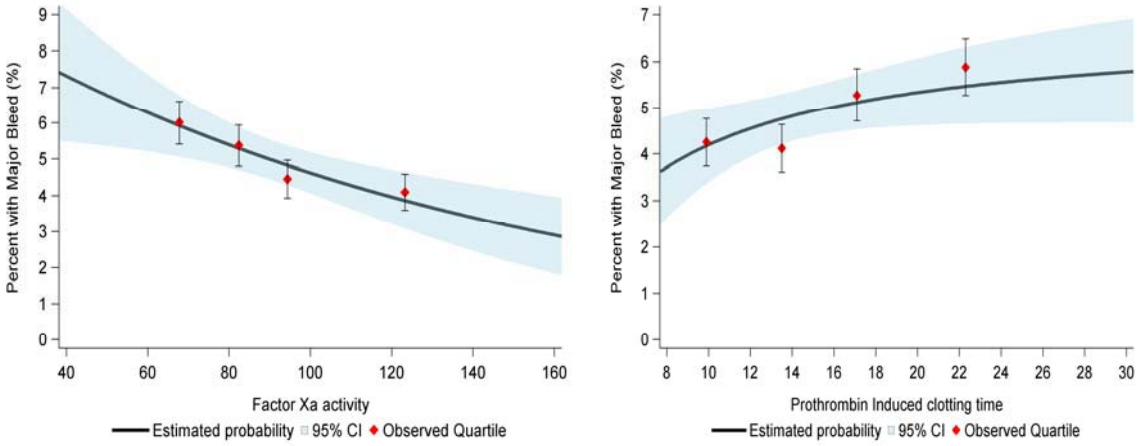


Figure 13 Probability of (A) TIMI major bleeding and (B) PLOT major bleeding as a function of pre-dose PT for rivaroxaban. The solid line represents the predicted probability from a E_{max} logistic regression and the shaded region represents the 95% confidence interval. The point represents observed probability at the median value of pre-dose PT and error bar represents standard error for a given quartile.

(A) FXa-Major Bleeding **(B) PiCT-Major Bleeding**



(C) PT-INR **(D) Last observed INR**

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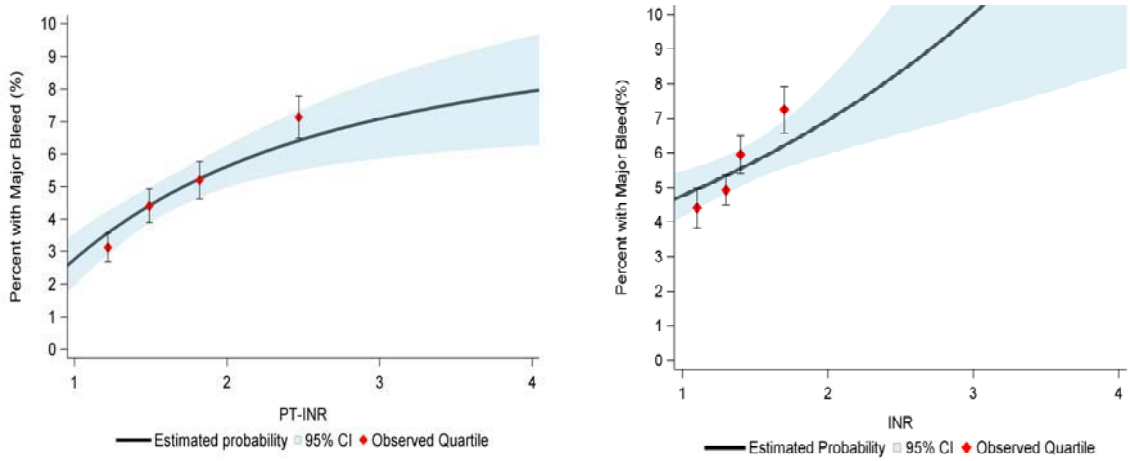

Figure 14 Probability of major bleeding as a function of (A) pre-dose FXa activity (B) pre-dose PiCT for rivaroxaban (C) PT-INR and (D) Last observed INR from the point of care device for rivaroxaban. The solid line represents the predicted probability from an E_{max} logistic regression and the shaded region represents the 95% confidence interval. The point represents observed probability at the median PD activity and error bar represents standard error for a given quartile.

Overall, all the results demonstrated that the risk of bleeding was associated with all pre-dose PD measurements for rivaroxaban. The results were consistent with the findings from our primary analysis of pre-dose PT-major bleeding relationship.

4.1.3.6 Last observed INR-Bleeding Relationship for Warfarin

The dataset used for this analysis comprised of all warfarin subjects in the per-protocol analysis set for whom there were available INR and major bleeding information. The last observed INR was defined as the last measured INR value prior to or on the date of first major bleeding event (censored date if no event). In the ROCKET-AF study, the INRs were measured using a point of care device at the study centers and an INR of greater than 6 was truncated to 6.1. To examine a fair relationship between continuous INR and major bleeding, those whose last observed INR equaling to 6.1 were excluded (n 82, 10 major bleeding events excluded). A total of 6,877 subjects with 365 major bleeding events were included in the final dataset (378/7046 major bleeding events in the per-protocol analysis set). Figure 15 illustrates the observed and predicted probability of major bleeding by the last observed INR. The result showed that major bleeding increased with the increase in the last observed INR for warfarin.

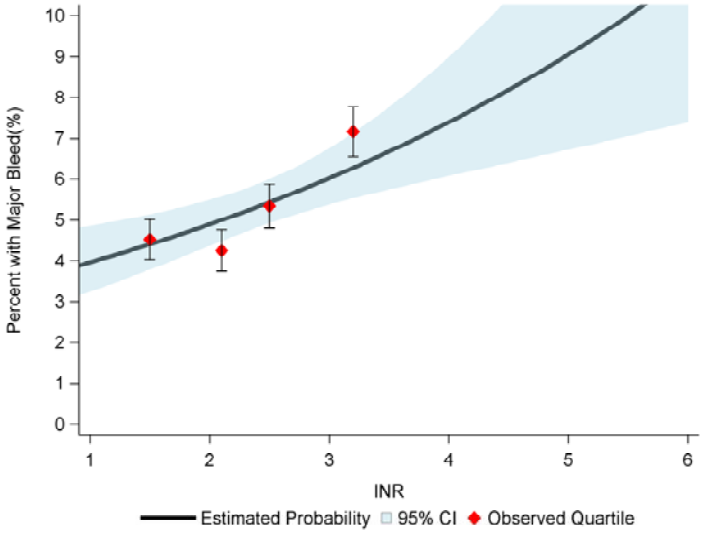

Figure 15 Probability of major bleeding as a function of the last observed INR for warfarin. The solid line represents the predicted probability from a linear logistic regression and the shaded region represents the 95% confidence interval. The red points represent the observed probability at the median value of INR and error bars represent standard errors for a given quartile.

The potential interaction between aspirin use (≥50% use) and the last observed INR for major bleeding risk was also explored. There were 1613/6877 (23%) subjects who had concomitant use of aspirin with warfarin during treatment period. Aspirin use was defined as ≥ 50% use during double blind treatment period. The combined effect of aspirin and INR on the major bleeding on warfarin seems more like an addictive effect instead of an interaction effect (changes of slope) observed for rivaroxaban (Figure 16).

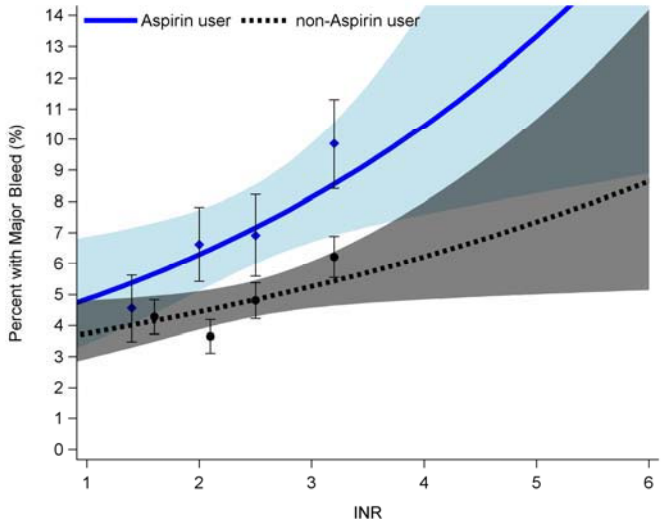

Figure 16 Predicted and observed probability of major bleeding as a function of the last observed INR and Aspirin use for warfarin in ROCKET-AF. The solid line represents the predicted probability from an unadjusted linear logistic regression and the shaded region

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represents the 95% confidence interval. The point represents observed probability at the median INR and the error bar is the standard error for a given quartile.

A Cox PH model was used to examine the relationship between INR and time to the first major bleeding event while controlling for potential covariates. Sex, baseline creatinine clearance, baseline proton pump inhibitor use, diabetes mellitus and age by aspirin use interaction were identified as significant risk factors. Interaction between INR and aspirin use was not significant (p 0.32). Table 10 shows the parameter estimates from the final Cox PH model. The mean predicted probability of major bleeding within one year according to the last observed INR and aspirin use was calculated from the model and illustrated in Figure 17.

Table 10 Parameter estimates from the Cox-Proportional Hazard model for the association between last observed INR and major bleeding for warfarin†

Parameter	Estimate (SE)	Hazard Ratio (95% CI) *	P value
Age (years)	0.02 (0.008)	1.20 (1.03-1.40)	0.02
Sex (female)	-0.27 (0.11)	0.77 (0.61-0.96)	0.02
Baseline creatinine clearance	-0.008 (0.003)	0.93 (0.88-0.98)	0.004
Diabetes mellitus (Yes vs. No)	0.27 (0.11)	1.32 (1.07-1.62)	0.01
Last observed INR	0.15 (0.07)	1.16 (1.02-1.32)	0.02
Aspirin use during double blind phase (Yes vs. No)	0.39 (0.11)	1.48 (1.18-1.85)	0.02

† The region was used as a stratification variable for model fitting to account for different baseline risk across regions

* Hazard ratio was calculated for 1 unit increase for last observed INR, and 10 units increase in age and baseline creatinine clearance

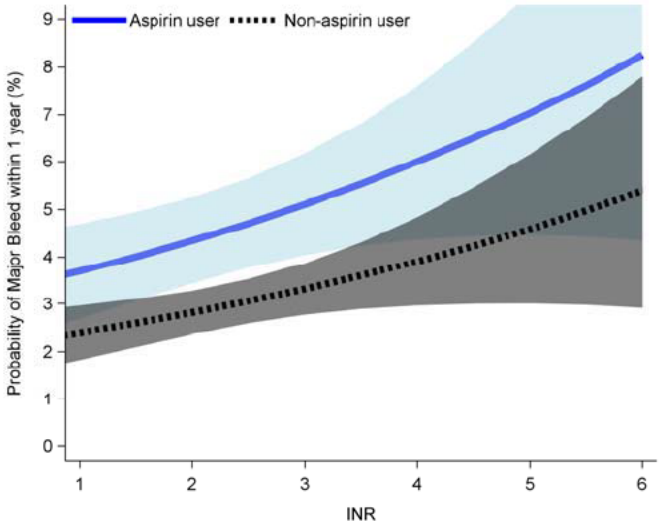

Figure 17 Probability of major bleeding within 1 year as a function of the last observed INR and aspirin use for warfarin in ROCKET-AF study. The shaded region represents the 95% confidence interval.

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4.1.5 Impact of concomitant aspirin use - Comparison of Rivaroxaban and Warfarin

The results from the PD-safety analyses showed that concomitant aspirin use during the double blind phase increases the risk of major bleeding in both rivaroxaban and warfarin treatment groups (See Figure 19). The use of aspirin seemed to modify the effect of pre-dose PT on the risk of major bleeding for rivaroxaban. That is, the risk of major bleeding significantly increased with PT among aspirin users but had a shallow relationship among non-aspirin user. However, the concomitant use of aspirin seemed not to affect the risk for ischemic stroke in both rivaroxaban and wafarin groups (aspirin use was not included in the final Cox PH models) (See Figure 19). These results might be partially due to insufficient power to identify risk factors for ischemic stroke. Although the risk of ischemic stroke is not statistically significant between aspirin users or non-aspirin users in rivaroxaban, a decreasing trend in risk reduction with increased PT was observed among aspirin users. There seemed to be no difference in ischemic stroke risk reduction between aspirin users and non-aspirin users in warfarin.

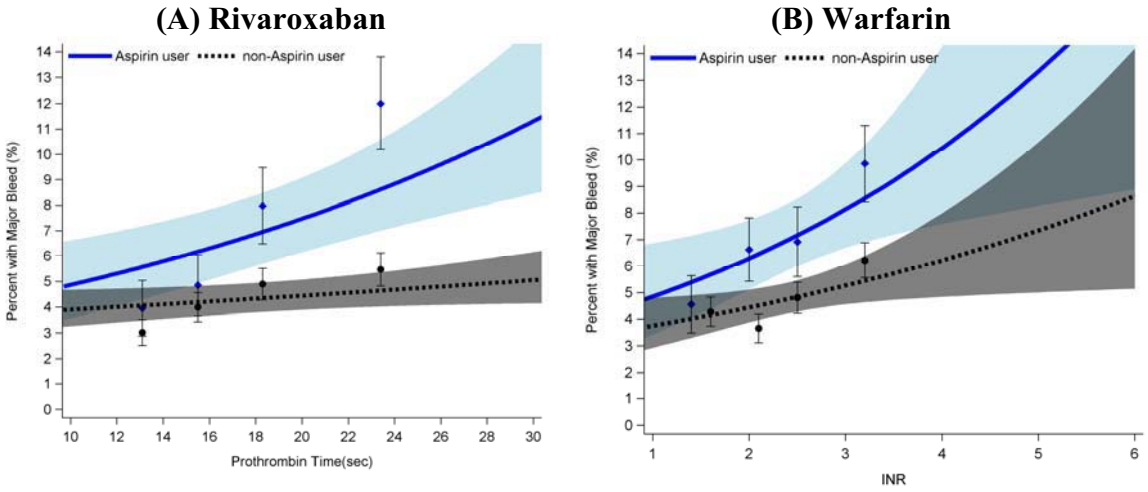

Figure 18 Predicted and observed probability of major bleeding by (**A**) Pre-dose PT and Aspirin use for rivaroxaban and (**B**) Last observed INR and Aspirin use from ROCKET-AF. Aspirin use is defined as ≥ 50% use during double blind period.

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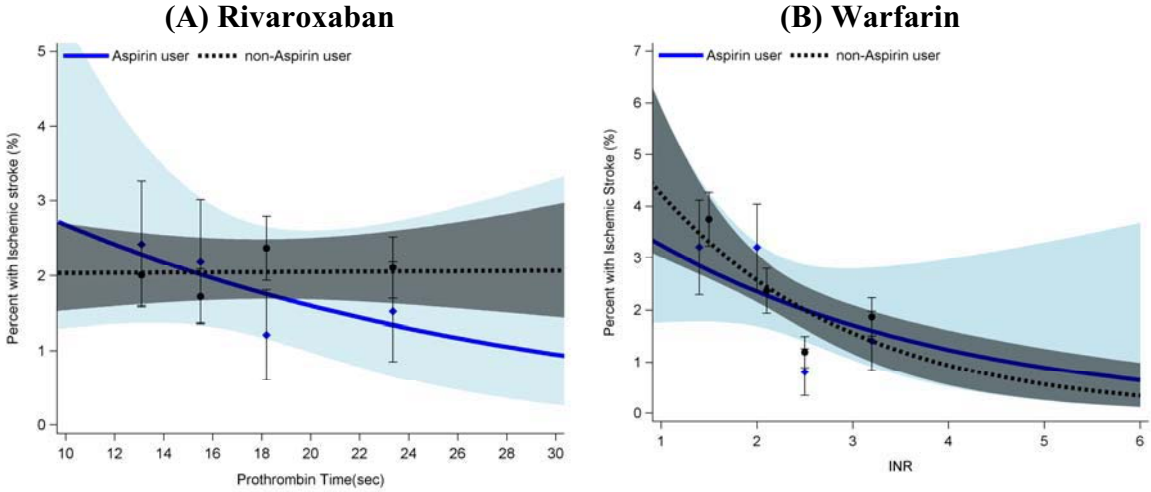

Figure 19 Predicted and observed probability of ischemic stroke by (**A**) Pre-dose PT and Aspirin use for rivaroxaban and (**B**) Last observed INR and Aspirin use from ROCKET-AF. Aspirin use is defined as ≥ 50% use during double blind period.

The analyses comparing the risk of major bleeding and ischemic stroke between aspirin and non-aspirin users are potentially confounded by the unobserved factors that govern the use of aspirin. It might be more reasonable to compare aspirin users and non-aspirin users between treatment arms with regards to risk of having efficacy and safety endpoints. In addition, it is important to know whether or not concomitant use of aspirin with rivaroxaban is associated with exceeding risk in major bleeding compared to that with warfarin.

Table 11 shows the incidence and event rate for efficacy and safety endpoints by treatment groups and aspirin use (≥ 50% use during double blind) in per-protocol analysis set. Between aspirin users treated with rivaroxaban and warfarin, the event rate for all the efficacy endpoints is numerically in favor of rivaroxaban, especially primary efficacy endpoint and hemorrhagic stroke. On the other hand, the event rate for major bleeding event is numerically in favor of warfarin. Specifically, the higher event rate of major bleeding in rivaroxaban is primary driven by the two components: hemoglobin drop ≥ 2 g/dl and transfusion ≥ 2 units. The aspirin users in rivaroxaban had significantly reduced risk of occurrence of major bleeding event in critical organ compared to those in warfarin (HR: 0.42, 95% CI: 0.24-0.76). Non-aspirin users between treatment groups have similar results across efficacy and safety endpoints.

Table 11 Incidence and event rate for efficacy and safety endpoints by treatment group, (A) Rivaroxaban and (B) warfarin, and aspirin use during double period.

Endpoint	(A) Rivaroxaban (N 7008)			
	Aspirin user (N 1577)		Non-Aspirin user (N 5431)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Primary efficacy endpoint	40 (2.5)	1.69	150 (2.8)	1.73
Ischemic Stroke	31 (2.0)	1.31	119 (2.2)	1.38
Hemorrhagic Stroke	6 (0.38)	0.25	23 (0.42)	0.27
Primary Safety Endpoint	407 (25.8)	19.9	1050 (19.3)	13.6
Major Bleeding	135 (8.6)	5.82	257 (4.7)	3.02
Hemoglobin drop	118 (7.5)	5.07	184 (3.4)	2.15
Transfusion	79 (5.0)	3.37	102 (1.9)	1.19
Critical Organ Bleeding	16 (1.0)	0.67	75 (1.4)	0.87
Death	7 (0.4)	0.29	20 (0.4)	0.23

Endpoint	(B) Warfarin (N 7046)			
	Aspirin user (N 1664)		Non-Aspirin user (N 5382)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Primary efficacy endpoint	57 (3.4)	2.26	185 (3.4)	2.13
Ischemic Stroke	37 (2.2)	1.47	124 (2.3)	1.43
Hemorrhagic Stroke	15 (0.9)	0.60	34 (0.6)	0.39
Primary Safety Endpoint	399 (24.0)	18.4	1034 (19.2)	13.4
Major Bleeding	118 (7.1)	4.76	260 (4.8)	3.03
Hemoglobin drop	76 (4.6)	3.05	172 (3.2)	2.0
Transfusion	50 (3.0)	2.0	96 (1.8)	1.11
Critical Organ Bleeding	40 (2.4)	1.59	90 (1.7)	1.04
Death	15 (0.9)	0.60	40 (0.7)	0.50

4.1.6 Impact of concomitant aspirin use –Analysis for Warfarin in RE-LY

To further explore the effects of concomitant use of aspirin with anticoagulants on efficacy and safety outcomes, we also conducted similar analysis using data from the control arm of the RE-LY study submitted in support of dabigatran (NDA 022-512) approval. The dataset used for this analysis comprised of all warfarin subjects for whom there were available INR and outcome information. The last observed INR was defined as the last measured INR value prior to or on the date of targeted event (censored date if no event). A total of 6011 subjects with 133 ischemic stroke events and 249 TIMI major bleeding events (central adjusted event) were included in the dataset. To conduct the exploratory analysis, subjects were first stratified by the aspirin use during the double period (Yes/No) and then divided into 4 quartiles within each stratum based on INR value. The observed probability of an outcome event in each quartile (number of event/ number of subjects in a quartile) by aspirin use was calculated. A logistic regression was used to predict the probability of an event as a function of the last observed INR. An overlay plot with an observed probability at the median INR for each quartile as well as

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the predicted probability from the regression model by the aspirin use was created to visually display the relationship (Figure 20).

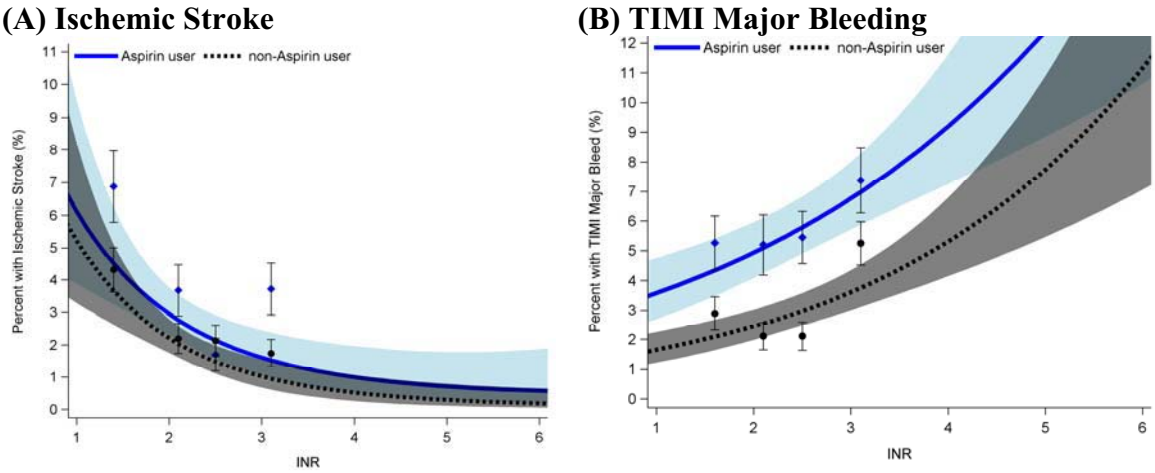

Figure 20 Predicted and observed probability of (A) ischemic stroke and (B) TIMI Major Bleeding by last observed INR and Aspirin use for warfarin in RE-LY study.

The exploratory analysis showed that the aspirin use did not seem to affect risk of ischemic stroke, while demonstrating an additive effect on the risk of TIMI major bleeding for warfarin arm in the RE-LY study. These results were in agreement with our findings for warfarin in the ROCKET-AF study.

4.1.7 SUMMARY

- A twice daily regimen for rivaroxaban provided lower peak to trough ratio in PK and PD for the same total daily dose. However, the clinical impact on safety and efficacy can not be assessed from the available information.
- There was no relationship between pre-dose PT (a surrogate for PK measurement; measured at steady state trough) and primary efficacy outcomes, including ischemic stroke, for rivaroxaban.
- The risk for bleeding with rivaroxaban increased with an increase in PT (mostly measured at steady state trough).
- Stroke reduction and the risk for bleeding were dependent on the last observed INR for warfarin in the ROCKET-AF study. The results were in agreement with the established PD-outcome relationship for warfarin.
- Concomitant aspirin use during the double blind phase significantly increased the risk for major bleeding with rivaroxaban. The risk is particularly higher in those with higher steady state trough PT. This increased risk is mainly driven by major bleeding components including hemoglobin drop ≥ 2 g/dl and transfusion ≥ 2 units.

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- Concomitant aspirin use with warfarin also increased the risk of major bleeding in the ROCKET-AF. Warfarin treated subjects in RE-LY study also had increased bleeding risk with concomitant aspirin administration.
- The risk of major bleeding among aspirin users in rivaroxaban compared to that of warfarin is similar.

4.2 TABULAR LISTING OF ANALYSIS SCRIPTS

File name	**Description**	**Location in\\cdsbas\pharmacometrics**
PD_outcome_macro.sas INR_outcome_macro.sas	Exploratory analysis on PD-outcome & INR-outcome relationship	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\Macro
PT_major.sas	Cox PH model for PT-Major Bleeding	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\Bleed
PT_stroke.sas	Cox PH model for PT-Ischemic stroke	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\Stroke
INR_major.sas.	Cox PH model for INR-Major Bleeding	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\Bleed
INR_stroke.sas	Cox PH model for INR-Ischemic stroke	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\Stroke
INR_outcome_rely	Exploratory analysis on Aspirin use in RE-LY	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\RELY

Reference ID: 2998583

5.1 DRUG-DRUG INTERACTION WITH FLUCONAZOLE

Study # 012606	**EDR Link:** \\cdsesub1\EVSPROD\NDA202439\0048\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\12606-fluconazole-ddi
Title	Randomized, open label, 2-fold cross-over study to investigate the influence of multiple doses of 400 mg fluconazole on safety, tolerability, and pharmacokinetics of a single oral dose of 20 mg rivaroxaban in healthy male subjects

Study Design: Multiple-Dose Fluconazole/Single-Dose Rivaroxaban Randomized Open-Label Cross-Over Healthy Vonuteers

Rationale: Rivaroxaban is metabolized via the CYP3A4/5 and 2J2 enzyme systems. It is also a substrate for Pgp and BCRP for its active renal secretion. In vitro data indicate that the antimycotic fluconazole, reported as a potent inhibitor for CYP2C9 (rivaroxaban is not metabolized via CYP2C9), but only a moderate CYP3A4 inhibitor, inhibited rivaroxaban oxidative metabolism in vitro much less than ketoconazole. This study was to explore the clinical impact and the maximal degree of a potential interaction between fluconazole 400 mg once-daily under steady state conditions on a single dose of 20 mg rivaroxaban.

Treatment A: 20 mg rivaroxaban single dose on day 0
Treatment B: 400 mg Fluconazole once daily (on days -4 to 1), and 20 mg rivaroxaban single dose (on day 0)
10 days wash out period

Sampling Times (for rivaroxaban treatment A/B):
0, 0.5, 1, 2, 3, 4, 6, 8, 12, 15 hr (Day 0), 12 hr(Day 1), 0 hr (Days 2, 3 & 4)

Analytical Method:

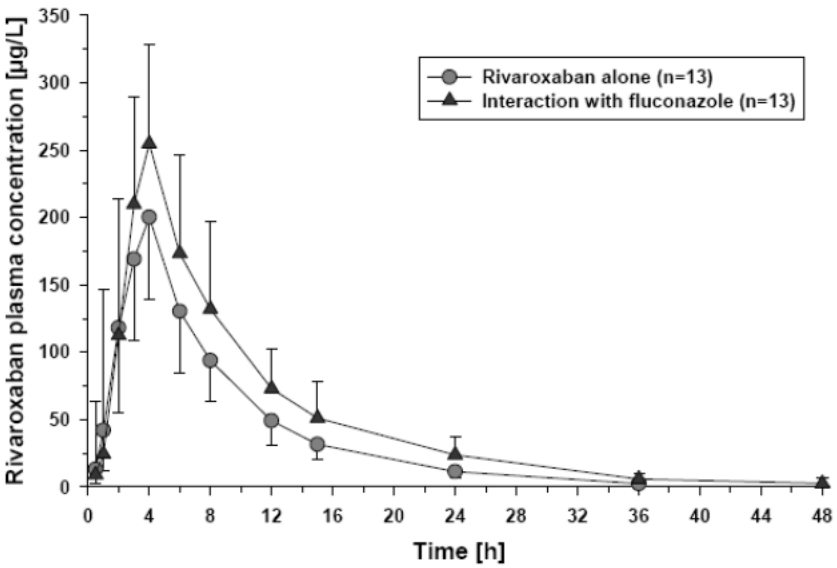
Analyte	Rivaroxaban	Rivaroxaban	Fluconazole
Method	HPLC-MS/MS	HPLC-UV	HPLC-MS/MS
Matrix	Plasma	Urine	Plasma
Range	0.5 ug/L-500 ug/L	0.1 mg/L-20 mg/L	0.1 mg/mL-100 mg/mL

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

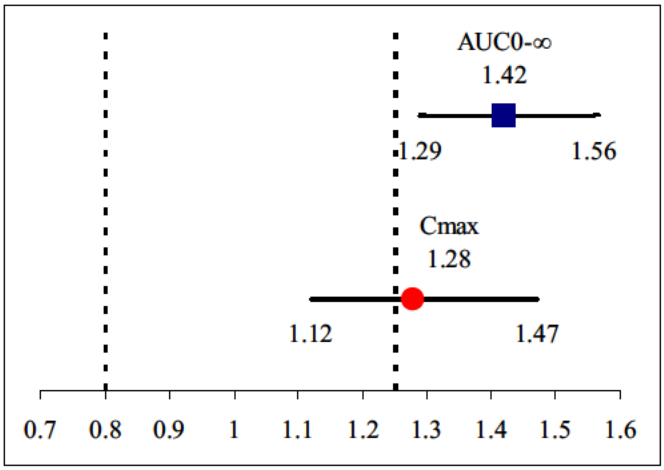
Study Population :

Randomized/Completed	13
Age [Median (range)] years	36 (20-45)
Male/Female	Male (100%)
Race (Caucasian/Black/Asian/Hispanic)	Caucasians (100%)

Results



Rivaroxaban plasma concentrations following oral administration of 20 mg alone (Treatment A) and following 20 mg rivaroxaban added to an on going Fluconazole 400 mg once daily treatment (Treatment B), geometric means, linear scale, N 13



Mean and 90% CI for AUC and Cmax ratio of rivaroxaban with fluconazole/alone

Safety

- Was there any death or serious adverse events? No

Conclusion

- Fluconazole is a moderate CYP3A4 inhibitor and can also inhibit BCRP
- Rivaroxaban AUC and Cmax had 1.42 and 1.28 fold increase respectively on co-administration with Fluconazole

Comments

No dose adjustments are warranted for rivaroxaban on co-administration with fluconazole similar to other scenarios such as mild renal impairment which are associated with similar increase in exposure.

5.2 DRUG-DRUG INTERACTION WITH OMEPRAZOLE

Study # 15232	**EDR Link:** \\cdsesub1\EVSPROD\NDA202439\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\rivarox-afl-1001
Title	Open-Label, 2-Way Crossover Study in Healthy Subjects to Determine the Effect of Multiple Doses of Omeprazole on the Pharmacokinetics, Pharmacodynamics, and Safety of a Single Dose of Rivaroxaban

Study Design: Multiple-Dose Omeprazole/Single-Dose Rivaroxaban Randomized Open-Label Cross-Over Healthy Vonuteers

Rationale: Omeprazole is a proton pump inhibitor, which suppresses gastric acid secretion by inhibition of the H^+/K^+ adenosine triphosphatase, thereby increasing intragastric pH. Due to omeprazole's different mechanism of action than ranitidine and Maalox, and because proton pump inhibitors are commonly prescribed to patients with atrial fibrillation and acute coronary syndromes, it was considered important to assess whether or not the use of proton pump inhibitors had the potential to alter the PK of rivaroxaban when co-administered.

Treatments:
Treatment A: single oral 20 mg dose of rivaroxaban administered in the fed state following a standardized breakfast on Day 1
Treatment B: omeprazole 40 mg administered orally once-daily for 5 consecutive days in the fasted state (Day -4 to Day 1) and a single oral dose of 20 mg rivaroxaban, administered in the fed state following a standardized breakfast between 1.5 hours to 2 hours after the fifth omeprazole dose on Day 1.
10 days wash out period

- **Sampling Times (for rivaroxaban)**

0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post rivaroxaban administration in each treatment period

Analytical Method

Analyte	Rivaroxaban	Omeprazole
Method	HPLC-MS/MS	HPLC-MS/MS
Matrix	Plasma	Plasma
Range	0.5 ug/L-500 ug/L	1.0-1000 ng/mL

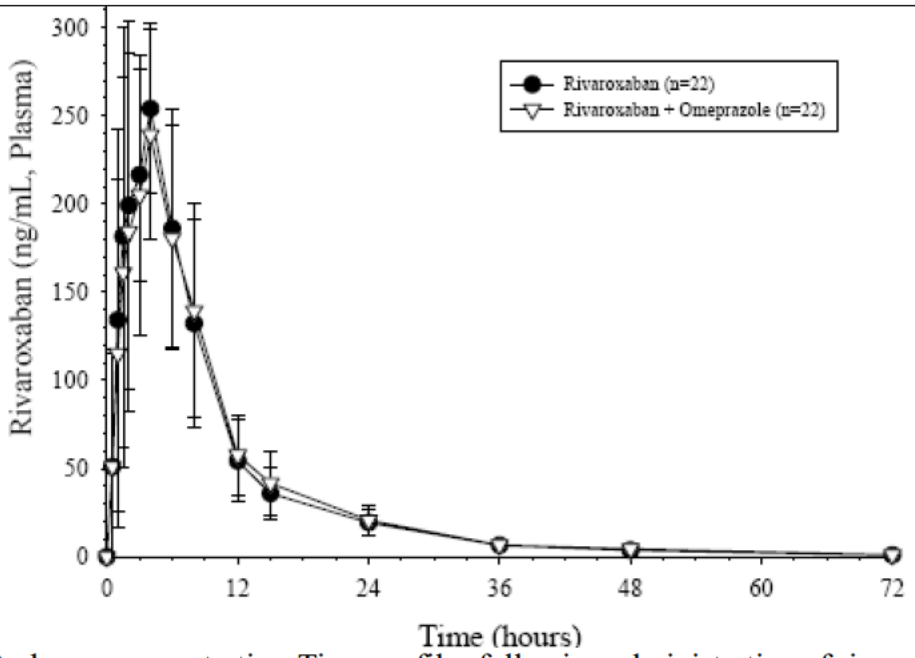
Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

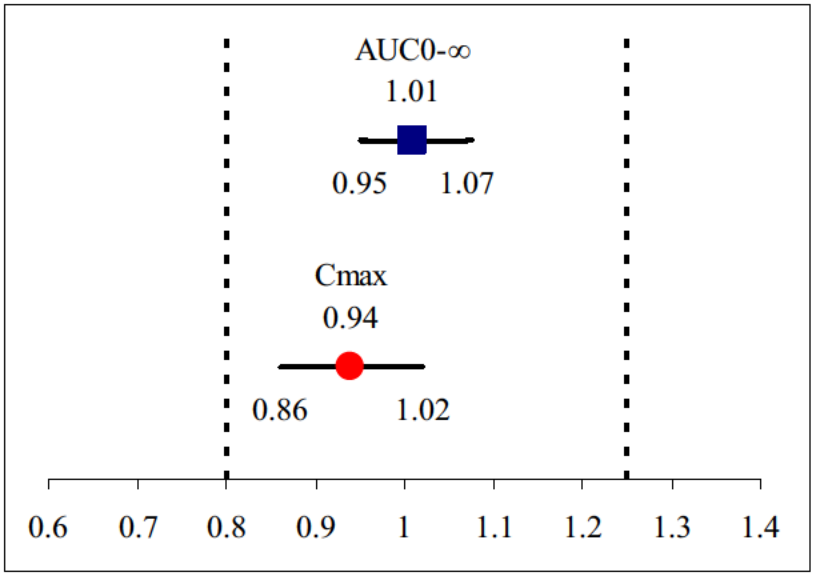
Randomized/Completed	22
Age [Median (range)] years	30.5 (18-43)
Male/Female	7/15
Race (Caucasian/Black/Asian/Hispanic)	Caucasians (100%)

Results

Reference ID: 2998583



Mean (SD) plasma concentration-Time profiles following administration of rivaroxaban alone and with omeprazole, N 22



Mean and 90% CI for AUC and Cmax ratio of rivaroxaban with omeprazole/alone

Safety

- Was there any death or serious adverse events? No

Conclusion

No clinically meaningful interaction was observed when rivaroxaban was co-administered with omeprazole. The 90% CIs of the ratios of the geometric means for rivaroxaban C_{max} and AUCs were contained within the bioequivalence criteria of 80% to 125%.

Comments

Omeprazole can be co-administered with rivaroxaban without significant changes to rivaroxaban exposure. No dose adjustments are required.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SREEDHARAN N SABARINATH
08/10/2011

TZU-YUN C MCDOWELL
08/10/2011

PRAVIN R JADHAV
08/10/2011

RAJANIKANTH MADABUSHI
08/10/2011
Concur with reviewers' findings and interpretation

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

Rivaroxaban is a direct factor Xa inhibitor. The sponsor is seeking approval for rivaroxaban for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The NDA consists of two phase III trials, ROCKET-AF and J-ROCKET-AF. The J-ROCKET-AF is designed for Japanese NDA and is not powered as a stand alone pivotal study. Rivaroxaban is also being developed for the prevention and treatment of venous thromboembolism (VTE). The NDA 22406, submitted based on data from RECORD studies for the prevention of VTE after major orthopedic surgeries received a complete response in January 2011. Some of the clinical pharmacology studies listed under the current NDA was reviewed as part of NDA 22406 (BA/BE/PK studies, intrinsic factor studies, and 18 of the 19 completed DDI studies). The current NDA lists 6 additional BA/BE/PK studies, one DDI study and 5 PK/PD/other clinical studies which are not reviewed earlier, in addition to ROCKET-AF, and J-ROCKET-AF.

	Information		Information
NDA/BLA Number	**202439**	**Brand Name**	**XARELTO**
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Rivaroxaban**
Medical Division	**DCRP**	**Drug Class**	**Direct FXa Inhibitor**
OCP Reviewer(s)	**Sreedharan Sabarinath**	**Indication(s)**	**Prevention of stroke and systemic embolism in patients with non-valvular atrial fribrillation**
OCP Team Leader	**Rajanikanth Madabushi**	**Dosage Form**	**IR Tablet**
Pharmacometrics Reviewer	**Sreedharan Sabarinath**	**Dosing Regimen**	**20 mg once daily**
Pharmacometrics Team Leader	**Pravin Jadhav**	**Route of Administration**	**Oral**
Date of Submission	**01/05/2011**	**Sponsor**	**Johnson & Johnson / Bayer Pharmaceuticals**
Estimated Due Date of OCP Review	**07/15/2011**	**Priority Classification**	**Standard**
Medical Division Due Date	**TBD**		
PDUFA Due Date	**11/05/2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies to be 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**			
I. Clinical Pharmacology	**X**			**All studies previously reviewed**
Healthy Volunteers-	**X**	**3**		**3 studies previously reviewed**
Patients-	**X**	**1**	**1**	**1 new**
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non fasting single dose:				
fasting / non fasting multiple dose:				

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Drug-drug interaction studies -				
In vivo effects on primary drug:	**X**	**18**	**1**	**17 studies previously reviewed /1 new**
In vitro:				
Subpopulation studies -	**X**	**14**		**14 studies previously reviewed**
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**12**	**5**	**5 new PK/PD studies**
Phase 3:	**X**			**ROCKET-AF, J-ROCKET-AF**
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**	**2**	**2**	**ROCKET-AF, J-ROCKET-AF**
Population Analyses -				
Data rich:				
Data sparse:	**X**			**2 previously reviewed / ROCKET AF is the new study**
II. Biopharmaceutics				**Previously reviewed**
Absolute bioavailability		**1**		
Relative bioavailability -		**17**	**3**	**14 previously reviewed/ 3 new**
Bioequivalence studies -		**2**	**2**	**2 x 5mg Vs 1 x 10 mg**
traditional design; single dose:				**2 formulations of 15 mg in Japan**
replicate design; single dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				**BCS2**
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies (completed)		**70**	**14**	
(ongoing)		**8**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Identical formulations – Phase 3 and commercial
2	Has the applicant provided metabolism and drug-drug interaction information?	X			18 DDI studies
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of	X			

Reference ID: 2900791

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	the NDA organized, indexed and paginated in a manner to allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reference ID: 2900791

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

There are no potential review issues identified at this time. We will contact the sponsor through the project manager if any issues come up during the review process.

Sreedharan Sabarinath	02/03/2011
Reviewing Clinical Pharmacologist	Date
Rajanikanth Madabushi	02/03/2011
Team Leader/Supervisor	Date

Reference ID: 2900791

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SREEDHARAN N SABARINATH
02/03/2011

RAJANIKANTH MADABUSHI
02/03/2011