CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206316Orig1Orig2s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY:

Application Number/eCTD Sequence No	NDA 206316/ eCTD 0000
Generic Name	Edoxaban tosylate
Formulation; Strength	Immediate release tablets: 15 mg, 30 mg , and 60 mg
Submission Date	8 Jan 2014
Submission Type	Original Efficacy Submission
Applicant	Daiichi Sankyo, Inc.
OCP Team Leaders	Jeffry Florian, Rajnikanth Madabushi
Clinical Division	DCRP/DHP

1 SUMMARY OF FINDINGS

1.1 Introduction

This document serves as an addendum to the primary Office of Clinical Pharmacology's review entered into DARRTS on 9/30/2014 by Dr. Divya Menon-Andersen and on 10/31/2014 by Dr. Young-Jin Moon. This addendum includes a recapitulation of the Advisory Committee questions and discussions, updated Office of Clinical Pharmacology recommendations based on these discussions, and additional supportive analyses to address questions raised at the Advisory Committee meeting and internally regarding the proposed recommendation. In addition, this addendum provides the Office perspective on the dose adjustment recommendations based on low body weight (<60 kg) and P-gp inhibitor use.

The primary focus of the original Office of Clinical Pharmacology review (9/30/2014) was to identify and characterize the factors that may explain the observed difference in edoxaban treatment effect in patients with normal renal function from a clinical pharmacology perspective. Those analyses identified edoxaban concentrations as determinant of both efficacy and safety. Based on these analyses, the Clinical Pharmacology Review Team proposed exposure matching in patients with normal renal function to that in patients with mild renal impairment (creatine clearance [CrCL] 50 – 80 mL/min) as a path forward for further dose optimization and evaluated projected efficacy and safety event rates based on potential dose adjustments in this population. These analyses were presented and discussed on October 30th, 2014 at a Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting. The CRDAC was asked to vote on the following question (Question 4):

> *Should edoxaban be approved to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation?*
>
> *If you recommend approval, please discuss the following options:*
>
> *a) Approval of the 60-mg dose for patients with normal or mildly impaired renal function.*
> *b) Approval of a dose higher than 60 mg for patients with normal renal function.*
> *c) Approval only for patients with mild and moderate renal impairment*
>
> *If you do not recommend approval, please discuss your thinking.*

The CRDAC vote on this question supported approval (vote results: 9 yes, 1 no), but the CRDAC members who voted for approval were split amongst the three options. Of note, multiple members mentioned the potential for increased GI bleeding with a higher edoxaban dose as a potential concern that warranted further investigation. Additionally, the committee noted that they were concerned with the findings in patients with normal renal function on edoxaban relative to warfarin (the hazard ratio for stroke/SEE was 1.41 (0.97 – 2.05), and that the analyses conducted by the Agency and the explanation offered of exdoxaban exposure as a causal factor was plausible and not a chance-finding.

Based on feedback and discussions from the CRDAC and internal discussions, the Office of Clinical Pharmacology conducted additional analyses to further characterize the relationship between dose/exposure and major GI bleeding and evaluated various CrCL cut offs to determine if 80 mL/min was an acceptable value for designating those patients who would benefit from a higher edoxaban dose. As a result of these analyses, the Office of Clinical Pharmacology concludes that systemic edoxaban exposure is the major contributor for major GI bleeding and that a CrCL cut off of 80 mL/min is appropriate to denote patients who would receive a higher edoxaban dose.

1.2 Recommendation

Dosing recommendations for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

In consideration of the findings presented in the primary clinical pharmacology review, discussion at the CRDAC, and additional analyses conducted following the Advisory Committee, the Office of Clinical Pharmacology recommends that a dose higher than 60 mg (e.g., 75-90 mg q.d.) should be approved for use in patients with CrCL > 80 mL/min for the indication of reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. This recommendation is based on the following observations and analyses:

1) Exposure-response analyses for edoxaban and both all strokes and ischemic strokes support that higher edoxaban exposures are associated with a reduction in the overall event rate. Combined with observations from ENGAGE AF-TIMI 48, these analyses support that higher edoxaban doses in patients with normal renal function offers a path for reducing the hazard ratio for all stroke and ischemic stroke relative to warfarin closer towards non-inferiority (see the clinical pharmacology review by Dr. Divya Menon-Andersen in DARRTS).

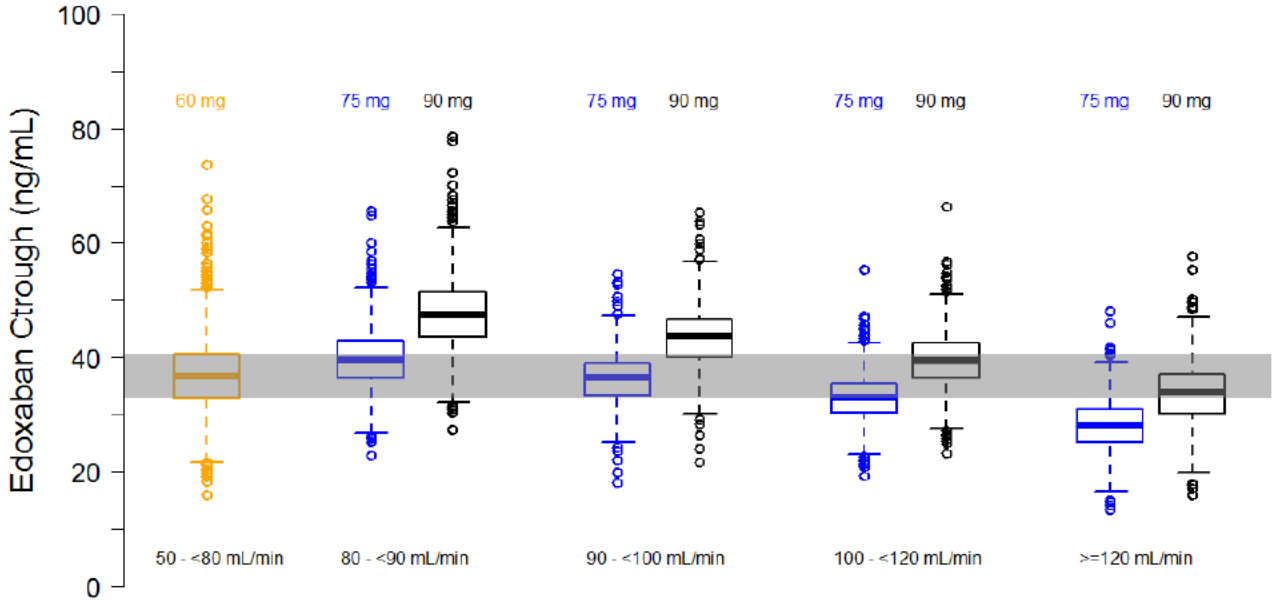
2) Exposure-response analyses for edoxaban and major bleeding and life-threatening/fatal bleeds support that the probability of the event increases with increasing edoxaban trough concentration. (b) (4)

3) Additional analyses of major GI bleeding indicate a similar event rate between subjects administered edoxaban 30 and 60 mg who had overlapping exposures. These analyses

suggest that systemic edoxaban exposure, and not local edoxaban exposure (i.e., dose) are the predominant factor associated with major GI bleeding (see Section 1.3.1)

4) Figure 1 suggests that from an exposure-matching perspective that patients with a creatinine clearance greater than 80 mL require a dose greater than 60 mg to achieve exposures observed in patients with mild renal impairment that received 60 mg edoxaban. A dose increase of this magnitude in patients with normal renal function is not projected to exceed exposures already observed in patients with mild renal impairment administered 60 mg in ENGAGE AF-TIMI 48.

Figure 1. Edoxaban doses of 75 mg or 90 mg are required to match exposures in patients with normal renal function (≥ 80 mL/min) to patients with mild renal impairment (50 - < 80 mL/min). The gray shaded region depicts the inter-quartile range for subjects with mild renal impairment that received 60 mg edoxaban (orange). Individual Bayesian post hoc estimates of trough concentration are shown for the 60 mg dose boxplots. Trough concentrations for edoxaban 75 mg and 90 mg are predictions based on the population PK model using the post-hoc PK parameters for patients with the corresponding creatinine clearance values denoted at the bottom of the plot.



In addition, the Office of Clinical Pharmacology recommends approval of edoxaban 60 mg q.d. for patients with mild renal impairment (CrCL 50 – 80 mL/min) and edoxaban 30 mg q.d. for patients with moderate renal impairment (CrCL 30 – 50 mL/min).

Dose adjustment recommendations based on low body weight (<60 kg) and P-gp inhibitor use

Consistent with the recommendations provided in the original Clinical Pharmacology Reviews for the atrial fibrillation (9/30/2014 by Dr. Divya Menon-Andersen) and deep vein thrombosis/pulmonary embolism (10/31/2014 by Dr. Young-Jin Moon) indications, the Office of Clinical Pharmacology recommends that dose reductions to edoxaban 30 mg are not necessary for patients with low body weight or in patients concomitantly treated with P-gp inhibitors. (b) (4) comparable exposures between those subjects receiving an unadjusted edoxaban dose and those subjects with

one or more of the factors prospectively identified for dose adjustment. An assessment of the observed pharmacokinetic data substantiates dose reduction only for subjects with moderate renal impairment (CrCL 30 – 50 mL/min) (Table 1).

Table 1. Observed Edoxaban Pre-Dose Concentrations in Hokusai VTE Based on Baseline Renal Function Category and Administered Edoxaban Dose.

Renal function category	Observed Edoxaban PK (pre-dose, day 29) (median, [interquartile range])		
	Edoxaban 60 mg	Edoxaban 30 mg	Ratio of Medians
Normal	17.3 (9.4; 34) n=2222	11 (6.0; 24.0)* n=223	0.64
Mild	27.9 (16.1; 51.9) n=516	17.2 (9.4; 33.8)* n=198	0.62
Moderate	34.9 (17.3; 60.1) n=42	19.8 (11.7; 38.8) n=124	0.57

* Dose reduction in these patients was due to low body weight or P-gp inhibitor use

Dose reduction in patients with low body weight or on concomitant P-pg inhibitors resulted in significantly lower edoxaban exposures. This pharmacokinetic finding is consistent between both Phase 3 studies. Dose reduction is only recommended in atrial fibrillation patients with moderate renal impairment based on the clinical observations from ENGAGE AF-TIMI 48. No dose reductions are necessary in this population based on body weight or concomitant P-gp use. Having different dose adjustment recommendations between the two indications may introduce unnecessary complexity to clinical practice. Given the pharmacokinetic findings and definitive clinical findings from ENGAGE AF-TIMI 48, this forms the basis of the Office perspective.

1.3 Supplemental Analyses to the Advisory Committee Discussion

Additional analyses were performed by the Office of Clinical Pharmacology based on the following:

- While the relationships between bleeding risks and edoxaban exposure had been previously discussed in the Clinical Pharmacology Review, additional concerns were raised at the CRDAC and internally of the possibility of a local, dose-related effect of edoxaban in the gut on major GI bleeding. (b) (4)

- The initial review had grouped patients as normal and mild renal function patients based on creatinine clearance measurements of >80 mL/min and 50-80 mL/min, respectively. An updated analysis based on renal function was conducted to assess whether 80 mL/min served as an appropriate cut off for designating those patients who would benefit most from an edoxaban dose greater than 60 mg. (Section 1.2.3).

1.3.1 What is the expectation of alterations to GI bleeding risk with administration of a higher dose?

Major GI bleeding is predominantly due to systemic exposure based on analyses presented in the original clinical pharmacology review for (Dr. Divya Menon-Andersen in DARRTS, 9/30/2014) and local edoxaban exposure does not appear to be a major contributor. A clear exposure-response relationship between major GI bleeds and edoxaban trough concentration is shown in the clinical pharmacology review in DARRTS (page 15, Figure 6). To further evaluate whether dose was a driver of major GI bleeding independent of edoxaban exposure a comparison of major GI bleeding event rates was made between edoxaban doses based on those subjects with overlapping edoxaban exposure (Table 2, higher exposure quartiles for edoxaban 30 mg compared to the lower exposure quartiles for edoxaban 60 mg). As the absolute major bleeding event rates differ between renal function categories and as edoxaban exposure is influence by renal function, the event rates are further grouped by renal function categories. There was no consistent dose-response relationship for major GI bleeds within each renal impairment subgroup while controlling for edoxaban exposure. In patients with normal renal function, the major GI bleeding event rate was similar between both edoxaban doses for those subjects with overlapping exposure (0.59% for 30 mg [Q2,3,4] and 0.68% for 60 mg [Q1,2]). Event rates were slightly higher for exposure-matched patients with mild renal impairment for 60 mg compared to 30 mg and slightly lower for exposure-matched patients with moderate renal impairment. Overall, there was not a consistent signal to suggest that edoxaban dose was the predominant factor for major GI bleeding as a large increase in major GI bleeding event rate was not observed for exposure-matched individuals administered edoxaban 60 mg versus those administered edoxaban 30 mg.

Table 2. Major GI bleeding rate is similar between subjects on 30 and 60 mg with similar exposures.

Renal Function Category	Dose/ Exposure	Major GI Bleeds (% events/year)	n/N	Edoxaban Ctough [min; max]
Moderate (30-50 mL/min)	15 mg, Q4	1.26 (0.46; 2.72)	6/261	[14.0; 25.0]
	30 mg, Q1,2	0.65 (0.26; 1.33)	7/533	[14.1; 25.5]
Mild (50-80 mL/min)	30 mg, Q2,3,4	1.12 (0.83; 1.47)	49/1864	[16.5; 37.1]
	60 mg, Q1,2	1.62 (1.19; 2.16)	46/1241	[16.0; 36.6]
Normal (>80 mL/min)	30 mg, Q2,3,4	0.59 (0.39; 0.85)	27/1884	[12.0; 26.6]

	60 mg, Q1,2	0.68 (0.42; 1.04)	21/1261	[10.7; 27.3]

In addition, it was identified that the fraction of major bleeds that were major GI bleeds were similar across the edoxaban 30 and 60 mg doses for each renal function subgroup (Table 3). As the contribution of major GI bleeding to overall bleeds was not related to edoxaban dose, this further supports that the major determinant of major GI bleeding was systemic rather than local exposures.

Table 3. Major GI bleeds comprise a similar fraction of overall major bleeds regardless of dose

Renal function category	Treatment arm		
	Edoxaban 60 mg	Edoxaban 30 mg	Warfarin
Moderate (30-50 mL/min)	51% (49/96)	56% (28/56)	33% (41/126)
Mild (50-80 mL/min)	60% (125/209)	52% (70/135)	34% (81/239)
Normal (>80 mL/min)	51% (56/109)	45% (31/69)	43% (66/154)

In summary, the major GI bleed event rate was similar between subjects administered 30 and 60 mg who had similar exposure after adjusting for renal function. Additionally, the percentage of major bleeds that are major GI bleeds is similar for 30 and 60 mg edoxaban. Thus, these analyses suggest that edoxaban systemic exposure is the predominant contributor for major GI bleeds rather than the dose administered (b) (4) by administering 60 mg edoxaban to patients with mild renal impairment.

1.3.2 What is an appropriate threshold of CrCL above which an increase in edoxaban dose may be required?

In the original clinical pharmacology review, analyses were conducted based on a CrCL cut point of 80 mL/min for differentiating between subjects with normal renal function and mild renal impairment. An 80 mL/min cut point is a typical metric for designating patients with renal function categories, but (b) (4) the review team considered whether an alternative CrCL cut point would better differentiate those subjects who would benefit from a higher edoxaban dose relative to warfarin. Table 3 show an additional analysis based on CrCL cut points of 70, 80, and 90 mL/min for stroke/SEE, ischemic strokes, and major bleeds. The hazard ratios of edoxaban 60 mg relative to warfarin for stroke/SEE and ischemic strokes increased from a cut point of 70 mL/min to 80 mL/min (1.04 to 1.4 and 1.21 to 1.57 for stroke/SEE and ischemic stroke) but were relatively consistent between 80 mL/min and 90 mL/min (1.4 to 1.43 and 1.57 to 1.64 for stroke/SEE and ischemic stroke).

There was a continual decline in the hazard ratio between edoxaban 60 mg and warfarin for major bleeding based on CrCL cut points of 70, 80, and 90 mL/min, which based on the previously developed relationships between efficacy and safety events suggests decreasing coagulation was achieved in subjects with higher CrCL values administered edoxaban 60 mg. These additional cut point analyses continue to support that 80 mL/min is appropriate for selecting subjects who would benefit from a higher edoxaban dose.

Table 4. Stroke/SEE, Ischemic Stroke, and Major Bleeding Event Rates and Hazard Ratios for Edoxaban 60 mg, Edoxaban 30 mg, and Warfarin from ENGAGE AF-TIME 48 Based on Difference Renal Function Cut Points

Endpoint (% patients with event/year)	Renal Function Cut Points	Edoxaban 60 mg	Edoxaban 30 mg	Warfarin	Hazard Ratio (Edoxaban 60/Warfarin)	Hazard Ratio (Edoxaban 30/Warfarin)	Hazard Ratio (Edoxaban 60/Edoxaban 30)
Stroke/SEE	>70 mL/min	1.02 (0.81; 1.26)	1.25 (1.02; 1.51)	0.98 (0.78; 1.21)	1.04	1.28	0.82
		85/3556	104/3532	82/3562	(0.77; 1.41)	(0.96; 1.71)	(0.61; 1.09)
	>80 mL/min	1.06 (0.82; 1.35)	1.23 (0.97; 1.53)	0.76 (0.56; 1.01)	1.4	1.62	0.86
		66/2633	77/2628	47/2608	(0.96; 2.04)	(1.13; 2.33)	(0.62; 1.20)
	>90 mL/min	1.00 (0.89; 1.55)	1.19 (0.89; 1.55)	0.69 (0.47; 0.98)	1.43	1.72	0.84
		45/1893	54/1897	31/1852	(0.91; 2.27)	(1.10; 2.67)	(0.56; 1.25)
Ischemic Stroke	>70 mL/min	0.78 (0.89; 1.35)	1.10 (0.89; 1.35)	0.64 (0.48; 0.84)	1.21	1.72	0.71
		65/3556	92/3532	54/3562	(0.84; 1.74)	(1.23; 2.40)	(0.51; 0.97)
	>80 mL/min	0.84 (0.62; 1.09)	1.12 (0.87; 1.41)	0.53 (0.37; 0.75)	1.57	2.1	0.75
		52/2633	70/2628	33/2608	(1.02; 2.43)	1.39; 3.18)	(0.52; 1.07)
	>90 mL/min	0.84; (0.60; 1.15)	1.08 (0.80; 1.42)	0.51 (0.33; 0.77)	1.64	2.1	0.78
		38/1893	49/1897	23/1852	(0.97; 2.74)	(1.28; 3.45)	(0.51; 1.19)
Major Bleed	>70 mL/min	2.07 (1.78; 2.41)	1.24 (1.01; 1.50)	2.67 (2.33; 3.04)	0.78	0.46	1.68
		171/3556	103/3532	221/3562	(0.64; 0.95)	(0.37; 0.58)	(1.31; 2.14)
	>80 mL/min	1.77 (1.46; 2.13)	1.10 (0.86; 1.39)	2.52 (2.14; 2.95)	0.7	0.44	1.61
		109/2633	69/2628	154/2608	(0.55; 0.90)	(0.33; 0.58)	(1.19; 2.17)
	>90 mL/min	1.38 (1.06; 1.77)	1.19 (0.89; 1.55)	2.32 (1.90; 2.81)	0.6	0.51	1.16
		62/1893	54/1897	102/1852	(0.44; 0.82)	(0.37; 0.71)	(0.81; 1.68)

2 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
ReviewAddendumMajorGIBleeds.R	Analysis code for Major GI Bleeds	\Reviews\PM Review Archive\2015\Edoxaban_NDA206316_JCE, DM\ER Analyses\AFib_JAF

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

/s/

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CLINICAL PHARMACOLOGY REVIEW

NDA Number	206316
Submission Type; Code	Original, N_00
Applicant Name	Daiichi Sankyo, Inc.
Submission Dates	01/08/14
Generic Name	Edoxaban tosylate
Dosage Form	Immediate release tablet
Dosage Strengths	15, 30, and 60 mg
Proposed Indication	For the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)
OCP Divisions	DCPI, DCPV, DPM
Primary Reviewers	Divya Menon-Andersen, Young Jin Moon, Justin Earp
Team Leaders	Julie Bullock, Jeffry Florian

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1 EXECUTIVE SUMMARY

In this new drug application, Daiichi Sankyo, Inc. is seeking approval of edoxaban (NDA 206316) for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Edoxaban is a direct factor Xa inhibitor. The Applicant is also seeing approval of edoxaban for the reduction in the risk of stroke in patients with atrial fibrillation (Afib) which was reviewed in detail in a separate clinical Pharmacology review (see review dated September 30, 2014)

In support of the DVT/PE indication being sought, the Applicant conducted an extensive clinical pharmacology program and a single phase 3 trial, Hokusai VTE. Hokusai VTE was a double dummy, warfarin controlled event driven trial in which one edoxaban dose level (60 mg given once daily; dose halved based on body weight, renal function and concomitant therapy with P-glycoprotein inhibitors) was evaluated. The phase 3 trial met the primary objective of non-inferiority on the symptomatic recurrent venous thromboembolism (VTE) compared to warfarin. For the primary safety endpoint (clinically relevant bleeding) edoxaban was superior to warfarin.

The exposure-response analysis suggests that patients with varying degrees of renal function have similar or improved efficacy and safety compared to warfarin. Based subgroup analysis of efficacy and safety, a dose reduction to 30 mg in patients with low body weight or who are taking concomitant P-gp inhibitors is not nessesary. The dose reduction to 30 mg in patients with moderate renal impairment as studied in Hokusai VTE is acceptable and will be included in product labeling.

1.1 Recommendations

The Office of Clinical Pharmacology, Divisions of Clinical Pharmacology 5 and Pharmacometrics have reviewed the information contained in BLA125423. From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the sponsor.

Decision	**Acceptable to OCP?**	**Comment**
Overall	☒ Yes ☐ No ☐ N/A	Pending labeling agreement with sponsor.
Evidence of Effectiveness	☒ Yes ☐ No ☐ N/A	1 positive registration trial; dose-response supportive
Proposed dose for general population	☒ Yes ☐ No ☐ N/A	60 mg QD is acceptable.
Proposed dose selection for others	☐ Yes ☒ No ☐ N/A	A dose reduction to 30 mg in patients with low body weight or who are taking concomitant P-gp inhibitors is not necessary. The dose reduction to 30 mg in patients with moderate renal impairment

		is acceptable
Labeling	☐ Yes ☒ No ☐ N/A	Pending satisfactory agreement with sponsor.

Post Marketing Requirements

None

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DCP V: Reviewer – Y Moon; TL - J Bullock; DD - A Rahman
DCP I: Reviewer- D Menon-Andersen; TL- R Madabushi
DPM: Reviewer- J Earp; TL- J Florian

1.1 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Key findings are listed below.

Pharmacokinetics and Pharmacodynamics

- The pharmacokinetics of edoxaban and its main active metabolite following oral administration of single and repeat doses are dose proportional in the range studied in healthy subjects (60 to 120 mg repeat doses).
- The absolute bioavailability of edoxaban following oral administration is 62%. It is a substrate of the efflux transporter, P-glycoprotein.
- Edoxaban undergoes minimal metabolism. Its main active metabolite is formed via hydrolysis by carboxyesterase 1.
- Edoxaban is eliminated mainly as unchanged drug in urine (60% of bioavailable drug) and to a lesser extent via biliary secretion.
- Clearance of edoxaban in patients with VTE is similar to that in healthy subjects (~ 30 L/h).
- Edoxaban exhibits a concentration dependent effect on anti-FXa activity, prothrombin time, and activated partial thromboplastin time.

Effect of intrinsic factors

- A 75% increase in total systemic exposure (AUC) to edoxaban was observed in subjects with moderate and severe renal impairment compared to subjects with normal renal function. A 30% increase in edoxaban AUC was observed in individuals with mild renal impairment compared to subjects with normal renal function.
- Total systemic exposure to edoxaban was ~ 28% and 15% higher in the elderly and females, respectively.
- After accounting for renal function and body weight, age and gender do not affect systemic exposure to edoxaban.

Effect of extrinsic factors

- Overall, increased peak and total systemic exposure to edoxaban was observed when edoxaban was co-administered with P-gp inhibitors. About 0.5% of the patients in Hokusai VTE received an adjusted dose because of concomitant therapy with P-gp inhibitors. Trough concentrations in these patients were lower (~10 ng/mL) than those observed in patients who received a full dose (~15 ng/mL).
- Co-administration of rifampin resulted in ~ 40% loss of total systemic edoxaban exposure (AUC). While an increase in systemic exposure to its equipotent active metabolite D21-2393 makes up for this loss in total systemic exposure, it is driven by an increase in peak systemic exposure (C_{max}) to D21-2393. At trough (end of inter-dosing interval), there still exists a ~ 80% reduction in exposure to both edoxaban and the metabolite combined.

Exposure-response relationships

- The probability of DVT/PE decreases with increasing edoxaban total systemic exposure.
- The probability of a major bleed increased with increasing edoxaban trough concentrations.
- Alternate dosing in patients with normal renal function is not being proposed as the risk ratio relative to warfarin on the primary efficacy endpoint was 1.05, suggesting that patients achieved comparable benefit on 60 mg edoxaban relative to warfarin.

2 QUESTION BASED REVIEW

This is an abbreviated question based review addressing issues specific to VTE. Please consult the review dated September 30, 2014 for general clinical pharmacology aspects of edoxaban.

2.1 General Attributes of the Drug

2.1.1 What are the proposed therapeutic indications?

The applicant is seeking an indication for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients (b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal phase 3 trial used to support dosing or claims?

A single phase 3 trial (Hokusai VTE) conducted in patients with documented acute symptomatic DVT and or PE was submitted in support of efficacy and safety of edoxaban in VTE. Hokusai VTE was a multi-center, double dummy, warfarin controlled, event driven trial. For most patients, a single edoxaban dose level (60 mg given once daily) was evaluated in this trial. Patients who had one or more of the following received a dose reduction to 30 mg in the trial:

- Creatinine clearance (CrCL) between 30 mL/min and 50 mL/min;
- Body weight ≤ 60 kg, and
- Concomitant use of the P-gp inhibitors verapamil or quinidine

Edoxaban was administered with or without food in this trial.

The primary efficacy endpoint in Hokusai VTE was symptomatic recurrent VTE (composite of DVT, non-fatal PE, fatal PE). The primary safety endpoint was clinically relevant bleeding, defined as the composite of major[1] or clinically relevant non-major[2] bleeding that occurred during treatment or within three days after interrupting or stopping study drug.

[1] A fall in hemoglobin level of 2.0 g/dL or more, or leading to transfusion of two or more units of packed red cells or whole blood; occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; contributing to death

[2] Defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, an unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with discomfort for the subject such as pain, or impairment of activities of daily life

2.3 Exposure-Response

2.3.1 What was the basis for dose selection for phase 3?

Dose and dosing regimen for the VTE phase 3 trial was selected based on PK/PD data from phase 1 and the safety results of a phase 2 trial conducted in patients with Afib as presented in the Clinical Pharmacology review dated September 30, 2014.

2.3.2 What are the characteristics of the exposure-response relationships for efficacy and safety for edoxaban?

Exposure-efficacy relationship

The exposure-response relationship for DVT/PE events for the overall study period (primary endpoint) is presented in **Figure 1**. The predicted event rate corresponding to exposures at the studied dose (60 mg QD) suggests the dosing produces numerically lower results than warfarin. Unlike the SAPF indication (see Clinical Pharmacology review dated September 30, 2014), a significant interaction between renal function and the overall efficacy results was not identified.

The exposure metric of significance from this analysis was the area under the plasma concentration-time curve at steady state (AUC), and the identified exposure-response efficacy relationship suggests that additional improvements in efficacy could be attainable with further increases in the edoxaban dose. This is further supported by the observed data where the efficacy event rate (DVT+PE+unexplained death) was numerically lower in patients with mild renal impairment (2.7% [24/879]), the subgroup with higher edoxaban exposures, compared to subjects with normal renal function (3.3% [93/2799]), the subgroup with lower edoxaban exposures. However, a higher dose is not being recommended in the subgroup of subjects with normal renal function as the risk ratio relative to warfarin was 1.05, suggesting that patients were achieving comparable benefit on 60 mg edoxaban relative to warfarin.

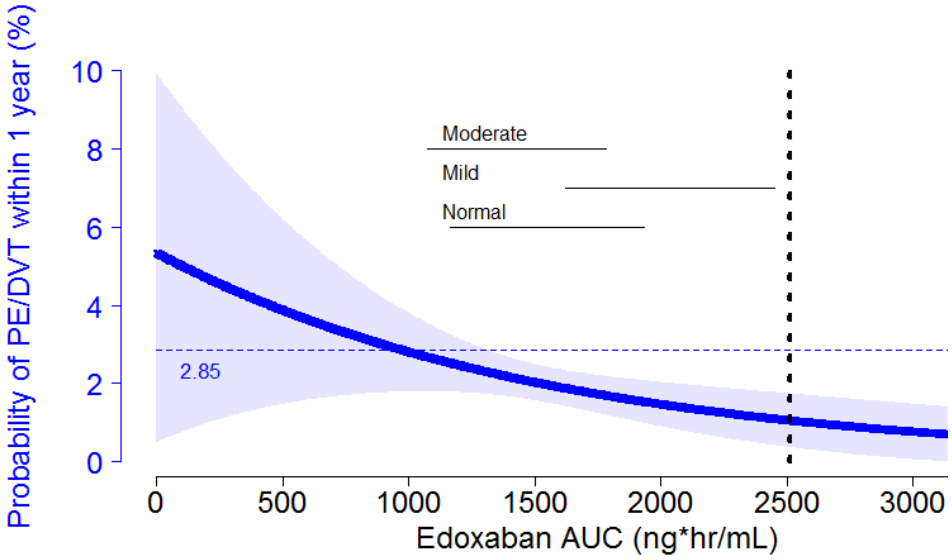


Figure 1 Exposure-Response relationship for DVT/PEevents suggests improved reduction in the event rate with increasing edoxaban AUC values.

Exposure-response relationship is shown for the typical DVT/PE patient. The blue dashed horizontal reference line indicates the observed rate of DVT/PE events for the warfarin treatment arm. The intersection of the exposure response relationship and the relevant warfarin reference line occurs at the concentration of edoxaban that is predicted to produce similar results to warfarin. The solid horizontal black lines indicate the exposure range (5th to 95th percentile) for edoxaban in each renal function group for those subjects in the high edoxaban dose arm. The vertical dashed line indicates the 99th percentile of edoxaban AUC values predicted by the population PK model for patients from the VTE trial.

Exposure-safety relationship

The exposure-response relationship for major bleeding events by renal function category is presented in Figure 2. The corresponding exposure range for each renal function group has a lower bleeding rate compared to warfarin. The identified exposure-response relationship for both the Afib (see Clinical Pharmacology review dated September 30, 2014) and VTE populations were conceptually similar; increasing edoxaban C_{trough} was associated with increase probability of major bleeding events across all renal function categories.

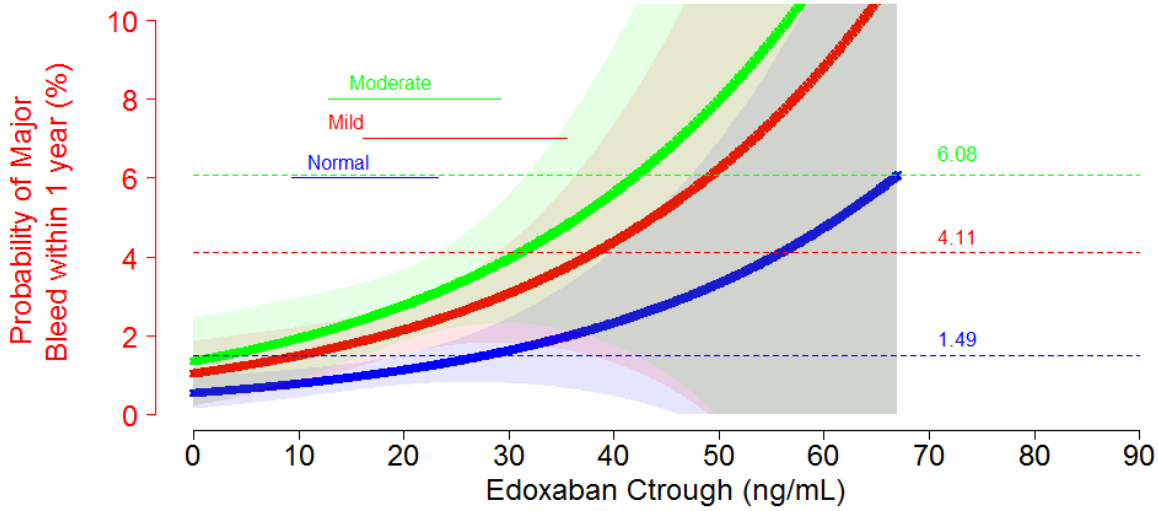


Figure 2 Exposure-Response relationship for major bleeds suggests increasing events with increasing edoxaban C_{trough} concentrations.

Cox proportional hazards relationships are shown for normal renal function (blue line), mild renal impairment (red line), and moderate renal impairment (green line). Horizontal reference lines indicate the observed rate of ischemic stroke for the warfarin treatment arm for the corresponding color coded renal function groups. The intersection of the exposure response relationship and the relevant warfarin reference line occurs at the concentration of edoxaban that is predicted to produce similar results to warfarin. The horizontal bands indicate the exposure range (5th to 95th percentile) for edoxaban in each renal function group.

2.3.3 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

The proposed dosing appears to produce exposures that are expected to give better efficacy (Figure 1) and less major bleeding (Figure 2) when compared to warfarin, despite differences in exposure by renal function. For conclusions on dosing in patients

with low body weight or those taking concomitant p-gp inhibitors see detailed discussion below (Section 2.5).

2.4 Pharmacokinetic characteristics

2.4.1 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

Edoxaban pharmacokinetics is similar between healthy subjects and patient population.

Table 1: PK parameters of edoxaban in healthy subjects and VTE patients

	Healthy subjects [a] (n=10)	VTE[b]
CL/F (mL/min)	33.7	33.4
Vc/F + Vp/F (L)	433[c]	301

a. Noncompartmental analysis from PRT001
b. Population PK parameter estimates in typical patients (70 kg) from TMPP010
c. Vz/F

Source: Adapted from Table 12.11, Clinical Study Report DU176-E-PRT001 and Population PK Study Report TMPP010

2.4.2 What is the inter- subject variability of PK parameters in healthy subjects and patients?

The inter- and intra-subject variability for clearance and volume of distribution of edoxaban is low (<30%) in healthy volunteers. In patients, only sparse PK samples were collected. Inter-individual variability for parameter estimates using PPK analysis were 14.9% and 23.2% in VTE patients (PPK Study Report TMPP010) for CL/F and Vc/F, respectively.

2.5 Intrinsic Factors

2.5.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Approximately 60% of a bioavailable dose of edoxaban is excreted in urine and the rest via biliary secretion. Given this, impaired renal (including because of advanced age) or hepatic function (with bile duct obstruction) are expected to impact edoxaban pharmacokinetics. Additionally, total body weight was found to be a predictor of bleeding (safety) in a phase 2 trial in patients with atrial fibrillation.

The effect of renal function, hepatic function, body weight, age, or gender on edoxaban pharmacokinetics was studied in dedicated pharmacokinetic trials. Please consult the clinical pharmacology review in DARRTS dated September 30, 2014 for a discussion of these covariates..

Renal function

Total systemic exposure to edoxaban increased to ~ 1.75X in individuals with moderate or severe renal impairment (Study U120). Increased exposure to edoxaban, as a consequence of impaired renal function may increase the risk for bleeding and therefore

edoxaban dose was prospectively reduced to 30 mg in patients with moderate renal impairment in phase 3. About 6.5% of the patients in Hokusai VTE received an adjusted edoxaban dose because of moderate renal impairment (approx. 4.5% because of moderate renal impairment alone) and systemic exposure to edoxaban were similar to those observed in patients who received the full dose (see Appendix section 3).

Hepatic function

Mild or moderate hepatic impairment did not affect edoxaban exposure (study A-E134). No dose adjustments are recommended in patients with mild hepatic impairment. Patients with moderately impaired hepatic function (Child-Pugh B) may have intrinsic coagulation abnormalities. That combined with the limited data available in this sub-population, dosing recommendations cannot be provided.

Body weight

About 10.6% of the population in Hokusai VTE received a reduced edoxaban dose because of low body weight (TBW ≤ 60 kg) alone. There are several factors to be considered in interpreting these data. First, as expected edoxaban trough concentrations in the dose adjusted group was lower than those in patients who received edoxaban 60 mg (pre-dose concentrations of 9 vs 15 ng/mL). Second, total systemic exposure to edoxaban was identified as an important predictor of both efficacy and safety. Finally, low TBW is often correlated with other factors that affect outcomes such as lower CrCL or increased age. Taken together, there does not appear to be a need for dose reduction in patients with a TBW ≤ 60 kg alone.

Age/gender

There was no clinically significant effect of age or gender (PPK analysis report TMPP010) on edoxaban exposure in VTE patients. In Hokusai VTE ~ 32% of the population was ≥ 75 years and ~ 42% of the population was female. There were no safety concerns identified in these groups. Hence, a dose reduction because of age or gender is not recommended.

2.6 Extrinsic Factors

2.6.1 What are the drug-drug interactions?

The potential for drug interaction with CYP3A/P-gp substrates/inhibitors, and other concomitant medication was evaluated in several dedicated trials conducted in healthy subjects. Please consult the clinical pharmacology review in DARRTS dated September 30, 2014 for a detailed discussion. Data from the phase 3 trial informing dosing recommendations are discussed below.

P-gp Inhibitors

Overall, increased peak and total systemic exposure to edoxaban was observed when edoxaban was co-administered with P-gp inhibitors. Generally, edoxaban dose was reduced to 50% when co-administration with a P-gp inhibitor that increased it exposure≥ 50% was required in phase 3. The exceptions were ketoconazole, itraconazole, clarithromycin or erythromycin (prohibited at randomization, subsequent use permitted with 50% reduced edoxaban dose), dronedarone (edoxaban dose reduced to 50%, but

prohibited subsequent to protocol amendment 2) and cyclosporin (prohibited) in Hokusai VTE.

About 0.5% of the patients in Hokusai VTE received an adjusted dose because of concomitant therapy with P-gp inhibitors alone. Trough concentrations in these patients were lower (~ 10 ng/mL) than those observed in patients who received a full dose (~15 ng/mL). Similar findings in reference to edoxaban exposure were reported in the phase 3 SPAF trial. Taken together, this suggests that a dose reduction is not necessary based on this factor alone.

P-gp Inducer

Rifampin

Co-administration of rifampin (600 mg QD for 7 days) and edoxaban (60 mg single dose on Day 7) decreased total systemic exposure to edoxaban by 40% without having an apparent effect on peak exposure (Study A-U137). Total and peak systemic exposure to the metabolite increased 2.86X and 5.06X, respectively. Metabolite to parent ratios increased approximately 4.5X from approximately 9 to 40% for AUC and from approximately 10 to 45% for C_{max}.

While an increase in systemic exposure to its equipotent active metabolite D21-2393 makes up for this loss in total systemic exposure, it is driven by an increase in peak systemic exposure (C_{max}) to D21-2393. At trough (end of inter-dosing interval), there still exists a ~ 80% reduction in exposure to both edoxaban and the metabolite combined. Loss in exposure is considered detrimental and therefore, concomitant therapy with rifampin and other P-gp inducers is not recommended.

Other co-administered drugs

The effect of co-administration of other drugs (digoxin, atorvastatin, esomeprazole, NSAIDs) on edoxaban are discussed in detail in the Afib review (see Clinical Pharmacology review dated September 30, 2014)

Esomeprazole (Proton pump inhibitor)

Co-administration of esomeprazole (40 mg QD for 5 days) and edoxaban (60 mg single dose 2 h after esomeprazole dosing on Day 5) resulted in no change in total exposure, but peak exposure decreased by 33% (Study A-U156). In Hokusai VTE ~ 28% of the population received therapy with a proton pump inhibitor.

Aspirin (antiplatelet agent)

About 8.5% of the population in Hokusai VTE received concomitant therapy with aspirin because of co-morbid conditions. The annualized event rate for major bleeds was higher than that in patients not receiving aspirin (7.8% vs. 14.9%). However, the annualized event rate was similar to that in patients receiving aspirin+warfarin (14.9% vs. 15.9%). Based on these data no dose adjustments or contraindication is required, however patients who use concomitant aspirin should be closely monitored for bleeding.

Naproxen (NSAID)

Co-administration of naproxen (500 mg BID for 2 days) with a single oral dose of edoxaban (60 mg) prolonged bleeding time (Study A-U128). Naproxen did not affect the

anti-coagulant effect of edoxaban (PT, anti-factor Xa or aPTT) or edoxaban pharmacokinetics.

About 19% of the Hokusai VTE trial population received concomitant therapy with an NSAID. No dose adjustments or contraindication is required; however patients who use concomitant NSAIDs should be closely monitored for bleeding.

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

Anti-platelet drugs such as aspirin, naproxen may be prescribed to patients with VTE. For VTE patients, heparin (unfractionated or low molecular weight heparin) will be initially used before edoxaban treatment. Patients may be switching to edoxaban from another oral anticoagulants such as apixaban, dabigatran and rivaroxaban.

APPENDIX I

Pharmacometrics review

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the proposed dose of edoxaban in patients with venous thromboembolism (VTE) acceptable from an efficacy and safety perspective when compared to warfarin?

Yes, the exposure-response analysis suggests that patients with varying degrees of renal function all exhibit concentrations that translate to similar or improved efficacy and safety compared to warfarin (Figure 3 and Figure 4).

Figure 3. Exposure-response relationships for pulmonary embolism (PE)/deep-vein thrombosis (DVT) (only edoxaban exposure was found to be a significant predictor of response) and the observed rate for warfarin (horizontal dashed lines). The corresponding observed edoxaban exposure range for varying degrees of renal impairment are shown by the solid black lines as the 5th to 95th percentiles (solid-filled rectangles). The black vertical dashed line indicates the 99th percentile of all edoxaban C_{trough} exposures.

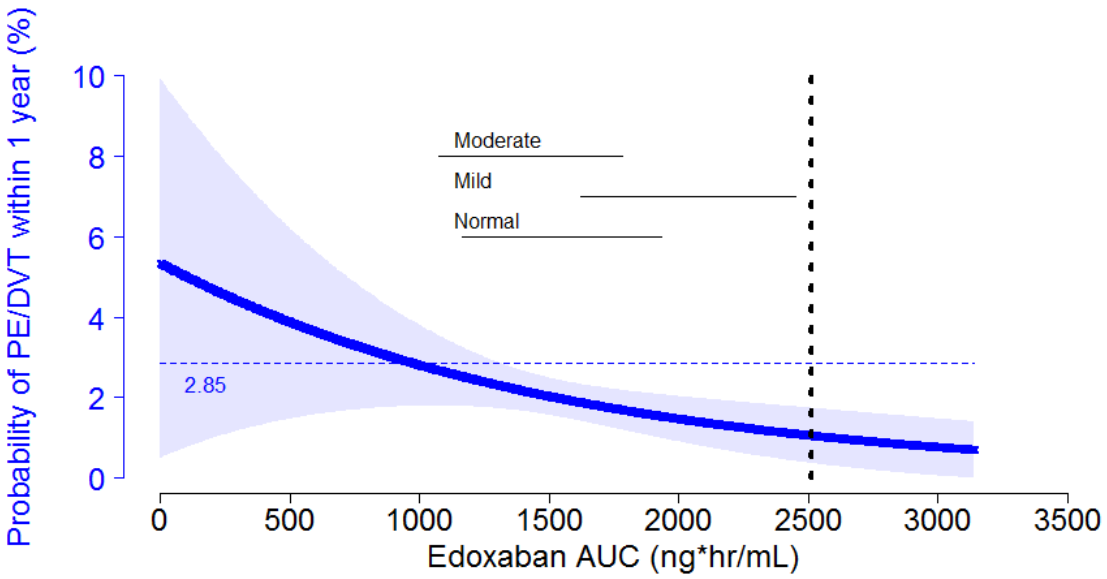


Figure 4. Exposure-response relationships for major bleeds for varying degrees of renal impairment and their corresponding observed rate for warfarin (horizontal

dashed lines) and their corresponding observed edoxaban exposure range as the 5th to 95th percentiles (solid-filled rectangles).

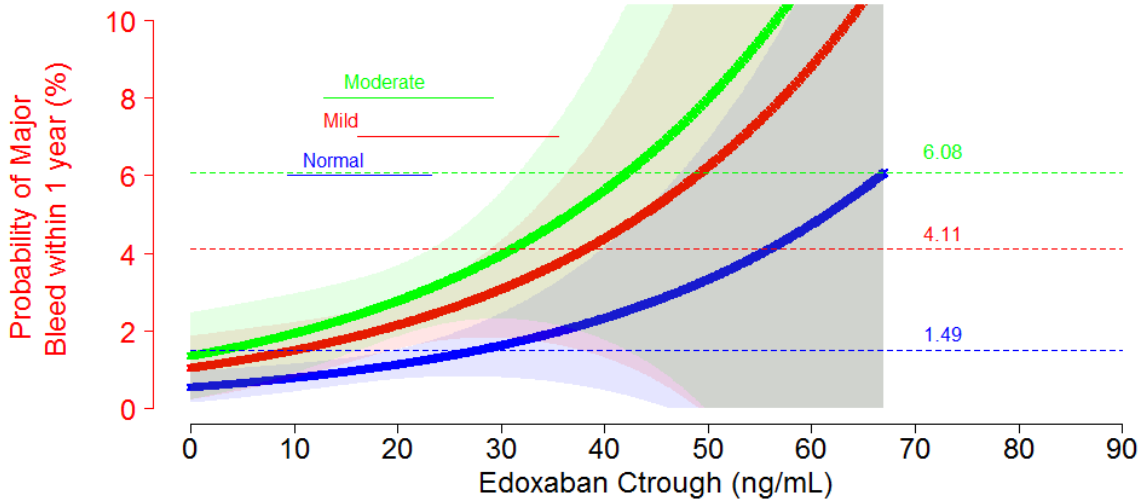


Table 2 supports the conclusion that no dose adjustment is required based on renal function as all renal function categories on edoxaban were comparable or showed improved efficacy and safety relative to warfarin. Summary results presented in the table below are based on an mITT analysis, baseline creatinine clearance values, and the overall treatment period. Not included in the table are 20 subjects (10 in each arm) who are baseline had creatinine clearance values of <30 mL/min (severe renal impairment).

Table 2. Observed Event Rates by Renal Function and Treatment Group suggest that patients with moderate renal impairment exhibit more benefit on edoxaban compared to warfarin.

Renal Function	Efficacy (DVT+PE+ unexplained death) Incidence			Safety (Major bleed) Incidence		
	Edoxaban	Warfarin	Risk Ratio	Edoxaban	Warfarin	Risk Ratio
Normal	3.3% (93/2799)	3.2% (88/2771)	1.045	0.9% (24/2799)	1.0% (29/2771)	0.819
Mild	2.7% (24/879)	4.2% (38/901)	0.647	2.7% (24/879)	2.8% (25/901)	0.984
Moderate	2.8% (6/218)	6.9% (15/216)	0.396	3.7% (8/218)	3.7% (8/216)	0.991

1.2 Recommendations

The Division of Pharmacometrics in the Office of Clinical Pharmacology has reviewed NDA206316 and found it acceptable.

2 PERTINENT REGULATORY BACKGROUND

Edoxaban is a new molecular entity that has been studied for the treatment and prevention of venous thrombo-embolism and the prevention of stroke in patients with atrial fibrillation.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1.1 Population PK:

3.1.1.1 Data

The PopPK analysis was performed using a dataset including relevant validated data from both Phase 1 (PRT016, A-U120, A-U127, A-U128, A-U129, A-U130, AU131, A-E132, A-E133, A-U136, A-U137, A-U138, A-U141) and Phase 3 (Hokusai VTE).

The following study conditions or patients were not included in the Phase 1 dataset: dose equal to 90 mg or 180 mg, routes of administration other than oral, drug formulations other than tablet, food effect, patients on dialysis, concomitant administration with other drugs apart from quinidine, verapamil, dronedarone, ketoconazole and erythromycin. Pharmacokinetic data following intravenous administration were not included since available data are limited and the aim of the Phase 1 data was to provide a structural model for the sparse Phase 3 data where only oral data are available.

3.1.1.2 Model

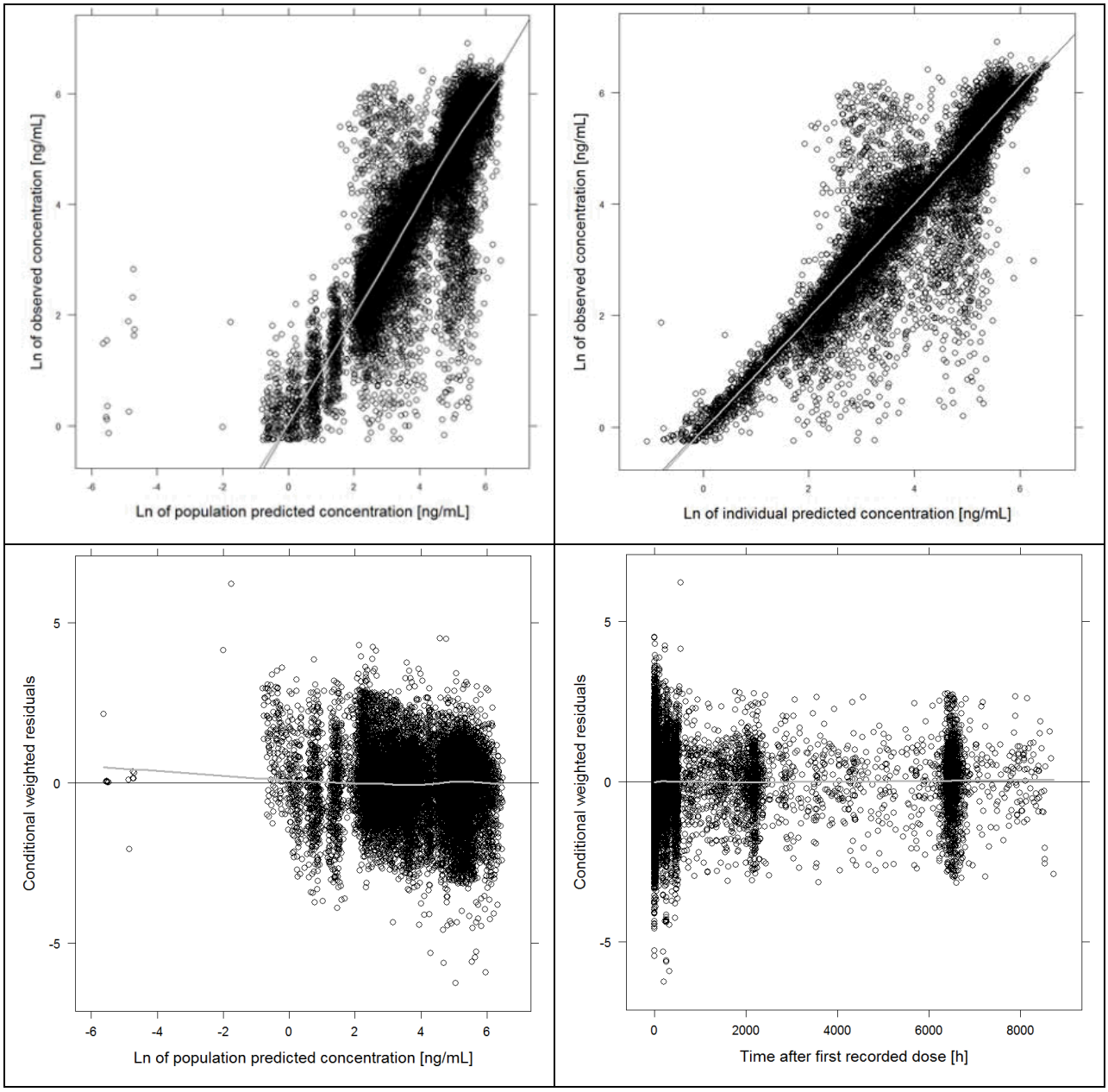
Table 3. Parameter Estimates of the Final VTE Population PK Model

Parameter		Estimate (%Rse[a])
Structural model		
Apparent non-renal clearance (CL_{nr}/F), L/h		15.2 (2.20)
Apparent non-renal clearance (CL_{nr}/F) study A-U141, L/h (θ_{16})		18.3 (3.73)
Apparent central volume of distribution (Vc/F), L		209 (1.61)
Apparent peripheral volume of distribution (Vp/F), L		92.3 (2.66)
Apparent inter-compartmental clearance (Q/F), L/h		5.91 (3.44)
First order absorption rate constant (k_a), h^{-1}		3.36 (4.74)
Fractional change in k_a study A-U141, h^{-1} (θ_{15}) [b]		-0.690 (1.19)
Lag-time (Tlag), h		0.250 fixed[c] (ne[d])
Covariate effects		
CLcr on CL_r, slope 1 (θ_{11})[e]		0.202 (2.22)
CLcr on CL_r, slope 2 (θ_{12})[e]		0.0321 (4.74)
Scaling parameter for CLcr on CL_r, slope 2 in Phase 3, % change (θ_{19}) [e]		274 (8.02)
P-gp inhibitors on CL (Phase 1 only, θ_{17}), % change [f]		33.4 (9.39)
P-gp inhibitors on F (Phase 1 only, θ_{18}), % change [f]		125 (5.19)
Scaling parameter for race on Vc/F (θ_{20}), % change for Asians[g]		22.6 (13.6)
Scaling parameter for Q/F in Phase 3 (θ_{21}), % change for patients[h]		64.6 (19.5)
Inter-individual variability		***Shrinkage[k] of etas (%)***
CL/F[i], %CV	14.9 (7.10)	57.2
Scaling parameter CL/F-Vc/F (θ_9)[i]	1.56 (2.47)	
Vc/F[i], %CV	23.2 (ne)	57.2
Vp/F[i], %CV	52.7 (8.57)	58.7
Scaling parameter Q/F-Vp/F (θ_{10})[i]	1.00 fixed (ne)	
Q/F[i], %CV	52.7 (ne)	58.7
Correlation η_1 and η_2[i]	42.7 (13.7)	
Tlag, %CV	58.5 (7.83)	30.4
Inter-individual variability on residual variability, %CV	33.3 (6.89)	23.2
Inter-occasion variability		***Shrinkage[k] of eta (% at occasion 1; 2; 3; 4; 5)***
CL/F, %CV	9.78 fixed (ne)	65.7; 78.5; 72.3; 41.5; 2.38
Vc/F, %CV	26.9 fixed (ne)	58.8; 66.4; 69.9; 24.9; -30.7
k_a, %CV	101 fixed (ne)	70.4; 65.0; 78.4; 40.5; 43.2
Residual variability		***Shrinkage[k] of epsilon (%)***
Proportional residual error, %CV	14.2 (2.80)	8.04
Incremental proportional residual error in Phase 3, %CV	54.4 (1.80)	

(Source: Sponsor's Population PK Report TMP010, Table 9.12)

3.1.1.3 Goodness of Fit Plots

Figure 5. Goodness of Fit plots for the sponsor's final population PK model.



(Source: Sponsor's Population PK Report TMP010, Figure 10.23 (top left panel), Figure 10.24 (top right panel), Figure 10.25 (bottom left panel), Figure 10.26 (bottom right panel))

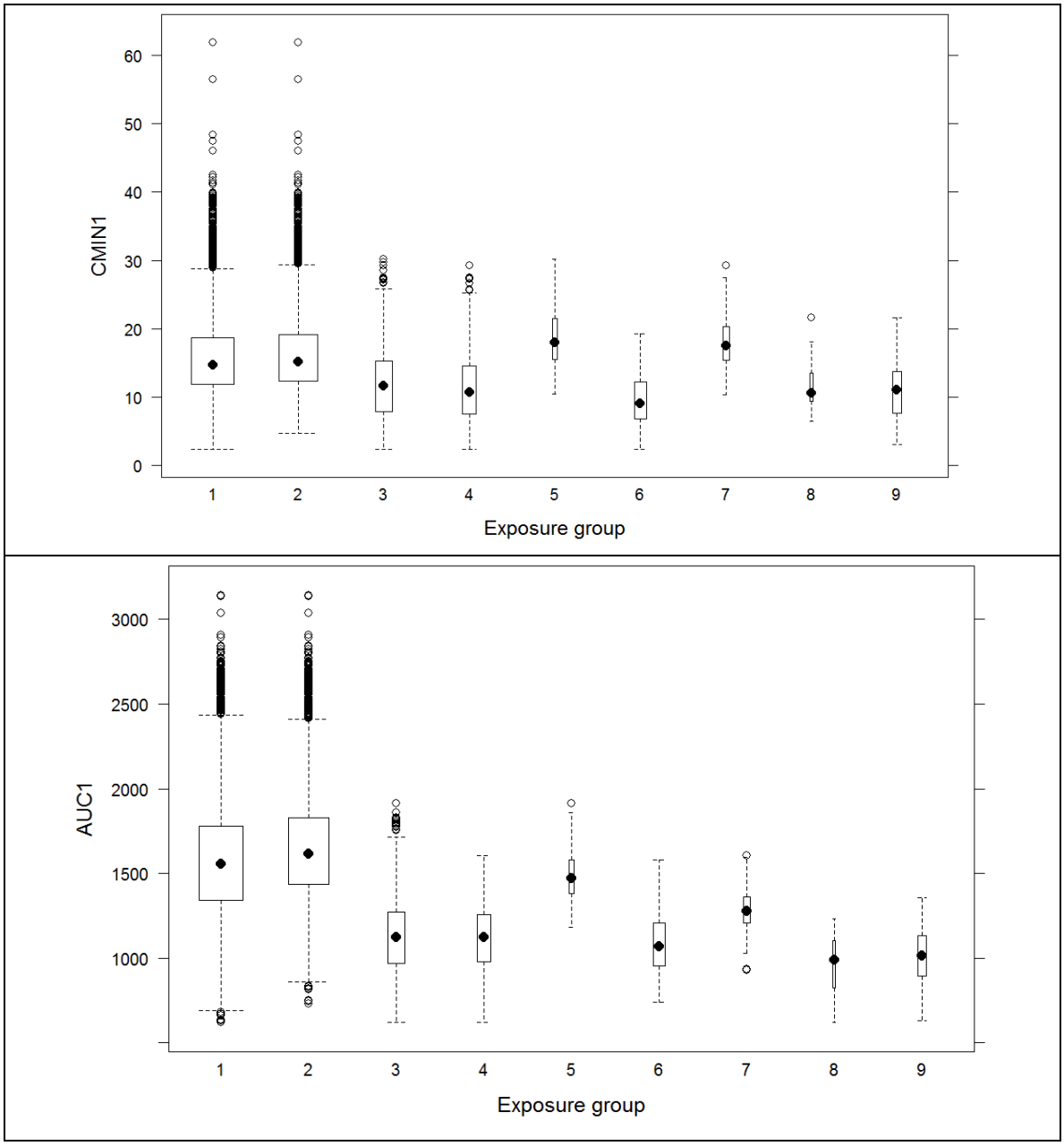
3.1.1.4 Exposure Metrics by Exposure Group:

(Source: Sponsor's Population PK Report TMP010, Figure 10.62)

Figure 6. Boxplots of individual predicted minimum concentration (CMIN1 = C24 h) and AUC24 hr at steady-state, in ng/mL. in various exposure groups.

1. **all data, i.e. 60 mg QD non-adjusted and 60 mg QD adjusted to 30 mg,**

2. **non-dose-adjusted 60 mg QD,**
3. **60 mg QD adjusted to 30 mg,**
4. **all single adjusted,**
5. **adjusted for 2 or more factors,**
6. **only body weight adjusted,**
7. **only P-gp inhibitor adjusted,**
8. **only CLcr adjusted,**
9. **no apparent reason for adjustment.**



(Source: Sponsor's Population PK Report TMP010, Figure 10.57 and Figure 10.58)

Table 4. Individual Predicted C_{min} based on the exposure prediction for each individual at the first occasion.

Exposure Group	Mean	Median	25th Percentile	75th Percentile	Min	Max	N
All	15.7	14.7	11.6	18.9	3.07	56.4	3687
Non-dose-adjusted 60 mg QD	16.4	15.3	12.1	19.4	4.84	56.4	3105
60 mg QD adjusted to 30 mg	12.1	11.5	7.98	15.2	3.07	30.1	582
All single adjusted	11.5	10.7	7.59	14.6	3.07	29.2	384
Adjusted for 2 or more factors	18.7	19.3	15.5	21.7	10.6	30.1	61
Only weight adjusted	9.58	9.28	6.68	12.3	3.07	19.3	288
Only P-gp inhibitor adjusted	11.2	10.0	8.96	11.9	6.48	21.6	16
Only CLcr adjusted	18.2	17.6	15.5	20.4	10.9	29.2	80
Adjusted for no apparent reason	11.0	11.1	7.59	13.8	3.26	21.6	137

(Source: Sponsor's Population PK Report TMP010, Table 11.2)

Table 5. Individual Predicted AUC0-24,SS based on the exposure prediction for each individual at the first occasion.

Exposure Group	Mean	Median	25th Percentile	75th Percentile	Min	Max	N
All	1572	1556	1340	1783	622	3035	3687
Non-dose-adjusted 60 mg QD	1653	1615	1433	1835	749	3035	3105
60 mg QD adjusted to 30 mg	1137	1126	973	1275	622	1858	582
All single adjusted	1123	1134	981	1258	622	1590	384
Adjusted for 2 or more factors	1493	1465	1383	1581	1198	1858	61
Only weight adjusted	1085	1079	953	1201	772	1541	288
Only P-gp inhibitor adjusted	950	902	816	1075	622	1233	16
Only CLcr adjusted	1295	1291	1210	1376	936	1590	80
Adjusted for no apparent reason	1016	1018	897	1128	635	1355	137

(Source: Sponsor's Population PK Report TMP010, Table 11.3)

Reviewer's Comments:

The sponsor's goodness of fit plots deviates from the line of identity in multiple locations. However, in general the central tendency is captured for the majority of the data and bias does not appear to arise over time in the model. The model is reasonable for generating post-hoc Bayesian estimates of C_{trough}, AUC and $C_{average}$ (AUC divided by dosing interval) for exposure response analyses. Based on the manner of the data collection, it does not

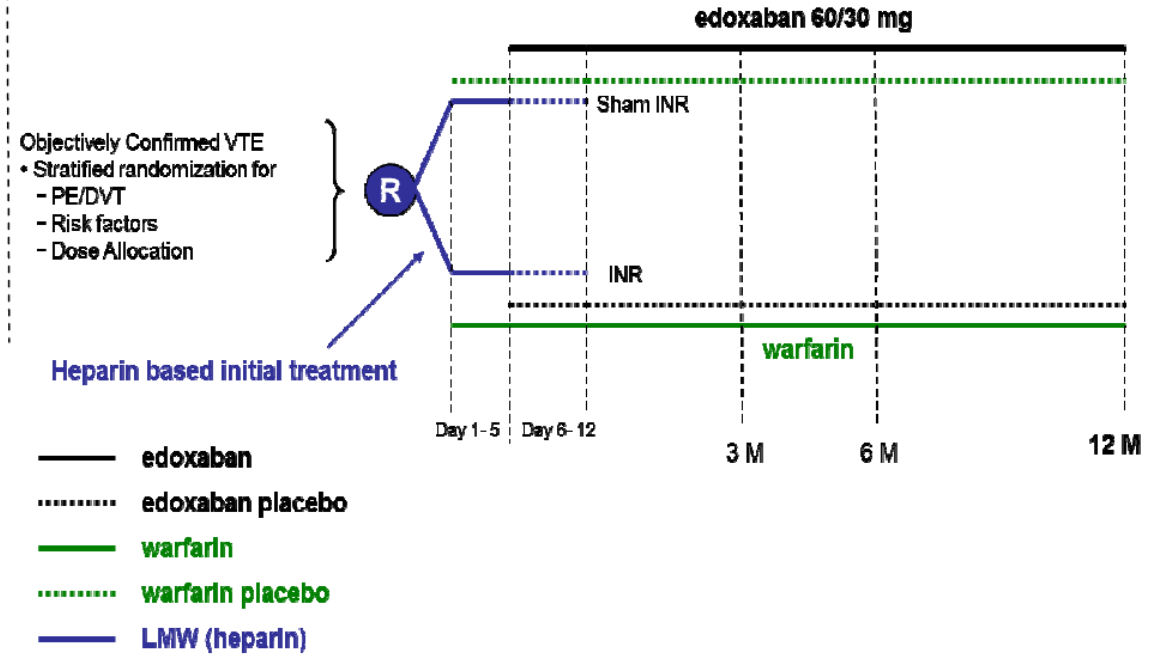
appear reasonable to use this model to estimate C_{max} for each individual; Therefore C_{max} was not used in the exposure-response analysis. The final model has large shrinkage on the eta for CL (57%), and thus only-post hoc Bayesian estimates should be used when possible for the exposure-response analyses.

3.1.2 Time-To-Event Exposure Response Analyses:

3.1.2.1 Clinical Trial DU176B-D-U305 (Pivotal VTE Phase 3 Study):

Study DU176B-D-U305 was a phase 3, randomized, double-blind, double-dummy, parallel-group, multi-center, multi-national study for the evaluation of efficacy and safety of heparin/edoxaban versus heparin/warfarin in subjects with symptomatic deep-vein thrombosis and/or pulmonary embolism.

Figure 7. Hokusai VTE Study Design Schematic



(Source: Sponsor's Clinical Study Report DU176B-D-305, Figure 9.1)

The primary objective was to evaluate whether initial low molecular weight heparin followed by edoxaban only is non-inferior to initial heparin overlapping with warfarin, followed by warfarin only in the treatment of subjects with acute symptomatic VTE for the prevention of symptomatic recurrent VTE during the 12-month study period.

The primary efficacy endpoint was symptomatic recurrent VTE (i.e., the composite of DVT, non-fatal PE, and fatal PE)

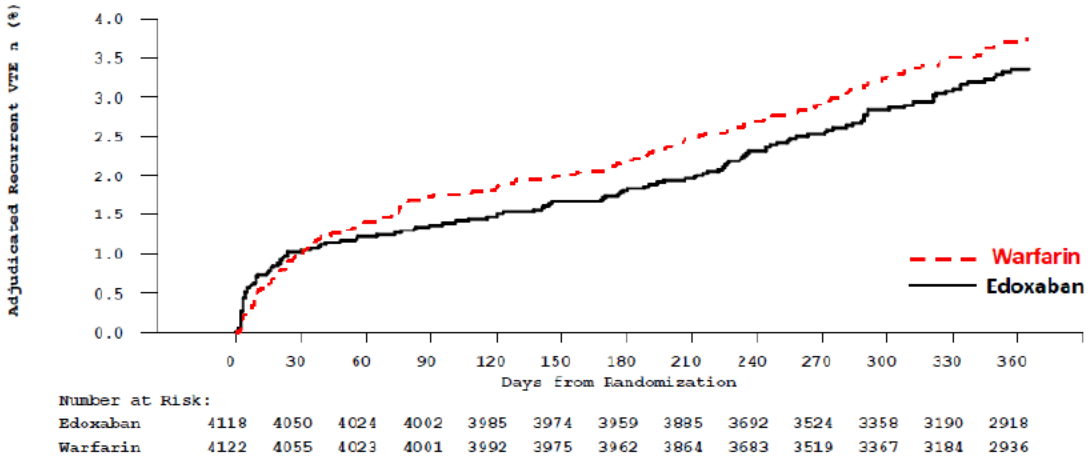
Heparin/edoxaban was found to be non-inferior to the standard therapy ([LMW] heparin/warfarin) since the upper limit of the two-sided 95% confidence interval (CI) for the Hazard Ratio ([LMW] heparin/edoxaban to standard therapy) was less than 1.5.

Blood samples were collected at Months 3 and 12 and in conjunction with an event for PK evaluation of edoxaban and its active metabolite, D21-2393. Blood samples were

collected at baseline (Day 1), Months 3 and 12, at follow-up, and in conjunction with an event for the measurement of PD markers including D dimer and anti-Factor Xa activity (Anti-FXa).

The primary efficacy analysis was based on a modified Intent-to-Treat (mITT) Analysis Set (subjects who are randomized and received at least one dose of study drug) using all primary efficacy events that occurred in the 12-month study period (i.e., primary efficacy events occurring from randomization through the end of the 12-month study period (or to the day of global end of treatment), regardless of whether the subject was taking study drug). Also included are subjects whose full 12-month study period was truncated due to declaration of the end of study. In this analysis, the time to the first event of the composite primary efficacy outcome was analyzed using a Cox proportional hazards model including treatment and the stratification factors as covariates. The (LMW) heparin/edoxaban: comparator Hazard Ratio (HR) was computed with a 95% CI (two-sided testing) based on this model. (LMW) heparin/edoxaban was considered noninferior to the comparator if the upper limit of the CI is less than 1.5.

Figure 8. Kaplan-Meier Cumulative Event Rate Estimates for Primary Endpoint (Adjudicated Symptomatic Recurrent VTE) – mITT Analysis Set, Overall Study Period.



(Source: Sponsor's Clinical Study Report DU176B-D-305, Figure 11.2)

3.1.2.2 Data

In the ER analysis, all evaluable patients in the DU176B-D-305 study taking at least one dose of edoxaban were included. Patients taking at least one dose of warfarin were used for the risk factor analysis.

Only time to first event was considered. The time to first event was defined as the time from the first dose of study drug to the first event experienced by a subject, for both efficacy and safety endpoints. Only data up until first study interruption plus 3 days was included. Study drug interruption of ≤3 days were allowed, as this was according to the protocol not considered to be study drug interruption, but rather missed doses. For subjects who did not experience an event, the time to first event was censored at the time of permanent discontinuation of drug plus 3 days, first drug interruption plus 3 days, or on the last day the subject had a complete assessment for study outcomes (or death, if a

subject died), whichever occurred first. If none of these rules were applicable, the individual was excluded.

In total, 4118 edoxaban patients and 4122 warfarin treated patients were included in the analysis. The total numbers of events and the number of patients are shown in Table 6.3.

Table 6. Disposition of All Subjects Randomized to Trial DU176B-D-305.

	Edoxaban N=4143 n (%)	Warfarin N=4149 n (%)	Overall N=8292 n (%)
Randomized, n	4143	4149	8292
Treated (mITT) [a]	4118 (99.4)	4122 (99.3)	8240 (99.4)
Completed Study [a,b]	3937 (95.6)	3955 (95.9)	7892 (95.8)
Full 12 Month Follow-Up	3058 (74.3)	3074 (74.6)	6132 (74.4)
<12 Month Follow-Up Due to Study Truncation [b]	879 (21.3)	881 (21.4)	1760 (21.4)
Did Not Complete Study Follow-Up [a]	181 (4.4)	167 (4.1)	348 (4.2)
Death	136 (3.3)	127 (3.1)	263 (3.2)
Withdrew Consent	32 (0.8)	33 (0.8)	65 (0.8)
Lost to Follow-Up	7 (0.2)	4 (<0.1)	11 (0.1)
Sponsor Decision	0 (0.0)	0 (0.0)	0 (0.0)
Other [c]	6 (0.1)	3 (<0.1)	9 (0.1)

Abbreviations: mITT=modified Intent-to-Treat, N = number of subjects in analysis set, n = number of subjects meeting event criteria.
[a] The denominator for percent treated is the number of subjects randomized; the denominator for percents completed and did not complete study follow-up is the mITT Population.
[b] Subjects were considered to have completed the study when they had a 12-month follow-up or < 12-month follow-up due to truncation of the study. Subjects completing less than 12 months of follow-up due to study truncation based on global study milestone dates announced in Protocol Amendment 4.
[c] Investigator or subject decision to not continue in lieu of withdrawn consent.
Source: Table 14.1.1.5 and Table 14.1.1.7.

(Source: Sponsor's Clinical Study Report DU176B-D-305, Table 10.1)

Table 7. Demographic and Baseline Characteristics by Edoxaban Dose at Randomization, mITT Analysis Set.

	Active Edoxaban		Active Warfarin	
	Edoxaban 30 mg [a] N=733 n (%)	**Edoxaban 60 mg N=3385 n (%)**	**Edoxaban Placebo 30 mg [a] N=719 n (%)**	**Edoxaban Placebo 60 mg N=3403 n (%)**
Age (years)	733	3385	719	3403
Mean (SD)	59.9 (19.19)	54.7 (15.43)	60.2 (19.45)	55.0 (15.24)
Median	64.0	56.0	64.0	56.0
Minimum	18	18	19	18
Maximum	106	93	95	93
<65 years	372 (50.8)	2412 (71.3)	363 (50.5)	2389 (70.2)
>=65 years	361 (49.2)	973 (28.7)	356 (49.5)	1014 (29.8)
>=75 years	208 (28.4)	352 (10.4)	216 (30.0)	328 (9.6)
>=80 years	107 (14.6)	145 (4.3)	125 (17.4)	140 (4.1)
Gender	733	3385	719	3403
Male	245 (33.4)	2115 (62.5)	241 (33.5)	2115 (62.2)
Female	488 (66.6)	1270 (37.5)	478 (66.5)	1288 (37.8)
Race	730	3379	718	3397
Caucasian	326 (44.5)	2541 (75.1)	323 (44.9)	2572 (75.6)
Black	22 (3.0)	134 (4.0)	22 (3.1)	122 (3.6)
Asian	337 (46.0)	529 (15.6)	331 (46.0)	530 (15.6)
Other	45 (6.1)	175 (5.2)	42 (5.8)	169 (5.0)
Presenting Diagnosis (IXRS)	733	3385	719	3403
Pulmonary Embolism	311 (42.4)	1360 (40.2)	309 (43.0)	1370 (40.3)
with DVT	97 (13.2)	514 (15.2)	80 (11.1)	480 (14.1)
without DVT	214 (29.2)	846 (25.0)	229 (31.8)	890 (26.2)
DVT Only	422 (57.6)	2025 (59.8)	410 (57.0)	2033 (59.7)
Risk Factors (IXRS)	733	3385	719	3403
Temporary	206 (28.1)	926 (27.4)	206 (28.7)	934 (27.4)
Other	527 (71.9)	2459 (72.6)	513 (71.3)	2469 (72.6)
Weight at Randomization (IXRS)(kg)	733	3385	719	3403
<=60	524 (71.5)	0 (0.0)	519 (72.2)	0 (0.0)
> 60	209 (28.5)	3385 (100.0)	200 (27.8)	3403 (100.0)
Creatinine Clearance at Randomization (IXRS) (mL/min)	733	3385	719	3403
>=30 to <=50	268 (36.6)	0 (0.0)	273 (38.0)	0 (0.0)
>50	465 (63.4)	3385 (100.0)	446 (62.0)	3403 (100.0)

Verapamil or Quinidine Use at Randomization (IXRS)	733	3385	719	3403
Yes	26 (3.5)	0 (0.0)	25 (3.5)	0 (0.0)
No	707 (96.5)	3385 (100.0)	694 (96.5)	3403 (100.0)

Abbreviations: DVT = deep vein thrombosis, IXRS = Interactive voice/web response system, N = number of subjects in analysis set, n = number of subjects meeting event criteria, SD = standard deviation.
[a] At randomization subjects with low body weight (≤60kg), moderate renal impairment (CrCL 30-50 ml/min), or pre-specified concomitant medications (e.g. verapamil. quinidine). in the edoxaban group received active edoxaban 30 mg (and placebo warfarin) while subjects in the warfarin group with the same low body weight, moderate renal impairment, or pre-specified concomitant medications received placebo edoxaban 30 mg (and active warfarin).
Note: Body weight, creatinine clearance and verapamil/quinidine use was derived from information recorded in the IXRS at randomization.
Note: Risk Factors and Presenting Diagnosis are per the Investigator at Randomization. Risk Factors are categorized temporary (e.g., trauma, surgery, immobilization, estrogen therapy, etc.) vs all others.
Source: Table 14.1.3.4.

(Source: Sponsor's Clinical Study Report DU176B-D-305, Table 10.3)

- The risk factor dataset consisted of all patients who had received at least one dose of warfarin or edoxaban. The dataset contained 8240 patients, of which only the 4122 warfarin treated patients were used in the RF modeling.
- The ER data set comprised all patients who had received at least one edoxaban dose. The data set contained 4118 patients.

Table 8. Description of PK Exposure Indices Predictions

PK Information	Total Number of Patients (%)	Exposure Prediction
Conventional	3687 (89.5%)	Individual prediction
All PK observations below limit of quantification	20 (0.5%)	Zero PK exposure
No PK observations available	411 (10.0%)	Typical prediction based on individual covariates[a]

a: Typical predictions inserted by Uppsala University Pharmacometric group (UUPM) to the ER datasets. The process is further described in Section 5.2.1.

(Source: Sponsor's Exposure Response Report TMP011, Table 6.1)

3.1.2.3 Exposure Metrics:

The full covariate PopPK model was used to predict individual PK exposure indices (Cavg, AUC0-24,ss, Cmin and Cmax) over time in each patient. The full covariate PopPK model was used since this model included all covariate relationships used for dose adjustment i.e. WT, CLcr and concomitant P-gp inhibitors.

- In patients with observed plasma concentrations on at least one occasion (i.e. those included in the PopPK dataset), PK exposure indices were predicted for each individual at each occasion where a plasma concentration was measured or a change in dose occurred. These predictions were based on the empirical Bayes estimates (EBE) of PK parameters derived from the full PopPK model. The predicted inter-occasion variability was included in the prediction of PK exposure indices.

- For patients in the PopPK dataset who only had observed concentrations below the limit of quantification (LLOQ) in the dataset, all PK exposure indices were set to 0.
- For patients in the ER dataset with no observed plasma concentrations (i.e. not included in the PopPK dataset), the typical PK exposure indices were used. These predictions were based on the full PopPK model, the protocol study design, the patient's dosing information at randomization and the WT, CLcr and concomitant medication of P-gp inhibitors at randomization.

3.1.2.4 Risk Factors Evaluated:

Table 9. Risk Factors Included in the Exposure-Response Analysis

	Endpoints	
Risk Factors	**Safety Endpoints**	**Efficacy Endpoints**
History of life-threatening bleeding (BLE)	X	
History of dyslipidemia (DYS)		X
History of cardiovascular disease (CAR)		X
History of cerebrovascular disease (CER)	X	
History of renal disease (REN)	X	X
History of hepatic disease (HEP)	X	X
History of pulmonary disease (PUL)	X	X
History of cancer (CAN)	X	X
Recent surgery, trauma or immobilization (SUR)	X	X
Use of estrogen containing drugs (EST)	X	X
Recent active cancer (RCAN)	X	X
Previous episode(s) of PE/DVT (PDVT)*	X	X
Prolonged sitting more than 4 hours (SIT)		X
Antithrombin deficiency (THR)*	X	X
Factor V Leiden (FAC)	X	X
Hyperhomocysteinaemia (HOM)*	X	X
Antiphospholipid antibodies (APLA)*	X	X
Protein c deficiency (PCD)*	X	X
Protein S deficiency (PSD)*	X	X
Prothrombin gene mutation (PGM)*	X	X
Concomitant intake of aspirin or anti-platelet agent (ASA)	X	X
AGE≥75 (AGE75)	X	X
Female Sex (SEX)	X	X

Note: Safety endpoint - CRB (i.e., major or clinically relevant non-major bleeding)
Efficacy endpoint - symptomatic recurrent VTE (i.e., the composite endpoint of DVT, non-fatal PE and fatal PE) *Excluded from the analysis (see sections 6.2.2 and 6.3.2).

(Source: Sponsor's Exposure Response Report TMP011, Table 4.1)

3.1.2.5 Exposure-Response for Efficacy:

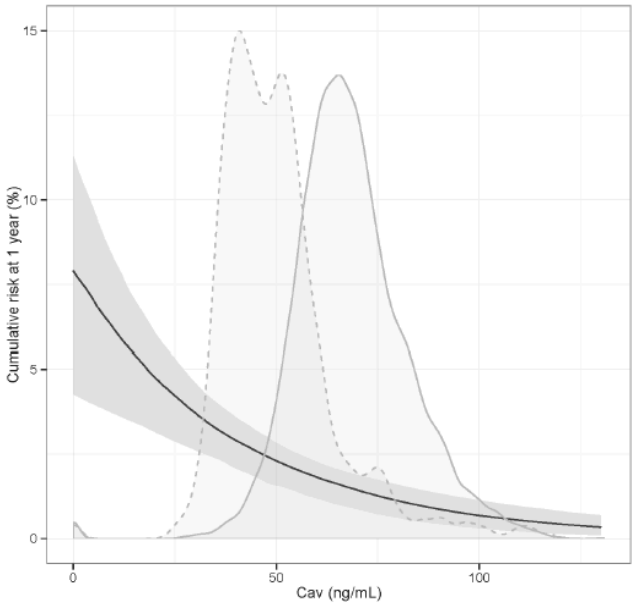
Table 10. Parameter Estimates of the Final Symptomatic Recurrent VTE Exposure-Response Model Using Edoxaban Patients

Parameter	Estimate[a]	90% Ci[b]	Hazard Ratio
λ [day^{-1}]	$2.624 \cdot 10^{-6}$	[$-4.256 \cdot 10^{-6}$ – $9.496 \cdot 10^{-6}$]	-
γ	0.3729	[0.2973 – 0.4487]	-
$\beta_{L,Cav}$ [(ng/ml)$^{-1}$]	-0.02181 [c]	[-0.03445 – $-9.151 \cdot 10^{-3}$]	0.98[d]

a: The estimates of the risk factor effects are parameterized as log hazard ratio.
b. CI obtained by observed Fisher information matrix
c. Decrease in the logarithmic hazard ratio with every 1 ng/ml of C_{av} of edoxaban
d. Decrease in the hazard ratio with every 1 ng/ml of C_{av} of edoxaban
C_{av} Average plasma concentration at steady state; λ Scale factor of the Weibull distribution; γ Shape factor of the Weibull distribution.

(Source: Sponsor's Exposure Response Report TMP011, Table 6.7)

Figure 9. Probability of a symptomatic recurrent VTE event within one year in an edoxaban patient versus $C_{average}$ edoxaban exposure.



(Source: Sponsor's Exposure Response Report TMP011, Figure 6.21)

Reviewer's Comments:

Similar to the atrial fibrillation population, it appears that with increasing edoxaban exposure there is a reduction in the probability of having an event. It is also apparent from the density plots in these figures that the same overcorrection in dose was made by reducing to 30 mg from 60 mg. Overall, despite difference in edoxaban PK between the atrial fibrillation and VTE populations, similar exposure-response relationships were identified, with increasing edoxaban exposure associated with a lower efficacy event rate and observations that the dose adjustment over-corrected for edoxaban exposures.

3.1.2.6 Exposure-Response for Safety:

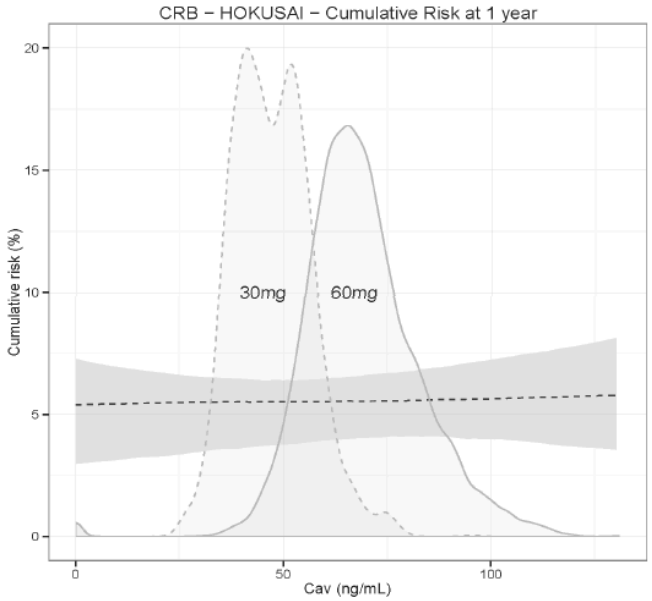
Table 11. Parameter Estimates of the Clinical Relevant Bleeding model used for the Clinical Utility Index.

Parameter	Estimate[a]	90% Ci[b]	Hazard Ratio
λ [day^{-1}]	$2.775 \cdot 10^{-5}$	[$7.203 \cdot 10^{-6}$ – $4.830 \cdot 10^{-5}$]	-
γ	0.6289	[0.5768 – 0.6810]	-
β_{AGE75}	0.2969	[0.06256 – 0.5311]	1.35
β_{ASA}	0.7613	[0.5457 – 9.769]	2.14
β_{CAN}	0.1091	[-0.2235 – 0.4416]	1.12
β_{PUL}	0.1683	[-0.05565 – 0.3922]	1.18
β_{RCAN}	0.7926	[0.3065 – 1.279]	2.21
β_{SUR}	0.3952	[0.1858 – 0.6047]	1.48
β_{SEX}	0.6778	[0.4964 – 0.8591]	1.97
$\beta_{L,Cav}$ [(ng/ml)$^{-1}$]	$9.272 \cdot 10^{-4}$ [c]	[$-4.617 \cdot 10^{-3}$ – $6.471 \cdot 10^{-3}$]	1.001[d]

a: The estimates of the risk factor effects are parameterized as log hazard ratio.
b. CI obtained by observed Fisher information matrix
c. Increase in the logarithmic hazard ratio with every 1 ng/ml of C_{av} of edoxaban
d. Increase in the hazard ratio with every 1 ng/ml of C_{av} of edoxaban
C_{av} Average plasma concentration at steady state; λ Scale factor of the Weibull distribution; γ Shape factor of the Weibull distribution.

(Source: Sponsor's Exposure Response Report TMP011, Table 6.8)

Figure 10. Probability of a Clinical Relevant Bleed within 1 year in an Edoxaban Patient versus $C_{average}$ Exposure of Edoxaban.



(Source: Sponsor's Exposure Response Report TMP011, Table 6.22)

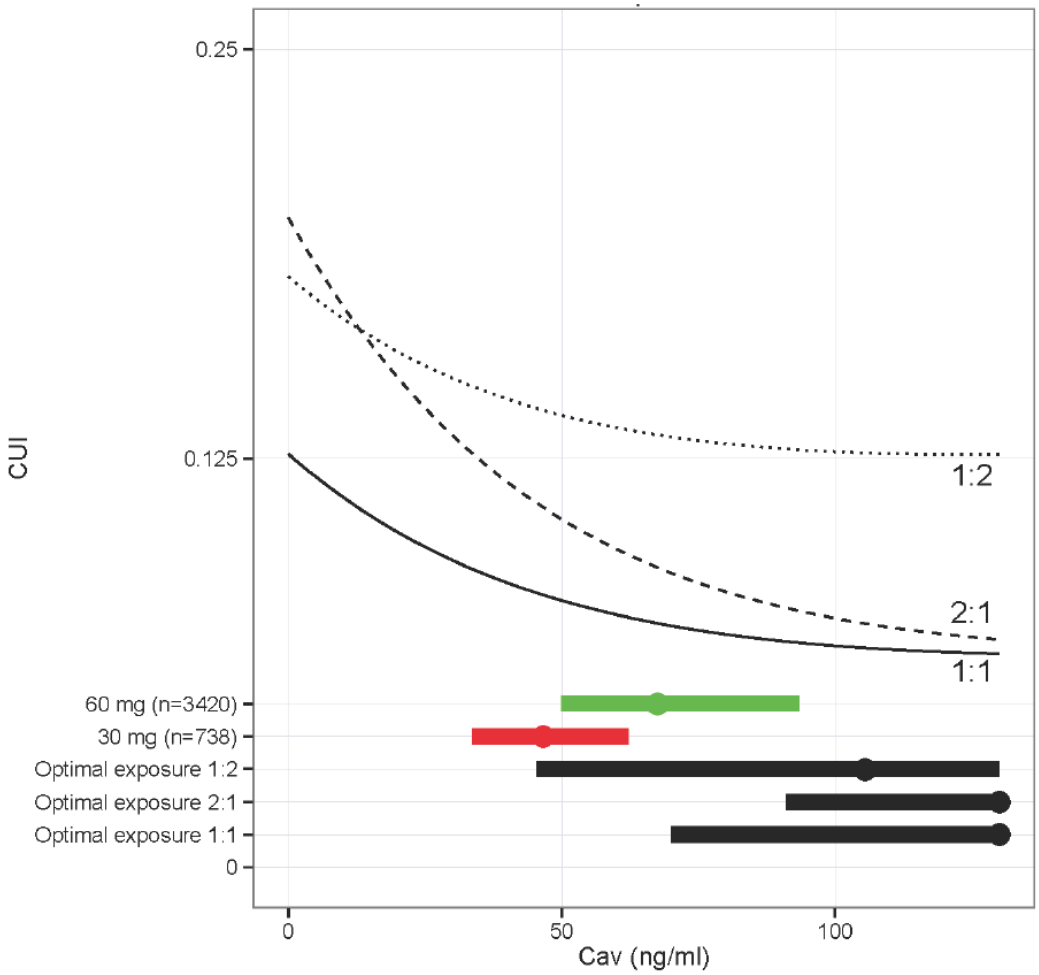
Reviewer's Comments:

The sponsor chose to use clinically relevant bleeds as the safety endpoint. The reviewer's analysis uses major bleeds.

3.1.2.7 Clinical Utility Analysis:

Figure 11. Clinical Utility Index based on Cumulative Risk of Symptomatic Recurrent VTE and Clinically Relevant Bleeds at One Year for Clinical Weights of

1:1, 2:1, and 1:2 versus PK exposure ($C_{average}$) visualized together with Optimal PK Exposure and Predicted PK Exposure in All Patients.



(Source: Sponsor's Exposure Response Report TMP011, Figure 6.26)

Reviewer's Comments:

The sponsor's analysis shows that for the same increase in edoxaban exposure between efficacy and safety events, there appears to be a benefit in reducing the probability of a pulmonary embolism or deep vein thrombosis compared to increasing the probability of a clinically relevant bleed for all three of the benefit-risk weighting schemes. This analysis suggests that a higher dose may offer more benefit without the additional bleeding burden, though it is acknowledged that different individuals may have different weights for the considered efficacy and safety events or may consider different safety events for such assessments. Taking that into consideration, the reviewer's analysis looks at this with regards to major bleeding events.

4 REVIEWER'S ANALYSIS

4.1 Introduction

Multi-variate exposure- and risk-factor analyses for efficacy endpoints and safety endpoints were conducted to inform a benefit-risk assessment of the proposed edoxaban dose (60 mg QD with dose adjustment to 30 mg QD for patients with low body weight, moderate or severe renal impairment, and concomitant P-gp Inhibitor use). The analysis served as a quality control to the sponsor's analysis and an opportunity to develop an independent scientific opinion on the sponsor's models as well as develop new models for endpoints not evaluated by the sponsor (major bleeds).

4.2 Objectives

Analysis objectives are:

1. Construct multi-variate exposure- and risk-factor- response models for efficacy
2. Construct multi-variate exposure- and risk-factor- response models for safety
3. Use the developed models to identify the expected yearly event-rates for different patient populations and to evaluate the net benefit at various dose levels

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 12.

Table 12. Analysis Data Sets

Study Number	Name	Link to EDR
DU176B-D-305	dm.xpt, basegrp.xpt, adjeff.xpt, adjsaf.xpt	\\Cdsesub1\evsprod\NDA206316\0000\m5\datasets\du176b-d-u305\analysis\legacy\datasets

4.3.2 Software

The statistical software R (version 2.15) was used for all dataset construction, time-to-event analyses, and for generating graphics.

4.3.3 Models

Multivariate Cox proportional hazards models were developed for the PE/DVT and bleeding events from Study 305. Models were evaluated for both warfarin and edoxaban in the same dataset and also for edoxaban data alone. The latter models (edoxaban) were explored in the subsequent analyses owing to their better estimation of the observed event rates for edoxaban and as a full model accounting for the treatment effect of warfarin and relevant covariates (i.e., INR) was not being developed. Model covariates tested included: treatment (warfarin vs. edoxaban), age, creatinine clearance (both Cockcroft-Gault and eGFR), edoxaban trough concentrations, log-transformed edoxaban trough concentrations, body weight, concomitant aspirin use, history of life-threatening bleeding, history of dyslipidemia, history of cardiovascular disease, history of cerebrovascular disease, history of renal disease, history of hepatic disease, history of pulmonary disease, history of cancer, recent surgery or immobilization, use of estrogen

containing drugs, recent active cancer, prior PE/DVT, prolonged sitting of more than 4 hours, antithrombin deficiency, factor V Leiden deficiency, hyperhomocysteinanemia, antiphopholipid antibodies, protein c deficiency, protein S deficiency, promthrombin gene mutation, and sex. Covariates were included into a full model if their univariate assessment indicated significance of the parameter at α=0.05. Covariates were eliminated from the model during a backwards elimination evaluation if based on a significance of the parameter at α=0.05. The efficacy and safety analyses were based on the full mITT population using the on-treatment censor for both efficacy and bleeding endpoints.

Table 13. Final Cox proportional hazards model (exponential distribution) for PE/DVT events using only edoxaban data from study DU176B-D-305.

PE/DVT Events				
	Estimate	Standard Error	z	p
Edoxaban AUC (ng*hr/mL)	-0.000663	0.000306	-2.17	0.03

Table 14. Final Cox proportional hazards model (exponential distribution) for major bleeds using only edoxaban data from study DU176B-D-305.

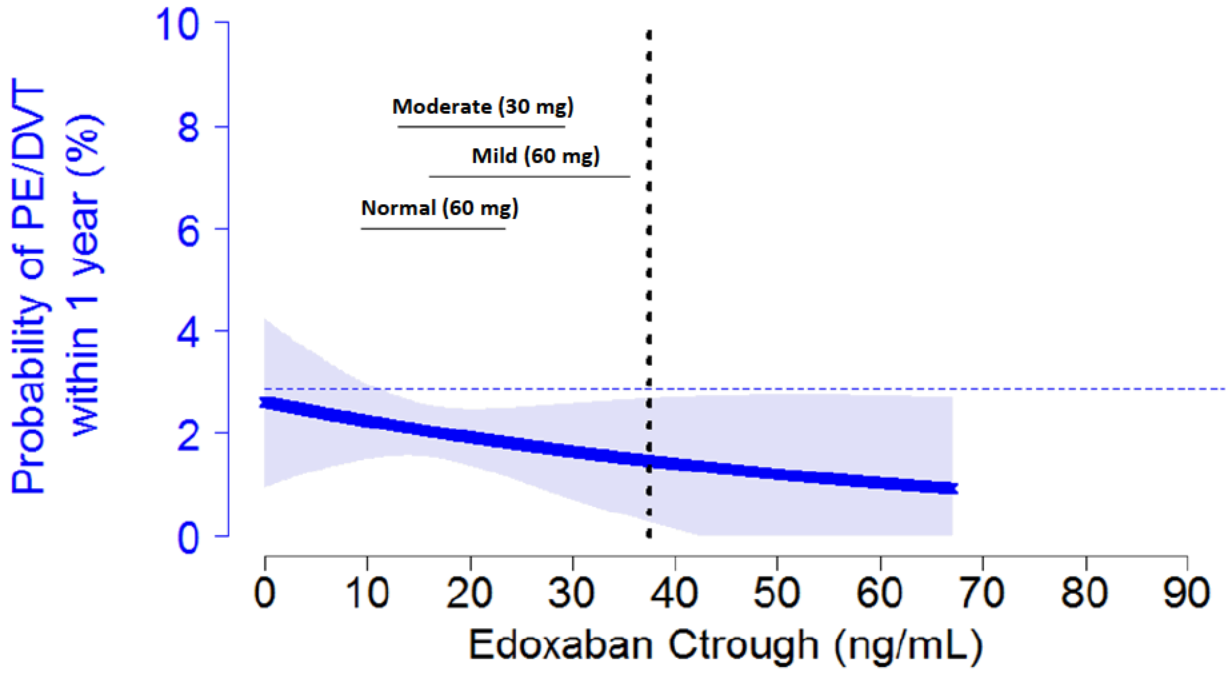
PE/DVT Events				
	Estimate	Standard Error	z	p
Edoxaban Ctrough (ng/ml)	0.0361	0.01746	2.07	3.90E-02
Concomitant Aspirin	0.7993	0.20669	3.87	1.10E-04
Age (years)	0.032	0.00676	4.74	2.20E-06
Sex	-0.4087	0.18124	-2.26	2.40E-02

4.4 Results

Refer to Section 1.1.1 for details on this analysis. Figure 12 is shown below for completeness. While there was a slight correlation between AUC and C_{trough} (0.61), C_{trough} was not a significant predictor for the probability of a PE/DVT event, whereas AUC was. However, for completeness the efficacy relationship based on C_{trough} is shown in Figure 12. Additionally the C_{trough} relationship for PE/DVT did not appear to qualitatively make sense below the evaluated concentrations. That is no concentrations of edoxaban or placebo appeared to be better or the same as warfarin. This was not the case with the AUC metric, which was a significant predictor. The intercept for the C_{trough} relationship was most due to the use of linear AUC as the exposure metric, a slightly lower event rate for edoxaban (particularly for the highest exposures), and projections of the relationship back to the y-axis over an interval (0 to 11 ng/mL) where there are few patients and events. Inclusion of a second edoxaban dose (i.e. 30 mg) in the study may have provided the necessary information to more accurately determine the edoxaban concentration at which PE/DVT event rates may have begun to increase relative to warfarin.

Figure 12. Exposure-response relationships for pulmonary embolism/deep-vein thromboses (only edoxaban exposure was found to be a significant predictor of response) and the observed rate for warfarin (horizontal dashed lines). The corresponding observed edoxaban exposure range for varying degrees of renal

impairment are shown by the solid black lines as the 5th to 95th percentiles (solid-filled rectangles). The black vertical dashed line indicates the 99th percentile of all edoxaban C_{trough} exposures.



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\Edoxaban_NDA206316_JCE,DM\
VTE_EfficacySafetyCombined.R	Exposure-response and data management for both efficacy and safety endpoints in the VTE population.	…\ER Analyses\VTE_JCE\

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

/s/

YOUNG J MOON
10/31/2014

DIVYA MENON ANDERSEN
10/31/2014

JEFFRY FLORIAN on behalf of JUSTIN C EARP
10/31/2014
Signing on behalf of Justin Earp

JEFFRY FLORIAN
10/31/2014

JULIE M BULLOCK
10/31/2014

CLINICAL PHARMACOLOGY REVIEW

NDA Number	206316
Submission Type; Code	Original, N_00
Applicant Name	Daiichi Sankyo, Inc.
Submission Dates	01/08/14, 08/22/2014
Generic Name	Edoxaban tosylate
Dosage Form	Immediate release tablet
Dosage Strengths	15, 30, and 60 mg
Proposed Indication	To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
OCP Divisions	DCPI, DCPV, DPM, GTTG
Primary Reviewers	Divya Menon-Andersen, Young-Jin Moon, Justin Earp, Robert Schuck
Team Leaders	Rajanikanth Madabushi, Julie Bullock, Jeffry Florian, Michael Pacanowski

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1 EXECUTIVE SUMMARY

In this new drug application, Daiichi Sankyo, Inc. is seeking approval of edoxaban (NDA 206316) for reduction in the risk of stroke and systemic embolic event (SEE) in patients with nonvalvular atrial fibrillation (Afib). Edoxaban is a third in class direct factor Xa inhibitor. In addition to warfarin, the following three products are approved for this indication: dabigatran, rivaroxaban, and apixaban.

In support of the indication being sought, the Applicant conducted an extensive clinical pharmacology program and a single Phase 3 trial, ENGAGE-AF, a double dummy, warfarin controlled event driven trial in which two edoxaban doses (dose halved based on body weight, renal function and concomitant therapy with P-glycoprotein inhibitors) were evaluated. The Phase 3 trial met the primary objective of non-inferiority on the composite endpoint of ischemic stroke/SEE but failed to demonstrate superiority compared to warfarin. Compared to warfarin-treated subjects, the hazard ratio (HR) in the edoxaban 60 mg (30 mg) group was 0.86 (97.5% CI: 0.719, 1.029) and in the edoxaban 30 mg (15 mg) group was 1.13 (97.5% CI: 0.955, 1.336). However, in the edoxaban 30 mg (15 mg) group, results were not favorable with a HR for ischemic stroke of 1.54 (1.25-1.9). For this reason, the Applicant is seeking to market only the 60 mg (30 mg) dose of edoxaban.

Subgroup analyses of ENGAGE-AF identified unfavorable findings in patients with normal renal function (CrCL $\geq$ 80 mL/min), who comprised a large fraction of the target population (~37% in ENGAGE-AF). The HR for stroke/SEE in this subgroup for edoxaban 60 mg was 1.41 (0.97 – 2.05). The treatment by renal function interaction was nominally significant ($p < 0.001$) for both edoxaban dose groups. Less favorable results were also observed for the components of the primary efficacy endpoint across edoxaban dose groups in patients with CrCL$\geq$80 mL/min. This unique finding for prevention of stroke with edoxaban, where alternative treatments are available, was identified as the most significant review issue with potential implications on regulatory action as well as labeling. Hence, the primary focus of this review was to identify and characterize the factors that may explain the observed difference in edoxaban treatment effect in patients with normal renal function from a clinical pharmacology perspective.

Our analyses indicate that the observed outcomes relative to warfarin appear to be the result of lower edoxaban concentrations achieved in patients with normal renal function. This conclusion is also supported by the observation that the most favorable reduction in stroke/SEE compared to warfarin is observed in patients with mild renal impairment (CrCL $\geq$50 – < 80 mL/min), the subgroup with highest edoxaban exposure in ENGAGE AF. Also, supportive is the observation that major bleeding rates (relative to warfarin) are lower in edoxaban patients with normal renal function as compared to that in patients with mild renal impairment. Hence we consider edoxaban exposure to be a determinant of efficacy and safety. Further, steady-state trough concentration (C_{trough}) attained in patients following administration of edoxaban was identified as a significant predictor of primary efficacy and safety endpoints in exposure–response analyses using multivariate Cox Proportional Hazards models. Similar exposure-response relationships have been

quantified for other thrombotic and safety events of interest including ischemic strokes, hemorrhagic strokes, life-threatening/fatal bleed, and major gastrointestinal bleed.

We believe that based on exposure-response analyses, a path forward for optimizing dose in patients with normal renal function can be derived by exposure-matching to that observed in patients with mild renal impairment. Dose adjustment based on exposure-matching is routinely applied by the Agency for deriving dosing in sub-populations that are not represented in the registration trials, accounting for exposure changes resulting from drug-drug interactions, or mitigating safety concerns while maintaining acceptable efficacy. The choice of an appropriate edoxaban dose using this approach depends on the benefit/risk that will be considered acceptable, a topic for discussion at the Cardiovascular and Renal Drugs Advisory Committee meeting on Oct 30, 2014. To facilitate this discussion risk ratio projections for efficacy and safety endpoints of edoxaban 75 mg and edoxaban 90 mg in patients with normal renal function are presented in Table 1. The exposures projected to be achieved with these doses are mostly covered by the overall experience in ENGAGE-AF in patients with mild renal impairment.

Table 1: Risk ratio based on event rates projected for edoxaban with doses greater than those studied in ENGAGE-AF for patients with normal renal function (CrCL≥80 mL/min).

Endpoint	Comparison	Risk Ratio
Stroke/SEE	Edoxaban 60 vs Warfarin*	1.41
	Edoxaban 75 vs Warfarin	1.14
	Edoxaban 90 vs Warfarin	1.05
Major Bleed	Edoxaban 60 vs Warfarin*	0.71
	Edoxaban 75 vs Warfarin	0.96
	Edoxaban 90 vs Warfarin	1.19
Ischemic Stroke	Edoxaban 60 vs Warfarin*	1.58
	Edoxaban 75 vs Warfarin	1.26
	Edoxaban 90 vs Warfarin	1.15
LT / Fatal Bleed	Edoxaban 60 vs Warfarin*	0.69
	Edoxaban 75 vs Warfarin	0.73
	Edoxaban 90 vs Warfarin	0.78

*Observed Hazard Ratio

1.1 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Key findings are listed below.

Pharmacokinetics and Pharmacodynamics

- The pharmacokinetics of edoxaban and its main active metabolite following oral administration of single and repeat doses are dose proportional in the range studied in healthy subjects (60 to 120 mg repeat doses) and in patients with atrial fibrillation.
- The absolute bioavailability of edoxaban following oral administration is 62%. It is a substrate of the efflux transporter, P-glycoprotein.
- Edoxaban undergoes minimal metabolism. Its main active metabolite is formed via hydrolysis by carboxyesterase 1.
- Edoxaban is eliminated mainly as unchanged drug in urine (60% of bioavailable drug) and to a lesser extent via biliary secretion.
- Clearance of edoxaban in patients with atrial fibrillation is similar to that in healthy subjects (~ 30 L/h).
- Edoxaban exhibits a concentration dependent effect on anti-FXa activity, prothrombin time, and activated partial thromboplastin time.

Effect of intrinsic factors

- A 75% increase in total systemic exposure (AUC) to edoxaban was observed in subjects with moderate and severe renal impairment compared to subjects with normal renal function. A 30% increase in edoxaban AUC was observed in individuals with mild renal impairment compared to subjects with normal renal function.
- Total systemic exposure to edoxaban was ~ 28% and 15% higher in the elderly and females, respectively.
- After accounting for renal function and body weight, age and gender do not affect systemic exposure to edoxaban.

Effect of extrinsic factors

- Overall, increased peak and total systemic exposure to edoxaban was observed when edoxaban was co-administered with P-gp inhibitors. About 4% of the patients in ENGAGE-AF received an adjusted dose because of concomitant therapy with P-gp inhibitors. Trough concentrations in these patients were ~ half those observed in patients who did not receive an adjusted dose (after accounting for renal function).
- Co-administration of rifampin resulted in ~ 40% loss of total systemic edoxaban exposure (AUC). While an increase in systemic exposure to its equipotent active metabolite D21-2393 makes up for this loss in total systemic exposure, it is driven by an increase in peak systemic exposure (C_{max}) to D21-2393. At trough (end of

inter-dosing interval), there still exists a ~ 80% reduction in exposure to both edoxaban and the metabolite combined.

Exposure-response relationships

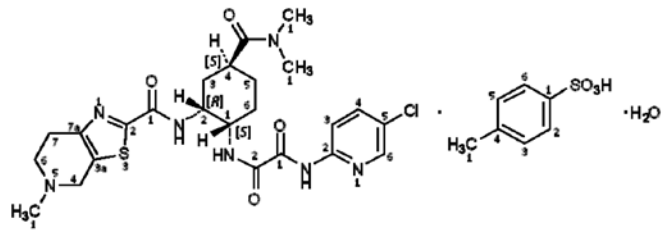
- For thrombotic events such as stroke/SEE and ischemic stroke, the probability of the event decreases with increasing edoxaban trough concentration.
- For bleeding events the probability of the event increases with increasing edoxaban trough concentration.
- In general, the model predictions by dose and degree of renal impairment appear to reasonably capture the central tendency of the observed data for both efficacy and safety endpoints of interest.
- The efficacy and safety findings in the subgroup of patients with normal renal function and patients with mild renal impairment in ENGAGE-AF can be attributed to edoxaban exposure achieved in the trial.
- Dose optimization based on exposure-matching is a viable option for optimizing the dose for patients with normal renal function.

2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Drug substance

Appearance	A white to pale yellowish-white powder
Chemical name	*N*-(5-Chloropyridin-2-yl)-*N*'-[(1*S*,2*R*,4*S*)-4-(*N*,*N*dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro [1,3] thiazolo [5,4-*c*]pyridine-2-carboxamido)cyclohexyl]oxamide mono(4-methylbenzenesulfonate) monohydrate
Molecular formula	$C_{24}H_{30}ClN_7O_4S \cdot C_7H_8O_3S \cdot H_2O$
Molecular weight	738.27 (548.06 as edoxaban anhydrous base)
Structural formula	 *Source: Quality Overall Summary for Drug Substance, Page 3*
Solubility	pH range / Descriptive term[1] / Concentration range 1.2 - 5 / Slightly soluble / 6.2 – 1.8 mg/mL 6 - 7 / Very slightly soluble / 0.54 – 0.14 mg/mL 9 / Practically insoluble / 0.08 mg/mL
pKa	6.7
Partition coefficients	Log $P_{o/w}$ at pH 4 = -0.91, Log $P_{o/w}$ at pH 8 = 1.72

Drug product

Edoxaban was formulated as round, film coated, unscored, debossed immediate release tablets in strengths of 15, 30, and 60 mg differentiated by color and debossing. The excipients were mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, and magnesium stearate. (b) (4) talc and carnauba wax.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

[1] USP definition

Edoxaban is a direct acting, competitive, selective inhibitor of free factor Xa (Ki=0.651 nM) and factor Xa in the prothrombinase complex (Ki= 0.903 nM) (Study R20020850 and R20060456). Factor Xa is the prime component of the prothrombinase complex (fXa+fVa) which catalyzes the conversion of prothrombin to thrombin. Thrombin catalyzes the conversion of fibrinogen to insoluble fibrin, the last step in clot formation. Hence, inhibition of factor Xa decreases clot formation[2].

The applicant is seeking an indication for stroke prevention in atrial fibrillation (SPAF).

2.1.3 What are the proposed dosages and routes of administration?

Edoxaban will be formulated as immediate release tablets (15, 30, and 60 mg) for oral administration. The applicant is seeking approval of 30 and 60 mg strengths.

2.2 General Clinical Pharmacology

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

The clinical pharmacology program for edoxaban included trials characterizing pharmacokinetics and pharmacodynamics following single and multiple doses of edoxaban, a mass balance trial, drug interactions trials, absolute and relative bioavailability trials, food effect trials, trials in specific populations, and Phase 2 trials in relevant patient populations [3]. Sixteen *in vitro* studies were conducted to identify the relevant enzymes and transporters involved in the metabolism and transport of edoxaban, and to determine the protein binding and RBC distribution characteristics of edoxaban. Thirty nine *in vivo* trials and 16 *in vitro* studies were considered relevant in understanding and interpreting Phase 3 data and therefore reviewed. The individual study reviews will be included in a separate addendum to this review.

A single Phase 3 trial conducted in atrial fibrillation (Afib) patients was submitted in support of efficacy and safety of edoxaban in SPAF. ENGAGE-AF was a multi-center, double dummy, warfarin controlled, event driven trial. Two edoxaban dose levels (30 and 60 mg given once daily) were evaluated in this trial.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology trials?

Anti-factor Xa activity, prothrombin time (PT), activated partial thromboplastin time (aPTT), and D-Dimer formation were the pharmacodynamic (PD) response endpoints measured in most trials in the edoxaban development program. Edoxaban is expected to exert its effect in SPAF by inhibiting factor Xa activity and thereby decreasing clot formation. Measuring anti-factor Xa activity provides a direct assessment of the drug's pharmacodynamic effect. Other coagulation measures with established reference range can be informative of edoxaban's effect on the various components of the coagulation pathway.

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[2] Hoffman, et al, Coagulation 2006: A modern view of hemostasis, Hematology and oncology clinics of North America, 21(1):1-11
[3] \\cdsesub1\evsprod\nda206316\0000\m5\52-tab-list\tabular-listing.pdf

The primary efficacy endpoint in ENGAGE-AF was a composite of stroke and systemic embolic event (SEE) and major bleeding[4] was the primary safety endpoint.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Edoxaban and its major active human specific metabolite D21-2393 (Ki=0.797 nM) are the active moieties in plasma. These were appropriately identified and measured in plasma (and urine where applicable) to permit adequate assessment of pharmacokinetics.

Poor practices at a bioanalytical site used in the edoxaban development program rendered data generated at that site unreliable. Appropriate measures to remedy this were proposed by the applicant and found acceptable. Please see bioanalytical validation reports or individual study reports for details (see Addendum to review).

2.3 Exposure-Response

2.3.1 What was the basis for dose selection for Phase 3?

Dose and dosing regimen for Phase 3 was selected based on PK/PD data from Phase 1 and the safety results of a Phase 2 trial conducted in patients with Afib.

A total daily dose of 60 mg appears to have been selected based on the pharmacokinetic / pharmacodynamic data from Phase 1. A dose dependent increase in anti-Xa activity, PT and aPTT was observed at doses up to 60 mg. At doses higher than 60 mg, the increase was less pronounced in some of the PD measures.

The choice of a dosing regimen was based on the safety results of the Phase 2 trial in patients with Afib (Study PRT018). This was a 12 week warfarin controlled trial in which patients with a $CHADS_2$ score of ≥ 2 were randomized to treatment with blinded edoxaban (30 mg QD, 60 mg QD, 30 mg BID, or 60 mg BID, n=230-240/group) or open label warfarin. Major bleeds was the primary endpoint (safety) of interest in this trial. The incidence of bleeding was found to be lower with the QD regimens as compared to the BID regimens (see Table 2**).**

Table 2 Incidence of major bleeds in Phase 2 dose selection trial.

	30 mg QD (n=235)	30 mg BID (n=244)	60 mg QD (n=234)	60 mg BID (n=180)	Warfarin (n=250)
Major bleed					
n	0	5	1	6	1
% (95% CI)	0 (0, 1.6)	2 (0.7, 4.7)	0.4 (0, 2.4)	3.3 (1.2, 7.1)	0.4 (0, 2.2)
All bleed					
n	13	31	17	33	20
% (95% CI)	5.5 (3, 9.3)	12.7 (8.8, 17.5)	7.3 (4.3, 11.4)	18.3 (13, 24.8)	8, (5, 12.1)

Source: Adapted from Table 15.2.8.1.1, Clinical Study Report DU176b-PRT018

[4] ISTH major bleed (fatal bleeding, symptomatic bleeding in a critical area or organ, transfusion adjusted Hg decrease ≥ 2 g/dL)

Further, as seen in Figure 1 the incidence of major bleeds increased with increasing pre-dose edoxaban concentration. The incidence of major bleeding in the QD regimens was lower than that in the warfarin treated group (dashed horizontal line).

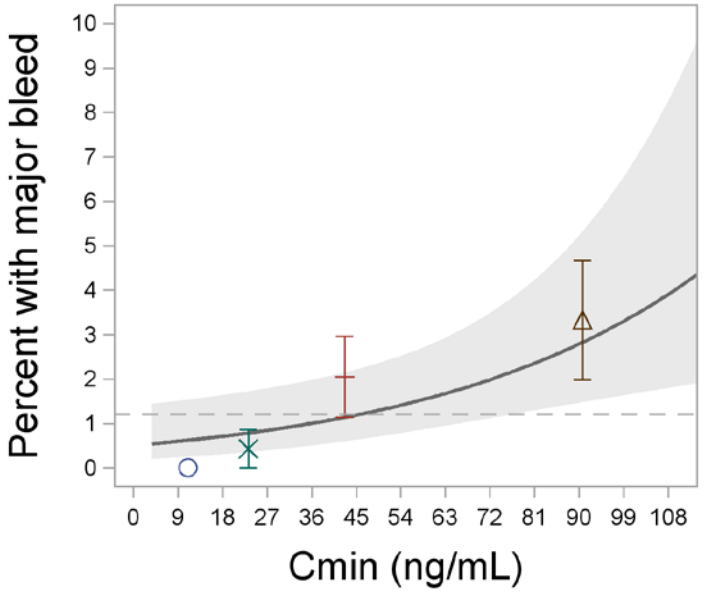


Figure 1: Pre-dose edoxaban concentration (Cmin) is a significant predictor of a major bleed.

The solid line and shaded region represent the predicted probability and 95% confidence limits, respectively. The filled circles represent the observed proportion (95% confidence limits) of patients with a major bleed by treatment group (30 mg QD (○), 60 mg QD (x), 30 mg BID (+), and 60 mg BID (Δ)). The dashed horizontal line represents the incidence of major bleeds in the warfarin treated group.

Source: FDA reviewer's analysis

Systemic exposure to edoxaban was found to be ~ 75% higher in subjects with moderate and severe renal impairment (see section 2.5). Additionally, a 50% to 90% increase in systemic exposure to edoxaban was observed in subjects receiving concomitant P-gp inhibitors (see section 2.6). A population pharmacokinetics/ pharmacodynamics (PK/PD) analysis of these data and data from the Phase 2 trial (Analysis report TMPP004) suggested a dose reduction by half in those with moderately impaired renal function or receiving concomitant therapy with strong P-gp inhibitors would provide exposures that may result in major bleed event rates comparable to or lower than that observed for warfarin. Also, the incidence of bleeding events was higher in the ≤60 kg subgroup than in the >60 kg subgroup in a Japanese Afib Phase 2 trial (Study C-J225).

Based on the above information, a pre-specified 50% dose reduction was utilized for patients meeting one or more of the following criteria in the Phase 3 trial: i) moderately impaired renal function (CrCL ≥30 - ≤ 50 mL/min); ii) receiving concomitant therapy with strong P-gp inhibitors; or iii) body weight ≤ 60 Kg. Two edoxaban doses were evaluated (30 mg QD and 60 mg QD) with accompanying 50% dose reductions (15 mg QD and 30 mg QD, respectively) in patients meeting one or more of the above criteria in Phase 3 (ENGAGE-AF).

2.3.2 What factors in ENGAGE-AF may have contributed to the observed thrombotic event rate in patients with normal renal function?

Sub-group analyses by baseline characteristics in ENGAGE-AF for the primary efficacy end point, identified a nominally significant interaction for treatment by renal function (interaction $p < 0.001$). The hazard ratio (HR) for edoxaban 60 mg versus the warfarin

group is greater than 1.0 in patients with normal renal function (CRCL ≥ 80 mL/min) as shown in Table 3. On the other hand, the HR in patients with mild renal impairment is not only less than 1.0 but is lowest among the three renal function categories. Similar results are also observed for the edoxaban 30 mg group.

Table 3: Hazard Ratio by renal function categories in ENGAGE-AF for stroke/SEE

Subgroup CRCL (mL/min)	Edoxaban 60 mg (30 mg DosAdj)
Overall	0.79 (0.61 – 1.02)
≥80	1.41 (0.97 – 2.06)
>50 - <80	0.53 (0.40 – 0.70)
30 - ≤50	0.88 (0.58 – 1.32)

Source: Adapted from Table 14.2.5.1; Clinical Study Report DU176B-C-U301

The subgroup analysis for the major bleed did not show a statistically significant treatment by renal function interaction. However, consistent with the efficacy finding, the risk for major bleeding, relative to warfarin, is numerically higher in patients with mild renal dysfunction compared to those with normal renal function as shown in Table 4.

Table 4: Hazard Ratio by renal function categories in ENGAGE-AF for major bleed

Subgroup CrCL (mL/min)	Edoxaban 60 mg (30 mg DosAdj) HR (95% CI)
Overall	0.80 (0.71 – 0.91)
≥80	0.71 (0.55 – 0.90)
>50 - <80	0.90 (0.75 – 1.08)
30 - ≤50	0.75 (0.38 – 0.96)

Source: Adapted from Table 14.2.5.1, Clinical Study Report DU176B-C-U301

These outcomes appear to be a result of lower edoxaban concentrations achieved in patients with normal renal function compared to the mild renal dysfunction group (CRCL ≥50 – <80 mL/min) as summarized in the Table 5.

Table 5: Steady-state edoxaban C_{trough} derived from POPPK analysis by renal function categories in ENGAGE-AF (Median and Interquartile Range)

Subgroup CrCL (mL/min)	Edoxaban Dose (mg)	Edoxaban Trough Conc. (ng/mL)
≥80	60	27.3 (23.8 – 30.8)
>50 - <80	60	36.6 (33.0 – 40.6)
30 - ≤50	30	27.0 (24.5 – 32.3)

Source: FDA Reviewer's Analysis

Further, in patients with moderate renal insufficiency, dose reduction to 30 mg QD seems to be an over correction based on a PK comparison between patients with mild renal impairment administered 60 mg and patients with moderate renal impairment administered 30 mg. A difference in edoxaban exposure with respect to renal function is

anticipated given that renal elimination is identified as a primary route of edoxaban elimination. These findings lead us to believe that systemic edoxaban exposures may be deterministic and prompted further characterization and quantification of the exposure-response relationship for both efficacy and safety endpoints.

2.3.3 What are the characteristics of the exposure-response relationships for efficacy and safety for edoxaban?

A clear dose-response relationship is observed for the primary efficacy & safety endpoints (Table 6).

Table 6: Comparison of the event rate (%/yr) across the treatment groups in ENGAGE-AF for stroke/SEE and major bleeding

Endpoint	Edoxaban 60 mg (30 mg DosAdj)	Edoxaban 30 mg (15 mg DosAdj)	Warfarin
First Stroke/SEE	1.61	1.18	1.50
Major Bleed	1.61	2.75	3.43

Source: Adapted from Table 11.5, Clinical Study Report DU176B-C-U301

A time-to-event approach was utilized for establishing exposure-response relationships for all stroke/SEE, ischemic stroke, hemorrhagic stroke, life-threatening and fatal bleeds, major bleeds, major GI bleeds, clinically-relevant non-major and major bleeds, and MACE events. A subset of these analyses are presented below under subsection headings of *Efficacy* (stroke/SEE, ischemic stroke) and *Safety* (major bleed, life-threatening/fatal bleed), and the remainder of the analyses along with technical details are located in the Pharmacometrics Review (Appendix I).

Exposure-efficacy relationships

The exposure-response analyses based on the multivariate Cox proportional hazards models are represented below. After adjusting for significant predictors of risk at baseline, the probability of all stroke/SEE and ischemic stroke decreases with increasing edoxaban trough concentrations (C_{trough}; $p<0.05$) as presented in Figures 2 and 3. This relationship is consistent across the three renal function categories.

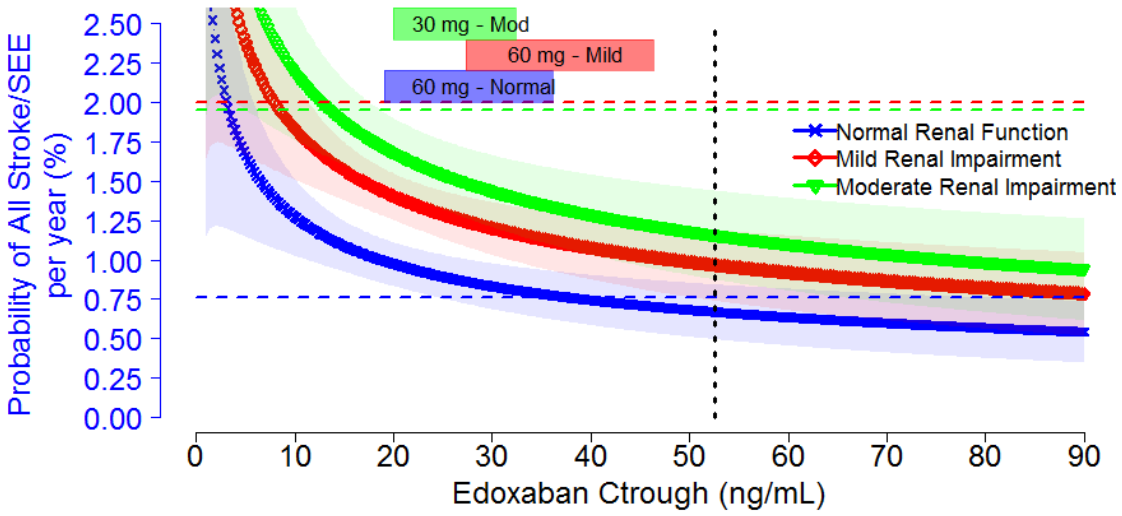


Figure 2: The exposure-response relationship for all stroke/SEE suggests a lower probability of stroke/SEE within 1 year with increasing edoxaban trough concentrations

Exposure-response relationships are shown for a typical patient with normal renal function (blue line), mild renal impairment (red line), and moderate renal impairment (green line) for individuals in the edoxaban high dose arm (60 mg). Horizontal reference lines indicate the observed rate of stroke/SEE for the warfarin treatment arm for the corresponding color coded renal function groups. The intersection of the exposure response relationship and the observed warfarin event rate (dashed lines) occurs at the concentration of edoxaban that is predicted to produce similar efficacy results to warfarin. The horizontal bands indicate the exposure range (5^{th} to 95^{th} percentile) for edoxaban in each renal function group. The vertical dashed line indicates the 99^{th} percentile of Edoxaban C_{trough} concentration.

Source: FDA Reviewer's Analysis

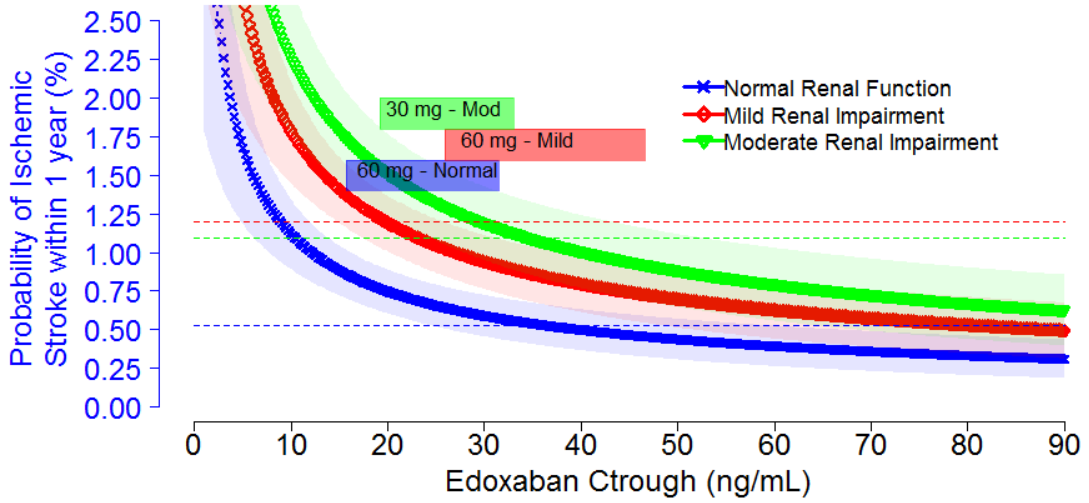


Figure 3: The exposure-response relationship for ischemic stroke suggests a lower probability of an ischemic stroke within 1 year with increasing edoxaban trough concentrations

Source: FDA Reviewer's Analysis

The model predictions by dose and degree of renal insufficiency appear to reasonably capture the central tendency of the observed data. The two groups with the lowest edoxaban exposures (normal renal function and moderate renal dysfunction) generally exhibit higher probability of ischemic stroke compared to warfarin across their range of exposures. See the Pharmacometrics Review for additional details.

Exposure-safety relationships

The exposure-response safety analyses based on the multivariate Cox proportional hazards models are represented below. After adjusting for significant predictors of risk at baseline, the probability of major bleeding and life-threatening/fatal[5] bleeding increases as a function of edoxaban C_{trough} achieved. These relationships are generally consistent across all renal function categories and are presented in Figures 4 and 5. It should be noted that the edoxaban exposures at the studied doses produced rates of bleeding that are less than those for warfarin in each respective renal function group. These findings are in agreement with observed data from ENGAGE-AF.

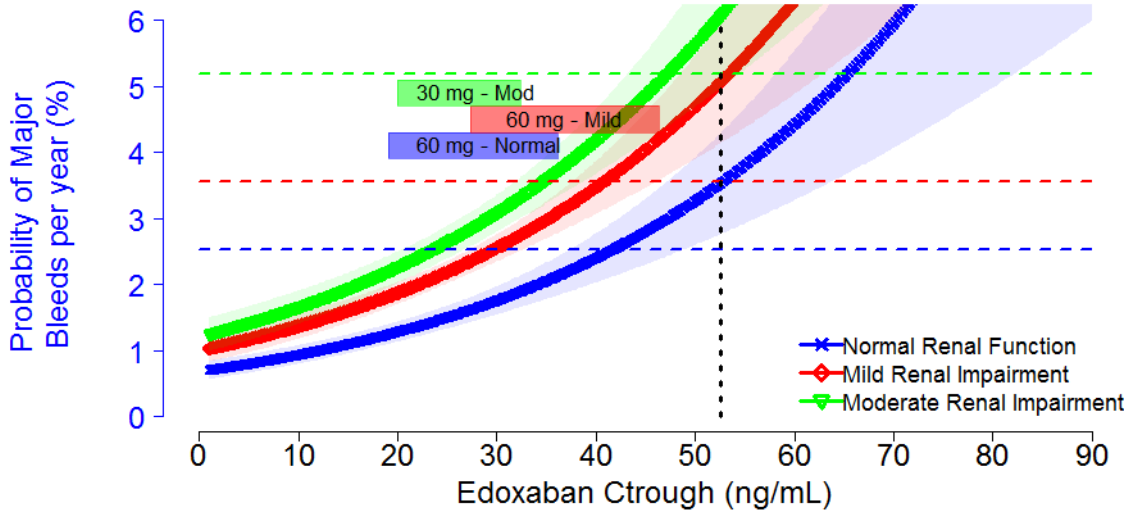


Figure 4: Exposure-Response relationship for major bleeds suggests increasing events with increasing edoxaban concentrations.

Exposure-response relationships are shown for a typical patient with normal renal function (blue line), mild renal impairment (red line), and moderate renal impairment (green line). Horizontal dashed reference lines indicate the observed rate of major bleeds in the warfarin treatment arm for the corresponding color coded renal function groups. The intersection of the exposure response relationship and the relevant warfarin reference line occurs at the concentration of edoxaban that is predicted to produce similar results to warfarin. The horizontal bands in the top center of the figure indicate the exposure range (5^{th} to 95^{th} percentile) for edoxaban in each renal function group in the edoxaban high dose arm. The vertical dashed line indicates the 99^{th} percentile of Edoxaban C_{trough} concentrations.

Source: FDA Reviewer's Analysis

[5] All non-fatal ICH and non-fatal non-intracranial major bleeds with hemodynamic compromise requiring intervention

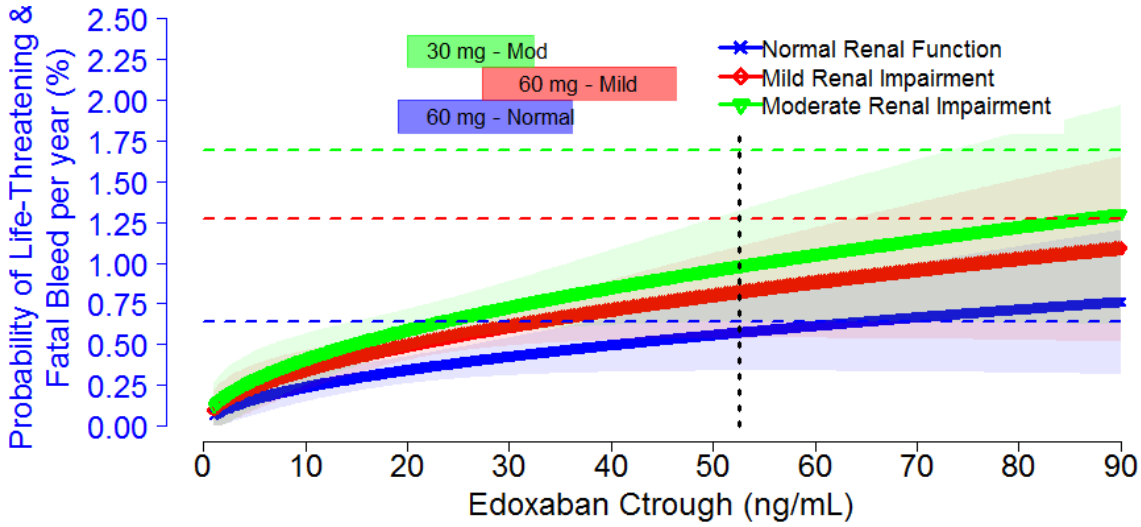


Figure 5: Exposure-Response relationship for life-threatening bleeds and fatal bleeds suggests increasing events with increasing edoxaban concentrations.

Source: FDA Reviewer's Analysis

The major gastrointestinal (GI) bleeding rate was significantly higher in edoxaban treated subjects (60 mg) compared to subjects who received warfarin. Consistent with the previous findings, there is an exposure dependent increase in the probability of major GI bleeding events as shown in Figure 6. The exposures attained at the studied doses produce event rates of major GI bleeding that are higher than those observed in subjects with mild or moderate renal impairment who were treated with warfarin. These findings are in agreement with observed data from ENGAGE-AF. The rate of major GI bleed observed with edoxaban is similar to some of the previously approved novel oral anticoagulants.

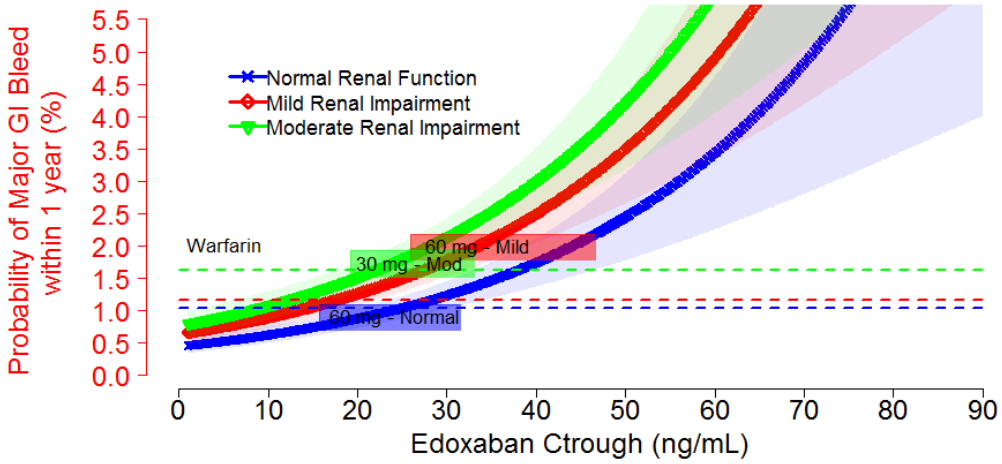


Figure 6: Exposure-Response relationship for major GI bleeds suggests increasing events with increasing edoxaban concentrations.

Source: FDA Reviewer's Analysis

See the Pharmacometrics Review for additional details.

2.3.4 Is it possible to optimize the dosing in patients with normal renal function based on the exposure-response relationships for efficacy and safety?

Based on the dose-response and exposure-response relationships described in sections 2.3.2 and 2.3.3, we believe the major driver of the findings in patients with normal renal function is sub-optimal edoxaban exposure. As such, dose optimization based on the principle of exposure-matching can be envisioned to improve the efficacy outcomes. The concept of exposure-matching is routinely applied by the Agency for deriving dosing in sub-populations that are not represented in the registration trials, accounting for exposure changes resulting from drug-drug interactions, or mitigating safety concerns while maintaining acceptable efficacy. In this instance, dosing in patients with normal renal function can be derived to match the exposures observed in patients with mild renal impairment administered 60 mg. This approach will allow for dose optimization within the confines of the clinical trial experience. The doses that can be considered for patients with normal renal function under these constraints are 75 mg QD and 90 mg QD. While these doses were not studied in ENGAGE-AF, the projected exposure in patients with normal renal function in general is covered by the overall experience in ENGAGE-AF as shown in Table 8.

Table 7: Projected Edoxaban Ctrough in patients with normal renal function for 75 mg QD and 90 mg QD

Subgroup CrCL (mL/min)	Edoxaban Dose (mg)	Edoxaban Trough Conc. (ng/mL)
≥80	60*	27.3 (23.8 – 30.8)
≥80	75	34.1 (29.8 – 38.5)
≥80	90	41.2 (35.9 – 46.2)
>50 - <80	60*	36.6 (33.0 – 40.6)

**These doses were studied in ENGAGE-AF.*

Source: FDA Reviewer's Analysis

Since the primary reason for focusing on the subgroup with normal renal function was the unfavorable hazard ratio between edoxaban and warfarin, Table 8 aims to provide the projected impact of edoxaban doses of 75 mg QD and 90 mg QD for both efficacy and safety endpoints. Risk ratios are shown for ischemic stroke, life-threatening/fatal bleeds, all stroke/SEE, and major bleeds to facilitate the discussion of the benefit/risk that can be considered acceptable for patients with normal renal function.

Table 8: Risk Ratios of predicted edoxaban event rates relative to the observed warfarin event rate for patients with normal renal function by dose, and event type.

Endpoint	Comparison	Risk Ratio
Ischemic Stroke	Edoxaban 75 vs Warfarin	1.26
	Edoxaban 90 vs Warfarin	1.15
LT/Fatal Bleed	Edoxaban 75 vs Warfarin	0.73
	Edoxaban 90 vs Warfarin	0.78
Stroke/SEE	Edoxaban 75 vs Warfarin	1.14
	Edoxaban 90 vs Warfarin	1.05
Major Bleed	Edoxaban 75 vs Warfarin	0.96
	Edoxaban 90 vs Warfarin	1.19

Source: FDA Reviewer's Analysis

A similar comparison is shown in Table 9 that aims to provide a net benefit quantification of the dose adjustments under consideration. Comparisons to warfarin are made to project the absolute numbers of events per 10000 patients per year.

Table 9: Projected difference in number of events per 10000 patients/year for patients with normal renal function: Stroke/SEE, Major Bleed, Ischemic Stroke and Life-Threatening/Fatal Bleeds.

Comparison	Stroke/SEE	Major Bleed	Ischemic Stroke	LT / Fatal Bleed
60 mg Observed vs Warfarin Observed	30	-75	31	-20
60 mg Predicted Vs Warfarin Observed	18	-59	22	-23
75 mg Predicted Vs Warfarin Observed	11	-11	14	-17
90 mg Predicted Vs Warfarin Observed	4	48	8	-14

Positive numbers indicate there are more events in the edoxaban arm than warfarin.

Source: FDA Reviewer's Analysis

2.3.5 What are the characteristics of the pharmacokinetic-pharmacodynamics relationships?

A concentration dependent effect of edoxaban was observed on all pharmacodynamic markers measured in the edoxaban development program. As seen in Figure 7, prothrombin time increases linearly with edoxaban concentrations. Similarly, the edoxaban – anti-factor Xa relationship is linear in the range to 200 ng/mL (see Figure 8).

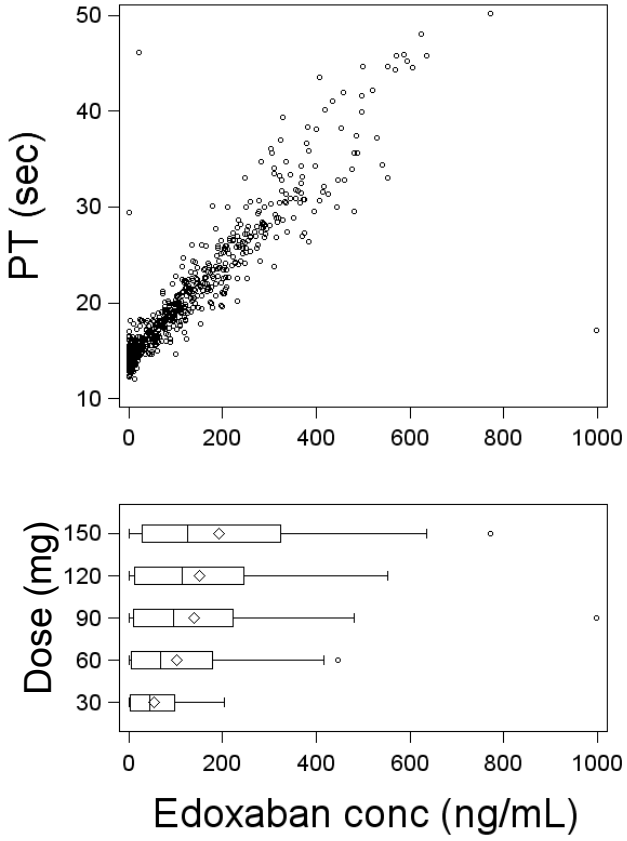


Figure 7: Edoxaban concentration – prothrombin time (PT) relationship in healthy subjects (n=10/group) following administration of a single oral dose of edoxaban tablet (Study PRT001).

Source: FDA Reviewer's Analysis

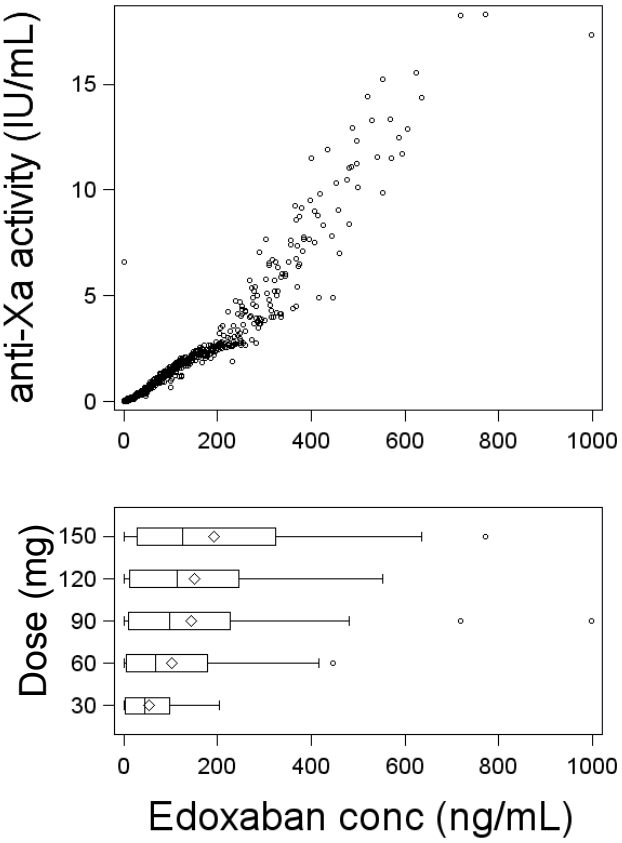


Figure 8: Edoxaban concentration - anti-Xa activity relationship in healthy subjects (n=5-10/group) following administration of a single oral dose of edoxaban tablet (Study PRT001).

Source: FDA Reviewer's Analysis

2.3.6 Does this drug prolong QT/QTc Interval?

No, edoxaban does not appear to prolong QTc interval. Please refer to the QT-IRT review (DARRTS date 11/10/2008).

2.4 Pharmacokinetic characteristics

2.4.1 What are the single and multiple dose PK parameters?

Single and multiple dose pharmacokinetics of edoxaban were evaluated over the dose range of 10 to 150 mg and 60 to 120 mg, respectively, in a trial conducted in healthy subjects (Study PRT001). Edoxaban exhibits close to dose proportional pharmacokinetics in the range of 10 to 150 mg (power model (AUC) - slope (95%CI) = 0.95 (0.85,1.04)).

On average, peak edoxaban plasma concentrations were observed within 2 hours following oral administration. Mean CL/F and terminal elimination half-life was estimated to be ~ 36 L/h (%CV=23) and 9 h (range=6, 11), respectively. The effective half-life is ~ 6 h.

Following repeat once daily administration 10-15% accumulation in total systemic exposure (AUC) to edoxaban was observed. However, pre-dose (C_{24} for QD administration) concentration following repeat QD administration was ~ 1.7X that observed after a single dose (31 vs 18 ng/mL). Similarly, following repeat twice daily administration, accumulation based on AUC was ~ 45% and pre-dose concentration (C_{12} for BID administration) was 2X that following the first dose. For the same total daily dose, trough concentration following twice daily dosing is 2X that following once daily dosing.

Following intravenous administration of a single dose in healthy subjects, mean CL of edoxaban was ~ 22 L/h (%CV=14). The terminal elimination half-life was estimated to be ~ 6.7 h (range=4.2 to 16.4 h) (Study A-U139).

Following oral administration of edoxaban, peak plasma D21-2393 concentrations were observed at about 2 h. The elimination half-life was similar to that of edoxaban. Following repeat once daily administration of edoxaban, 35% accumulation in total systemic exposure to D21-2393 was observed (Study A-U151). Total systemic exposure to D21-2393 was less than 10% of parent drug.

2.4.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

Edoxaban pharmacokinetics is similar between healthy subjects and patient population.

Table 10: PK parameters of edoxaban in healthy subjects and Afib patients

	Healthy subjects [a] (n=10)	Afib[b]
CL/F (mL/min)	33.7	29.4
Vc/F + Vp/F (L)	433[d]	283

a. Noncompartmental analysis from PRT001
b. Population PK parameter estimates in typical patients (70 kg) from TMPP008
c. Vz/F

Source: Adapted from Table 12.11, Clinical Study Report DU176-E-PRT001 and Population PK Study Report TMPP008

2.4.3 What are the characteristics of drug absorption?

Following oral administration peak edoxaban concentrations are achieved within 1-2 h. The absolute bioavailability is approximately 62%. Edoxaban appears to be predominantly absorbed in the upper GI tract.

Compared to oral administration, both rate and extent of absorption of edoxaban were reduced to 10-15 % when administered to the distal small intestine or ascending colon. Hence, a method that could deposit drug directly into distal small intestine will result in decreased systemic exposure to edoxaban.

2.4.4 What are the characteristics of drug distribution?

Edoxaban appears to be widely distributed in the body, with an average (SD) steady-state volume of distribution of 107 (±19.9) L (Study A-U139). The *in vitro* total plasma

protein binding for edoxaban at concentrations from 0.2 to 5 µg/mL[6] is about 55%, and D21-2393 is about 80% bound to plasma proteins over a concentration range of 0.2 µg/mL to 2 µg/mL. Edoxaban partitions almost equally in blood (46%) and plasma.

Edoxaban is a substrate of the efflux transporter, P-glycoprotein (P-gp), but not a substrate for uptake transporters such as organic anion transporting polypeptide (OATP1B1), organic anion transporters (OAT1 and OAT3), or organic cation transporter (OCT2) (Study AM10-C0129-R01).

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

Edoxaban appears to be eliminated mainly as unchanged drug in urine and to a lesser extent via biliary secretion. A small fraction of the drug is metabolized and excreted in urine and feces.

Following oral administration of [^{14}C]-edoxaban as a solution (Study PRT019), about 35% and 62% of the administered dose[7] was recovered in urine and feces, respectively. Elimination via the renal route appears to be the faster of the two elimination routes. About 16 and 17% of the administered dose was recovered in urine within 0-4 and 4-24 hours, respectively, as unchanged drug and metabolites. In comparison, only ~ 2% of the administered dose was recovered in feces within 24 hours of administration. The major fraction, ~ 50% of the administered dose, was eliminated in feces over the time interval of 24 to 72 hours post-oral administration of edoxaban. Additionally, < 5% of the administered dose was recovered as metabolites in urine (0-48h) or feces (0-144h).

Edoxaban was the major component in plasma (see Figure 9).

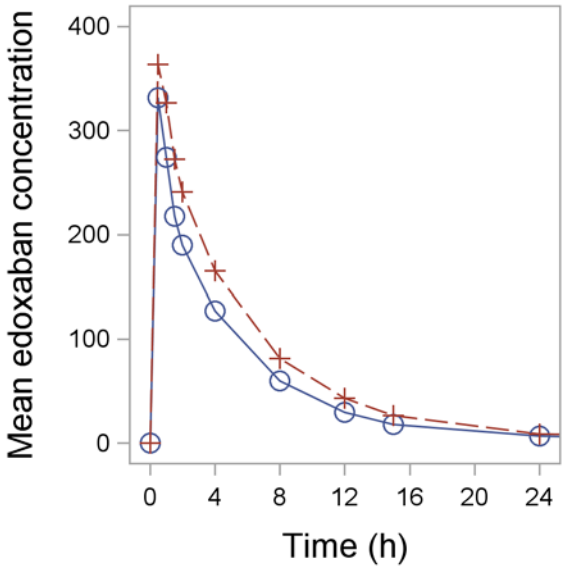


Figure 9: Mean plasma total radioactivity (+, ng eq/mL) and edoxaban (○, ng/mL) concentration versus time profile following administration of 60 mg 14C-edoxaban solution in six healthy individuals.

Source: FDA Reviewer's Analysis

[6] Edoxaban Cmax @ 60 mg is ~ 0.3 µg/mL
[7] F=0.62

2.4.6 What are the characteristics of drug metabolism?

Edoxaban is metabolized mainly by carboxyesterase 1 (CES1) and Cytochrome P450 3A (CYP3A). The major human specific active metabolite of edoxaban, D21-2393, is formed by hydrolysis at the carbonyl carbon of the N,N-dimethylcarbamoyl group by CES1 (Study AM10-C0146-R01). Metabolism by CYP3A results in formation of several other metabolites, including the two other active metabolites D21-1402 and D21-2135 (Study AM09-C0101-R01). Glucuronidated metabolites of edoxaban were also detected. Total systemic exposure to D21-2393 was ~ 10% that of edoxaban in healthy individuals. The remaining metabolites were detected in trace amounts and together equal < 5% of total systemic exposure to edoxaban. A schematic of the metabolic pathway is presented in Figure 10.

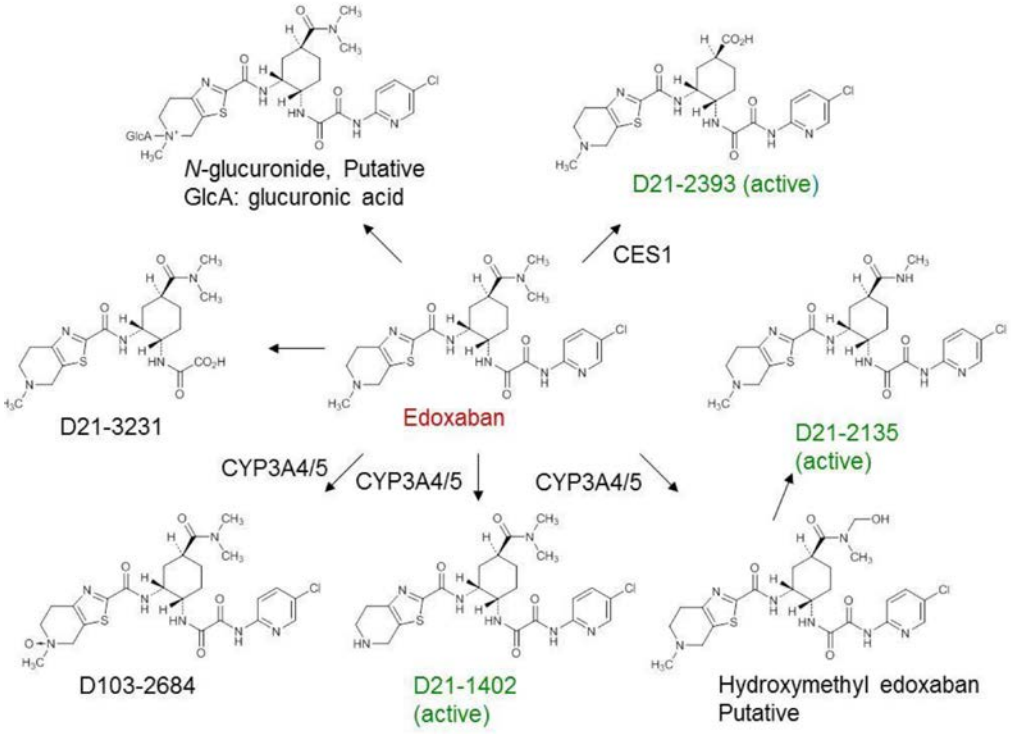


Figure 10: A schematic of the metabolic pathway of edoxaban in humans.

Source: Figure 1.3 of Summary of Clinical Pharmacology Studies

2.4.7 What are the characteristics of drug elimination?

Edoxaban appears to be eliminated mainly as unchanged drug in urine and to a lesser extent via biliary secretion. A small fraction of the drug is metabolized and excreted in urine and feces. Please see section 2.4.5.

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

Edoxaban exhibits close to dose proportional pharmacokinetics in the range of 10 to 150 mg (slope (AUC) (95%CI) = 0.95 (0.85, 1.04)).

2.4.9 What is the inter- subject variability of PK parameters in volunteers and patients?

The inter- and intra-subject variability for clearance and volume of distribution of edoxaban is low (<30%) in healthy volunteers. In patients, only sparse PK samples were collected. Inter-individual variability for parameter estimates using PPK analysis were 13.6% and 21.5% in Afib patients (PPK Study Report TMPP008) for CL/F and Vc/F, respectively.

2.5 Intrinsic Factors

2.5.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Approximately 60% of a bioavailable dose of edoxaban is excreted in urine and the rest via biliary secretion. Given this, impaired renal (including because of advanced age) or hepatic function (with bile duct obstruction) are expected to impact edoxaban pharmacokinetics. Additionally, total body weight was found to be a predictor of bleeding (safety) in a Phase 2 trial.

Renal function

The effect of renal impairment on edoxaban pharmacokinetics was assessed following administration of a single dose of 15 mg of edoxaban (Study A-U120). Subjects with normal, mild, moderate, severe renal impairment or end stage renal disease (ESRD) undergoing peritoneal dialysis were enrolled in the trial (n=8/group). As seen in Figure 11 total systemic exposure (AUC) to edoxaban increased 1.75X in individuals with moderate or severe renal impairment, and close to 2X in individuals with ESRD. Peak systemic exposure (C_{max}) was not affected. Systemic exposure (AUC and C_{max}) to the major active metabolite, D21-2393, was also higher in subjects with impaired renal function. The metabolite to parent ratio ranged from 0.05 in individuals with normal renal function and to 0.13 in individuals with severely impaired renal function and is similar to that reported in other trials in healthy subjects (~ 0.1).

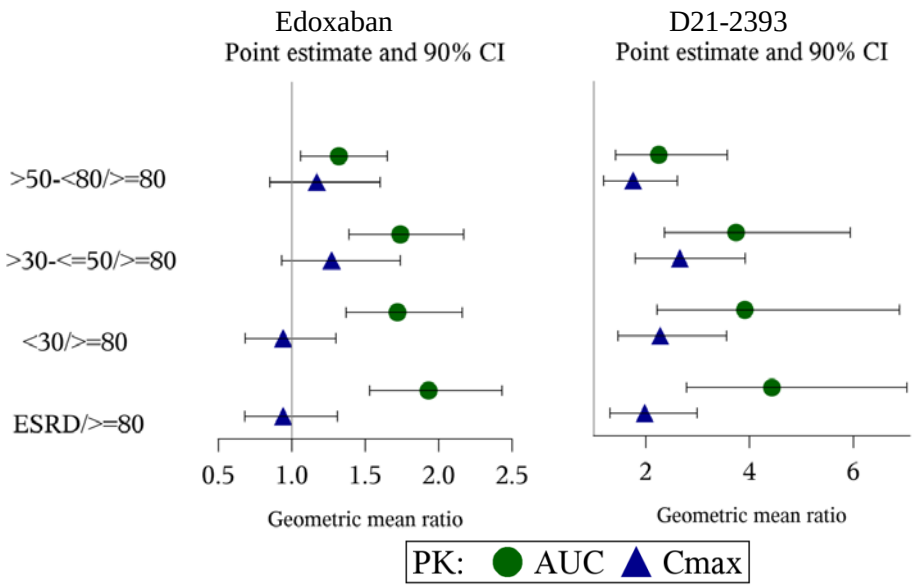


Figure 11: Total systemic exposure to edoxaban and D21-2393* is increased in individuals with impaired renal function. The closed circles represent the geometric mean ratio (test/reference) for AUCinf and Cmax and the horizontal line represents the 90%CI associated with the mean. * *considered exploratory because of bioanalytical problems*

Source: FDA Reviewer's Analysis

Increased exposure to edoxaban, as a consequence of impaired renal function may increase the risk for bleeding. Please see section 2.3 for information on dose adjustments for impaired renal function.

Hepatic function

The effect of hepatic impairment on edoxaban pharmacokinetics was assessed following oral administration of a single dose of 15 mg edoxaban conducted in subjects with mild or moderate hepatic impairment and matched controls with normal hepatic function (n=8/ group) (Study A-E134). As seen in Figure 12 there was no meaningful difference in systemic exposure to edoxaban or its metabolite in subjects with mild or moderate hepatic impairment.

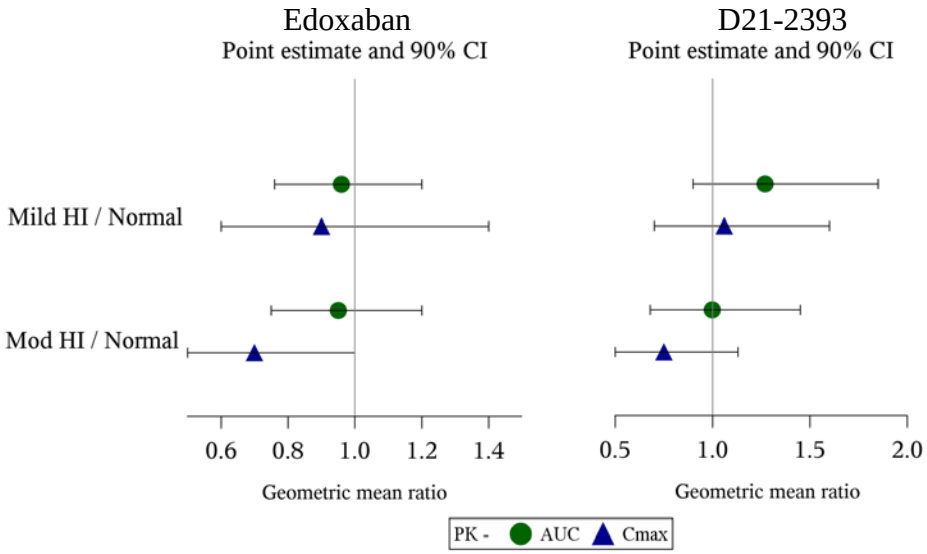


Figure 12: Total systemic exposure to edoxaban and D21-2393 in individuals with impaired hepatic function is similar to that in individuals with normal hepatic function. The closed circles represent the geometric mean ratio (test/reference) for AUCinf and Cmax; horizontal line represents the 90%CI associated with the mean.

Source: FDA Reviewer's Analysis

Patients with moderately impaired hepatic function (Child-Pugh B) may have intrinsic coagulation abnormalities. That combined with the limited data available in this sub-population, dosing recommendations cannot be provided.

Age

The impact of age on the PK and PD of edoxaban was assessed in Study PRT002. In this trial, the peak exposure was similar in elderly males and young males, but the total exposure was up to 28% higher in elderly males. The higher total exposure is considered to be related to a decline in renal function with age. Consistent with similar values for peak exposure, the maximum observed effects for PT and aPTT were similar between elderly males and young males.

After accounting for body weight and renal function, age did not have a clinically or statistically significant effect on edoxaban PK in Afib patients (PPK Study Reort TMPP008). Additionally, the median age in ENGAGE-AF was 72 years and ~ 40% were ≥ 75 years. There were no safety concerns identified in this group. Hence, for the above reasons, a dose reduction because of age is not recommended.

Gender

In a PPK analysis (PPK Study Report TMPP014) using data from Phase 1 studies, the apparent clearance and volume were found to be slightly lower in healthy females than in males. However, the difference was less than 15% and was not significant when other factors such as body weight were taken into account. In AF patients, after accounting for body weight, gender did not have an additional clinically or statistically significant effect

on edoxaban PK (PPK Study Report TMPP008). Thus, no dose modification is necessary based on gender.

Ethnicity

The effect of race on edoxaban pharmacokinetics was assessed in healthy Caucasian and Japanese males (Study J01). Creatinine clearance and age were similar between races, but weights were little bit higher in the Caucasian group (76-81 kg) than the Japanese group (62-67 kg). The point estimate of the ratio of Caucasians to Japanese (Caucasians/Japanese) in the geometric mean of each PK parameter was 0.7 to 1.6, showing no evident difference between Japanese and Caucasians in a dose range of 60 to 120 mg.

Genetics

The effect of a common polymorphism in the gene encoding P-gp (*ABCB1 C3435T*) on edoxaban PK was evaluated by the Applicant in healthy subjects in a post-hoc analysis using pooled data from 14 single-dose PK trials (Study Report TMPG0001). No significant differences were observed between genotypes for any evaluated PK parameters, including AUC_{Inf} and C_{max} (Table 11).

Table 11: PK Parameters by ABCB1 Genotype

PK Parameter	***ABCB1 345 C/C***	***ABCB1 345 C/T***	***ABCB1 345 T/T***
AUC_{inf}	1789.4 (25.2)	1845.2 (22.6)	1862.7 (23.4)
C_{max}	245.78 (39.3)	268.09 (35.5)	261.31 (38.8)

Source: Study Report TMPG002, Data presented as mean (CV%)

The applicant evaluated the impact of genetic variants in *CYP2C9* and *VKORC1* on major and clinically relevant non-major bleeding in their Phase 2 (study report TMPG0002) and Phase 3 (study report TMPG0003) atrial fibrillation studies. Subjects were characterized as warfarin "Normal Responders" and "Sensitive Responders" based on their *CYP2C9* and *VKORC1* genotype (see Genomics and Targeted Therapy Review in the Addendum). Among warfarin treated patients, bleeding rates were numerically higher during the first 90 days of treatment in the Sensitive Responder group (5.9%) compared to the Normal Responder group (4.6%). Within the edoxaban 60 mg (high exposure) treatment group, bleeding rates were similar in the Normal Responder (5.1%) and Sensitive Responder (4.2%) groups, suggesting that predicted warfarin phenotype does not impact edoxaban safety.

Body weight

Total body weight was identified as a predictor of bleeding in a Phase 2 trial conducted in Japan in the Afib population. This was a 12 week warfarin controlled trial in which patients with at least one risk factor for an embolism ($CHADS_2$ score of ≥ 1) were randomized to treatment with blinded edoxaban (30 mg QD, 45 mg QD or 60 mg QD, n=130-135/group) or open label warfarin (Study J-225). The probability of a bleeding event in those with a TBW $\leq$ 60 Kg was ~ 2X that in patients who had a TBW > 60 Kg (all other factors being equal). Hence, TBW of 60 Kg was used as a threshold for dose reduction in Phase 3.

A very small proportion of the population in ENGAGE-AF (~ 4%) received a reduced edoxaban dose because of low body weight (TBW ≤ 60 Kg) alone. There are several factors to be considered in interpreting these sparse data. First, edoxaban trough concentrations in the dose adjusted group was about half those in patients with received edoxaban 60 mg (median pre-dose concentrations of 21 ng/mL (n=291) vs 37 ng/mL (n=5251)), indicating that the pharmacokinetics of edoxaban in patients with low body weight was similar to those with body weight > 60 kg. As such, the final population PK model did not identify body weight as a significant predictor of edoxaban clearance. Second, while TBW was identified as an independent predictor of efficacy (low TBW associated with increased risk for events) it was not a significant predictor of safety. Finally, low TBW is often correlated with other factors that affect outcomes such as lower CrCL or increased age. Taken together, there does not appear to be a need for dose reduction in patients with a TBW ≤ 60 Kg alone.

2.5.2 What pregnancy and lactation use information is there in the label?

There are no adequate and well-controlled trials in pregnant women. Edoxaban should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

2.6 Extrinsic Factors

2.6.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Potential drug interactions may affect exposure and or response and are presented in the below section.

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

Results of in vitro studies suggest that pharmacokinetic drug interactions between edoxaban and CYP3A/P-gp inhibitors, CYP3A inducers, CES1 inhibitors, and OATP1B1 substrates are likely.

Edoxaban is metabolized by CES1 and CYP3A. The major active metabolite of edoxaban, D21-2393, is formed via hydrolysis by CES1 (Study AM10-C0146-R01). Two other active metabolites, D21-1402 and D2135, as well as several other inactive metabolites (D103-2684, D21-3231) are formed via metabolism by CYP3A (Study AM09-C0101-R01, R20050248). Edoxaban does not inhibit any of the major CYPs (IC_{50} > 100 μM) (Study R20040467).

Edoxaban is a substrate of the efflux transporter P-gp (Study AM08-C0045-R01). The active metabolite, D21-2393, is a substrate of uptake transporter OATP1B1 (Study AM10-C0061-R01).

Additionally, pharmacodynamic drug interactions via potentiation of its anti-coagulant effect are expected with other anti-coagulant or anti-platelet agents.

2.6.3 What are the drug-drug interactions?

The potential/extent for drug interaction with CYP3A/P-gp substrates/inhibitors, and other concomitant medication was evaluated in several dedicated trials conducted in healthy subjects. Additionally, data from the Phase 3 trials also inform dosing recommendations.

P-gp Inhibitors

Overall, increased peak and total systemic exposure to edoxaban was observed when edoxaban was co-administered with P-gp inhibitors. Generally, edoxaban dose was reduced to 50% when co-administration with a P-gp inhibitor that increased it exposure≥ 50% was required in Phase 3. The exceptions were ketoconazole, itraconazole or erythromycin (required edoxaban treatment interruption) and cyclosporin (prohibited) in ENGAGE-AF.

About 4% of the patients in ENGAGE-AF received an adjusted dose because of concomitant therapy with P-gp inhibitors. Trough concentrations in these patients were ~ half those observed in patients who did not receive an adjusted dose (after accounting for renal function). This suggests that a dose reduction is not necessary based on this factor alone.

Results of the dedicated Phase 1 drug interactions studies with P-gp inhibitors are presented below.

Quinidine

The effect of repeat administration of quinidine (300 mg tid) on a single oral dose of edoxaban (60 mg) was evaluated in a dedicated pharmacokinetic trial conducted in healthy subjects (Study U-129). As seen in Figure 13 both peak (C_{max}) and total systemic exposure (AUC) to edoxaban and D21-2393 increased ~ 1.75X. The increase in exposure to D21-2393 was proportional to that of edoxaban.

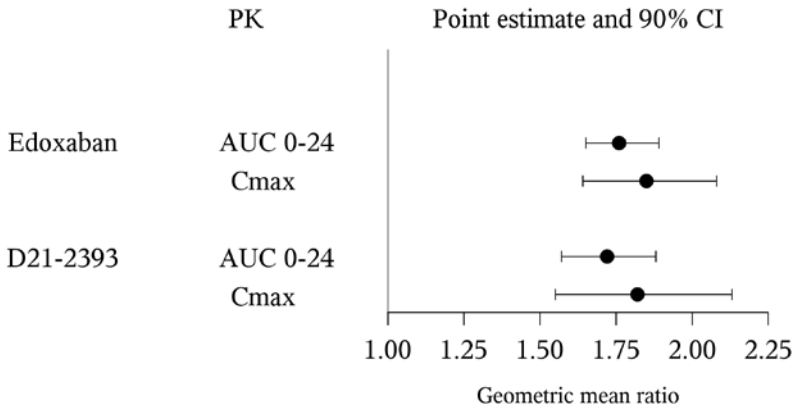


Figure 13: Co-administration of quinidine and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean

Source: FDA Reviewer's Analysis

Additionally, the effect of repeat co-administration of quinidine on a single IV dose of edoxaban was also assessed (Study U-139). Mean CL following administration of IV edoxaban was 22 (SD=3) L/h and decreased to 16 (SD=3) L/h when co-administered with quinidine. Taken together, the above data suggest that quinidine affects both absorption and elimination of edoxaban.

Dronedarone

The effect of repeat administration of dronedarone (400 mg bid) on a single oral dose of edoxaban (60 mg) was evaluated in healthy subjects (Study U-141). Total and peak systemic exposure to edoxaban increased 1.84X and 1.45X, respectively (see Figure 14). Total and peak systemic exposure to the metabolite increased 1.3X and 1.07X, respectively. Plasma edoxaban concentrations 24 hours post dose (C_{trough}) following co-administration edoxaban and dronedarone was 2.6X (14.4 vs 5.5 ng/mL) that following administration of edoxaban alone.

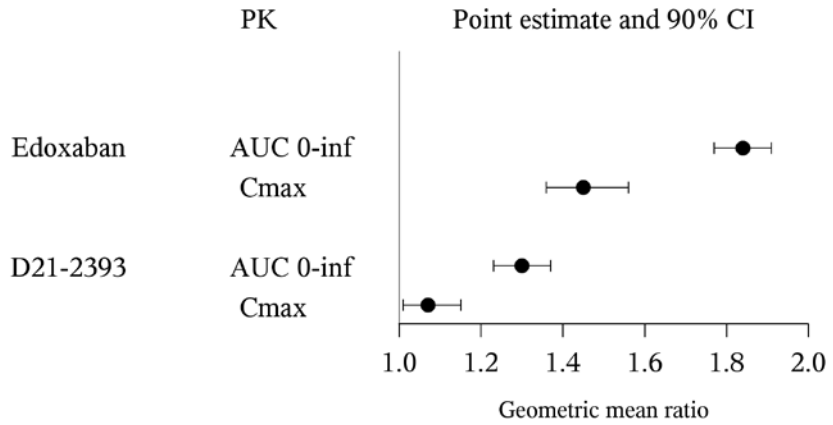


Figure 14: Co-administration of dronedarone and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

Source: FDA Reviewer's Analysis

Based on the above observed increase in trough edoxaban concentrations and the results of an interim exposure-safety analysis, the dose of edoxaban was reduced to half in individuals requiring concomitant therapy with dronedarone in ENGAGE-AF.

Amiodarone

Co-administration of amiodarone (400 mg QD for 4 days) and edoxaban (60 mg single dose) increased total and peak systemic exposure to edoxaban 1.4X and 1.6X, respectively (Study U-131). Plasma edoxaban concentrations 24 hours post dose (C_{trough}) following co-administration edoxaban and amiodarone were similar (EDX+AMIO - 7.8 vs EDX - 9.9 ng/mL).

Ketoconazole

The effect of repeat administration of ketoconazole (oral dose of 400 mg QD for 7 days) on a single oral dose of edoxaban (60 mg) was evaluated in healthy subjects (Study

PRT016). Total and peak systemic exposure to edoxaban increased 1.87X and 1.89X, respectively. Total and peak systemic exposure to the metabolite increased 1.46X and 1.56X, respectively (see Figure 15).

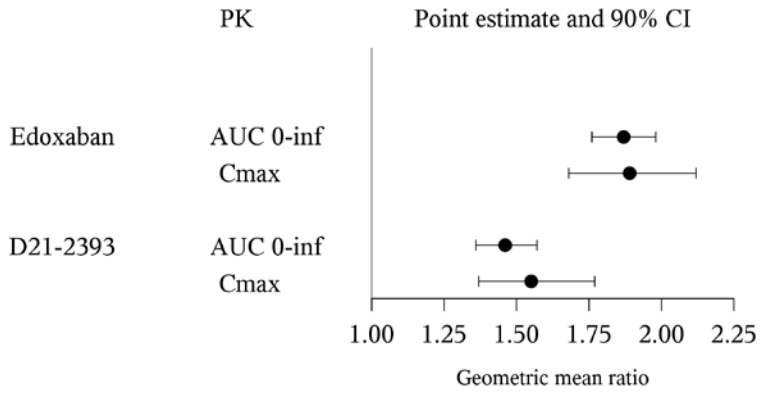


Figure 15: Co-administration of ketoconazole and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

Source: FDA Reviewer's Analysis

Erythromycin

The effect of repeat administration of erythromycin (oral dose of 500 mg four times daily for 8 days) on a single oral dose of edoxaban (60 mg) on Day 7 was evaluated in healthy subjects (Study E132). Total and peak systemic exposure to edoxaban increased 1.85X and 1.68X, respectively. Total and peak systemic exposure to the metabolite increased 1.78X and 1.75X, respectively (see Figure 16).

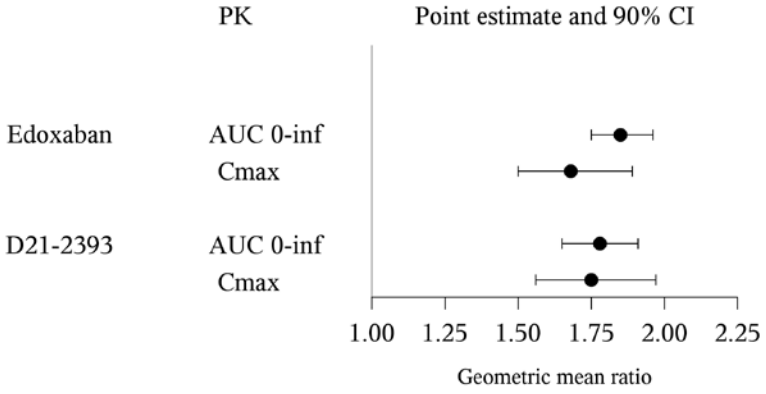


Figure 16: Co-administration of erythromycin and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

Source: FDA Reviewer's Analysis

Verapamil

The effect of repeat administration of verapamil (240 mg Verapamil SR Tablets (Calan® SR) QD for 11 Days) on a single oral dose of edoxaban (60 mg) on the morning of Day 10 was evaluated in healthy subjects (Study U130). Total and peak systemic exposure to edoxaban increased 1.53X and 1.53X, respectively. Total and peak systemic exposure to the metabolite increased 1.31X and 1.28X, respectively (see Figure 17).

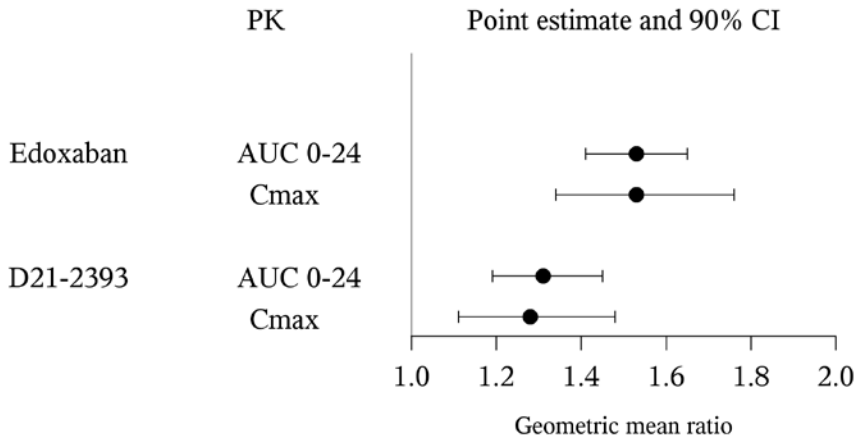


Figure 17: Co-administration of verapamil and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

Source: FDA Reviewer's Analysis

Cyclosporin

The effect of single oral dose of cyclosporin 500 mg on a single oral dose of edoxaban (60 mg) was evaluated in healthy subjects (Study U138). Total and peak systemic exposure to edoxaban increased 1.73X and 1.74X, respectively. Total and peak systemic exposure to the metabolite increased 6.87X and 8.71X, respectively (see Figure 18).

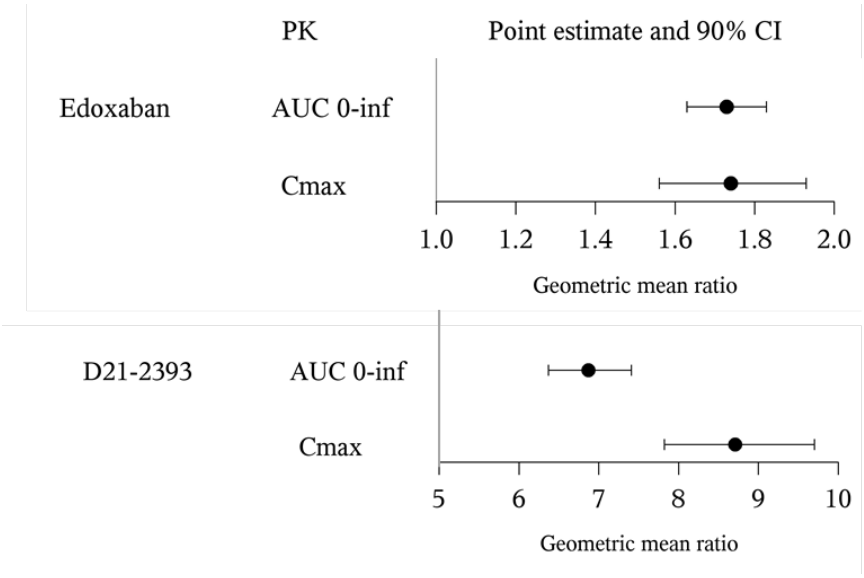


Figure 18: Co-administration of cyclosporine and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

Source: FDA Reviewer's Analysis

Metabolite to parent ratios increased from approximately 10 to 39% for AUC and from approximately 10 to 49% for Cmax. The reason why there was a significant increase in D21-2393 exposure is probably because cyclosporin (inhibitor of OATP1B1) inhibits the uptake of D21-2393 (substrate of OATP1B1) by liver.

P-gp Inducer

Rifampin

Co-administration of rifampin (600 mg QD for 7 days) and edoxaban (60 mg single dose on Day 7) decreased total systemic exposure to edoxaban by 40% without having an apparent effect on peak exposure (Study U-137). Total and peak systemic exposure to the metabolite increased 2.86X and 5.06X, respectively. Metabolite to parent ratios increased approximately 4.5X from approximately 9 to 40% for AUC and from approximately 10 to 45% for C_{max}.

While an increase in systemic exposure to its equipotent active metabolite D21-2393 makes up for this loss in total systemic exposure, it is driven by an increase in peak systemic exposure (C_{max}) to D21-2393. At trough (end of inter-dosing interval), there still exists a ~ 80% reduction in exposure to both edoxaban and the metabolite combined. Loss in exposure is considered detrimental and therefore, concomitant therapy with rifampin and other P-gp inducers is not recommended.

Other co-administered drugs

Digoxin (P-gp substrate)

Co-administration of digoxin (600 mg QD for 7 days) and edoxaban (60 mg single dose on Day 7) increased peak systemic exposure to edoxaban 1.17X without having an apparent effect on total exposure (Study PRT014). The pharmacodynamic effect of

edoxaban (prolongation of PT, INR and aPTT) was not influenced by its co-administration with digoxin. No dose reduction is necessary when edoxaban is administered with digoxin.

Atorvastatin (substrate of OATP1B1, OATP1B3; weak inhibitor of CYP3A4)

Co-administration of atorvastatin (80 mg QD for 8 days) and edoxaban (60 mg single dose on Day 7) decreased peak systemic exposure to edoxaban 1.14X without having an apparent effect on total exposure (Study E-133). Peak systemic exposure to the metabolite decreased 1.19X without having an apparent effect on total exposure. Concentration 24 h post administration was not significantly changed. The pharmacodynamic effect of edoxaban (prolongation of PT, INR and aPTT) was not influenced by its co-administration with atorvastatin.
No dose reduction is necessary when edoxaban is administered with atorvastatin.

Esomeprazole (Proton pump inhibitor)

Co-administration of esomeprazole (40 mg QD for 5 days) and edoxaban (60 mg single dose 2 h after esomeprazole dosing on Day 5) resulted in no change in total exposure, but peak exposure decreased by 33% (Study U156). In ENGAGE-AF ~ 17% of the population received therapy with a proton pump inhibitor. Trough edoxaban concentrations were similar across the various PPI treated groups and also to those not receiving a PPI. Given that systemic exposure to edoxaban is not affected by concomitant therapy with a PPI, no dose adjustment is necessary when edoxaban is administered with esomeprazole.

Aspirin (antiplatelet agent)

The effect of co-administration of low (Study U-127) and high dose aspirin (Study PRT017) on the pharmacokinetics and pharmacodynamics of edoxaban was evaluated in healthy subjects following repeat administration for 5 days. Co-administration of low dose aspirin (100 mg qd) and edoxaban (60 mg QD) for 5 days prolonged bleeding time by ~ 30%. A similar effect on bleeding time was observed following co-administration of high dose aspirin (325 mg qd) and edoxaban (60 mg QD). While edoxaban pharmacokinetics was not affected when administered with low dose aspirin, total and peak systemic exposure to edoxaban increased ~ 1.3X. The anti-factor Xa activity of edoxaban was not affected.

About 30% of the population in ENGAGE-AF received concomitant therapy with aspirin because of co-morbid conditions. While aspirin is known to increase risk for bleeds and the annualized event rate for major bleeds was higher than that in patients not receiving aspirin (3.87% vs. 2.13%). However, the risk for bleeds in patients receiving edoxaban 60 mg on a background of aspirin was lower than that for warfarin on a background of aspirin (HR 0.78 (95%CI 0.65,0.94. Based on these data no dose adjustments/contraindications are required.

Naproxen (NSAID)

Co-administration of naproxen (500 mg bid for 2 days) with a single oral dose of edoxaban (60 mg) prolonged bleeding time (Study U-128). Naproxen did not affect the anti-coagulant effect of edoxaban (PT, anti-factor Xa or aPTT) or edoxaban pharmacokinetics.

About 1% of the trial population received concomitant therapy with an NSAID. Similar to aspirin, the annualized event rate for major bleeds was higher than that in patients not receiving aspirin (3.7% vs. 2.1%), the point estimate was lower that for warfarin (HR 0.97 (95%CI 0.74, 1.27) for edoxban 60 mg).

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

Cardiovascular drugs that are known P-gp substrates (digoxin, atorvastatin, quinidine, and verapamil) and/or inhibitors (quinidine, digoxin, amiodarone, dronedarone, verapamil, and atorvastatin) may be prescribed to patients with Afib.

2.7 General Biopharmaceutics

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

Edoxaban tosylate has low aqueous solubility above pH 6.0 and is not rapidly dissolving. In vitro transport study using Caco-2 cell monolayers showed that the mean Papp [the mean of Papp in basal to apical direction] / [the mean of P_{app} in apical to basal direction at 1, 3, 10, 30 and 100 µmol/L was 4.53, 4.13, 3.97, 3.77 and 2.28 x 10^{-6} cm/s, respectively, suggesting that edoxaban is a low-permeability compound.

2.7.2 What is the effect of food on the bioavailability of the drug from the dosage form?

Food effect on the bioavailability was evaluated in study A-U148 using the 60 mg commercial formulation. Administration of a high-fat meal did not significantly affect the $AUC_{last\ and}$ AUC_{inf} of edoxaban but increased the C_{max} by 40% (90% CI: 124-159%). The C_{24h} of edoxaban was decreased by 22% (90% CI: 71-87%) (Study A-U148).Administration of a high-fat meal did not affect the AUC_{last} and AUC_{inf} and peak C_{max} exposures of D21-2393 but C_{24} of D21-2393 was decreased C24 of D21-2393 by 22% (90% CI: 70-86%) (Study A-U148). In ENGAGE-AF study medication could be administered fed or fasted.

2.8 Analytical Section

2.8.1 How are the active moieties identified and measured in the plasma?

Plasma and urine concentrations of edoxaban and metabolites were measured using LC/MS/MS methods at two sites of (b) (4) and at a single site at (b) (4) Audit findings and investigations at (b) (4) have led to revisions in the plasma concentration dataset. The approach for remediating the impact of bioanalytical findings on estimates of pharmacokinetics for edoxaban, and the overall plan Daiichi Sankyo, Inc. took for ensuring the fidelity of reported data were discussed with the FDA and considered acceptable (Type C meeting, October 2012).

A total of 18 of the earlier Phase 1 trials were analyzed at (b) (4) Among them, remediation actions included exclusion or amendment of plasma and/or urine

concentrations for edoxaban and metabolites were required for the following clinical pharmacology trials: PRT001, PRT002, PRT003, PRT004, PRT005, PRT008, PRT010, PRT012, PRT013, PRT014, PRT017, PRT020, A-U120, and A-J135. Bioanalytical findings did not impact data from the Phase 3 and 25 Phase 1 trials, as these were analyzed at (b) (4)

Long-term storage stability was validated up to 793 days under -20 °C (longer storage time was not tested). For all bioanalytical studies, the time from sample collection to analysis was within the validated long-term storage stability period with the following exception: for ENGAGE AF trial, PK samples from subjects experiencing a clinical event of either stroke/ systemic embolic event (SEE)/ major atherosclerotic cardiovascular events (MACE) or major bleeding were analyzed and reported, even though the collection-to-analysis time could have exceeded validated long-term storage stability period. There was a total of 335 "events samples" analyzed outside the established stability for edoxaban in this trial. They represent 4.16% of the 8,044 event samples analyzed. A sensitivity analysis was conducted to evaluate the impact of above. The results confirmed that there was no bias introduced because of this discrepancy.

Other than above-mentioned, the analytical procedures used to determine drug concentrations in this NDA appear generally acceptable per FDA Bioanalytical Method Validation guidance.

2.9 APPENDIX I

Pharmacometrics Review

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1. What factors in ENGAGE-AF may have contributed to the observed thrombotic event rate in patients with normal renal function?
2. What are the characteristics of the exposure-response relationships for efficacy and safety for edoxaban?
3. Is it possible to optimize the dosing in patients with normal renal function based on the exposure-response relationships for efficacy and safety?

These questions have been addressed in the body of the Clinical Pharmacology Review under Sections 2.3.2, 2.3.3, and 2.3.4. Additional details regarding questions 2.3.4 in the QBR are discussed under Key Question 1.1.1.

1.1.1 Should atrial fibrillation patients with normal renal function and moderate renal impairment receive a higher dose of edoxaban?

Yes, patients with normal renal function administered edoxaban 60 mg once daily exhibited a higher incidence of stroke/SEE (point estimate exceeding the non-inferiority margin of 1.38) and ischemic stroke relative to patients with normal renal function administered warfarin. Exposure-response analyses conducted by the review team, which are in agreement with analyses conducted by the Applicant, support that higher exposures of edoxaban would be associated with a decrease in the efficacy event rates with an accompanying increase in the safety event rates. Such observations are consistent with the known benefit-risk characteristics of warfarin and other approval oral anticoagulants (e.g., dabigatran, apixaban, rivoroxaban).

In conjunction with these observations, it was noted that patients with normal renal function exhibited lower concentrations of edoxaban with 60 mg once-daily, owing to higher renal clearance of the drug relative to patients with decreased renal function. Given the totality of the observations, we conducted analyses evaluating the impact of edoxaban dose adjustments on key primary and secondary efficacy and safety events. Many of the results discussed in this section will be discussed in the context that increasing the edoxaban dose in patients with normal renal function to achieve edoxaban exposures similar to that observed in patients with mild renal impairment may, in turn, 1) provide an improvement in stroke/SEE and ischemic stroke trending to achieve non-inferiority compared to warfarin and 2) result in a non-inferior bleeding profile relative to warfarin especially for life-threatening and fatal bleeds (which include hemorrhagic stroke). Other bleeding events are anticipated to increase with such a dose adjustment compared to warfarin (20% more for major bleeds primarily driven by increase in major GI bleeds). Such a dose adjustment in patients with normal renal function will still retain

a major part of the target product profile the Applicant intended. A similar case can also be made for supporting a dose increase to 45 mg QD in patients with moderate renal impairment as the utilized dose adjustment (50 % decrease to 30 mg QD) was an over-correction for the anticipated exposure increase in these patients in the phase 3 trial. However, final assessment of the benefit-risk characteristics for edoxaban in this population will be informed by discussions at the Cardiovascular and Renal Drugs Advisory Committee Meeting scheduled for October 30th, 2014.

The following describes in detail the motivation for embarking on characterizing the exposure-response relationship and touches on benefit-risk characteristics determined from the observed data as well as the benefit-risk characteristics for various projected edoxaban dosing regimens.

Sub-group analyses from study 301, identified renal function as a significant predictor for reduction of stroke/SEE (interaction p = 0.0002). Of note, subjects with normal renal function (CRCL ≥ 80 mL/min) in the edoxaban 60 mg did not exhibit relative benefit over warfarin and numerically appears worse than warfarin (HR: 1.41, 95% CI: 0.97-2.06). Similar results were also found in the edoxaban 30 mg group. This outcome appears to be the result of lower edoxaban concentrations (Mean population PK estimated trough exposure for normal renal function at 60 mg QD is 27.4 ng/mL) compared to the mild impairment group (CRCL ≥50 – <80 mL/min) that received 60 mg (Mean exposure is 36.8 ng/mL). Consistent with this finding, the risk for major bleeding, relative to warfarin, is numerically higher in patients with mild renal impairment compared to those with normal renal function. Further, in patients with moderate renal impairment, dose reduction to 30 mg QD seems to be an over correction based on a PK comparison between patients with mild renal impairment administered 60 mg (Mean exposure is 36.8 ng/mL) and patients with moderate renal impairment administered 30 mg (Mean exposure is 30.4 ng/mL).

Table 12 and Source: FDA *Reviewer's Analysis*

Figure 19 show the population PK predicted trough concentration for each of the renal function categories discussed above, in addition to concentrations in patients with low-body weight and concomitant P-gp use, which are two demographics that are relevant for the edoxaban dosing instructions. It is apparent that the dose reduction in patients with low body weight and concomitant P-gp use was an over correction as the 2-fold reduction in dose resulted in lower C_{trough} and AUC exposures compared to subjects in the same renal function category without a dose adjustment.

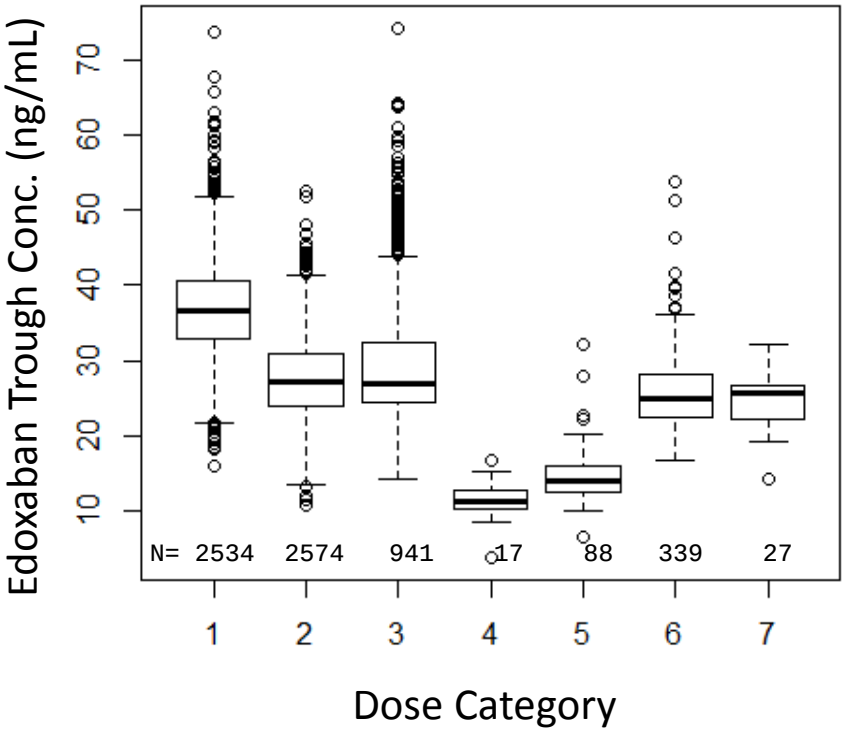
Table 12. Summary of edoxaban PK parameters C_{trough} and AUC by dose and patient demographic.

Patient Description					Ctrough				AUC			
Dose Group	Dose (mg)	Renal Function Cat.	Body Weight Cat.	P-gp Inhibitor Use?	Mean	Median	25%	75%	Mean	Median	25%	75%
High (60/30 mg)	60	Mild Insufficiency	≥ 60 kg	No	36.8	36.6	33.0	40.6	2296	2291	2138	2476
Low (30/15 mg)	30	Mild Insufficiency	≥ 60 kg	No	18.4	18.3	16.5	20.2	1158	1158	1076	1244
High (60/30 mg)	60	Normal Function	≥ 60 kg	No	27.4	27.3	23.8	30.8	1739	1765	1604	1922
Low (30/15 mg)	30	Normal Function	≥ 60 kg	No	13.7	13.7	12.0	15.4	875	886	809	958
High (60/30 mg)	30	Moderate Insufficiency	≥ 60 kg	No	30.4	27.0	24.5	32.3	1760	1513	1401	1726
Low (30/15 mg)	15	Moderate Insufficiency	≥ 60 kg	No	15.2	13.5	12.3	16.5	890	760	702	885
High (60/30 mg)	30	Mild Insufficiency	< 60 kg	No	18.2	17.6	15.8	20.1	1383	1363	1306	1467
Low (30/15 mg)	15	Mild Insufficiency	< 60 kg	No	9.3	9.2	8.1	10.6	694	690	662	731
High (60/30 mg)	30	Mild Insufficiency	≥ 60 kg	Yes	20.3	20.0	17.6	22.2	1374	1367	1289	1451
Low (30/15 mg)	15	Mild Insufficiency	≥ 60 kg	Yes	9.9	9.7	8.8	10.8	672	675	633	717
High (60/30 mg)	30	Normal Function	< 60 kg	No	11.4	11.3	10.3	12.7	1067	1084	1055	1121
Low (30/15 mg)	15	Normal Function	< 60 kg	No	5.6	5.7	4.1	6.5	548	549	522	576
High (60/30 mg)	30	Normal Function	≥ 60 kg	Yes	14.6	14.0	12.4	15.7	999	1015	920	1106
Low (30/15 mg)	15	Normal Function	≥ 60 kg	Yes	7.0	6.8	6.0	7.7	501	504	458	552

Source: FDA Reviewer's Analysis

Figure 19. Observed edoxaban trough concentrations by renal impairment, body weight, and concomitant P-gp demographic.

1. Patients with Mild Renal Impairment (60 mg) – *Group to Match Exposures to*
2. Patients with Normal Renal Function and no dose reduction (60 mg)
3. Patients with Moderate Renal Impairment only (30 mg)
4. Patients with Low Body Weight (<60 kg) only (30 mg)
5. Patients with concomitant P-gp only (30 mg)
6. Patients with Moderate Renal Impairment and Low Body Weight (30 mg)
7. Patients with Moderate Renal Impairment and concomitant P-gp Use (30 mg)



Source: FDA Reviewer's Analysis

As a result of the above finding, exposure-response relationships were established for all stroke/SEE, ischemic stroke, hemorrhagic stroke, life-threatening and fatal bleeds, major bleeds, major GI bleeds, clinically-relevant non-major and major bleeds, and MACE events. These relationships were then evaluated to assess alternative edoxaban doses and the resulting impact of such dosing on efficacy and safety relative to warfarin.

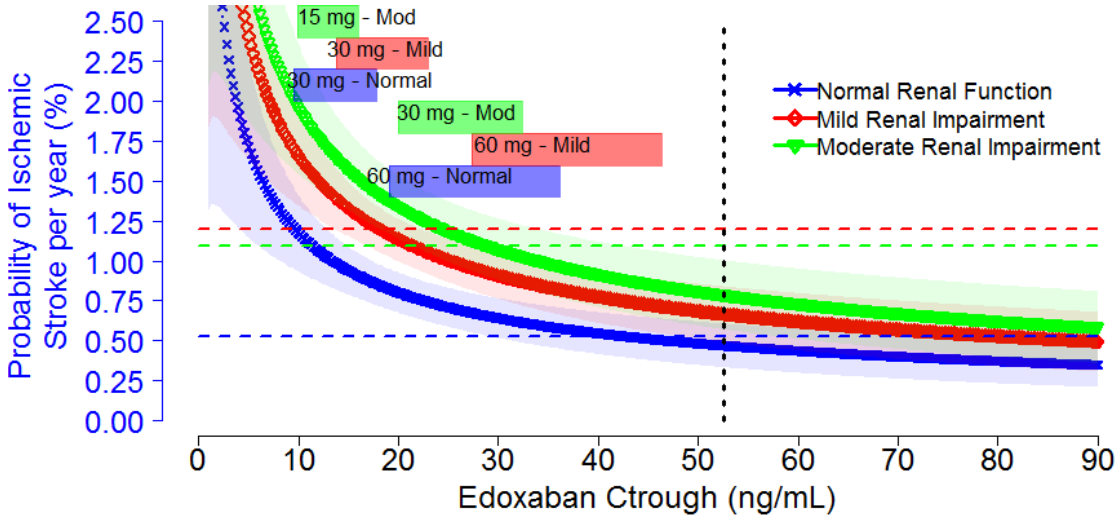
The analysis that has carried the most weight to date has been the comparison of ischemic stroke with life-threatening and fatal bleeds.

- Ischemic stroke was chosen over all stroke/SEE as all stroke/SEE contains hemorrhagic stroke which is bleeding related and is also incorporated into the life-threatening bleed category (i.e., double counting of events)
- Life-threatening and fatal bleeds were chosen as the severity of these events appears to be more in line with the severity of the ischemic stroke endpoint. Further discussion on this may be found in the clinical review by (Dr. Melanie Blank).

Exposure response relationships across renal function groups of interest for ischemic stroke are shown in Figure 20. The relationships illustrate two important points:

1. With increasing exposure, the probability of an ischemic stroke decreases. The nature of this relationship is such that the benefit of increased exposure on stroke reduction is diminishing with further increases along the concentration gradient.
2. Additionally this figure suggests that lower exposure with edoxaban 60 mg is the most likely explanation for findings observed in patients with normal renal function and moderate renal impairment compared to patients with mild impairment of renal function in ENGAGE-AF. Further, if these subgroups had exposures similar to those patients with mild renal impairment at 60 mg, their ischemic stroke reduction profile is predictive to improve and is likely to achieve at least non-inferiority compared to warfarin.

Figure 20. Exposure-response relationships for ischemic stroke for varying degrees of renal impairment and their corresponding observed rate for warfarin (horizontal dashed lines) and their corresponding observed edoxaban exposure range as the 5th to 95th percentiles (solid-filled rectangles). The black vertical dashed line indicates the 99th percentile of all edoxaban C_{trough} exposures.

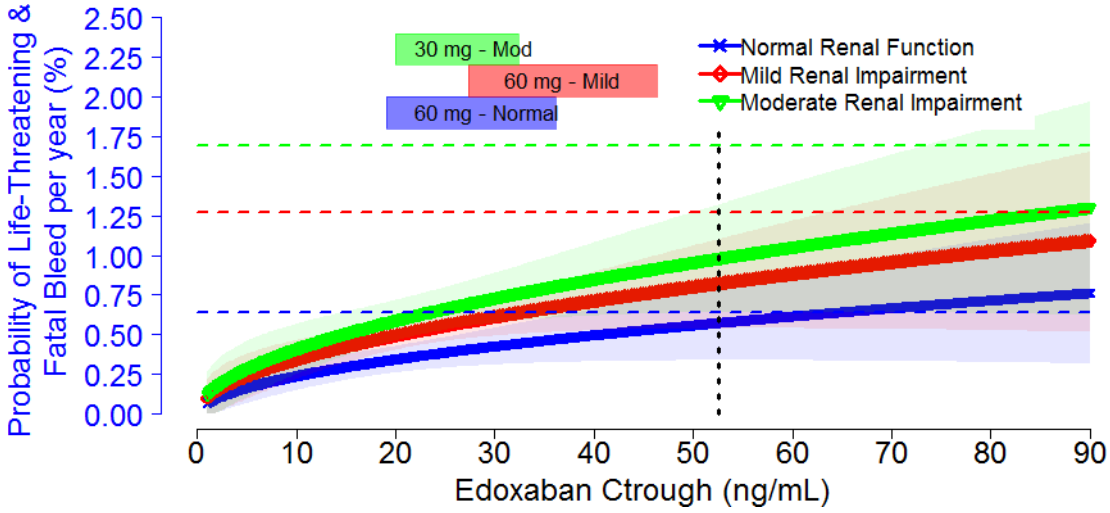


Source: FDA Reviewer's Analysis

Exposure-response relationships for life-threatening/fatal bleeds are shown in Figure 21. Two points are clear from this relationship.

1. There is an exposure dependent increase in the risk for life-threatening/fatal bleeds.
2. Increasing exposures in patients with normal renal function and moderate renal impairment to match exposures in patients with mild renal impairment (60 mg) is not predicted to exceed the life-threatening/fatal bleeding rate for warfarin.

Figure 21. Exposure-response relationships for life-threatening/fatal bleeds for varying degrees of renal impairment and their corresponding observed rate for warfarin (horizontal dashed lines) and their corresponding observed edoxaban exposure range as the 5th to 95th percentiles (solid-filled rectangles). The black vertical dashed line indicates the 99th percentile of all edoxaban C_{trough} exposures.



Source: FDA Reviewer's Analysis

Based on the exposure response relationships and edoxaban pharmacokinetics, exposure-matching to that observed in patients with mild renal impairment administered 60 mg QD would suggest the following dosing:

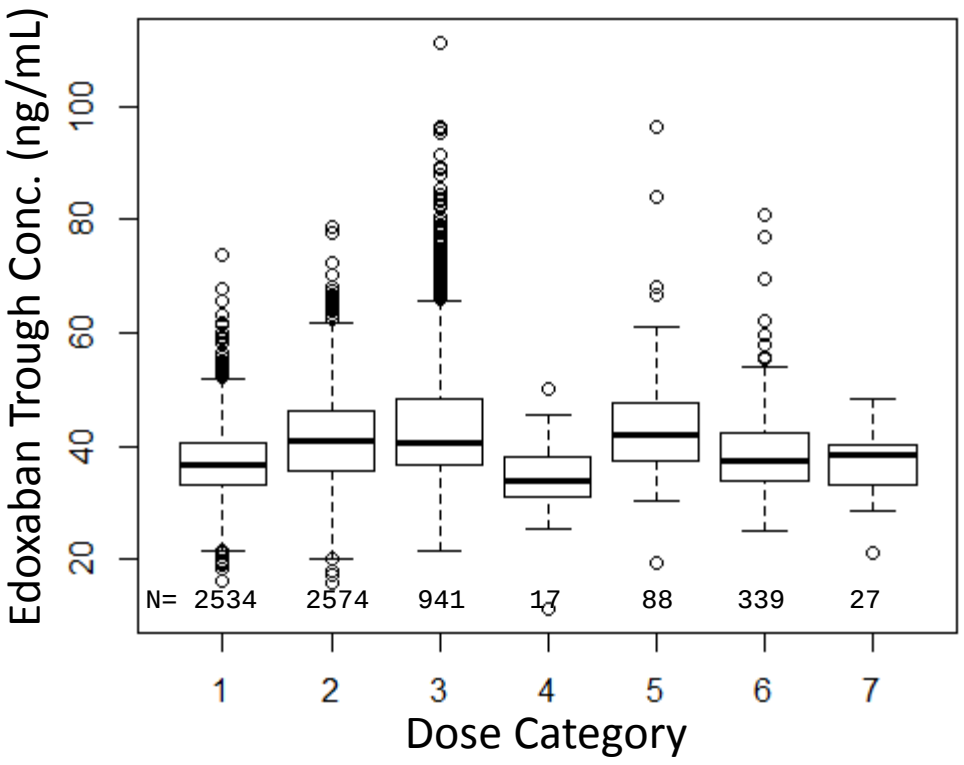
- 90 mg QD for patients with normal renal function
- 60 mg QD for patients with mild renal impairment
- 45 mg QD for patients with moderate renal impairment
- No dose reduction for patients with normal renal function or mild renal impairment based on body weight < 60 kg OR concomitant p-gp use

Figure 22 shows the projected exposures in each of the categories mentioned above (inSource: FDA *Reviewer's Analysis*

Figure 19) based on their population PK post-hoc Bayesian estimates compared against exposures in mild renal impairment patients who received 60 mg QD. This regimen appears reasonable in achieving exposures similar to 60 mg QD in patients with mild renal impairment.

Figure 22. Projected exposures at the dosing regimens listed above (groups 2 - 7) compared to the observed exposures in patients with mild renal impairment who received 60 mg edoxaban (group 1).

1. Patients with Mild Renal Impairment (60 mg) – Group to Match Exposures to
2. Patients with Normal Renal Function and no dose reduction (90 mg)
3. Patients with Moderate Renal Impairment only (45 mg)
4. Patients with Low Body Weight (<60 kg) only (no adjustment except for renal function category)
5. Patients with concomitant P-gp only (no adjustment except for renal function category)
6. Patients with Moderate Renal Impairment and Low Body Weight (45 mg)
7. Patients with Moderate Renal Impairment and concomitant P-gp Use (45mg)



Source: FDA Reviewer's Analysis

Since the primary reason for focusing on the subgroup with normal renal function was the unfavorable hazard ratio estimate between edoxaban relative to warfarin, Table 1 provides the projected impact on the risk ratio (edoxaban event rate/ observed warfarin event rate) of the various dose adjustments of edoxaban for both efficacy and safety endpoints. Risk ratios are shown for ischemic stroke, life-threatening/fatal bleeds, all stroke/SEE, and major bleeds. The projected risk ratio for the proposed dose adjustment are below the NI margin without an inferior trend for life-threating/fatal bleeds. The cost of such dose adjustment is manifested in ~20% increase in the risk for major bleeds; a risk we believe can be communicated via appropriate labeling.

Table 13. Relative Risk Ratios (90% Prediction Interval) of Predicted Edoxaban Event Rates Relative to the Observed Warfarin Event Rate by Renal Category, Dose, and Event Type.

Endpoint	Renal Category	Comparison	Relative Risk Ratio
Ischemic Stroke	Normal (≥ 80 mL/min)	Edoxaban 60 vs Warfarin	1.42 (1.21, 1.62)
		Edoxaban 75 vs Warfarin	1.26 (1.06, 1.49)
		Edoxaban 90 vs Warfarin	**1.15 (0.92, 1.40)**
	Mild (≥50 - <80 mL/min)	**Edoxaban 60 vs Warfarin**	**0.80 (0.67, 0.93)**
		Edoxaban 75 vs Warfarin	0.72 (0.60, 0.86)
		Edoxaban 90 vs Warfarin	0.64 (0.53, 0.82)
	Moderate (≥30 - <50 mL/min)	Edoxaban 30 vs Warfarin	1.15 (0.96, 1.34)
		Edoxaban 37.5 vs Warfarin	0.98 (0.82, 1.17)
		Edoxaban 45 vs Warfarin	**0.93 (0.73, 1.12)**
LT/Fatal Bleed	Normal (≥ 80 mL/min)	Edoxaban 60 vs Warfarin	0.64 (0.53, 0.80)
		Edoxaban 75 vs Warfarin	0.73 (0.58, 0.94)
		Edoxaban 90 vs Warfarin	**0.78 (0.56, 1.05)**
	Mild (≥50 - <80 mL/min)	**Edoxaban 60 vs Warfarin**	**0.49 (0.39, 0.58)**
		Edoxaban 75 vs Warfarin	0.56 (0.43, 0.71)
		Edoxaban 90 vs Warfarin	0.61 (0.43, 0.82)
	Moderate (≥30 - <50 mL/min)	Edoxaban 30 vs Warfarin	0.41 (0.34, 0.52)
		Edoxaban 37.5 vs Warfarin	0.45 (0.37, 0.62)
		Edoxaban 45 vs Warfarin	**0.50 (0.39, 0.61)**
Stroke/SEE	Normal (≥ 80 mL/min)	Edoxaban 60 vs Warfarin	1.24 (1.00, 1.46)
		Edoxaban 75 vs Warfarin	1.14 (0.95, 1.36)
		Edoxaban 90 vs Warfarin	**1.05 (0.91, 1.28)**
	Mild (≥50 - <80 mL/min)	**Edoxaban 60 vs Warfarin**	**0.63 (0.56, 0.73)**
		Edoxaban 75 vs Warfarin	0.57 (0.50, 0.68)
		Edoxaban 90 vs Warfarin	0.54 (0.45, 0.64)
	Moderate (≥30 - <50 mL/min)	Edoxaban 30 vs Warfarin	0.83 (0.73, 0.96)
		Edoxaban 37.5 vs Warfarin	0.76 (0.64, 0.88)
		Edoxaban 45 vs Warfarin	**0.71 (0.57, 0.84)**
Major Bleed	Normal (≥ 80 mL/min)	Edoxaban 60 vs Warfarin	0.77 (0.71, 0.83)
		Edoxaban 75 vs Warfarin	0.96 (0.84, 1.10)
		Edoxaban 90 vs Warfarin	**1.19 (1.03, 1.41)**
	Mild (≥50 - <80 mL/min)	**Edoxaban 60 vs Warfarin**	**0.94 (0.82, 1.02)**
		Edoxaban 75 vs Warfarin	1.23 (1.08, 1.44)
		Edoxaban 90 vs Warfarin	1.69 (1.40, 1.99)
	Moderate (≥30 - <50 mL/min)	Edoxaban 30 vs Warfarin	0.67 (0.57, 0.72)
		Edoxaban 37.5 vs Warfarin	0.85 (0.76, 0.96)
		Edoxaban 45 vs Warfarin	**1.10 (0.93, 1.27)**

Source: FDA Reviewer's Analysis

A similar comparison is shown below (Table 14) that aims to put both efficacy and safety in perspective and attempts to provide a net benefit quantification of the dose adjustments. Comparisons to warfarin with both observations and predictions are made to project the absolute numbers of events per 10000 patients per year. This table maintains that dose adjustment to 90 mg brings the ischemic stroke event rate comparable to warfarin and does not push the life-threatening/fatal bleed beyond warfarin's rate.

Table 14. Difference in Events per 10000 patients/year – Ischemic Stroke and Life-Threatening/Fatal Bleeds. Positive numbers indicate there are more events in the edoxaban arm than warfarin arm.

Renal Function	Comparison	Ischemic Stroke	LT / Fatal Bleed
	60 mg Observed vs Warf Observed	31	-20
Normal (>80 mL/min)	60 mg Predicted Vs Warf Observed	22	-23
	75 mg Predicted Vs Warf Observed	14	-17
	90 mg Predicted Vs Warf Observed	8	-14
	30 mg Observed Vs Warf Observed	10	-92
Moderate (30 - 50 mL/min)	30 mg Predicted Vs Warf Observed	16	-99
	37.5 mg Predicted Vs Warf Observed	-2	-93
	45 mg Predicted Vs Warf Observed	-8	-84

Source: FDA Reviewer's Analysis

The results shown thus far have been in the context of ischemic stroke and life-threatening/bleeds for reasons mentioned above. While these have been the primary focus of the exposure-response analysis, other endpoints have been evaluated including all stroke/SEE, hemorrhagic stroke, major bleed, major GI bleed, clinically relevant non-major bleed, and MACE events. All of these results are described in detail in Section 2 and provide a broader perspective on how various event rates may change with edoxaban exposure.

2 REVIEWER'S ANALYSIS

2.1 Introduction

Sub-group analyses from study 301 (Figure 11.3 in CSR), identified renal function as a significant predictor for reduction of stroke/SEE (interaction p = 0.0002). Of note, subjects with normal renal function (CRCL ≥ 80 mL/min) in the edoxaban 60 mg did not exhibit relative benefit over warfarin and numerically appears worse than warfarin (HR: 1.41, 95% CI: 0.97-2.06). Similar results were also found in the edoxaban 30 mg group. As expected, this outcome appears to be the result of lower edoxaban concentrations (Mean population PK estimated trough exposure for normal renal function at 60 mg QD is 27.4 ng/mL) compared to the mild impairment group (CRCL ≥50 – 80 mL/min) that received 60 mg (Mean exposure is 36.8 ng/mL). Consistent with this finding, the risk for major bleeding, relative to warfarin, is numerically higher in patients with mild impairment of renal function compared to those with normal renal function. Further, in patients with moderate impairment of renal function, dose reduction to 30 mg QD seems to be an over correction based on a PK comparison between patients with mild renal impairment administered 60 mg (Mean exposure is 36.8 ng/mL) and patients with moderate renal impairment administered 30 mg (Mean exposure is 30.4 ng/mL).

Multivariate exposure- and risk-factor analyses for efficacy endpoints and safety endpoints were conducted to gain a benefit-risk assessment of the proposed edoxaban dose (60 mg QD with dose adjustment to 30 mg QD for patients with low body weight, moderate or severe renal impairment, and concomitant P-gp Inhibitor use) for patients with atrial fibrillation. The analysis served as a quality control to the Applicant analysis and an opportunity to develop an independent scientific opinion on the Applicant's models (all stroke/SEE, ischemic stroke, hemorrhagic stroke) as well as develop new models for endpoints not evaluated by the Applicant (life-threatening/ fatal bleeds, major GI bleeds, clinically relevant non-major & major bleeds, and MACE events). The reviewer's analysis also evaluated the population PK model to ensure the exposure metrics used in the analyses were robust and the model was sufficient to propose doses based on exposure matching.

2.2 Objectives

Analysis objectives are:

1. Construct multi-variate exposure- and risk-factor- response models for efficacy
2. Construct multi-variate exposure- and risk-factor- response models for safety
3. Use the developed models to identify the expected yearly event-rates for different patient populations to evaluate the net benefit at various dose levels
4. Review the Applicant's population PK model to determine its sufficiency for proposing new doses based on edoxaban exposure matching

2.3 Methods

2.3.1 Data Sets

Data sets used are summarized in Table 15.

Table 15. Analysis Data Sets

Study Number	Name	Link to EDR
DU176B-C-301	dm.xpt, basegrp.xpt	\\Cdsesub1\evsprod\NDA206316\0000\m5\datasets\du176b-c-u301\analysis\legacy\datasets
DU176B-C-301	adjeffca.xpt, adjsafca.xpt	\\Cdsesub1\evsprod\NDA206316\0009\m5\datasets\du176b-c-u301\analysis\legacy\datasets
DU176B-D-305	dm.xpt, basegrp.xpt, adjeff.xpt, adjsaf.xpt	\\Cdsesub1\evsprod\NDA206316\0000\m5\datasets\du176b-d-u305\analysis\legacy\datasets

2.3.2 Software

The statistical software R (version 2.15) was used for all dataset construction, time-to-event analyses, and for generating graphics. The software NONMEM (version 7.3) was used to evaluate the Applicant's population PK model.

2.3.3 Models

Edoxaban Population Pharmacokinetic Model:

The structure of the population PK model and its covariates were not changed during this analysis. Instead the model was reevaluated using an updated dataset to include data from patients with valid PK information who were inadvertently excluded from the original analysis.

It was observed that the majority (~90%) of patients with stroke/SEE events and bleeding events were not included in the final population PK model assessment. Such subjects had PK values predicted from the population PK model rather than calculated from posthoc Bayesian estimates (Table 16), which were subsequently used in the exposure-response analyses. The exclusion of these subjects from the initial population PK analysis as well as a subset of other subjects without events was due to a data assembly error in the construction of the population PK dataset. The FDA noted this observed and sent an information request dated July 31st, and the applicant clarified this observation on August 22nd with a written amendment to the population PK report:

> "The initial intention was to exclude samples that are considered compromised or might be compromised from the population PK analysis, and corresponding to this purpose, to code ERROR=1 for samples that fall in these categories. However, upon further review of the dataset (**DBL_3u**), a coding error was identified for the bioanalytical sample condition related variables (ERROR, SAAFIL, SAAFIH, SAAFIF, ESRD, VOL, DUP, NOICE, HEMO, OUTSTAB, EVENT). As a result, 8155 observations (out of a total of 37920 observations that are above LLOQ) were accidentally excluded from the population PK analysis."

As a consequence of this the Applicant's dataset was revised to include those observations from patients who had stroke or bleeding events that were excluded for

reasons other than sample handling errors. The population PK model was rerun using the revised dataset. This revision permitted Bayesian post-hoc estimates to be used, rather than simulated values, for these patients where the data was originally excluded. This was of particular interest given that the shrinkage of the eta for clearance was 63%. The Applicant's model parameters are shown alongside the revised model parameters in Table 16. The important distinction is that the clearance parameter was not influenced by this adjustment to the dataset since clearance and dose are what determine the C_{trough} and AUC used for the exposure-response analyses.

Table 16. Applicant's and FDA Revised Edoxaban Population PK Model Structural Parameters

Parameter	Applicant's Final Estimate	Final Estimate based on the Revised Dataset
Clearance (L/hr)	13.9	13.7
Central Volume of Dist. (L)	193	165
Peripheral Volume of Dist. (L)	88.3	270
Inter-Compartmental Clearance (L/hr)	5.74	16.5
1^{st} order Absorption Rate Constant (1/hr)	2.16	1.53
Absorption Lag Time	0.25	0.25

Multivariate Edoxaban Exposure- and Risk Factor- Time-to-Event Analyses:

Multivariate Cox proportional hazards models were developed for the stroke and bleeding events described above from Study 301. Models were evaluated for both warfarin and edoxaban in the same dataset and also for edoxaban data alone. The latter models (edoxaban) were explored in the subsequent analyses owing to their better estimation of the observed event rates for edoxaban and as a full model accounting for the treatment effect of warfarin and relevant covariates (i.e., INR) was not being developed. C_{trough} values were updated from a revised population PK analysis as described above. Model covariates tested included: treatment (warfarin vs. edoxaban), age, creatinine clearance, prior stroke/transient ischemic attack history, diabetes status, edoxaban trough concentrations, log-transformed edoxaban trough concentrations, body weight, concomitant aspirin use, continuous CHADS2, CHADS2 based on binary cut points between 2 and >2 or ≤3 and >3, and congestive heart failure. Covariates were included into a full model if their univariate assessment indicated significance of the parameter at α=0.05. Covariates were eliminated from the model during a backwards elimination evaluation if based on a significance of the parameter at α=0.05. The efficacy and safety analyses were based on the full mITT population and on-treatment censored events (time to first event) for all endpoints.

Models were developed for both edoxaban and warfarin data combined, as well as for edoxaban independent of the warfarin data. However, as the primary focus of these analyses is to inform dosing for edoxaban and as a complete model for warfarin was not being developed, it was decided that an analysis based on the edoxaban observed data would be the focus of the final analyses. Similar to the approach presented by the Applicant in their atrial fibrillation exposure-response analyses, data from all three treatment arms was used to inform potential covariates, but only data from the edoxaban treatment arms was used for final covariate identification.

Weibull distribution proportional hazards models were evaluated for every scenario and in general fit the data better for the first two years. However, the Weibull model was inefficient to simulate from in the software R and did not affect the model results significantly. Thus exponential distribution proportional hazards models were utilized to simulate and determine the event rate per year for different doses and degrees of renal impairment. The parameter estimates for various models tested are listed below.

Table 17. Final Cox proportional hazards model (exponential distribution) for All Stroke/SEE events using only edoxaban data from study DU176B-C-301.

All Stroke/SEE				
Covariate	Estimate	Standard Error	z	p
Age (years)	0.0155	5.84E-03	2.66	7.90E-03
Prior Stroke (strktia)	0.5432	1.27E-01	4.26	2.00E-05
Log Edoxaban Ctrough (ng/ml)	-0.3936	1.08E-01	-3.64	2.70E-04
CHAD Score (chadcut1)	0.3036	1.34E-01	2.27	2.30E-02
Body Weight (kg)	-0.0089	2.72E-03	-3.29	1.00E-03

Table 18. Final Cox proportional hazards model (exponential distribution) for ischemic stroke events using only edoxaban data from study DU176B-C-301.

Ischemic Stroke				
Covariate	Estimate	Standard Error	z	p
Age (years)	0.0153	6.36E-03	2.4	1.60E-02
Prior Stroke (strktia)	0.6002	1.39E-01	4.32	1.50E-05
Log Edoxaban Ctrough (ng/ml)	-0.5597	1.19E-01	-4.72	2.40E-06
CHAD Score (chadcut1)	0.2932	1.45E-01	2.02	4.40E-02
Body Weight (kg)	-0.0078	2.93E-03	-2.66	7.90E-03

Table 19. Final Cox proportional hazards model (exponential distribution) for hemorrhagic stroke events using only edoxaban data from study DU176B-C-301.

Hemorrhagic Stroke				
Covariate	Estimate	Standard Error	z	p
Body Weight (kg)	-0.0207	7.87E-03	-2.63	8.60E-03
Concomitant Aspirin	0.5303	2.68E-01	1.98	4.80E-02
Log Edoxaban Ctrough (ng/ml)	0.7102	3.02E-01	2.35	1.90E-02

Table 20. Final Cox proportional hazards model (exponential distribution) for life-threatening and fatal bleeds using only edoxaban data from study DU176B-C-301.

Life Threatening & Fatal Bleeds				
Covariate	Estimate	Standard Error	z	p
Age (years)	0.0363	9.91E-03	3.67	2.50E-04
Log Edoxaban Ctrough (ng/ml)	0.5339	1.91E-01	2.8	5.10E-03

Table 21. Final Cox proportional hazards model (exponential distribution) for major bleeds events using only edoxaban data from study DU176B-C-301.

Major Bleeds				
Covariate	Estimate	Standard Error	z	p
Age (years)	0.0364	4.77E-03	7.62	2.50E-14
Edoxaban Ctrough (ng/ml)	0.0323	3.54E-03	9.12	0.00E+00
Concomitant Aspirin	0.3671	7.92E-02	4.63	3.60E-06
CHAD Score (chadcut1)	0.2626	8.61E-02	3.05	2.30E-03

Table 22. Final Cox proportional hazards model (exponential distribution) for major GI bleeds events using only edoxaban data from study DU176B-C-301.

Major GI Bleeds				
Covariate	Estimate	Standard Error	z	p
Age (years)	0.0395	6.57E-03	6	1.90E-09
Concomitant Aspirin	0.4361	1.07E-01	4.06	4.90E-05
Edoxaban Ctrough (ng/ml)	0.0413	4.77E-03	8.67	0.00E+00

Table 23. Final Cox proportional hazards model (exponential distribution) for clinically-relevant, non-major & major bleeds using only edoxaban data from study DU176B-C-301.

Clinically Relevant Non-Major & Major Bleeds				
Covariate	Estimate	Standard Error	z	p
Age (years)	0.0237	2.86E-03	8.28	1.10E-16
Creatinine Clearance (mL/min)	-0.0044	1.18E-03	-3.74	1.80E-04
Body Weight (kg)	0.0063	1.35E-03	4.71	2.40E-06
Prior Stroke (strktia)	0.1502	4.24E-02	3.54	4.00E-04
Edoxaban Ctrough (ng/ml)	0.0175	1.87E-03	9.35	0.00E+00
Concomitant Aspirin	0.3027	4.03E-02	7.51	6.00E-14
Diabetes	0.1425	4.05E-02	3.52	4.40E-04

Table 24. Final Cox proportional hazards model (exponential distribution) for MACE events using only edoxaban data from study DU176B-C-301.

MACE Events				
	Estimate	Standard Error	z	p
Creatinine Clearance (mL/min)	-0.0094	1.25E-03	-7.54	4.50E-14
Edoxaban Ctrough (ng/ml)	-0.0137	0.00332	-4.13	3.60E-05
Sex	-0.2911	6.81E-02	-4.27	1.90E-05
Concomitant Aspirin	0.1775	6.72E-02	2.64	8.30E-03
CHAD Score (chadcut1)	0.4836	6.93E-02	6.98	2.90E-12

Source: FDA Reviewer's Analysis

2.4 Results

2.4.1.1 Time to Event Exposure-Response Analysis of the Efficacy Endpoints

The exposure-response analysis based on the Cox proportional hazards models are represented below in two formats. The first is a prediction of the exposure-response relationship for the typical patient with normal renal function, mild renal impairment, or moderate renal impairment (Figure 23) based on demographics from DU176B-C-301. Each line was generated for a typical patient in each renal function category. The second component of this analysis is the event rates per year for each dose and renal impairment demographic.

The key points of this analysis are:

1.) Edoxaban exposure correlates with all endpoints evaluated.

2.) For clotting related events such as stroke/SEE and ischemic Stroke, the probability of the event decreases with increasing edoxaban exposure.

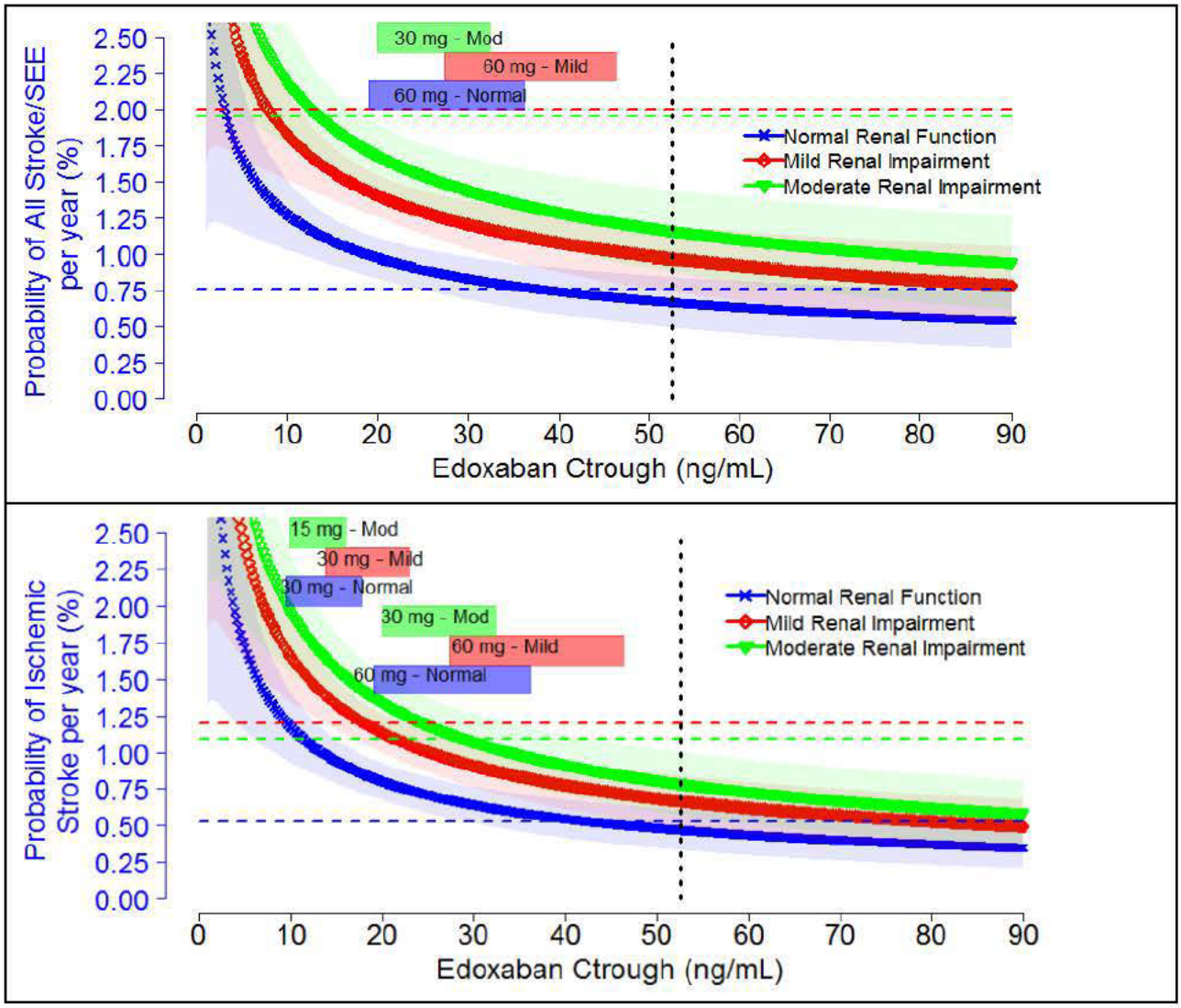
3.) For bleeding related stroke events (i.e, hemorrhagic stroke) the probability of the event increases with increasing concentration. Thus, ischemic stroke appears to be the most relevant endpoint for benefit gained from an anti-coagulant. Whereas all stroke/SEE also contains hemorrhagic strokes. In the safety analysis, life threatening bleeds also contain hemorrhagic strokes.

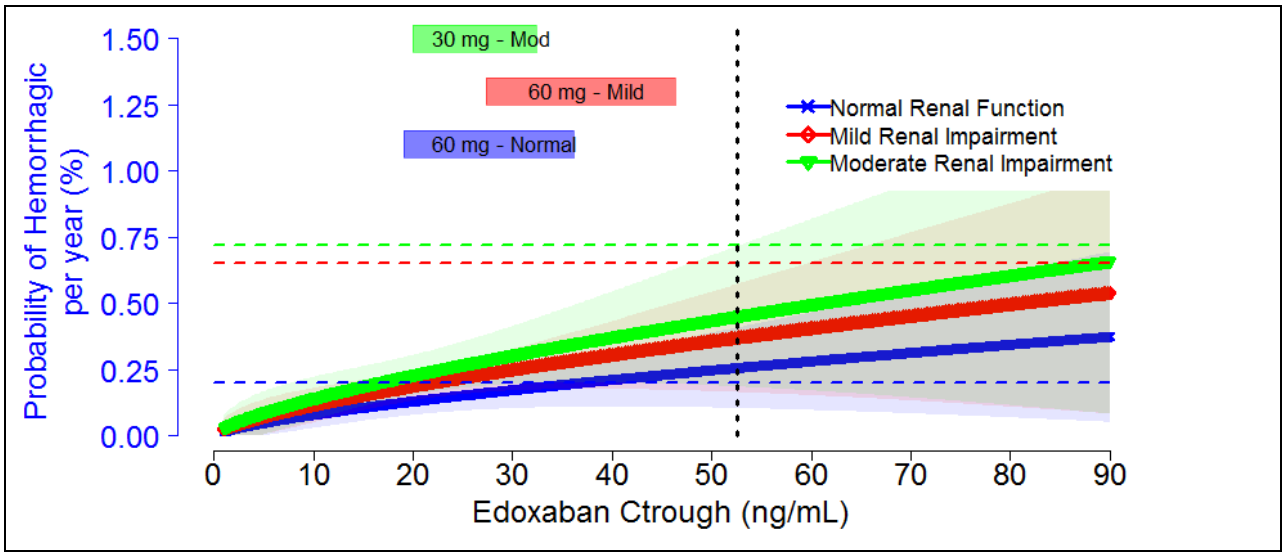
4.) Patients with normal renal function and moderate renal impairment appeared to have lower exposures compared to patients with mild renal impairment who were not dose adjusted for body weight or concomitant P-gp use. These patients may achieve further reduction in ischemic stroke compared to warfarin by increasing the dose to 45 mg in patients with moderate renal impairment and 90 mg in patients with normal renal function.

5.) The proposed exposure range of the 45 mg dose in patients with moderate renal impairment and 90 mg in patients with normal renal function in general does not exceed the exposure range evaluated in study DU176B-C-301.

6.) The model predictions by dose and degree of renal impairment appear to capture the central tendency of the observed data (Table 25 and Table 26).

Figure 23. Exposure-response relationships for all stroke/SEE (top panel), ischemic stroke (middle panel), and hemorrhagic stroke (bottom panel) for varying degrees of renal function and impairment and their corresponding observed rate for warfarin (horizontal dashed lines) and their corresponding observed edoxaban exposure range as the 5th to 95th percentiles (solid-filled rectangles). The black vertical dashed line indicates the 99th percentile of all edoxaban C_{trough} exposures.





Source: FDA Reviewer's Analysis

In an effort to 1) evaluate the benefit of the proposed dose adjustment in terms of absolute numbers of patients and 2) assess the model's goodness of fit, an event rate per year was calculated from both the observed data and model predictions by dose and degree of renal impairment (Table 25 and Table 26). Values were generated by bootstrapping the model fitting on a dataset resampled 100 times and obtaining a simulated probability of the event over time (survival function) at each iteration. Linear regressions from the survival functions gave the event rates per year (slope of survival function) and the reported values are the 50% percentile and the 5^{th} and 95^{th} percentiles of the slopes determined for each bootstrap iteration.

Table 25. Observed and predicted Stroke/SEE event rates per year by dose and degree of renal impairment.

Event rate (% patients/year)		Stroke/SEE	
		Observed	Predicted
Overall	Warfarin	1.49 (1.31; 1.70)	---
	30/15 mg	1.60 (1.41; 1.81)	1.6 (1.45,1.78)
	60/30 mg	1.18 (1.01; 1.36)	1.22 (1.04,1 39)
	75 mg	---	1.11 (0.97, 1.27)
	90 mg	---	1.05 (0.88,1 23)
Normal	Warfarin	0.76 (0.56; 1.01)	---
	30 mg	1.23 (0.97; 1.53)	1.25 (1.05,1.46)
	60 mg	1.06 (0.82; 1.35)	0.94 (0.76,1.11)
	75 mg	---	0.87 (0.72, 1.03)
	90 mg	---	0.8 (0.69,0.97)
Mild	Warfarin	2.00 (1.68; 2.36)	---
	30 mg	1.66 (1.38; 1.99)	1.67 (1.5,1.87)
	60 mg	1.06 (0.83; 1.34)	1.26 (1.11,1.45)
	75 mg	---	1.14 (1, 1.36)
	90 mg	---	1.07 (0.89,1 27)
Moderate	Warfarin	1.95 (1.44; 2.57)	---
	15 mg	2.34 (1.78; 3.01)	2.15 (1.84,2.5)
	30 mg	1.73 (1.25; 2.32)	1.61 (1.42,1.87)
	37.5 mg	---	1.48 (1.24, 1.71)
	45 mg	---	1.39 (1.11,1.64)

Source: FDA Reviewer's Analysis

Table 26. Observed and predicted ischemic stroke (left) and hemorrhagic stroke (right) event rates per year by dose and degree of renal impairment.

Event rate (% patients/year)		Ischemic Stroke	
		Observed	Predicted
Overall	Warfarin	0.93 (0.78; 1 09)	---
	30/15 mg	1.43 (1 25; 1.63)	1.4 (1.26,1.57)
	60/30 mg	0.87 (0.73; 1 03)	0.93 (0 81,1.06)
	75 mg	---	0.85 (0.7, 0.99)
	90 mg	---	0.77 (0.65,0.94)
Normal	Warfarin	0.53 (0 37; 0.75)	---
	30 mg	1.12 (0 87; 1.41)	1.13 (0 96,1.31)
	60 mg	0.84 (0.62; 1 09)	0.75 (0.64,0.86)
	75 mg	---	0.67 (0.56, 0.79)
	90 mg	---	0.6 (0.49,0.74)
Mild	Warfarin	1.22 (0 97; 1 51)	---
	30 mg	1.42 (1.15; 1.72)	1.45 (1.3,1.64)
	60 mg	0.78 (0 58; 1 02)	0.98 (0 82,1.13)
	75 mg	---	0 88 (0.73, 1.05)
	90 mg	---	0.78 (0.64,1)
Moderate	Warfarin	1.10 (0.72; 1 59)	---
	15 mg	2.22 (1.67; 2 87)	1.85 (1 59,2.09)
	30 mg	1.20 (0 81; 1.72)	1.26 (1 05,1.47)
	37.5 mg	---	1.08 (0 9, 1.29)
	45 mg	---	1 02 (0.8,1.23)

Event rate (% patients/year)		Hemorrhagic Stroke	
		Observed	Predicted
Overall	Warfarin	0.48 (0 38,0.6)	---
	30/15 mg	0.11 (0.07,0.18)	0.13 (0 09,0.19)
	60/30 mg	0 25 (0.18,0.34)	0.23 (0.17,0.29)
	75 mg	---	0.27 (0 2, 0.37)
	90 mg	---	0.29 (0 21,0.48)
Normal	Warfarin	0.2 (0.11,0 35)	---
	30 mg	0.11 (0.04,0.22)	0.1 (0.06,0.14)
	60 mg	0.17 (0.09,0.31)	0.15 (0.11,0 2)
	75 mg	---	0.17 (0.13, 0.25)
	90 mg	---	0.21 (0.13,0.31)
Mild	Warfarin	0.65 (0.47,0.86)	---
	30 mg	0.15 (0.08,0.27)	0.16 (0.11,0.21)
	60 mg	0.25 (0.14,0.4)	0.25 (0.19,0.32)
	75 mg	---	0.3 (0.2, 0.46)
	90 mg	---	0.35 (0 24,0.48)
Moderate	Warfarin	0.72 (0.43,1.13)	---
	15 mg	0 (0,0.15)	0.17 (0.11,0.25)
	30 mg	0.43 (0.21,0.77)	0.3 (0 2,0.41)
	37.5 mg	---	0 34 (0.21, 0.45)
	45 mg	---	0.38 (0 24,0.54)

Source: FDA Reviewer's Analysis

2.4.1.2 Time-to-Event Exposure-Response Analysis of Safety Endpoints:

The exposure-response safety analyses based on the Cox proportional hazards models are represented below similarly to that for the stroke endpoints. (Figure 24, Table 27, Table 28, and Table 29).

The key points of the safety analysis are:

1.) Edoxaban exposure correlates with all endpoints evaluated.

2.) For clotting related events such as MACE events, the probability of the event decreases with increasing edoxaban exposure.

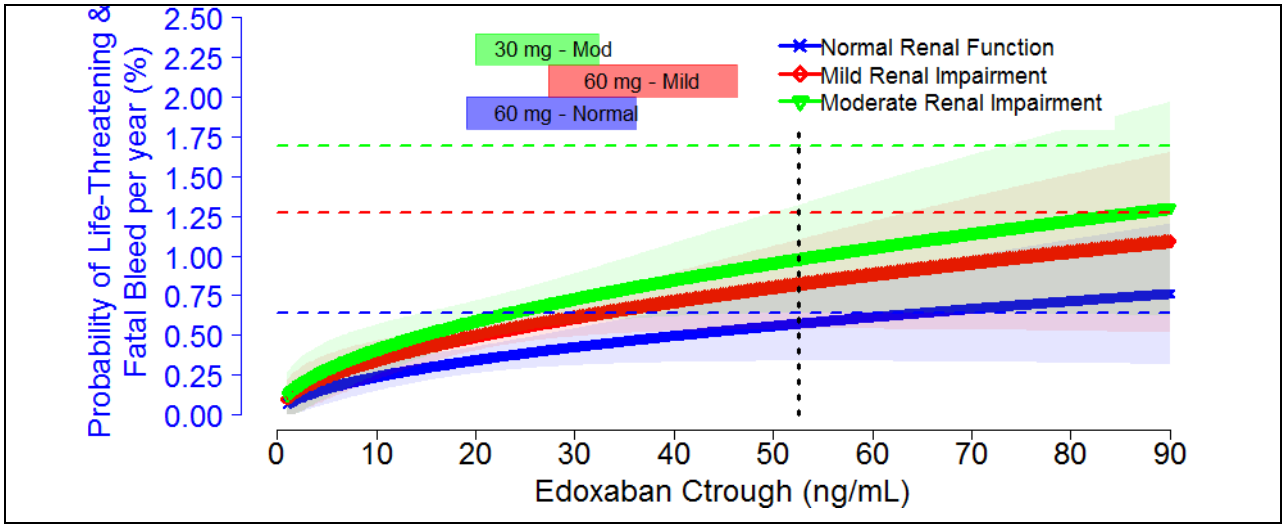
3.) For bleeding related events the probability of the event increases with increasing concentration.

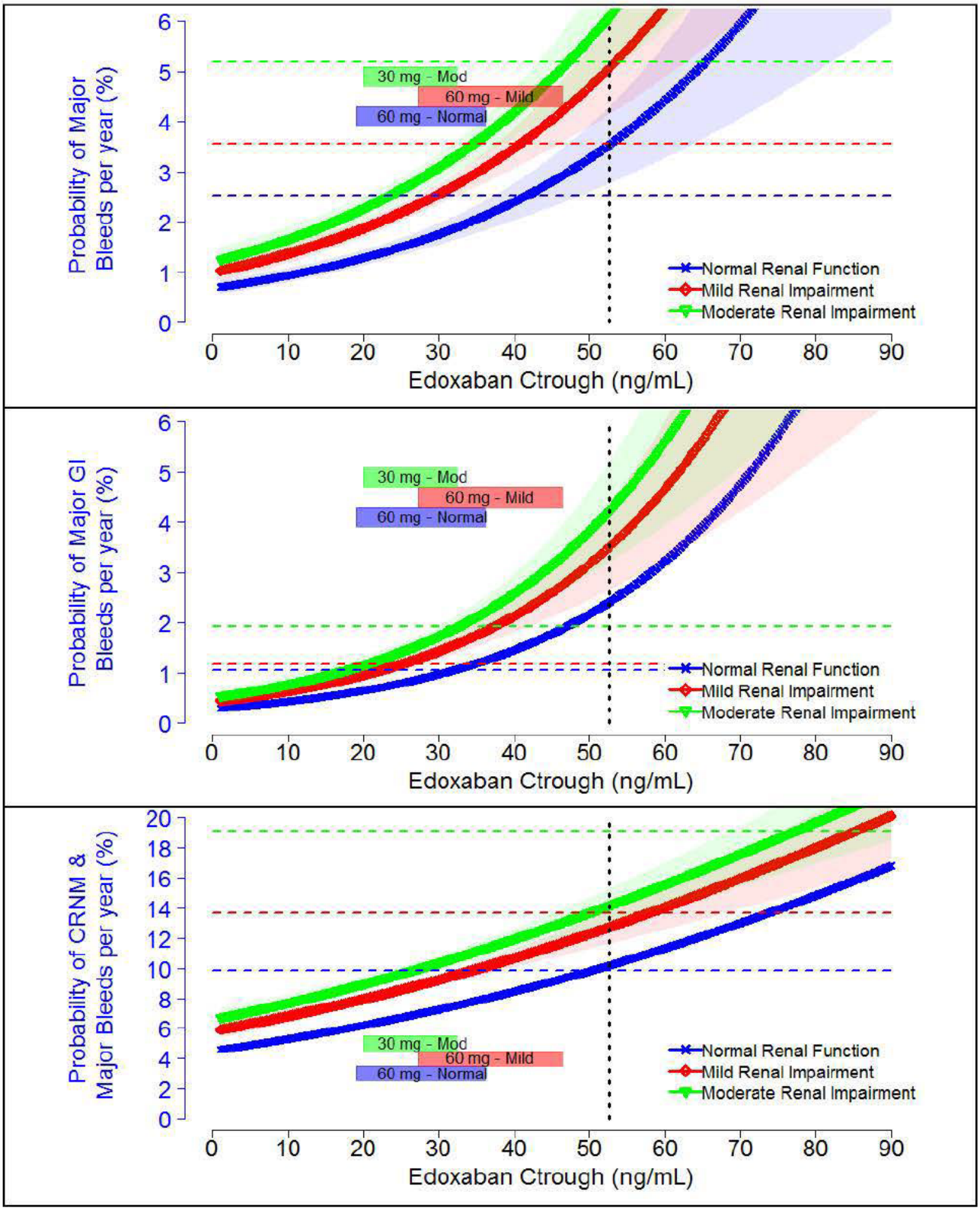
4.) In most bleeding events, it appears that a dose increase to 45 mg in patients with moderate renal impairment or normal renal function will not produce bleeding rates higher than warfarin. Whereas, for major GI bleeds, this is the only event that is expected to have a higher rate of events than warfarin.

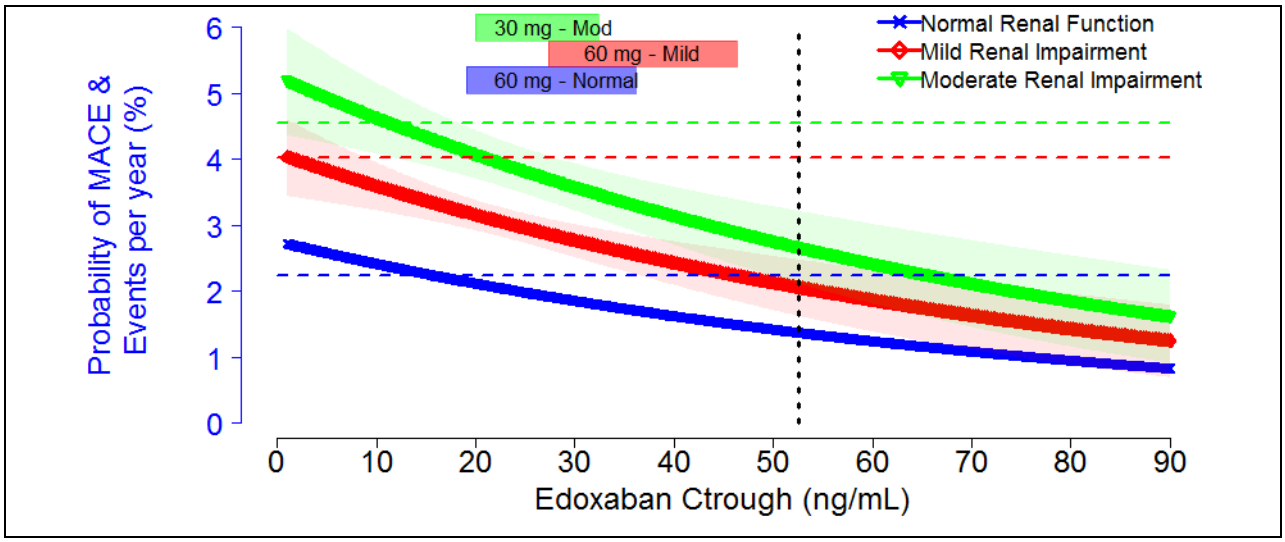
5.) It is apparent that there is a greater margin to increase the dose for those with moderate renal impairment compared to those with normal renal function when comparing the projected rate of events against the observed warfarin rate.

6.) The model predictions by dose and degree of renal impairment appear to capture the central tendency of the observed data.

Figure 24. Exposure-response relationships for safety endpoints for varying degrees of renal impairment and their corresponding observed rate for warfarin (horizontal dashed lines) and their corresponding observed edoxaban exposure range as the 5th to 95th percentiles (solid-filled rectangles). The black vertical dashed line indicates the 99th percentile of all edoxaban C_{trough} exposures.




Probability of Major Bleeds per year (%)
30 mg - Mod
60 mg - Mild
60 mg - Normal
Normal Renal Function
Mild Renal Impairment
Moderate Renal Impairment
Edoxaban Ctrough (ng/mL)
Probability of Major GI Bleeds per year (%)
30 mg - Mod
60 mg - Mild
60 mg - Normal
Normal Renal Function
Mild Renal Impairment
Moderate Renal Impairment
Edoxaban Ctrough (ng/mL)
Probability of CRNM & Major Bleeds per year (%)
30 mg - Mod
60 mg - Mild
60 mg - Normal
Normal Renal Function
Mild Renal Impairment
Moderate Renal Impairment
Edoxaban Ctrough (ng/mL)



Source: FDA Reviewer's Analysis

Event rates per year for the safety endpoints are shown in Table 27 through Table 29.

Table 27. Observed and predicted life-threatening and fatal bleeds (left) and major bleeds (right) event rates per year by dose and degree of renal impairment.

Event rate (% patients/year)		Life-threatening & Fatal bleed	
		Observed	Predicted
Overall	Warfarin	1.09 (0 94; 1.27)	---
	30/15 mg	0.34 (0 26; 0.45)	0.39 (0.3,0.47)
	60/30 mg	0.58 (0.47; 0.71)	0 55 (0.46,0.67)
	75 mg	---	0.6 (0.51, 0.79)
	90 mg	---	0.69 (0.53,0.95)
Normal	Warfarin	0.64 (0.46; 0.87)	---
	30 mg	0.25 (0.14; 0.40)	0 29 (0.21,0.35)
	60 mg	0.44 (0 29; 0.63)	0.41 (0.34,0.51)
	75 mg	---	0.47 (0.37, 0.6)
	90 mg	---	0.5 (0 36,0.67)
Mild	Warfarin	1.27 (1.02; 1.56)	---
	30 mg	0.43 (0 29; 0.61)	0.43 (0.36,0.52)
	60 mg	0.63 (0.45; 0.84)	0.62 (0.5,0.73)
	75 mg	---	0.71 (0.54, 0.9)
	90 mg	---	0.77 (0.54,1.04)
Moderate	Warfarin	1.69 (1 22; 2.26)	---
	15 mg	0.35 (0.16; 0.66)	0.48 (0.34,0.6)
	30 mg	0.77 (0.47; 1.19)	0.7 (0 58,0.87)
	37.5 mg	---	0.76 (0.62, 1.04)
	45 mg	---	0.85 (0.65,1.03)

Event rate (% patients/year)		Major Bleed	
		Observed	Predicted
Overall	Warfarin	3.43 (3.14; 3.73)	---
	30/15 mg	1.61 (1.42; 1.82)	1.65 (1.5,1.86)
	60/30 mg	2.75 (2.49; 3.02)	2.83 (2.59,3.08)
	75 mg	---	3.67 (3.12, 4.09)
	90 mg	---	4.83 (4.03,5.69)
Normal	Warfarin	2 52 (2.14; 2.95)	---
	30 mg	1.10 (0.86; 1.39)	1.2 (1.1,1 35)
	60 mg	1.77 (1.46; 2.13)	1.93 (1.78,2.1)
	75 mg	---	2.41 (2.11, 2.76)
	90 mg	---	3 (2 59,3.54)
Mild	Warfarin	3 56 (3.13; 4.04)	---
	30 mg	1 94 (1.63; 2.29)	1.89 (1.68,2.04)
	60 mg	3.19 (2.77; 3.64)	3.35 (2.92,3.64)
	75 mg	---	4.39 (3.86, 5.13)
	90 mg	---	6.03 (4.99,7.07)
Moderate	Warfarin	5 20 (4.35; 6.16)	---
	15 mg	2.02 (1.50; 2.66)	2.06 (1.85,2.34)
	30 mg	3 93 (3.20; 4.78)	3.46 (2.96,3.72)
	37.5 mg	---	4.43 (3.95, 5)
	45 mg	---	5.73 (4.84,6.59)

Source: FDA Reviewer's Analysis

Table 28. Observed and predicted major GI bleed (left) and clinically relevant non-major & major bleeds (right) event rates per year by dose and degree of renal impairment.

Event rate (% patients/year)		Major GI bleed	
		Observed	Predicted
Overall	Warfarin	1.20 (1.03; 1.38)	---
	30/15 mg	0.80 (0.66; 0.94)	0.78 (0.68,0.88)
	60/30 mg	1.47 (1 29; 1.68)	1 53 (1.35,1.72)
	75 mg	---	2.21 (1.83, 2.64)
	90 mg	---	3.19 (2.47,3.75)
Normal	Warfarin	1.04 (0.81; 1.32)	---
	30 mg	0.48 (0 33; 0.68)	0 54 (0.45,0.65)
	60 mg	0.88 (0.67; 1.14)	0 99 (0.89,1.18)
	75 mg	---	1.38 (1.17, 1.61)
	90 mg	---	1.85 (1.48,2.21)
Mild	Warfarin	1.16 (0 92; 1.44)	---
	30 mg	0.98 (0.76; 1.23)	0.9 (0.78,1.03)
	60 mg	1.85 (1 54; 2.20)	1.9 (1.64,2.15)
	75 mg	---	2.76 (2.24, 3.35)
	90 mg	---	4 (3.11,5.51)
Moderate	Warfarin	1.92 (1.42; 2.53)	---
	15 mg	1.09 (0.73; 1.57)	0.94 (0.8,1.1)
	30 mg	1.62 (1.16; 2.19)	1.86 (1.67,2.13)
	37.5 mg	---	2.61 (2.24, 3.06)
	45 mg	---	3.63 (2.85,4.83)

Event rate (% patients/year)		CRNM + Major Bleed	
		Observed	Predicted
Overall	Warfarin	12.95 (12.39,13.52)	---
	30/15 mg	7.98 (7.55,8.43)	8.02 (7.74,8.34)
	60/30 mg	11.09 (10.57,11.62)	10.62 (10.15,11.06)
	75 mg	---	12.04 (11.25, 13.05)
	90 mg	---	13.77 (12.71,15.26)
Normal	Warfarin	9.85 (9.09,10.66)	---
	30 mg	5.98 (5.39,6.61)	6.43 (5.97,6.89)
	60 mg	8.65 (7.94,9.41)	8.23 (7.63,8.72)
	75 mg	---	9.25 (8.51, 9.87)
	90 mg	---	10.25 (9.47,11.29)
Mild	Warfarin	13.7 (12.84,14.6)	---
	30 mg	9.15 (8.46,9.87)	8.73 (8.31,9.23)
	60 mg	12.41 (11.58,13.27)	11.86 (11.27,12.37)
	75 mg	---	13.81 (12.73, 14.95)
	90 mg	---	15.94 (14.35,17.69)
Moderate	Warfarin	19.07 (17.41,20.81)	---
	15 mg	9.85 (8.66,11.13)	9.53 (8.81,10.28)
	30 mg	13.68 (12.29,15.17)	12.43 (11.76,13.19)
	37.5 mg	---	14 27 (13.27, 15.04)
	45 mg	---	16.22 (14.66,17.81)

Source: FDA Reviewer's Analysis

Table 29. Observed and predicted MACE event rates per year by dose and degree of renal impairment.

Event rate (% patients/year)		MACE Events	
		Observed	Predicted
Overall	Warfarin	3.41 (3.13,3.7)	---
	30/15 mg	3.49 (3.21,3.78)	3.6 (3.24,3.81)
	60/30 mg	2.9 (2.65,3.18)	2.9 (2.69,3.1)
	75 mg	---	2.64 (2.33, 2.91)
	90 mg	---	2.4 (2.02,2.81)
Normal	Warfarin	2 23 (1.88,2.62)	---
	30 mg	2 55 (2.18,2.97)	2.72 (2.44,2.98)
	60 mg	2 52 (2.15,2.93)	2.23 (2.03,2.49)
	75 mg	---	2.04 (1.79, 2.37)
	90 mg	---	1.87 (1.63,2.17)
Mild	Warfarin	4.03 (3.58,4.53)	---
	30 mg	3.64 (3.21,4.1)	3.82 (3.51,4.13)
	60 mg	2.74 (2.36,3.16)	3.06 (2.73,3.31)
	75 mg	---	2.75 (2.37, 3.15)
	90 mg	---	2.39 (2.04,2.92)
Moderate	Warfarin	4 55 (3.77,5.45)	---
	15 mg	5.4 (4.55,6.36)	4.79 (4.34,5.35)
	30 mg	4 21 (3.47,5.07)	3.95 (3.69,4.32)
	37.5 mg	---	3.58 (3.25, 3.9)
	45 mg	---	3.26 (2.8,3.78)

Source: FDA Reviewer's Analysis

2.4.1.3 Net-benefit for the proposed edoxaban doses

In an effort to evaluate the net-benefit of edoxaban at different doses in patients with normal renal function and moderate renal impairment, the following tables were generated. These tables present net benefit as the numbers of events per 10000 patients per year. Table 30 puts the Applicant's primary efficacy endpoint side-by-side with their primary safety endpoint. Positive numbers indicate that warfarin has fewer events than edoxaban. Other endpoints are shown in Table 31 through Table 33.

Table 30. Difference in Events per 10000 patients/year: Stroke/SEE and Major Bleed

Renal Function	Comparison	Stroke/SEE	Major Bleed
	60 mg Observed vs Warf Observed	30	-75
Normal (>80 mL/min)	60 mg Predicted Vs Warf Observed	18	-59
	75 mg Predicted Vs Warf Observed	11	-11
	90 mg Predicted Vs Warf Observed	4	48
	30 mg Observed Vs Warf Observed	-22	-127
Moderate (30 - 50 mL/min)	30 mg Predicted Vs Warf Observed	-34	-174
	37.5 mg Predicted Vs Warf Observed	-47	-77
	45 mg Predicted Vs Warf Observed	-56	53

Source: FDA Reviewer's Analysis

Table 31. Difference in Events per 10000 patients/year: Ischemic Stroke and Life-Threatening/Fatal Bleeds

Renal Function	Comparison	Ischemic Stroke	LT / Fatal Bleed
	60 mg Observed vs Warf Observed	31	-20
Normal (>80 mL/min)	60 mg Predicted Vs Warf Observed	22	-23
	75 mg Predicted Vs Warf Observed	14	-17
	90 mg Predicted Vs Warf Observed	8	-14
	30 mg Observed Vs Warf Observed	10	-92
Moderate (30 - 50 mL/min)	30 mg Predicted Vs Warf Observed	16	-99
	37.5 mg Predicted Vs Warf Observed	-2	-93
	45 mg Predicted Vs Warf Observed	-8	-84

Source: FDA Reviewer's Analysis

Table 32. Difference in Events per 10000 patients/year – Hemorrhagic Stroke and Major GI Bleeds

Renal Function	Comparison	Hemorrhagic Stroke	Major GI Bleed
	60 mg Observed vs Warf Observed	-3	-16
Normal (>80 mL/min)	60 mg Predicted Vs Warf Observed	-5	-5
	75 mg Predicted Vs Warf Observed	-3	34
	90 mg Predicted Vs Warf Observed	1	81
	30 mg Observed Vs Warf Observed	-29	-30
Moderate (30 - 50 mL/min)	30 mg Predicted Vs Warf Observed	-42	-6
	37.5 mg Predicted Vs Warf Observed	-38	69
	45 mg Predicted Vs Warf Observed	-34	171

Source: FDA Reviewer's Analysis

Table 33. Difference in Events per 10000 patients/year – Clinically-Relevant, Non-Major Bleeds & Major Bleeds and MACE Events

Renal Function	Comparison	CRNM + Major Bleed	MACE Events
	60 mg Observed vs Warf Observed	-120	29
Normal (>80 mL/min)	60 mg Predicted Vs Warf Observed	-162	0
	75 mg Predicted Vs Warf Observed	-60	-19
	90 mg Predicted Vs Warf Observed	40	-38
	30 mg Observed Vs Warf Observed	-539	-34
Moderate (30 - 50 mL/min)	30 mg Predicted Vs Warf Observed	-664	-60
	37.5 mg Predicted Vs Warf Observed	-480	-97
	45 mg Predicted Vs Warf Observed	-285	-129

Source: FDA Reviewer's Analysis

3 RESULTS OF APPLICANT'S ANALYSIS

3.1.1 Population PK:

3.1.1.1 Data

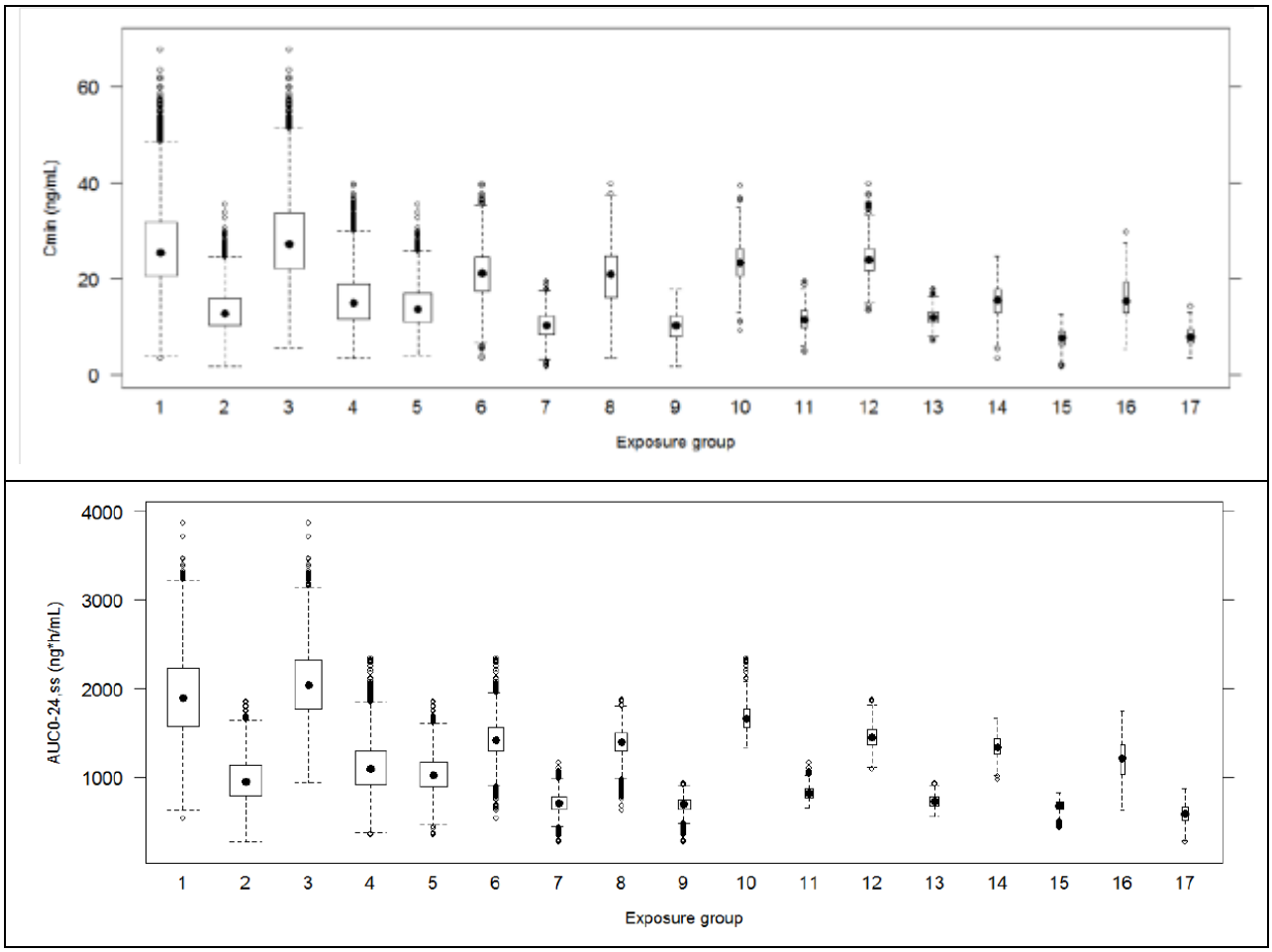
This PopPK analysis was performed using a dataset including relevant data from both Phase 1 (PRT016, AU120, AU127, AU128, AU129, AU130, AU131, AE132, AE133, AU136, AU137, AU138, AU141) (see: Table 9.1) and Phase 3 (ENGAGE-AF) studies. The Phase 1 studies were selected to inform and stabilize the structural PK model. Only the parent compound was included in the PopPK analysis.

The following effects, patients, or study conditions were not investigated: drug administration routes other than oral, drug formulations other than tablet, influence of food intake relative to drug intake, patients on dialysis, and concomitant administration of drugs other than verapamil, quinidine and dronedarone. PK data from Phase 1 studies with intravenous administration were limited, as Phase 1 data were selected to support and inform a structural model for the ENGAGE study where only oral data is available.

3.1.1.2 Edoxaban Exposure Metrics by Dose Group:

Figure 25. Boxplots of individual predicted Cmin (top panel) and AUC (bottom panel) in various exposure groups.

1. high exposure treatment group
2. low exposure treatment group
3. non-dose adjusted 60 mg QD
4. combined non-dose adjusted and dose-adjusted 30 mg QD
5. non-dose adjusted 30 mg QD
6. dose-adjusted 30 mg QD
7. dose-adjusted 15 mg QD
8. all single adjusted high exposure treatment group
9. all single adjusted low exposure treatment group
10. adjusted for multiple factors high exposure treatment group
11. adjusted for multiple factors low exposure treatment group
12. Only CLcr adjusted high exposure treatment group
13. Only CLcr adjusted low exposure treatment group
14. Only WT adjusted high exposure treatment group
15. Only WT adjusted low exposure treatment group
16. Only P-gp adjusted high exposure treatment group
17. Only P-gp adjusted low exposure treatment group



(Source: Applicant's Population PK Report, TMP009, Figure 10.65 & Figure 10.66)

Table 34. Individual predicted C_{min} for observation in the analysis dataset.

Exposure Group	Mean	Median	25th Percentile	75th Percentile	Min	Max	Observation
Based on all observations in Analysis Dataset							
All observations	19.84	18.01	12.43	25.35	1.810	67.58	26676
Observations in high exposure treatment group (60 mg QD non-adjusted and 60 mg QD adjusted to 30 mg)	26.50	25.34	20.58	31.73	3.508	67.58	13232
Observations in low exposure treatment group (30 mg QD non-adjusted and 30 mg QD adjusted to 15 mg)	13.29	12.70	10.28	15.98	1.810	35.39	13444
Observations with non-dose-adjusted 60 mg QD	28.13	27.26	21.99	33.68	5.672	67.58	10272
Observations with both non-dose-adjusted and dose-adjusted 30 mg QD	15.63	14.91	11.64	18.95	3.508	39.81	13432
Observations with non-dose-adjusted 30 mg QD	14.16	13.73	11.07	16.95	3.982	35.39	10472
Observations with dose-adjusted 30 mg QD	20.82	21.04	17.39	24.53	3.508	39.81	2960
Observations with dose-adjusted 15 mg QD	10.23	10.34	8.446	12.08	1.810	19.34	2972
Observations with single reason for adjustment in high exposure treatment group	20.45	20.95	16.15	24.60	3.508	39.81	1885
Observations with single reason for adjustment in low exposure treatment group	10.04	10.35	7.964	12.13	10.810	17.92	1891
Observations with multiple reasons for adjustment in high exposure treatment group	23.52	23.25	20.56	26.33	9.148	39.36	640
Observations with multiple reasons for adjustment in low exposure treatment group	11.63	11.48	10.02	13.24	4.798	19.34	646
Observations with dose-adjustment due to CLcr ≤ 50 only in high exposure treatment group	24.09	23.89	21.65	26.29	13.22	39.81	1072
Observations with dose-adjustment due to CLcr ≤ 50 only in low exposure treatment group	12.03	11.94	10.90	13.07	6.940	17.92	1010
Observations with dose-adjustment due to WT ≤ 60 only in high exposure treatment group	15.23	15.48	12.86	17.72	3.508	24.59	478
Observations with dose-adjustment due to WT≤ 60 only in low exposure treatment group	7.599	7.707	6.236	8.913	1.810	12.81	530
Observations with dose-adjustment due to concomitant P-gp inhibitor only in high exposure treatment group	16.24	15.40	12.93	19.27	5.476	29.76	335
Observations with dose-adjustment due to concomitant P-gp inhibitor only in low exposure treatment group	7.977	7.908	6.501	9.464	3.466	14.25	351
Observations with dose-adjustment due to CLcr + WT in high exposure treatment group	23.20	23.02	20.46	25.71	9.148	39.36	555
Observations with dose-adjustment due to CLcr + WT in low exposure treatment group	11.48	11.35	10.01	12.88	4.798	18.62	532
Observations with dose-adjustment due to CLcr + P-gp inhibitor in high exposure treatment group	27.60	27.12	25.37	28.92	22.89	36.64	38
Observations with dose-adjustment due to CLcr + P-gp inhibitor in low exposure treatment group	14.05	13.95	12.22	15.66	8.143	19.34	54
Observations with dose-adjustment due to WT + P-gp inhibitor in high exposure treatment group	18.86	18.28	17.38	20.46	14.94	24.59	14
Observations with dose-adjustment due to WT + P-gp inhibitor in low exposure treatment group	9.088	9.505	7.923	10.53	5.083	11.48	36
Observations with dose-adjustment due to CLcr + WT + P-gp inhibitor in high exposure treatment group	26.25	27.80	21.40	31.54	11.25	36.71	33
Observations with dose-adjustment due to CLcr + WT + P-gp inhibitor in low exposure treatment group	9.088	9.505	7.923	10.53	5.083	11.48	36
Observations with dose-adjustment due to no obvious reasons in high exposure treatment group	18.46	18.87	16.82	20.74	3.917	26.90	435
Observations with dose-adjustment due to no obvious reasons in high exposure treatment group	8.973	9.220	8.102	10.17	2.748	13.11	435
Observations with CLcr≤30 in high exposure treatment group	32.39	33.52	28.71	34.74	25.90	39.81	14

Observations with CLcr≤30 in low exposure treatment group	18.71	15.88	15.55	16.75	14.82	33.79	12
Observations with CLcr>30 in high exposure treatment group	26.49	25.32	20.57	31.69	3.508	67.58	13218
Observations with CLcr>30 in low exposure treatment group	13.28	12.70	10.27	15.98	1.810	35.39	13432
Observations with CLcr≤50 in high exposure treatment group	27.82	24.91	21.98	29.75	9.148	67.58	2107
Observations with CLcr≤50 in low exposure treatment group	14.15	12.48	11.01	15.29	4.798	35.39	2058
Observations with CLcr>50 in high exposure treatment group	26.24	25.45	20.21	31.95	3.508	61.85	11125
Observations with CLcr>50 in low exposure treatment group	13.13	12.77	10.10	16.03	1.810	26.87	11386
Based on baseline observation in Analysis Dataset[3]							
Observations(Patients) with no dose-adjustment at baseline in high exposure treatment group	27.69	26.94	21.48	33.11	5.672	67.58	4035
Observations(Patients) with no dose-adjustment at baseline in low exposure treatment group	13.96	13.53	10.85	16.78	4.118	35.39	4101
Observations(Patients) with dose-adjustment at baseline in high exposure treatment group	20.53	20.76	16.81	24.41	5.325	37.74	1149
Observations(Patients) with dose-adjustment at baseline in low exposure treatment group	10.11	10.18	8.246	12.01	2.094	19.34	1147

[1)] Summary is based on PK exposure measures that were created for each dosing occasion with a PK observation in the DBL Analysis Dataset.
[2)] Reasons are based on the information in the DBL Analysis Dataset with respect to CLcr, WT and concomitant P-gp inhibitor.
[3)] Baseline refers to the first PK observation the DBL Analysis Dataset.
CLcr = creatinine clearance, WT = body weight

[1] Summary is based on PK exposure measures that were created for each dosing occasion with a PK observation in the DBL Analysis Dataset.
[2] Reasons are based on the information in the DBL Analysis Dataset with respect to CLcr, WT and concomitant P-gp inhibitor.
[3] Baseline refers to the first PK observation the DBL Analysis Dataset.
CLcr = creatinine clearance, WT = body weight

(Source: Applicant's Population PK Report, TMP008, Table 9.15)

Reviewer's Comments:

The Applicant's population PK model appears reasonable for calculating the C_{trough} and AUC of edoxaban for each individual. Based on the manner of the data collection, it does not appear reasonable to use this model to estimate C_{max} for each individual; Therefore C_{max} was not used in the reviewer's exposure-response analysis.

The degree of shrinkage in the Applicant's original analysis on CL (63%) is sufficient to cause concern for using this model for simulating data in an unstudied population based solely on patient demographic variables. Thus, whenever possible, post-hoc Bayesian estimates for each individual should be used in the exposure-response analyses.

3.1.2 Time-to-event Exposure Response Analyses:

This was a Phase 3, randomized, double-blind, double-dummy, parallel group, multicenter, multi-national study for evaluation of efficacy and safety of edoxaban versus warfarin in subjects with AF. The primary objective was to compare edoxaban to warfarin with regard to the composite primary endpoint of stroke/SEE.

Eligible subjects were stratified by CHADS2 risk score at randomization in two strata:

1: CHADS2 risk score 2 and 3

2: CHADS2 risk score 4, 5, and 6.

Within each CHADS2 stratum, subjects were further stratified with respect to factors requiring edoxaban dosage adjustment (CLcr ≤50 mL/min, WT ≤60 kg, concomitant verapamil, quinidine) Subjects were randomized to one of three treatment groups:

- Warfarin (once daily with dose adjusted to maintain INR between 2.0 and 3.0, inclusive);
- Edoxaban High Exposure (60 mg QD with dosage adjustment to 30 mg QD for moderate renal impairment (CLcr ≥ 30 and ≤ 50 mL/min), low WT (≤ 60 kg), and/or specified concomitant medications (verapamil, quinidine);
- Edoxaban Low Exposure (30 mg QD with dosage adjustment to 15 mg QD for moderate renal impairment (CLcr ≥ 30 and ≤ 50 mL/min), WT (≤ 60 kg), and/or specified concomitant medications (verapamil, quinidine).

After randomization was complete, concomitant dronedarone was added to the list of P-gp inhibitors for which the edoxaban dose was reduced. A subject with multiple factors requiring edoxaban dosage adjustment received the halved edoxaban dosage regimen, same as a subject with only one factor requiring edoxaban dosage adjustment.

Up to five blood samples were collected for PK per subject: pre-dose and between 1h and 3h post-dose on Day 29, any time at Month 3 visit; any time at Month 12 visit; and if a subject experienced a clinical event of either stroke/SEE/MACE. Only edoxaban-treated subjects' blood samples were analyzed. For each subject given edoxaban, the two samples on Day 29 and either the Month 3 or the Month 12 sample, were utilized for bioanalytical analysis. In addition, if a subject in one of the edoxaban arms experienced a clinical endpoint of either stroke/SEE/MACE or major bleeding, then all plasma samples from that subject were analyzed. All samples were analyzed for patients that progressed to severe renal impairment during the study. Edoxaban plasma concentrations from edoxaban treatments were included in the PopPK analysis.

3.1.2.1 Data

In the ER analysis, all evaluable patients in study DU176B-C-301 taking at least one dose of edoxaban were included (mITT population). Patients taking at least one dose of warfarin were used for the risk factor analysis.

Only time to first event was considered. The time to first event was defined as the time from the first dose of study drug to the first event experienced by a subject for both efficacy and safety endpoints, e.g. first time of a major bleeding. Only data up until first study drug interruption plus 3 days was included. Study drug interruption of ≤3 days were allowed as this was according to the protocol not considered to be study drug interruption but rather missed doses. For subjects who did not experience an event, the time to first event was censored at the time of permanently discontinuing drug plus 3 days, first drug interruption plus 3 days or on the last day the subject had a complete assessment for study outcomes (or death, if a subject died), whichever came first. If none of these rules were applicable, the individual was excluded.

- The risk factor dataset was comprised of all patients who had received at least one dose of warfarin or edoxaban, with the exception of the three patients described Section 4.2.1. The dataset contained 21026 patients, of which only the 7012 warfarin treated patients were used.
- The dataset used for the ER analysis was comprised of all patients who have received at least one edoxaban dose. The dataset contained 14014 patients.

In total, 14014 edoxaban patients were included in the ER analysis of all four endpoints. In the ER datasets provided (b) (4) 745 patients did not have any PK observations (i.e. not included in the PopPK dataset).

3.1.2.2 Exposure Metrics

The full population PK model included covariate relationships of covariates that were used for dose-adjustments, i.e. WT, CLcr and concomitant P-gp inhibitors and therefore the obtained full PopPK model was used to predict the individual Cav , AUC0-24,ss, C_{min} and C_{max}.

- In patients with observed plasma concentrations on at least one occasion (i.e. those included in the PopPK dataset), PK exposure indices were predicted for each individual at each occasion where a plasma concentration was measured or a change in dose occurred. These predictions were based on the empirical Bayes estimates (EBE) of PK parameters derived from the full PopPK model. The predicted inter-occasion variability was included in the prediction of PK exposure indices.
- For patients in the PopPK dataset that only had observed concentrations below limit of quantification (LLOQ) in the dataset, all PK exposure indices were set to 0. Further, for patients with samples reported to be compromised (i.e. sample handling errors that occurred prior to bioanalysis) and no other observed concentrations above the LLOQ, the typical PK exposure indices were derived from the full PopPK model, while taking into account the individual covariate values (WT, CLcr and concomitant medication of verapamil, quinidine and dronedarone) and dosing histories.
- For patients in the ER dataset not having any observed plasma concentrations (i.e. not being included in the PopPK dataset), the typical PK exposure indices were predicted. These predictions were based on the full PopPK model, the protocol study design, the patient's dosing information at randomization and the WT, CLcr and concomitant medication of verapamil, quinidine and dronedarone at randomization.

3.1.2.3 Risk Factors Evaluated

Table 36. Risk Factors Included in the Exposure-Response Analysis

		Endpoints	
Risk Factor	**Abbreviation**	**Safety**	**Efficacy**
Age (as continuous value)	AGE	X	X
Age ≥75	AGE75	X	X
Female sex	SEX	X	X
Body weight	WT	X	X
Congestive heart failure	CHF	X	X
Hypertension requiring medication	HYP	X	X
Diabetes mellitus	DIAB	X	X
Prior stroke or TIA	TIA	X	X
Composites of $CHADS_2$ scores ($CHADS_2$ 2-3 versus 4-6)	CHAD	X	X
Anemia	ANE	X	
History of any bleeding	HBLE	X	
Serum creatinine ≥1.5 mg/dL	CREA	X	
History of cancer	CANC	X	
Prior stroke	STR	X	
VKA-naïve vs. VKA-experienced	VKA	X	X
Concomitant use of aspirin or anti-platelet agent	ASA	X	
Concomitant use of NSAID	NSA	X	X
Ethnicity	ETHN	X	X
Race	RACE	X	X
Diuretics	DIUR		X
Dyslipidemia	DYS		X
Concomitant use lipid lowering therapy	LLT		X

(Source: Applicant's Exposure-Response Report TMP 009, Table 4.1)

3.1.2.4 Exposure-Response for Efficacy:

Four endpoints were analyzed using a time-to-event approach: all stroke/SEE, ischemic stroke, hemorrhagic stroke, and major bleeds. Only time to first event, if occurring after first dose, was considered. Time (days) to first event (major bleeding, stroke or SEE, ischemic stroke or SEE and hemorrhagic stroke) or censoring time since first dose was included in the analysis. Censoring time was set to date of common study end visit, subject's last assessment (or death, if a subject died), 3 days after first study interruption or 3 days after final dose, whichever came first. Event time was set to difference between event day and day of first dose +1.

Initially an exponential as well as a Weibull distribution was applied to the data without risk factors. The assumption of distribution was re-evaluated, using graphical evaluation, for the final model including risk factor and ER relationships.

Final model estimates for each endpoint and exposure response relationships are shown in the following tables and figures.

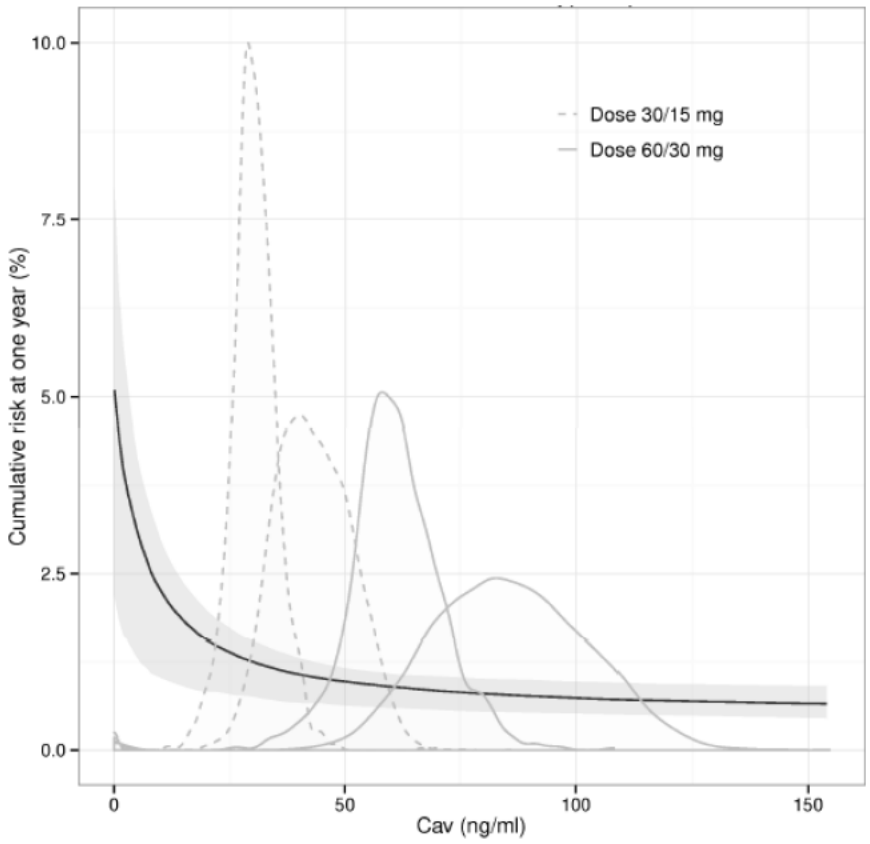
Table 37. Parameter Estimates of the Final Stroke or SEE Exposure-Response Model Using Edoxaban Patients

Parameter	Estimate[a]	90% Ci[b]	Hazard Ratio
λ [day^{-1}]	$9.978 \cdot 10^{-5}$	[$3.437 \cdot 10^{-5}$ - 0.0001652]	-
γ	0.8885	[0.8163 - 0.9607]	-
β_{AGE} [year^{-1}]	0.01749	[0.007285 - 0.02771]	1.02
β_{TIA}	0.9185	[0.7342 - 1.103]	2.51
$\beta_{E_{max}}$	-2.268	[-2.915 - -1.621]	-
$\beta_{EC_{50}}$ [ng/mL]	20.4	[2.999 - 37.80]	-

a: The estimates of the risk factors are parameterised as log hazard ratio
b: C.I. confidence interval obtained from the Fisher information matrix
λ Scale factor of the Weibull distribution; γ Shape factor of the Weibull distribution; *AGE* age at baseline in years; *TIA* history of ischemic/embolic stroke and/or TIA

(Source: Applicant's Exposure-Response Report TMP 009, Table 6.9)

Figure 26. Probability of a stroke or SEE within 1 year in an edoxaban patient versus $C_{average}$ exposure of edoxaban.



(Source: Applicant's Exposure-Response Report TMP 009, Figure 6.16)

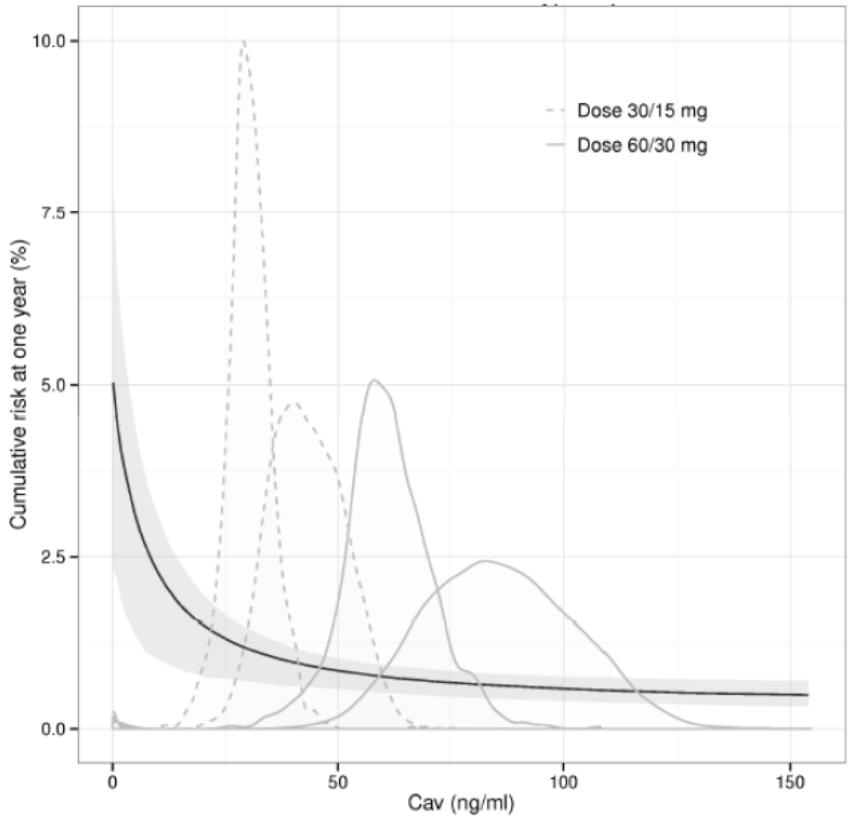
Table 38. Parameter Estimates of the Final Ischemic Stroke or SEE Exposure-Response Model Using Edoxaban Patients

Parameter	Estimate[a]	90% Ci[b]	Hazard Ratio
λ [day^{-1}]	$9.177 \cdot 10^{-5}$	[$3.028 \cdot 10^{-5}$-$1.533 \cdot 10^{-4}$]	-
γ	0.8625	[0.7867 - 0.9373]	-
β_{AGE} [year^{-1}]	0.01740	[0.006494 - 0.02831]	1.02
β_{TIA}	0.9567	[0.7596 - 1.154]	2.60
$\beta_{E_{max}}$	-2.752	[-3.457 - -2.043]	-
$\beta_{EC_{50}}$ [ng/mL]	27.72	[6.481 - 48.92]	-

a: The estimates of the risk factors are parameterised as log hazard ratio
b: CI confidence interval obtained by the observed Fisher information matrix
λ Scale factor of the Weibull distribution; γ Shape factor of the Weibull distribution; *AGE* Age at baseline; *TIA* History of ischemic/embolic Stroke and/or TIA

(Source: Applicant's Exposure-Response Report TMP 009, Table 6.11)

Figure 27. Probability of an Ischemic stroke of SEE within 1 year in an edoxaban patient versus $C_{average}$ exposure of edoxaban.



(Source: Applicant's Exposure-Response Report TMP 009, Figure 6.24)

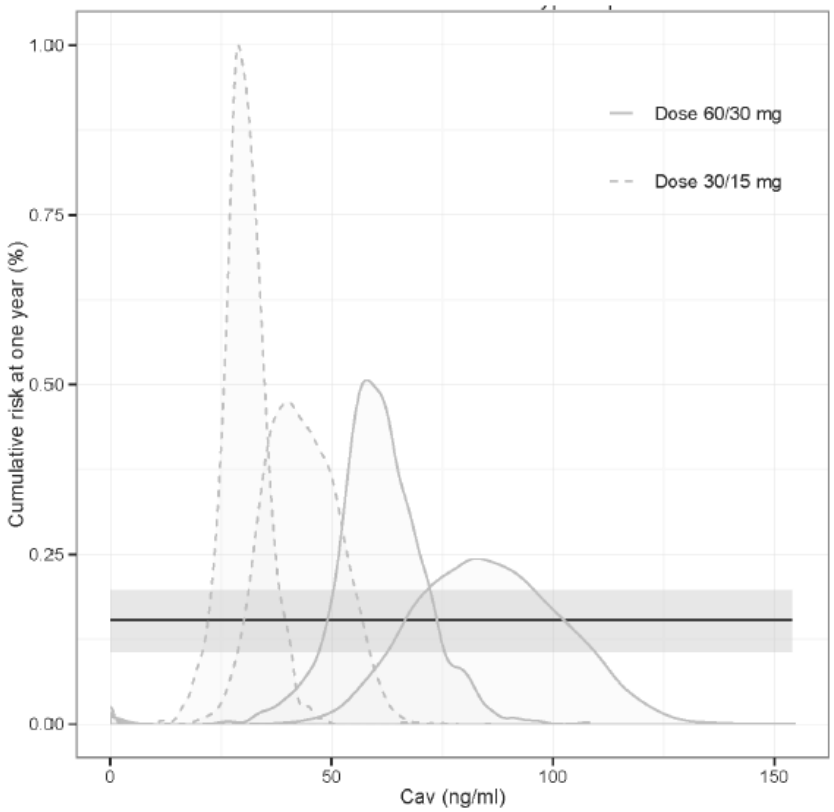
Table 39. Parameter estimates of the final hemorrhagic stroke exposure-response model using edoxaban patients.

Parameter	Estimate[a]	90% Ci[b]	Hazard Ratio
λ [day^{-1}]	$4.192 \cdot 10^{-6}$	$[2.954 \cdot 10^{-6} - 5.431 \cdot 10^{-6}]$	-
RACE	0.8660	[0.3067 – 1.425]	2.38

a: The estimates of the risk factors are parameterized as log hazard ratio
b: CI confidence interval obtained by the observed Fisher information matrix
λ baseline hazard for the exponential distribution; *RACE*: non-Asian vs Asian

(Source: Applicant's Exposure-Response Report TMP 009, Table 6.13)

Figure 28. Probability of hemorrhagic stroke event within 1 year in an edoxaban patient versus total $C_{average}$ exposure of edoxaban.



(Source: Applicant's Exposure-Response Report TMP 009, Figure 6.32)

Reviewer's Comments:

These figures reveal two salient points.

1. *The probability of ischemic stroke decreases with increasing edoxaban concentration.*
2. *The Applicant's dose adjustment for low body weight, concomitant P-gp inhibitor use, and/or moderate renal impairment results appears to reduce exposures in this subset of patients compared to patients without a dose adjustment. This plot does not inform whether the dose adjustment was warranted for the intrinsic/extrinsic factor the adjustment was made on (i.e. renal impairment, concomitant Pgp inhibitor use, and low body weight.*

3.1.2.5 Exposure-Response for Safety:

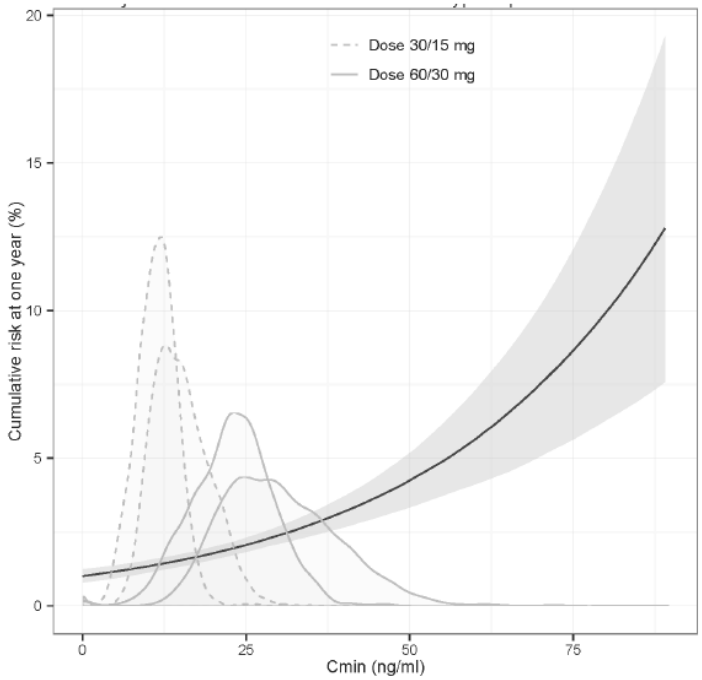
Table 40. Parameter estimates of the final major bleeding exposure-response model using edoxaban patients.

Parameter	Estimate[a]	90% CI[b]	Hazard Ratio[c]
λ [day^{-1}]	$1.142 \cdot 10^{-5}$	[$7.045 \cdot 10^{-6}$ - $1.579 \cdot 10^{-5}$]	-
γ	0.8348	[0.7791 - 0.8906]	-
β_{AGE} [year^{-1}]	0.03786	[0.0285 – 0.0472]	1.04
β_{ASA}	0.4709	[0.3147 – 0.6271]	1.60
$\beta_{L,Cmin}$ [(ng/mL)$^{-1}$]	0.02902	[0.02198 – 0.03607]	1.03

a: The estimates of the risk factor effects are parameterised as log hazard ratio
b: CI obtained from the observed Fisher information matrix
γ Shape factor of the Weibull distribution; *AGE* Age at baseline; *ASA* Concomitant use of aspirin or anti-platelet agent; C_{min} Minimum plasma concentration within one dosing interval at steady state included as a linear ER relationship; λ Scale factor of the Weibull distribution.

(Source: Applicant's Exposure-Response Report TMP 009, Table 6.7)

Figure 29. Probability of a major bleeding event within 1 year in an edoxaban patient versus C_{min} exposure of edoxaban.



(Source: Applicant's Exposure-Response Report TMP 009, Figure 6.8)

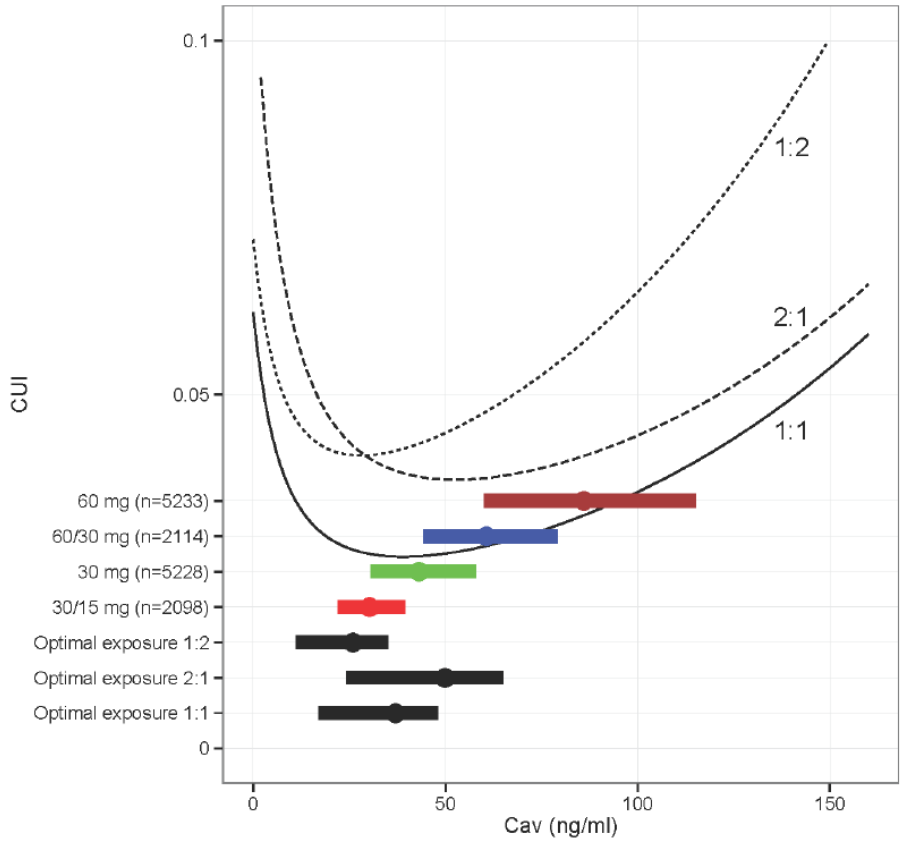
Reviewer's Comments:

As expected, the probability of major bleeds increases with edoxaban exposure and the studied dose groups appear to fall in the part of the relationship where there is the smallest rate of increase of events with increasing edoxaban concentrations (smallest slope). This plot does not show the rate of warfarin for comparison. Additionally the Applicant used C_{trough} for this bleeding relationship and $C_{average}$ for the efficacy endpoint.

C_{trough} has appeared to be a better metric for bleeding consistently between the phase 2 and phase 3 programs. However, because C_{trough} and $C_{average}$ and AUC are correlated, C_{trough} was used for consistency for both efficacy and safety endpoints in the reviewer's analysis.

3.1.2.6 Clinical Utility Analysis

Figure 30. Applicant's Clinical Utility Index for All Stroke/SEE against Major Bleeding Events at one year for clinical weights of 1:2, 2:1, and 1:1 versus PK exposure ($C_{average}$) visualized together with predicted exposure in all patients and the Applicant's optimal exposure for each weight.



(Source: Applicant's Exposure-Response Report TMP 009, Figure 6.37)

Reviewer's Comments:

The Applicant's clinical utility index assumes that one stroke is either equal to 0.5, 1, or 2 major bleeds. As this type of benefit-risk weighting is difficult to obtain consensus regarding two different approaches were considered in the review's analysis to evaluate the net-benefit-risk of edoxaban at different concentrations/doses – 1) the probability of having an event (stroke or bleeding) was compared to the probability for the warfarin control arm and 2) multiple efficacy and safety endpoints (all stroke/SEE, ischemic stroke, hemorrhagic stroke, life-threatening and fatal bleeds, major bleeds, major GI bleeds, clinically relevant non-major & major bleeds, and MACE events) were evaluated to gain a more complete picture of where edoxaban offers benefit compared to warfarin at different edoxaban doses.

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

/s/

DIVYA MENON ANDERSEN
09/29/2014

DIVYA MENON ANDERSEN on behalf of YOUNG J MOON
09/29/2014

JEFFRY FLORIAN on behalf of JUSTIN C EARP
09/29/2014

ROBERT N SCHUCK
09/29/2014

MICHAEL A PACANOWSKI
09/29/2014

JULIE M BULLOCK
09/30/2014
Concur regarding review of general PK caracterisitcs. Defer SPAF dose and exposure-response conclusions to DCP1 and Pharmacometrics teams.

JEFFRY FLORIAN
09/30/2014

RAJANIKANTH MADABUSHI
09/30/2014

BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 206-316 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DCRP		
Applicant:	Daiichi Sankyo Pharma Development	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	Savaysa ™ Tablets	**Acting Biopharmaceutics Supervisor:** Paul Seo, Ph.D.	
Generic Name:	Edoxaban Immediate Release Tablets	**Date Assigned:**	Jan 13, 2014
Indication:	Various cardiovascular disorders	**Date of Review:**	Sep 8, 2014
Formulation/strength	IR Tablets 15 mg, 30 mg and 60 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	Date of informal/Formal Consult	Primary Review Due in DARRTS
01/13/14 04/03/14 04/18/14 04/30/14 08/18/14 09/04/14 09/05/14	Jan 13, 2014	Sep 09, 2014

Type of Submission:	Original NDA (Priority Review)
Key review points	1. Dissolution method and acceptance criterion 2. Data supporting appropriate bridging throughout drug development 3. BE study supporting the 60 mg strength 4. Role of dissolution is supporting the proposed design space 5. (b) (4)

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12. Is dissolution testing appropriate as a tool to monitor for solid state? What data are available to support this claim?

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES **29**

13. What are the highlights of the drug product formulation development?

14. Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

15. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

D) DISSOLUTION APPLICATIONS **38**

D.1 BIOWAIVERS

16. Is there a waiver request of in vivo BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?

17. Is there any IVIVC information submitted? What is the regulatory application of the IVIVC in the submission? What data are provided to support the acceptability of the IVIVC model?

18. Is there any in vitro alcohol dose-dumping information submitted? What data are provided to support the Applicant's claim (e.g., lack of dose-dumping in the presence of alcohol)?

D.2 SURROGATES IN LIEU OF DISSOLUTION **38**

19. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

D.3 DISSOLUTION AND QBD **38**

20. Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?

21. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

22. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

23. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

BIOPHARMACEUTICS ASSESSMENT

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Daiichi Sankyo is seeking approval of edoxaban IR tablets, 15 mg, 30 mg, and 60 mg for the treatment of several cardiovascular anomalies such as pulmonary embolism, deep vein thrombosis, reduce the risk of stroke, systemic embolism, etc. The recommended dose is 60 mg once daily. The three strengths of edoxaban tablets are manufactured from [redacted] (b) (4) and are dose proportional to one another.

The pivotal Phase 3 clinical trials in atrial fibrillation (AF) and venous thromboembolism (VTE) indications used 15 mg and 30 mg strength tablets. The proposed commercial strengths include 15 mg, 30 mg, and 60 mg tablets to provide maximum flexibility for dose adjustment. A BE Study (A-U142) was conducted to support the bridging between the 30 mg and 60 mg tablets.

The manufacturing process development of edoxaban tablets was conducted according to a Quality by Design (QbD) approach [redacted] (b) (4)

This Biopharmaceutics review focuses on the evaluation of:

1. The acceptability of the dissolution method and acceptance criterion;
2. The data supporting appropriate bridging throughout drug development;
3. BE study A-U142 supporting the approval of the 60 mg strength;
4. The use of dissolution to support the drug product design space for [redacted] (b) (4)
5. [redacted] (b) (4)

1. **Dissolution Method and Acceptance Criterion:**

The following dissolution method and dissolution acceptance criterion have been found ***acceptable on an interim basis only*** (refer to submission dated Sep 5, 2014):

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Recommended Acceptance Criterion
II	50 rpm	900 mL	37°C	Citrate/phosphate buffer pH 6.0	Q≥ (b) (4)% in 30 min

The Applicant did not submit adequate/sufficient information to support the discriminating ability of the dissolution method. The following summarizes the concerns about the dissolution method:

a. The proposed dissolution method does not reflect the (b) (4)

(b) (4)

(b) (4)

The Biopharmaceutics team believes that many of these discrepancies are due to the (b) (4)

In a tecon dated Sep 4, 2014 and in a submission dated Sep 05, 2104, the Applicant agreed to have a Post-Marketing Commitment to be fulfilled within 15 months from action date for: i) development of a new dissolution method, which shows greater discriminating ability (b) (4) and ii) setting of the final dissolution acceptance criterion of their drug product using the new method and the overall dissolution profile data from a minimum of 12 commercial batches.

A summary of the **RISK ANALYSIS** for dissolution is presented in Table 15 (refer to page 43 of this review).

2. Appropriate Bridging throughout the Phases of Drug Development

Edoxaban tablets were developed as an IR tablet formulation using common excipients and conventional manufacturing procedures. The tablets developed for clinical studies were 5 mg (Phase 1, Phase 2b); 15 mg (Phase 2a, 2b and 3); and 30 mg (Phase 1, 2a, 2b and 3). The proposed commercial formulations for the 15 mg and 30 mg tablets have the same composition as the Phase 3 tablets, with the exception of the colorants used in the film coats. Additionally, a 60 mg tablet was later developed for commercial use. Based on data from the pilot bioavailability study (A-U145), and a subsequent BE study (A-U142), the proportional 60 mg round tablet formulation was chosen as the proposed commercial formulation. Note that some major changes were implemented to the formulation tested in Phase 1 and Phase 2 studies; however, these studies are considered not pivotal from the biopharmaceutics perspective for the approval of the proposed drug product, because there are PK data for the phase 3/TBM formulation (15 mg and 30 mg) and a BE study between the 30 mg and 60 mg tablet.

There were no manufacturing changes implemented to the clinical trial formulation. The product will be manufactured by Daiichi Sankyo Propharma Co., Ltd., Hiratsuka, Japan.

3. Bioequivalence Study A-U142 Supporting the Approval of the 60 mg Strength

The 60 mg tablets were not tested in Phase 3 Clinical Trials. Its approval is based on the results of BE study A-U142. This study was an single-center, open-label, randomized, two-treatment, four-period, two-sequence, replicated crossover study in 30 healthy subjects to investigate the bioequivalence of the round 60 mg proposed commercial tablet formulation to the Phase 3 tablet formulation (30 mg round tablets), when both tablets are dosed at 60 mg under fasting conditions. Subjects were randomized to 1 of 2 sequences (ABAB or BABA) and received both treatments as follows:

Treatment A: Single oral dose of round tablet (1 x 60 mg tablet),
Treatment B: Single oral dose of Phase 3 formulation (2 x 30 mg tablets), on separate occasions.

This Reviewer run the average BE and the scaled-average BE (ASBE) analysis for the PK data provided during the review cycle using the Phoenix software. ASBE was run given the nature of the data; specifically the study design was replicated and the %CV for Cmax was higher than 30%. The pharmacokinetic parameters Cmax, AUCt, and AUCinf met the criteria for BE for both edoxaban and its major metabolite.

It is noted that the inspection report from the Office of Scientific Investigations (OSI) for the analytical and clinical sites of BE study **A-U142** is pending.

4. The Role of Dissolution Supporting the Construction and Proposed Ranges of the Design Space

As part of the control strategy for edoxaban tablets, the design and control spaces were constructed (b) (4)

According to the Applicant and later confirmed by the CMC review team during several internal meetings, (b) (4)

(b) (4)

In the Email submissions dated July 1, 2014 and Sep 5, 2014, the Applicant agreed on (b) (4)

15 mg tablets: from (b) (4) mg/mm
30 mg tablets: from mg/mm^3
45 mg tablets: from mg/mm^3

A summary of the control space ranges agreed upon is provided in the Table below.

Control Space to Assure the (b) (4) of Dissolution for Edoxaban Tablets

Tablet strength	15 mg tablets	30 mg tablets	60 mg tablets
(b) (4)			

(b) (4)

It should be noted that the design space ranges for the (b) (4) are based on passing an acceptance criterion of Q≥ (b) (4)% at 30 min and on a dissolution method that is considered less than adequate. Therefore, the design space should be revised as appropriate, once the results of the post marketing commitment are submitted.

5. (b) (4) Dissolution Model

(b) (4)

The (b) (4) dissolution models developed by the Applicant for the 15mg, 30 mg, and 60 mg tablets are not acceptable for the following reasons:

(b) (4)

The above concerns and deficiencies for the proposed dissolution model were communicated to the Applicant in a submission dated Aug 26, 2014 and in a teleconference dated Sep 5, 2014. The Applicant agreed to withdraw the dissolution model from the NDA submission and to take into consideration the FDA's recommendation for future dissolution model submissions.

II) RECOMMENDATION

ONDQA-Biopharmaceutics had reviewed NDA 206-316. The following dissolution method and acceptance criterion are acceptable on an **INTERIM BASIS** for release and on stability.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	50 rpm	900 mL	37°C	Citrate/phosphate buffer pH 6.0	Q≥ (b) (4) % in 30 min

From the Biopharmaceutics perspective, NDA 206-316 for Edoxaban Toxylate IR tablets, 15 mg, 30 mg and 60 mg, is recommended for an **APPROVAL action with a post-marketing commitment***, provided the inspection report from OSI, which is currently pending does not report any objections for accepting the analytical and clinical data from BE study **A-U142** .

**PMC to develop an improved discriminating and canonical method and set the final acceptance criterion for the drug product using this method).*

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) QUESTION BASED REVIEW APPROACH

A) GENERAL ATTRIBUTES

1. ***What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?***

Drug Substance

According to the Applicant, edoxaban is a highly selective, direct and reversible inhibitor of factor Xa (FXa), the serine protease located in the final common pathway of the coagulation cascade. Edoxaban inhibits free FXa, and prothrombinase activity leading to the coagulation cascade which reduces thrombin generation and prolongs clotting time and reduces the risk of formation or provoked thrombus formation.

Edoxaban (DU-176), the active moiety, is an anhydrous free form with a molecular mass of 548.06. The active pharmaceutical ingredient (API) is a monohydrate tosylate salt. Edoxaban tosylate monohydrate (also referred to as DU-176b) has a molecular weight of 738.27.

The solubility of the 60 mg strength was evaluated in aqueous media over a pH range (b) (4) The solubility profile of edoxaban tosylate in various aqueous solutions is summarized in Figure 1 and Table 1 (b) (4)

(b) (4)

Figure 1. Solubility Profile of Edoxaban Tosylate in Aqueous Solutions of Various pH at 37°C (Batch No. MH401)

Table 1. Solubility Profile of Edoxaban Tosylate in Aqueous Solutions at Various pHs (Batch No. MH401)

(b) (4)

Edoxaban tosylate has a (b) (4) (refer to CMC review by Dr. Ghosh for details on this matter).

The following comments were conveyed to the Applicant regarding the potential change in (b) (4)

1. ***If edoxaban undergoes change in*** (b) (4)
    - ***Demonstration of the same physicochemical properties (e.g. solubility profile, melting point, hygroscopicity, intrinsic dissolution, etc.) of the*** (b) (4)
    - ***If there are clear differences in these physicochemical properties, then you should provide data/justification for the lack of impact on the bioavailability of the drug product due to presence of*** (b) (4) ***Alternatively, monitor the*** (b) (4) ***of the drug product at release and during stability using the following approaches:***

i. ***As per ICH Q6A guidance, it is recommended that you use dissolution testing to monitor for the amount/type of*** (b) (4) ***at release and on stability. For this purpose, provide information/data showing that your proposed dissolution testing methodology and proposed acceptance criterion are able to reject batches with inadequate amount/type of*** (b) (4) ***Submit dissolution profiles as a function of*** (b) (4) ***In addition, the setting of an acceptable specification limit of*** (b) (4) ***allowed by the dissolution acceptance criterion should be supported by clinical information (i.e., bioavailability, exposure-response, etc.).***

ii. ***Alternatively, monitor the*** (b) (4) ***at release and on stability using a*** (b) (4) ***Note that the setting of an acceptable limit of the*** (b) (4) ***should be supported by clinical information (i.e., bioavailability, exposure-response, etc.).***

On April 30, 2014, the Applicant responded that the (b) (4) ***data provided (refer to CMC review) confirmed that*** (b) (4) ***is maintained during the*** (b) (4) ***and that the*** (b) (4)

Drug Product

Edoxaban tosylate drug product is an IR, round-shaped, film-coated, and debossed tablet. The tablets are available in three strengths (15 mg, 30 mg, and 60 mg) and are not scored. Tablet strength is expressed as amount of edoxaban, which is the free base of the drug substance, edoxaban tosylate. According to the Applicant, all three tablet strengths are produced from (b) (4) and are differentiated by tablet size, film-coating color, and debossed information. The quantitative composition of the edoxaban IR tablets is provided in Table 2. The three strengths are proportionally similar in composition.

Table 2. Unit Formula of Edoxaban Tablets 15 mg, 30 mg, and 60 mg

Ingredient	Function	Reference to Standards	15 mg tablets		30mg tablets		60 mg tablets	
			mg/tablet	wt/wt%	mg/tablet	wt/wt%	mg/tablet	wt/wt%
Edoxaban tosylate (as edoxaban free base)	Drug substance	Section 3.2.S.4.1 Specifications	20.20 (15)	(b) (4)	40.41 (30)	(b) (4)	80.82 (60)	(b) (4)
Mannitol	(b) (4)	USP/Ph. Eur./JP						
Pregelatinized starch		NF/Ph. Eur./JPE						
Crospovidone		NF/Ph. Eur./JP						
Hydroxypropyl cellulose		NF/Ph. Eur./JP						
(b) (4)		USP/Ph. Eur./JP						
Magnesium stearate		NF/Ph. Eur./JP						
(b) (4)								
(b) (4) (Orange)		In-house [b)]						
(b) (4) (Pink)		In-house [b)]						
(Yellow)		In-house [b)]						
		USP/Ph. Eur./JP						
Carnauba wax		NF/Ph. Eur./JP						
Talc		USP/Ph. Eur./JP						
Total Tablet Weight (mg)			105.0		210.0		420.0	

2. Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?

As mentioned above, edoxaban tosylate is considered a low solubility compound according to the BCS criterion. The permeability of edoxaban was assessed using in vitro transport across Caco-2 cell. The transport of edoxaban exhibited saturable kinetics with reduced apparent permeability coefficient (P_{app}) ratio at higher concentrations. The mean P_{app} [the mean of P_{app} in basal to apical direction] / [the mean of P_{app} in apical to basal direction at 1, 3, 10, 30 and 100 µmol/L was 4.53, 4.13, 3.97, 3.77 and 2.28 x 10^{-6} cm/s, respectively. Based on the mass balance study and the absolute bioavailability study, the extent of absorption in humans was less than 90% of the administered dose. Together, these in vitro and clinical pharmacology studies suggest that edoxaban is a low-permeability compound. Therefore, edoxaban may be classified as BCS class 4.

B) DISSOLUTION INFORMATION

B1) Dissolution Method

3. What is the proposed dissolution method?

The dissolution method proposed as a quality control tool for edoxaban IR Tablets is summarized below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
II	50 rpm	900 mL	37°C	Citrate/phosphate buffer pH 6.0

4. ***What data are provided to support the adequacy of the proposed dissolution method (e.g., medium, apparatus selection, etc.)?***

Dissolution Method Development

The dissolution method was evaluated during the IND stage. At that stage of development, the review team[1] considered the method acceptable. However, the data submitted as part of the pre-NDA meeting (May 17, 2013) showed that the method does not follow the (b) (4)

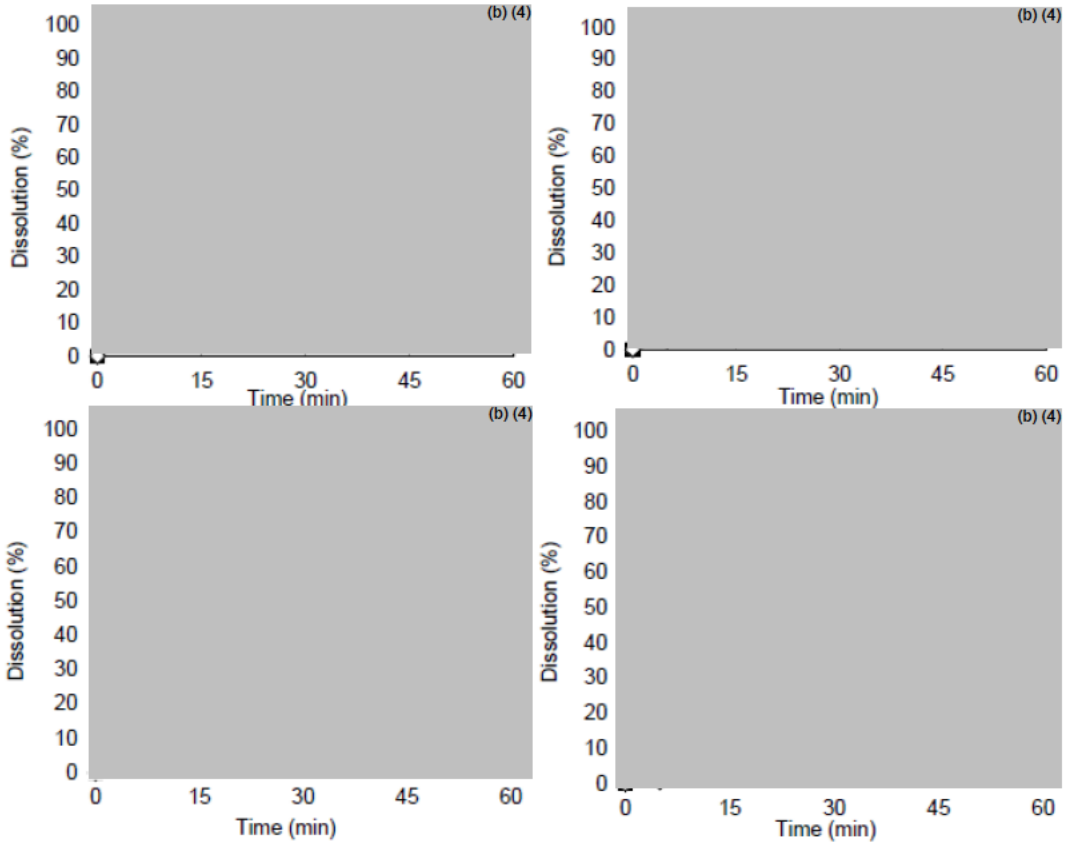

Figure 2. (b) (4)

[1] Biopharmaceutics review for IND 77,254 and IND 63,266 entered in DARRTS by Dr. Lakhani on Feb 2010.

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(b) (4)

5. ***What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?***

Dissolution Method Validation

The Applicant provided enough information to support the validity of the analytical method for dissolution testing for edoxaban tablets (refer to CMC review for more details; also see bionalytical-procedures.pdf at \\cdsesub1\evsprod\NDA206316\0000\m3\32-body-data\32p-drug-prod\edoxaban-tablets\32p5-contr-drug-prod\32p53-val-analyt-proc).

6. ***What data are available to support the discriminating power of the method?***

According to the Applicant, the discriminating capability and robustness of the dissolution method as a QC test were established through evaluation of factors that affect tablet dissolution (b) (4)

(b) (4)

Reviewer's Comments

(b) (4)

Therefore, the following comments were conveyed to the Applicant on an IR letter dated and discussed in a tecon dated July 01/2014:

1. ***Based on the evaluation of the overall dissolution and clinical data submitted in your original NDA and further amendments, we have the following issues/concerns regarding the proposed dissolution method:***
   a. ***The method does not reflect the*** (b) (4)

(b) (4)

(b) (4)

(b) (4)

2. ***Based on the above issues/concerns, we recommend that new dissolution methodology showing adequate discriminating ability reflective of meaningful changes in the*** (b) (4) ***be developed for your drug product. We remind you that the discriminating ability of a dissolution method is not only determined by the dissolution method testing conditions but also by the selection of the acceptance criterion, which include specification-sampling time point and limit value.***

3. ***Please provide your proposal for pathways to move forward with the review of your proposed drug product.***

During the teleconference, the Applicant agreed to submit information to address the FDA's concerns about the (b) (4)

In a submission dated Aug 18, 2014 (\\cdsesub1\evsprod\NDA206316\0076\m1\us\111-info-amend), the Applicant provided a report reiterating the selection of the originally proposed dissolution method. This report consisted on a compilation of the data already submitted during the IND and during the original NDA submission and some additional data, which included:

(b) (4)

The results of these experiments showed that:

1. (b) (4)

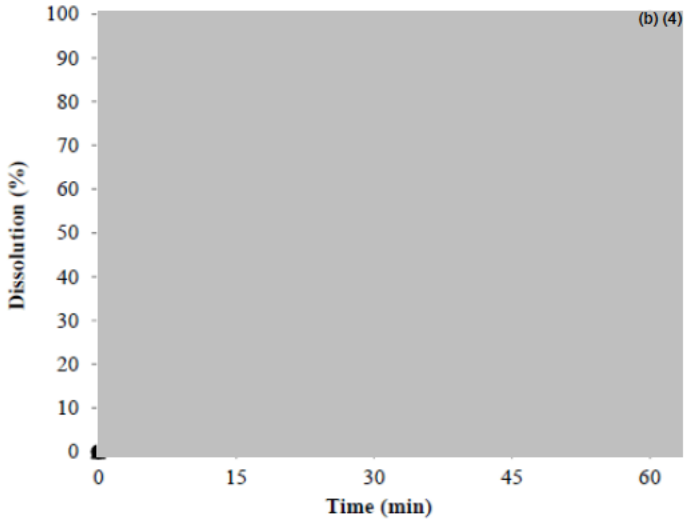

Figure 7. (b) (4)

2. (b) (4)

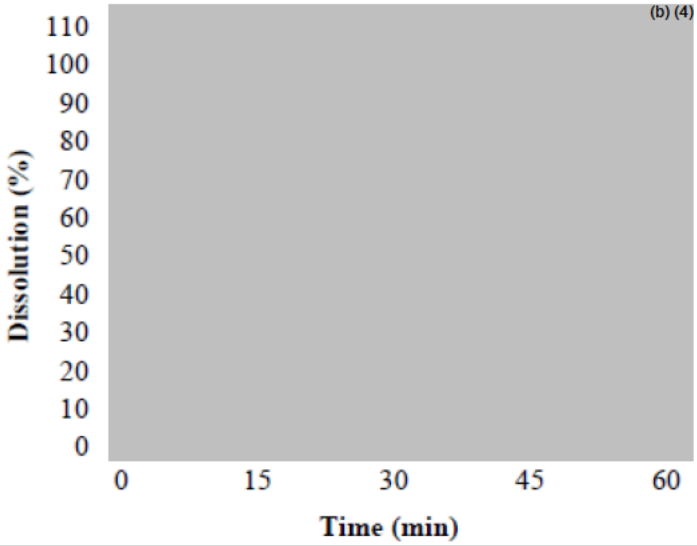

Figure 8. (b) (4)

3. (b) (4)

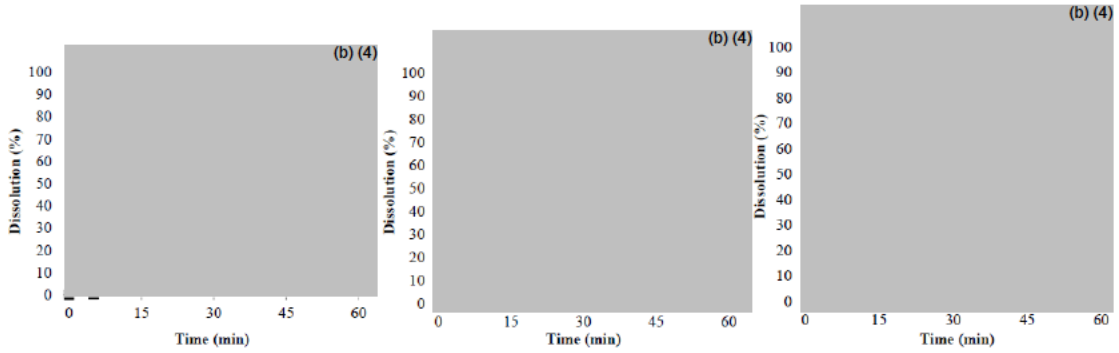

Figure 9. (b) (4)

Reviewer's Comments

(b) (4)

(b) (4)

The Applicant concluded that (b) (4)

Thus, the data provided did not address the fundamental problem of [redacted] Therefore, the following comments were conveyed to the Applicant in a submission dated Aug 26, 2014:

1. ***The dissolution of your drug product using the current dissolution method does not conform to the*** [redacted]

2. ***FDA has concerns that the current dissolution method does not account for*** [redacted] ***Overall, we consider that the proposed dissolution model developed with the current dissolution method cannot support the proposed*** [redacted] ***for your drug product.***

3. ***FDA considers that to support the approval of your drug product from the Quality perspective (Biopharmaceutics and CMC) the next pathway should be followed:***

   A. Withdraw from your NDA submission the dissolution model [redacted] ***for dissolution.***

   B. Implement on an interim basis the current dissolution method with an acceptance criterion of Q= [redacted] ***% at 30 minutes for release and on stability.***

   C. Modify the remaining design spaces to account for removing the dissolution model as follows:

      a. ***The data submitted on April 3, 2014, showed that f2 values for the comparison of some batches with the respective reference batch failed the similarly testing.*** [redacted]

   D. Agree to the following post-marketing commitment:

a. ***Within one year from NDA's action date, develop and implement a new dissolution method, which shows greater discriminating ability and*** [redacted] ***Also, within one year set the final dissolution acceptance criterion for your drug product using the new method and the overall dissolution profile data from a minimum of 12 commercial batches.***

b. ***We remind you that the discriminating ability of the method is not only determined by the dissolution method conditions but also by the time point and specification value. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e., ±*** [redacted] ***% change to the specification-ranges of these variables) for the most relevant manufacturing variables (e.g.*** [redacted] ***.***

E. ***If you develop a new*** [redacted] ***dissolution model with the new dissolution method, please consider the following:***

a. ***In order to mitigate the risk that is not addressed by the model, include*** [redacted] ***in the model. Alternatively, provide rationale with supporting data justifying the use of an alternative approach.***

b. [redacted] ***construct and validate the model using 'individual mean' values of the relevant variables measured throughout the manufacturing run (e.g., 6 mean values of tablet density).*** [redacted]

Therefore, the model should predict 'individual mean dissolution', where the inputs to the model are the 'individual means' of selected input variables measured throughout the manufacturing run.

c. ***For model prediction purposes, it is recommended that the 95% one-sided lower confidence limit for the individual mean prediction be ≥*** [redacted] ***% for the dissolution acceptance criterion. This acceptance criterion is consistent with USP <711> Stage 1 criterion of Q+5 for each individual tablet.***

F. ***As part of drug product's Continuous Process Verification, we recommend that you track all process variables and in-process attributes that have a potential to impact dissolution during routine production in a multivariate manner e.g. via use of MSPC (multivariate statistical process control).***

These results and additional data claiming presence of (b) (4) [3] *submitted on Sep 3, 2014, were discussed with the Applicant in a teleconference dated Sep 4, 2014. During the teleconference the review team reiterated the FDA's position as described on the comments above; specifically, the Biopharmaceutics review team communicated that the dissolution method specifications (method and criterion) are not adequate and can only be approved on an interim basis at this time. In addition, since the dissolution model relies on an adequate method and acceptance criterion, it renders the dissolution model unacceptable as well. At the conclusion of the teleconference, the Applicant agreed on the following:*

- *Accepting the dissolution method and acceptance criterion of Q=* (b) (4) *% in 30 min on an interim basis*
- *withdrawing the dissolution model*
- *Work with the FDA on the details and due dates of a PMC to develop an improved discriminating and canonical method and set the final acceptance criterion for the drug product using this method.*

7. *Is the proposed dissolution method biorelavant? What data are available to support this claim?*

There were no data in the submission to help in the assessment of the biorelavancy of the method; however, based on the results of BE study A-U140 and dissolution data submitted during the review cycle (\\cdsesub1\evsprod\NDA206316\0031\m1\us\111-info-amend) for batches tested in this BE study, this Reviewer concludes that the method is not biorelevant because it did not reject a batch failing Cmax. Specifically, Figure 10 shows that the method and proposed acceptance criterion will not reject a batch (DU176F1H10M07; A-U140) which was shown to fail Cmax (Table 4).

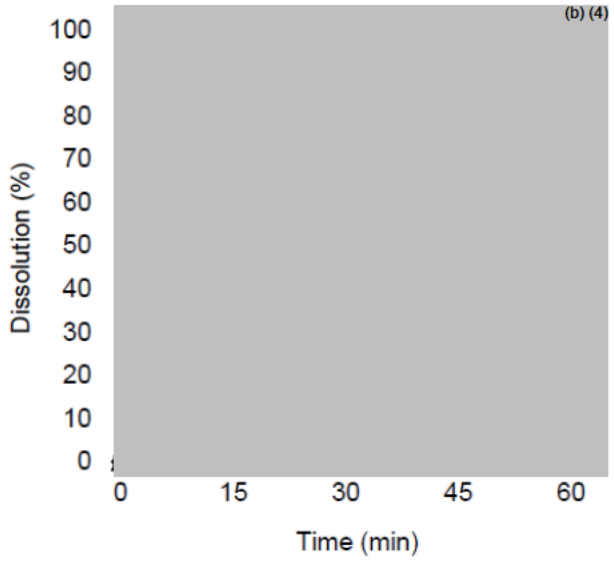

Figure 10. (b) (4)

Study AU140 was an open-label, randomized, crossover study in 44 healthy subjects comparing the bioavailability of a 60 mg [redacted] shaped tablet and the 30 mg round tablets used in Phase 3. These tablets differed in the amount of [redacted] On separate occasions, subjects received a single 60 mg oral dose of the [redacted] shaped formulation or 2 x 30 mg round tablets. Blood samples were collected over 72 h for PK analyses. The peak exposure of the [redacted] 60 mg tablet was 17% lower, with the lower bound of the 90% CI falling outside the 80% to 125% interval (Table 4).

Table 4. Statistical Comparisons (ANOVA) of PK Parameters of Edoxaban between Teardrop-Shaped 60 mg Tablets and Phase 3 Formulation (2 x 30 mg Tablets) (A-U140)

PK Parameters of Edoxaban	Geometric LS Means		Ratio of Geometric LS Means (%)	90% CI (%)
	[redacted] 60 mg Tablet (1 Tablet)	2 x 30 mg Tablets	[redacted] 60 mg Tablet / 2 x 30 mg Tablets)	
C_{max} (ng/mL)	[redacted]			
AUC_{last} (ng·h/mL)				
AUC_{0-inf} (ng·h/mL)				

8. Is the proposed method acceptable? if not, what are the deficiencies?

The method was found acceptable only on an interim basis for the reasons stated above under B1.6. In a tecon dated Sep 4, 2014 the Applicant accepted the method and acceptance criterion on an interim basis.

B.2. ACCEPTANCE CRITERION

9. What is the proposed dissolution acceptance criterion for this product?

The following dissolution acceptance criterion was originally proposed by the Applicant as a QC for edoxaban IR tablets:

Proposed Dissolution Acceptance criterion
Q= [redacted] in 30 min

10. What data are available to support it?

During the pre-NDA meeting held on May 17, 2013 this Reviewer recommended that the Applicant consider [redacted] the proposed acceptance criterion to Q= [redacted] This recommendation was based on the dissolution profiles observed for all strengths of the product (Figure 11). The FDA added during the face-to-face meeting that a more

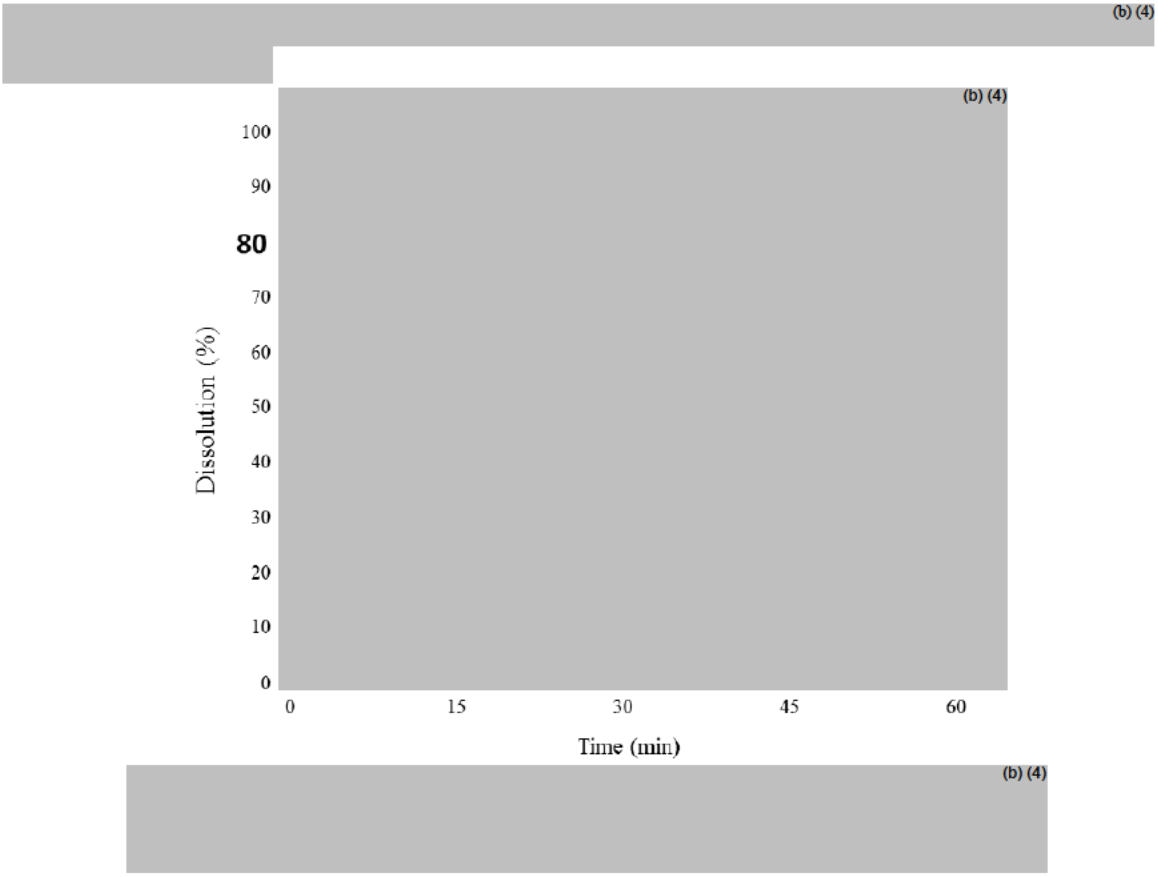

Figure 11. Batch Data Summary (Mean Dissolution Profiles) of Phase 3 Clinical and Registration Batches of 15 mg, 30 mg, and 60 mg Tablets in pH 6.0 citrate/Phosphate Buffer Solution with 50 rpm Paddle Rotation Speed.

According to the Applicant, the proposed criterion of Q (b) (4) % in 30 min is based on release data from batches tested in clinical trials formulations and commercial batches manufactured at both manufacturing sites. In addition, the Applicant claims that the criterion is supported by the results of two BA studies which were performed to compare edoxaban (b) (4) vs. 2 x 30-mg tablets (b) (4) The dissolution data (Figure 12, same as Figure 6), show that the profile for (b) (4) Batch No. S02049- 2A, was (b) (4) Batch No. S03048-3A. The Applicant concludes that because (b) (4)

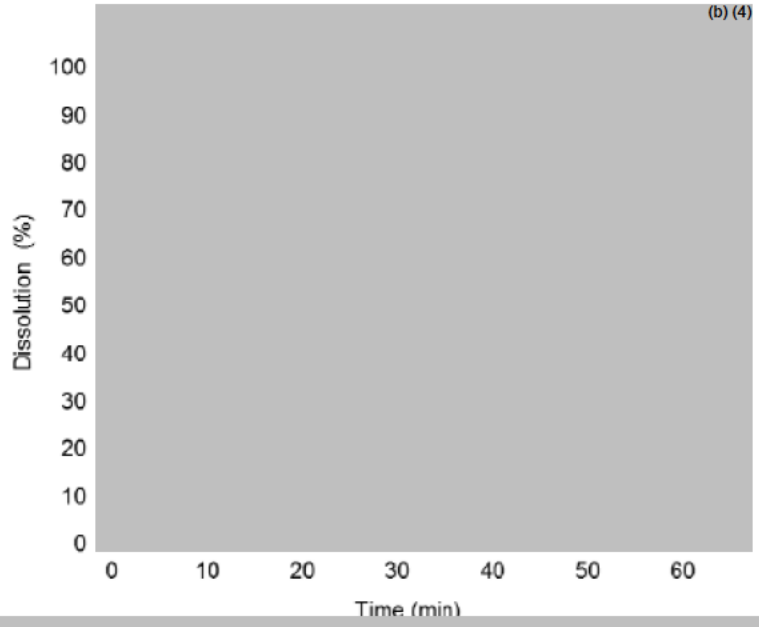

Figure 12. (b) (4)

Reviewer's comments

(b) (4) *dissolution data should not be used to support the justification for a more permissive criterion due to the following:*

(b) (4)

However, since Cmax was not identified as a significant predictor of the exposure-response relationship (Email communication with The Clinical Pharmacology review team), Cmax may not be critical for the efficacy profile of the drug product; therefore, the Biopharmaceutics review team decided to consider the proposed acceptance dissolution criterion of Q= (b) (4) *in 30 min. Specifically, BE failed due to a lower Cmax value for a batch passing acceptance criterion and the risk of accepting this is low since it seems that Cmax does not contribute to the efficacy of the drug product.*

11. Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches?

The following acceptance criterion has been agreed upon with the Applicant on an interim basis:

Proposed Dissolution Acceptance criterion
Q= (b) (4) in 30 min

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

12. What are the highlights of the drug product formulation development?

Figure 13 gives a Schematic Overview on the edoxaban Formulation Development and the data provided to bridge across stages. Note that some major changes were implemented to the formulation tested in Phase 1 and Phase 2 studies; however, these studies are considered not pivotal from biopharmaceutics perspective for the approval of the drug since there is PK data for the phase 3/TBM formulation (15 mg and 30 mg) and a BE study between the 30 mg and 60 mg tablet.

Figure 13. Schematic Overview on the Edoxaban Formulation Development.

Edoxaban tablets were developed as IR tablet formulation using common excipients and conventional manufacturing procedures. Tablets developed for clinical studies were 5 mg (Phase 1, Phase 2b); 15 mg (Phase 2a, 2b and 3); and 30 mg (Phase 1, 2a, 2b and 3). The proposed commercial formulations for the 15 mg and 30 mg tablets have the same composition as the Phase 3 tablets, with the exception of the colorants used in the film coats. Additionally, a 60 mg tablet was later developed for commercial use. During the development of the 60 mg tablet, different shapes ((b) (4) round tablets) were investigated. These three formulations had minor differences in composition. The 60 mg round tablets were proportionally similar in composition to the 30 mg round

tablets, [redacted] ased on data from the pilot bioavailability study (A-U145), and a subsequent BE study (A-U142), the proportional 60 mg round tablet formulation was chosen as the proposed commercial formulation. The review of this study is summarized below on question 14. A description of tablets used in the clinical studies is listed in Table 5.

Table 5. Tablet Formulations Used During Clinical Development

Main purpose of use[a]	Descriptions[b]	Tablet Strength
Phase 1	White [redacted] tablet Pale brownish white [redacted] tablet	5 mg 30 mg
Phase 1	White [redacted] tablet	30 mg
Phase 2a	Yellow [redacted] tablet	15 mg, 30 mg
Phase 2b	Yellow [redacted] tablet	5 mg, 15 mg, 30 mg
Phase 3	Yellow film coated tablet	15 mg, 30 mg
Proposed commercial formulation [redacted]	Orange film coated tablet	15 mg
	Pink film coated tablet	30 mg
	Yellow film coated tablet	60 mg
Commercial formulation (Japan)[c]	[redacted] tablet	15 mg
	[redacted] tablet	30 mg
	[redacted] tablet (proposed commercial formulations through Partial Change Approval Application)	60 mg

13. Are there any manufacturing changes implemented (e.g., formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

There were no manufacturing changes implemented to the clinical trial formulation. The 60 mg tablet was approved based on an in vivo BE study. The product will be manufactured by Daiichi Sankyo Propharma Co., Ltd., Hiratsuka, Japan

14. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

As mentioned above, edoxaban tablets were developed as IR tablet formulation using common excipients and conventional manufacturing procedures. The proposed commercial formulations for the 15 mg and 30 mg tablets have the same composition as the Phase 3 tablets, with the exception of the colorants used in the film coats.

Additionally, a 60 mg tablet was later developed for commercial use. The 60 mg round tablets were proportionally similar in composition to the 30 mg round tablets. Based on data from the pilot bioavailability study (A-U145), and a subsequent BE study (A-U142), the proportional 60 mg round tablet formulation was chosen as the proposed commercial formulation.

Study A-U142: Bioequivalence Study between Round 60 mg Tablets and Phase 3 Formulations (2 Tablets of 30 mg)

This was an single-center, open-label, randomized, two-treatment, four-period, two-sequence, replicated crossover study in 30 healthy subjects to investigate the bioequivalence of the round 60 mg proposed commercial tablet formulation to the Phase 3 tablet formulation (30 mg round tablets), when both tablets are dosed at 60 mg under fasting conditions. Subjects were randomized to 1 of 2 sequences (ABAB or BABA) and received both treatments as follows:

Treatment A: Single oral dose of round tablet (1 x 60 mg tablet),
Treatment B: Single oral dose of Phase 3 formulation (2 x 30 mg tablets), on separate occasions.

Blood samples for the analysis of plasma concentrations of edoxaban (DU-176) and its metabolite D21-2393 were collected prior to edoxaban dosing (within approximately 60 minutes prior to dosing) and at the following times: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 60, and 72 h postdose.

The following PK parameters were calculated from the individual plasma concentrations of edoxaban and its active metabolite, D21-2393 following the administration of the round shape tablet and the current tablet formulation of edoxaban under fasting conditions using a noncompartmental approach: AUClast, AUC0-inf, AUCextr, C24, Cmax, tmax, λz and t1/2 for both and CL/F and Vz/F for edoxaban only.

The inclusion/exclusion criteria and concomitant medications were described in detail under \\cdsesub1\evsprod\NDA206316\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\du176b-a-u142).

Statistical Methods

As the primary endpoints, AUClast, AUC0-inf, and Cmax (and C24 for information purposes only) were compared between Treatment A and Treatment B using an appropriate mixed effect model for replicated measurements on the *ln*-transformed AUClast, AUC0-inf, and Cmax values (and C24). Bioequivalence (BE) between the two treatments (A versus B) was concluded if the 90% confidence intervals (CIs) of the geometric mean ratios of AUClast, AUC0-inf, and Cmax of edoxaban were entirely contained within the BE interval of 80 to 125%.

Non-parametric analysis of tmax, and t1/2 were performed, to compare Treatment A to Treatment B. The statistical analyses described above were also performed for the edoxaban metabolite, D21-2393, as a secondary objective.

Safety

Safety assessments included physical examination findings, vital signs, 12-lead electrocardiograms (ECGs), adverse events (AEs), and clinical laboratories [hematology, serum chemistry, urinalysis (UA), fecal occult blood, and coagulation parameters: prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT)].

Results

The results of the bioanalytical analysis are summarized in Table 6 and demonstrate the robustness of the test.

Table 6. Assay Performance for Study DU176b-A-U142 (Edoxaban and Metabolite)

Bioanalytical Runs	Comprehensive list of bioanalytical runs for Study DU176b-A-U142 including run number, analysis date, subject numbers, and run status.	
DU-176 (parent) QC Samples	Accepted Runs 34 (Overall pass rate 91.9%)	Rejected Runs 3
Calibration Standards	Precision (%CV)* 1.7 to 2.9% Precision (%CV) 1.6 to 3.8%	Accuracy (%Dev) 0.0 to 3.3% Accuracy (%Dev) –1.0 to 1.0%
D21-2393 (metabolite) QC Samples	Accepted Runs 34 (Overall pass rate 91.9%)	Rejected Runs 3
Calibration Standards	Precision (%CV)* 2.1 to 3.3% Precision (%CV) 1.6 to 4.2%	Accuracy (%Dev) –6.9 to –1.5% Accuracy (%Dev) –2.3 to 1.9%
Room temperature in plasma	plasma 24 hours	
Freeze/thaw at –20 °C	6 cycles	
Reinjection reproducibility at approximately 3 °C	112 hours	
Processed extract stability stored at approximately 3 °C	95 hours	
Freezer at –20 °C in plasma	311 days for DU-176 277 days for D21-2393	

Thirty subjects were enrolled and 25 subjects completed the study. A summary of the pharmacokinetics results is presented in Table 7 and 8, for edoxaban and it major metabolite, respectively. The mean plasma concentration time profiles for both formulations were virtually superimposed (not shown in here). The individual edoxaban Cmax and AUCt values are shown in Figures 14 and 15, respectively. The individual Cmax and AUCt discretion is very similar across treatments. Note that the graphs for the metabolite are not shown here, but similar pattern in the distribution is observed as that for the parent compound.

Table 7. Overall Summary of Pharmacokinetic Parameters for Edoxaban in Plasma

PK Parameters Edoxaban	**Treatment A (Test) (Overall N=57)**	**Treatment B (Reference) (Overall N=57*)**
AUC_{last} (ng·h/mL) Arithmetic Mean ± SD Geometric Mean (Geo%CV)	1744 ± 460 1680 (29.1)	1718 ± 503 1649 (29.5)
$AUC_{0\text{-}inf}$ (ng·h/mL) Arithmetic Mean ± SD Geometric Mean (Geo%CV)	1769 ± 461 1706 (28.5)	1754 ± 501 1687 (28.7)
$\%AUC_{extr}$ (%) Arithmetic Mean ± SD	1.51 ± 1.43	1.39 ± 0.91
C_{max} (ng/mL) Arithmetic Mean ± SD Geometric Mean (Geo%CV)	249.5 ± 84.5 229.8 (49.2)	242.4 ± 93.4 223.6 (44.0)
t_{max} (h) Arithmetic Mean ± SD Median (Min, Max)	1.273 ± 0.451 1.00 (0.50, 2.50)	1.378 ± 0.536 1.50 (0.50, 2.98)
C_{24} (h) Arithmetic Mean ± SD Geometric Mean (Geo%CV)	11.69 ± 5.11 10.72 (43.3)	11.11 ± 4.08 10.43 (37.3)
$t_{½}$ (h) Arithmetic Mean ± SD Median (Min, Max)	13.33 ± 6.87 10.49 (5.10, 33.3)	12.84 ± 6.83 10.74 (5.22, 36.0)
CL/F (L/h) Arithmetic Mean ± SD	36.66 ± 11.73	37.00 ± 10.95
V_z/F (L) Arithmetic Mean ± SD	701 ± 429	675 ± 403

Table 8. Overall Summary of Pharmacokinetic Parameters for D21-2393 in Plasma

PK Parameters D21-2393	**Treatment A (Test) (Overall N=57)**	**Treatment B (Reference) (Overall N=57*)**
AUC_{last} (ng·h/mL) Arithmetic Mean ± SD Geometric Mean (Geo%CV)	140.3 ± 54.4 129.9 (42.4)	140.2 ± 62.5 128.0 (44.9)
$AUC_{0\text{-}inf}$ (ng·h/mL) Arithmetic Mean ± SD Geometric Mean (Geo%CV)	142.6 ± 54.6 132.5 (41.3)	143.8 ± 62.9 131.8 (43.8)
$\%AUC_{extr}$ (%) Arithmetic Mean ± SD	1.94 ± 1.61	1.66 ± 0.90
C_{max} (ng/mL) Arithmetic Mean ± SD Geometric Mean (Geo%CV)	20.96 ± 9.85 18.42 (61.0)	20.92 ± 11.17 18.31 (56.8)
t_{max} (h) Arithmetic Mean ± SD Median (Min, Max)	1.975 ± 0.511 2.00 (1.00, 3.50)	2.036 ± 0.624 2.00 (1.00, 4.00)
C_{24} (h) Arithmetic Mean ± SD Geometric Mean (Geo%CV)	0.9962 ± 0.4573 0.9068 (45.6)	0.9824 ± 0.4555 0.8956 (44.7)
$t_{½}$ (h) Arithmetic Mean ± SD Median (Min, Max)	13.03 ± 8.22 9.57 (4.93, 42.7)	11.53 ± 6.86 8.976 (4.92, 41.1)

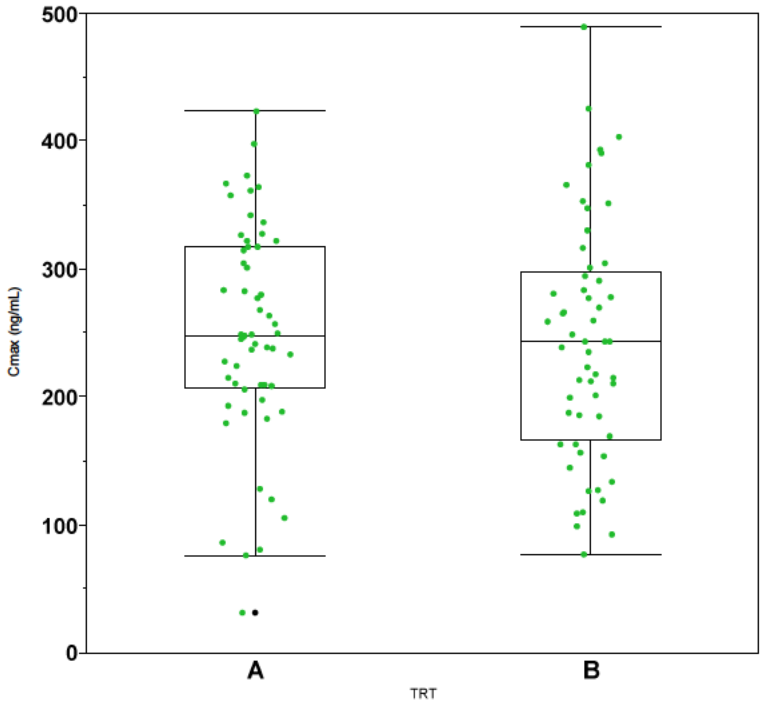

Figure 14. Box plot for the individual edoxaban Cmax values following single administration of the treatments. Constructed using data provided on Aug 13, 2014 in response to IR letter.

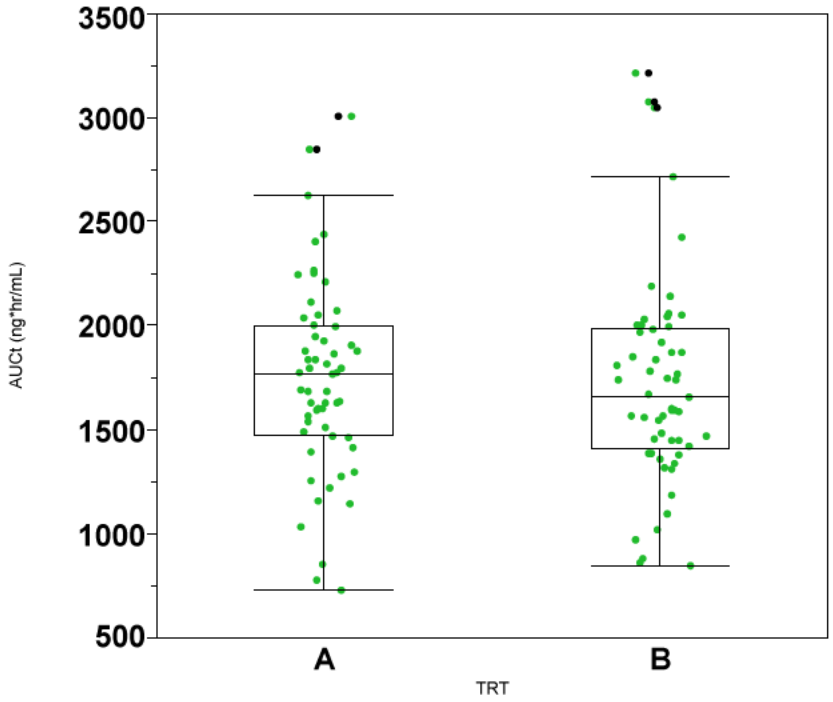

Figure 15. Box plot for the individual edoxaban AUCt values following single administration of the treatments. Constructed using data provided on Aug 13, 2014 in response to IR letter.

The statistical results reported by the Applicant are summarized in Table 9 and 10 for the parent compound and metabolite, respectively. This Reviewer run average BE and scaled-average BE analysis using Phoenix software given the nature of the data (replicated design and the %CV for Cmax was higher than 30%). The results of these analyses are summarized on Tables 11, 12, and 13 for the Cmax, AUCt, and AUCinf, respectively.

Table 9. Statistical Comparisons of the PK Parameters of **Edoxaban** between Treatments A and B

PK Parameters Edoxaban	**Geometric LSM**		**Ratio A/B (%)**	**90% CI (%)**	**Intra-Subject CV%**	
	Treatment A (Test)	**Treatment B (Reference)**			**Treatment A (Test)**	**Treatment B (Reference)**
AUC_{last} (ng·h/mL)	1668	1632	102.18	(96.37,108.35)	18.5	19.0
$AUC_{0\text{-}inf}$ (ng·h/mL)	1695	1670	101.50	(95.88, 107.44)	18.4	17.9
C_{max} (ng/mL)	227.3	220.9	102.90	(91.77, 115.39)	35.6	36.5
C_{24} (ng/mL)	10.62	10.37	102.34	(92.84, 112.82)	28.8	27.3

Table 10. Statistical Comparisons of the PK Parameters of **D21-2393** between Treatments A and B

PK Parameters D21-2393	**Geometric LSM**		**Ratio A/B (%)**	**90% CI (%)**	**Intra-Subject CV%**	
	Treatment A (Test)	**Treatment B (Reference)**			**Treatment A (Test)**	**Treatment B (Reference)**
AUC_{last} (ng·h/mL)	129.8	128.1	101.26	(94.61, 108.38)	23.0	20.6
$AUC_{0\text{-}inf}$ (ng·h/mL)	132.5	131.5	100.70	(94.28, 107.56)	22.3	19.5
C_{max} (ng/mL)	18.35	18.21	100.75	(89.73, 113.11)	38.3	37.1
C_{24} (ng/mL)	0.9019	0.8962	100.64	(91.27, 110.97)	28.6	27.1

Table 11. Statistical Analysis for **Edoxaban Cmax** between Treatments A and B

	Reviewer's BE analysis for CMAX*					
	Average Bioequivalence (ABE)			Referenced Scaled Average Bioequivalence (RSABE)		
Assessment	Ratio (%)	90% CI Lower	90% CI Upper	sWR [>=0.294]	Point Estimate [0.80, 1.25]	Critical Bound [<=0]
USE RSABE: **Criteria Met**	102.90	91.77	115.39	0.359	1.0253	-0.0634

* Run based data provided on Aug 13, 2014 in response to IR letter using Phoenix software.

Table 12. Statistical Analysis for **Edoxaban AUCt** between Treatments A and B

	Reviewer's BE analysis for AUCt*					
	Average Bioequivalence (ABE)			Referenced Scaled Average Bioequivalence (RSABE)		
Assessment	Ratio (%)	90% CI Lower	90% CI Upper	sWR [>=0.294]	Point Estimate [0.80, 1.25]	Critical Bound [<=0]
USE UNSCALED ABE: sWr < 0.294	102.18	96.37	108.35	0.189	1.0319	-0.0157

*Run based data provided on Aug 13, 2014 in response to IR letter using Phoenix software.

Table 13. Statistical Analysis for **Edoxaban AUCinf** between Treatments A and B

	Reviewer's BE analysis for AUCinf*					
	Average Bioequivalence (ABE)			Referenced Scaled Average Bioequivalence (RSABE)		
Assessment	Ratio (%)	90% CI Lower	90% CI Upper	sWR [>=0.294]	Point Estimate [0.80, 1.25]	Critical Bound [<=0]
USE UNSCALED ABE: sWr < 0.294	101.50	95.88	107.44	0.174	1.0257	-0.0131

*Run based data provided on Aug 13, 2014 in response to IR letter using Phoenix software.

Reviewer's Comments

The results summarized in Tables 9 through 13 showed that the 60 mg tablet meets the requirements for BE in terms of Cmax, AUCt and AUCinf when compared to the 30 mg tablets. Note that the CV for Cmax was higher than 30% and therefore, this Reviewer ran scaled average BE analysis. Since the intra-subject standard deviation (sWR) was lower than 0.294 for the AUCt and AUCinf, unscaled ABE should be used to make conclusions in terms of bioequivalency for the parent compound of this product. The BE analysis for the metabolite shows that the BE criteria is also met for this component (Table 10).

D) DISSOLUTION APPLICATIONS

D.1 BIOWAIVERS

15. Is there a request for waiver of in vivo BE data (Biowaiver)? What is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?

There were no biowaivers being request in this submission.

16. Is there any IVIVC information submitted? What is the regulatory application of the IVIVC in the submission? What data is provided to support the acceptability of the IVIVC?

There were no IVIVC models included.

17. Is there any in vitro alcohol dose-dumping information submitted? What data are provided to support the Applicant's claim (e.g. lack of dose-dumping in the presence of alcohol)?

Not applicable.

D.2 SURROGATES IN LIEU OF DISSOLUTION

18. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data is available to support this claim?

No. In laboratory dissolution testing is being implemented.

D.3 DISSOLUTION AND QBD

19. ***If the application contains QbD elements, is dissolution identified as a CQA for defining design space?***

The manufacturing process development of edoxaban tablets was conducted according to a quality by design (QbD) principles (b) (4)

[redacted]

21 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

4. *Since the dissolution method and acceptance criterion were found unacceptable, the input variables should be revised based on an assessment of the variables* (b) (4) (b) (4) *is based on passing an acceptance criterion of Q≥* (b) (4) *at 30 min and on a dissolution method that is considered less than optimum. Therefore, the design space should be revised once the results of the post marketing commitment are submitted.*

Therefore, the following comments were conveyed to the Applicant on an IR letter dated Aug 26, 2014:

1. ***Withdraw from your NDA submission the dissolution model and*** (b) (4) ***for dissolution.***

   Daiichi Sankyo's Response received on Sep 05, 2014 are as follows: "Yes, we agree to withdraw the dissolution model and (b) (4) e for dissolution from the NDA submission. To effect the withdrawal, we agree to amend Section 3.2.P.2.3, Section 3.2.P.3.3, and Section 3.2.P.3.4 noting that the dissolution model is withdrawn and subsequent necessary changes. We will also revise Section 3.2.P.5.1 Specifications, delete methods used for dissolution (b) (4) and, where necessary, create new IPC method files under Section 3.2.P.3.4"

2. ***If you develop a new*** (b) (4) ***dissolution model with the new dissolution method, please consider the following:***

   a. ***In order to mitigate the risk that is not addressed by the model, include*** (b) (4) ***in the model. Alternatively, provide rationale with supporting data justifying the use of an alternative approach.***

   b. (b) (4) ***construct and validate the model using 'individual mean' values of the relevant variables measured throughout the manufacturing run (e.g., 6 mean values of tablet density).*** (b) (4) ***Therefore, the model should predict 'individual mean***

dissolution, where the inputs to the model are the 'individual means of selected input variables measured throughout the manufacturing run.

c. ***For model prediction purposes, it is recommended that the 95% one-sided lower confidence limit for the individual mean prediction be ≥ (b) (4) % for the dissolution acceptance criterion. This acceptance criterion is consistent with USP <711> Stage 1 criterion of Q+5 for each individual tablet.***

d. ***As part of drug product's Continuous Process Verification, we recommend that you track all process variables and in-process attributes that have a potential to impact dissolution during routine production in a multivariate manner e.g. via use of MSPC(multivariate statistical process control).***

Daiichi Sankyo's Response received on Sep 6, 2014 is as follows:

"Should we develop a new (b) (4) dissolution model, we will take the FDA's recommendations into consideration and further consult with the FDA concerning their recommendations".

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

/s/

SANDRA SUAREZ
09/09/2014

ANGELICA DORANTES
09/09/2014

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

In this submission Daiichi Sankyo Co. is seeking authorization to market edoxaban, a factor Xa (FXa) inhibitor, for the following indications (1) risk reduction of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (Afib) (2) treatment of deep vein thrombosis (DVT) (b) (4) pulmonary embolism (PE) (b) (4) The proposed dose is 60 mg to be administered orally once daily. A dose reduction to 30 mg once daily is proposed in patients with one or more of the factors listed below.

- (b) (4)
- Body weight < 60 Kg
- Concomitant use of P-gp inhibitors (except amiodarone)

Edoxaban immediate release tablets will be marketed in strengths of 15, 30 and 60 mg.

Sixteen *in vitro* studies (metabolism, transport, protein binding), 43 *in vivo* clinical pharmacology studies (pharmacokinetics and pharmacodynamic, effect of intrinsic and extrinsic factors, transitioning to and from other anticoagulants), six biopharmaceutics studies, nine Phase 2 studies (five Afib/ four VTE) and two warfarin controlled Phase 3 studies (ENGAGE-AF and Hokusai VTE) are submitted in support of safety and claims. Plasma concentrations of edoxaban and its major active metabolite D21-2393 were collected in most Phase 1 / 2 studies and in all subjects in Phase 3. Anti FXa activity, D-dimer and PT/INR were assessed in all subjects in Phase 3. Details of the submission are presented below.

	Information		Information
NDA/BLA Number	206316	**Brand Name**	Savaysa
OCP Division (I, II, III, IV, V)	I, V, DPM, genomics	**Generic Name**	Edoxaban
Medical Division	DCRP, DHP	**Drug Class**	FXa inhibitor
OCP Reviewer(s)	Young-Jin Moon, Robert Schuck, Divya Menon-Andersen	**Indication(s)**	SPAF, treatment of DVT and PE
OCP Team Leader(s)	Julie Bullock, Mike Pacanowski, Nitin Mehrotra, Jeff Florian, Raj Madabushi	**Dosage Form**	Immediate release tablet
Pharmacometrics Reviewer(s)	Justin Earp, Jiang Liu	**Dosing Regimen**	Once daily
Date of Submission	01/08/2014	**Route of Administration**	Oral
Estimated Due Date of OCP Review	09/08/2014	**Sponsor**	Daiichi Sankyo Co.
Medical Division Due Date	09/08/2014	**Priority Classification**	Standard
PDUFA Due Date	01/08/2015		

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 identifiers
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	14	14	DPC/10, DPC/10A, DPC/10B, QBR113951, QB01- Plasma (b) (4) 07670VDAC DEN, 080091PVKLN_DEN_R2 –Plasma (b) (4) DPC/73, QBR103759/1, QBR103223/2, 090568XVJB_DEN- Plasma ((b) (4) cross validation), DPC/11, DPC/11A, QBR113951QB01- Urine (b) (4)
I. Clinical Pharmacology				

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

Mass balance:	X	1	1	PRT019 –60 mg ^{14}C edx
Isozyme characterization:	**X**	2	2	B041111, PBC314-473
Blood/plasma ratio:	**X**	1	1	AE-3868-G
Plasma protein binding:	**X**	1	1	AE-3867-G, AM10-C0090-R01
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**X**	3	3	PRT001, J01, A-U147
multiple dose:	**X**	2	1	PRT001
Patients-				
single dose:				
multiple dose:	**X**	7	4	PRT018, J307, PRT007, PRT011 Sparse PK/PD sampling in Phase 2 studies
Dose proportionality -				
fasting / non-fasting single dose:	**X**	1	1	A-U147
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	16	16	A-U139 (Quindine/IV edx), A-U129 (Quinidine), A-U131 (Amiodarone), A-U141 (Dronedarone), A-U128 (Naproxen), PRT017 (ASA LD), A-U127 (ASA HD), PRT016 (Keto), A-U130 (Verapamil), A-E132 (Erythromycin), A-U138 (CsA), A-U156 (Esomeprazole), PRT012 (Esomeprazole), A-U137 (Rif), PRT014 (Dig), A-E133 (Atorvastatin)
In-vivo effects of primary drug:	**X**	4	4	PRT017, A-U127, A-U129, PRT014
In-vitro:				
Subpopulation studies -				
ethnicity:	**X**	3	3	PRT020 (Japanese/Caucasian), A-A123 (Chinese), PRT010 (Japanese)
gender:	**X**	1	1	PRT002 (Age/gender)
pediatrics:				
geriatrics:				
renal impairment:	**X**	2	2	A-U120 (Normal/Mild/Mod/Severe/ESRD), A-U146 (receiving dialysis)
hepatic impairment:	**X**	1	1	A-E134 (Normal/CP A/CP B)
PD –				
Phase 1	X	3	3	PRT003(Shed blood model), PRT005(Badimon perfusion chamber), PRT009 (comparison with dalteparin, ximelagatran)
Phase 2:	**X**	9	4	PRT018, J307, PRT007, PRT011 (Sparse PK/PD sampling)
Phase 3:	**X**	6	2	ENGAGE-AF (C-U301), Hokusai VTE (D-U305) (Sparse PK/PD sampling)
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	11	6	PRT001, J-01, PRT018, J307, PRT007, PRT011
Phase 3 clinical trial:	**X**	2	2	ENGAGE-AF (C-U301), Hokusai VTE (D-U305)
Population Analyses -				
Data rich:	**X**	8	8	
Data sparse:	**X**	5	5	
II. Biopharmaceutics				
Absolute bioavailability	**X**	1	1	A-U139
Relative bioavailability -				
solution as reference:	**X**	3	2	PRT001 (SAD/MAD), PRT004 (absorption site)
alternate formulation as reference:	**X**	1	0	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	**X**	2	-	A-U142 (pivotal BE) will be reviewed by ONDQA BPH as per MoU dated 02/04/2014
Food-drug interaction studies	**X**	5	1	A-U148 (to-be marketed formulation)
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				

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

Genotype/phenotype studies	**X**	1	1	Analyses of data from multiple studies
Chronopharmacokinetics				
Pediatric development plan				
Switching/reversal studies	**X**	5	5	A-U136 (Enoxaparin), C-U122 (Warf), A-U151 (Riv/Dabi), A-E152 (Apx), A-U150 (PCC)
***In vitro* transport/CYP inhibition or induction**	**X**	8	8	
Literature References				
Total Number of Studies		55 11 (Phase 2)	38 (Phase 1) 4 (Phase 2) 2 (Phase 3)	Only *in vivo* studies counted

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			To be reviewed by ONDQA BPH as per MoU dated 02/04/2014
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
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			Please see footnote[1]
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
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		Please submit patient-level genotype results as a SAS XPORT file. If these data have already been submitted then please identify the file location.
	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	X			

[1] The applicant discovered and subsequently remedied irregularities at (b) (4) one of the two bioanalytical sites. This issue was presented to DCRP and DHP, and there was agreement on the proposed remedial measures. Relevant information can be found in DARRTS (IND 77254, date 10/25/2012) and in section 5.3.5.4 of the submission.

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

	designed and analyzed dose-ranging or pivotal studies)?				
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			Please see footnote[2]
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.

Young-Jin Moon, Divya Menon-Andersen	02/18/2014
Reviewing Clinical Pharmacologist	Date
Julie Bullock, Raj Madabushi	02/18/2014
Team Leader	Date

[2] A full waiver was granted for the SPAF indication (IND 77254, DARRTS date 11/25/2013) and a PPSR was submitted and reviewed for VTE (IND 63266 DARRTS date 11/01/2013).

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

/s/

DIVYA MENON ANDERSEN
02/18/2014

YOUNG J MOON
02/18/2014

JULIE M BULLOCK
02/19/2014

RAJANIKANTH MADABUSHI
02/19/2014