

FDA Draft Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

Meeting Date: 30 October 2014

NDA: 206316

Sponsor: Daiichi Sankyo

Drug: SAVAYSA (edoxaban) Tablets

Indication for Use: SAVAYSA is indicated for the prevention of stroke and systemic embolism (blood clots other than in the head) in patients with nonvalvular atrial fibrillation (A Fib; abnormally rapid and chaotic contractions of the atria, the upper chambers of the heart)

Title of Study: **ENGAGE AF-TIMI 48** - A Phase 3 Randomized, Double-Blind, Double-Dummy, Parallel Group, Multi-Center, Multi-National Study for Evaluation of Efficacy and Safety of DU-176b versus Warfarin in Subjects with Atrial Fibrillation - Effective anticoaGulation with factor xA next Generation in Atrial Fibrillation (DU176b-C-U301/TIMI 48)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the edoxaban New Drug Application (NDA) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

This document is based on the applicant's information as submitted up to 24 September 2014

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FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

FDA White Oak Campus, Building 31, the Great Room (Rm. 1503)

White Oak Conference Center, Silver Spring, Maryland

October 30, 2014

DRAFT POINTS TO CONSIDER

The Advisory Committee will consider the approvability of edoxaban, an oral antagonist of activated coagulation factor X (FXa), for use to reduce the rate of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAf). Edoxaban is also proposed for use in the treatment of venous thromboembolism, but that indication is not being considered at this meeting.

The applicant conducted one large outcome trial relevant to the proposed NVAf indication: ENGAGE-AF-TIMI 48. This large event-driven, non-inferiority, double-dummy trial compared two dosing regimens of edoxaban, a high-exposure and a low-exposure arm, to warfarin in adult patients with NVAf and a baseline CHADS₂ score of 2 or more (signifying at least a moderately elevated risk of stroke and a need for treatment with an oral anticoagulant per current treatment guidelines for NVAf). In the edoxaban high exposure arm, the dose for most subjects was 60 mg once daily (OD); in the low exposure arm it was 30 mg OD. In both arms, subjects who met one or more of the three dose reduction criteria (creatinine clearance ≤ 50 mL/min, weight ≤ 60 kg, or use of specified P-gp inhibiting drugs) were treated with half the usual dose (i.e., with 30 mg OD and 15 mg OD in the high exposure and low exposure arms, respectively). Warfarin dosing was based on INR, with a target of 2.0 to 3.0.

The primary efficacy endpoint in ENGAGE-AF was the time to the composite of stroke (any type) or systemic embolism, similar to the primary endpoints of the confirmatory trials of the three other direct acting oral anticoagulants approved in the US since 2011. The non-inferiority margin in ENGAGE-AF was a hazard ratio of 1.38, consistent with FDA's recommendation.

ENGAGE was a well-conducted trial with no important deficiencies in execution. Both the edoxaban high exposure (E60/30) regimen and the edoxaban low exposure (E30/15) regimen were non-inferior to warfarin for the primary endpoint. It should be noted that the rather wide non-inferiority margin associated with warfarin's large effect on preventing ischemic stroke allows a drug with substantially less efficacy than warfarin to meet the test of non-inferiority. In fact, the point estimate for the HR for E30/15 vs. warfarin comparison was > 1 , and the results were not far from meeting conventional superiority criteria favoring warfarin over E30/15. Results for the comparison of E60/30 vs. warfarin numerically favored E60/30 and supported non-inferiority, but narrowly fell short of establishing superiority of edoxaban in the prespecified superiority analysis (Table 1). In the primary safety analyses of time to major bleeding on treatment, both edoxaban dosing regimens were superior to warfarin. Only the high-exposure regimen is recommended for use in proposed labeling.

Table 1 ENGAGE-AF Primary Endpoint Results

E30/15 (KM %)	E60/30 (KM %)	Warfarin (KM %)	HR (95% CI)*	P
<i>Non-inferiority analysis (MITT population, on treatment)</i>				
1.61	1.18	1.50	1) 1.07 (0.87, 1.31) 2) 0.79 (0.63, 0.98)	1) 0.0055 ^a 2) <0.0001 ^a
<i>Superiority analysis (ITT population, overall study period)</i>				
2.04	1.57	1.80	1) 1.13 (0.98, 1.31) 2) 0.87 (0.74, 1.02)	1) 0.10 ^b 2) 0.08 ^b

MITT population: all randomized subjects who received at least one dose of study treatment

* 1): E30/15 vs. warfarin; 2): E60/30 vs. warfarin

^a p for non-inferiority

^b p for superiority

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Although the above overall findings support effectiveness, efficacy outcomes by baseline renal function have potential implications for approval or labeling. In subjects with normal renal function, defined as estimated creatinine clearance (CrCl) ≥ 80 mL/min, the hazard ratio for the primary endpoint favored warfarin over the edoxaban high exposure regimen (HR=1.41, 95% CI: 0.97, 2.05). This is a directional reversal of the results observed in the overall trial results and subgroups with impaired renal function. Results for the low exposure arm showed the same pattern of worsened results for edoxaban in patients with normal renal function, but with consistently less favorable results for edoxaban than with high exposure (Table 2).

Table 2 Primary Endpoint Results by Renal Function Subgroup
 MITT Population, On Treatment

Stroke/SEE		n(N)	Event Rate %/yr	HR vs. W
overall	W	232 (7012)	1.50	
	E30	253 (7002)	1.61	1.07 (0.87, 1.31)
	E60	182 (7012)	1.18	0.79 (0.63, 0.98)
30 -<=50	W	49 (1297)	1.98	
	E30	58 (1274)	2.33	1.19 (0.81, 1.74)
	E60	43 (1287)	1.73	0.88 (0.59, 1.33)
>50- <80	W	135 (3030)	2.01	
	E30	115 (3034)	1.66	0.82 (0.64, 1.05)
	E60	69 (2985)	1.04	0.51 (0.38, 0.69)
≥ 80	W	47 (2595)	0.76	
	E30	76 (2611)	1.22	1.61 (1.12, 2.32)
	E60	66 (2612)	1.07	1.41 (0.97, 2.05)

E30 = Low exposure arm; E60 = High Exposure Arm

Note that most subjects in the lowest Cr Cl had a dose reduction to 50% of the usual dose, resulting in substantially reduced exposure to edoxaban despite their reduced renal function.

Results for stroke subtypes overall and across renal function subgroups are shown in Table 3. The effect of edoxaban on ischemic stroke compared to warfarin was neutral overall for the high exposure group but was substantially reduced in subjects with normal renal function. However, in the mild renal impairment group (i.e., creatinine clearance >50 to <80 mL/min), the results favored the edoxaban high exposure arm. Overall and in each renal function subgroup, ischemic stroke rates favored warfarin over the low exposure arm, most notably in the normal renal function subgroup.

Consistent with the results in studies of the approved direct acting anticoagulants, analyses of hemorrhagic stroke favored both the edoxaban low and high exposure arms compared to warfarin overall and in each renal function subset, but the number of strokes in each renal function subgroup is small in the edoxaban arms, making it difficult to understand trends across these subgroups. Overall results for the low dose regimen were more favorable than for the high dose regimen for hemorrhagic stroke. Analyses of major bleeding overall favored both edoxaban exposure arms over warfarin, with better results for the low exposure arm: (low exposure arm vs. warfarin, HR=0.47 ((0.41, 0.55); high exposure arm vs. warfarin, HR=0.80 (0.71, 0.91). The renal function subgroup data for major bleeding had a reversed pattern from the efficacy results, i.e., the edoxaban subgroup with the most

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DRAFT POINTS TO CONSIDER (cont.)

favorable results for efficacy (the mild renal impairment subgroup) had the least favorable results for safety compared to warfarin (Figure 2). In the subset of subjects from ENGAGE-AF who had PK samples and who were not dose adjusted, geometric mean pre-dose Edoxaban exposure levels were about 30% less in the normal renal function subgroup than in the mild renal impairment subgroup for both doses. Therefore, the interaction of renal function with drug effects is consistent with the effect of renal function on edoxaban exposure. These results suggest that patients with normal renal function did not receive a fully effective dose of edoxaban.

Table 3 Time to Stroke Subtypes by Renal Function Subgroup
 MITT population, on treatment

Ischemic Stroke/ Cr Cl subgroup		n(N)	%/yr	HR vs. W
overall	W	144 (7012)	0.93	
	E30	226 (7002)	1.43	1.55 (1.26, 1.91)
	E60	135 (7012)	0.87	0.94 (0.75, 1.19)
30-≤50	W	28 (1348)	1.09	
	E30	55 (1274)	2.21	2.04 (1.29, 3.24)
	E60	30 (1287)	1.29	1.12 (0.67, 1.89)
>50- <80	W	83 (3030)	1.23	
	E30	98 (3034)	1.42	1.13 (0.85, 1.51)
	E60	51 (2985)	0.77	0.62 (0.43, 0.87)
≥80	W	33 (2595)	0.53	
	E30	69 (2611)	1.11	2.09 (1.38, 3.16)
	E60	52 (2612)	0.84	1.58 (1.02, 2.45)
Hemorrhagic Stroke/ Cr Cl subgroup		n(N)	%/yr	HR vs. W
overall	W	76 (7012)	0.49	
	E30	18 (7002)	0.11	0.23 (0.13, 0.38)
	E60	40 (7012)	0.26	0.53 (0.36, 0.77)
30-≤50	W	18 (1297)	0.72	
	E30	0 (1274)	0	---
	E60	11 (1287)	0.44	0.61 (0.29, 1.28)
>50- <80	W	45 (3030)	0.66	
	E30	11 (3034)	0.16	0.24 (0.12, 0.46)
	E60	16 (2985)	0.24	0.36 (0.20, 0.64)
≥80	W	13 (2595)	0.21	
	E30	7 (2611)	0.11	0.53 (0.21, 1.34)
	E60	11 (2612)	0.18	0.85 (0.38, 1.9)

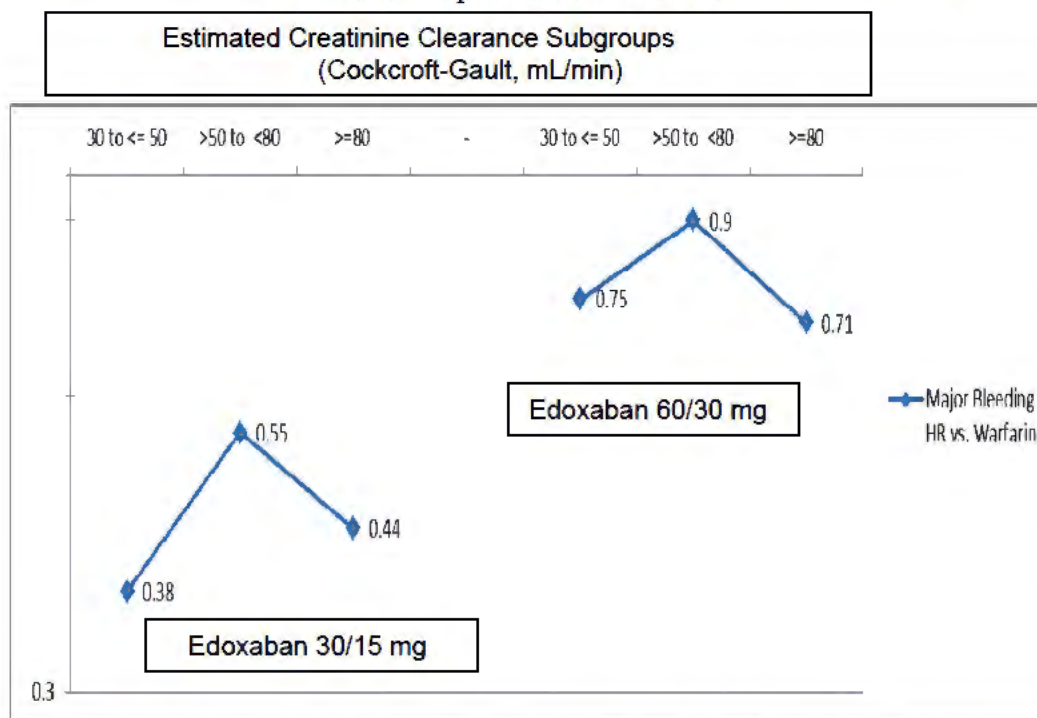
W= warfarin arm; E30 = edoxaban low exposure arm; E60 = edoxaban high exposure arm

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DRAFT POINTS TO CONSIDER (cont.)

Figure 1 ENGAGE AF: Major Bleeding Results by Renal Function Subgroup
 MITT Population on Treatment



Note that most subjects in the lowest Cr Cl subgroup had a dose reduction to 50% of the usual dose, resulting in substantially reduced exposure to edoxaban.

We would like the CRDAC to consider regulatory options here in the context of available treatments for edoxaban's proposed indication, which is the same as for 3 marketed products in the same or a closely related pharmacologic class. Each of these marketed drugs was approved on the basis of a confirmatory trial with a warfarin control arm and the same primary endpoint as ENGAGE-AF. All 3 drugs had substantially lower rates of hemorrhagic stroke than warfarin, but only one (dabigatran) had a lower rate of thromboembolic stroke, and this finding was dose-dependent. Two of the drugs (dabigatran and apixaban) had a lower rate of the composite primary endpoint (stroke or systemic embolism, but the vast majority of events were strokes) than warfarin, while one was non-inferior. One (apixaban) had a lower rate of major bleeding than warfarin, while the other two had rates similar to warfarin's at their marketed doses. While only dabigatran has substantial concentration-response data, these data are consistent with the data for edoxaban suggesting that there are concentration-related effects on bleeding and ischemic stroke that go in opposite directions. Also, as with edoxaban, there was a substantially reduced rate of hemorrhagic stroke compared to warfarin for all studied doses of the 3 approved direct acting anticoagulants (Table 3). While the effect on hemorrhagic stroke was similar both studied doses of dabigatran, for edoxaban the rate of hemorrhagic was higher in the high exposure arm than with low exposure.

Table 4 Summary of Findings for Key Outcomes in Trials of Marketed Direct-Acting Oral Anticoagulants
 Hazard Ratio and 95% CI vs. warfarin for each outcome

Drug	Stroke/SE	Ischemic Stroke	Hemorrh. Stroke	Major Bleeding
Dabigatran 110 mg bid	0.90 (0.74, 1.10)	1.13 (0.89, 1.42)	0.31 (0.17, 0.56)	0.80 (0.70, 0.93)
Dabigatran 150 mg bid	0.65 (0.52, 0.81)	0.75 (0.58, 0.97)	0.26 (0.14, 0.49)	0.93 (0.81, 1.07)
Rivaroxaban 20 mg OD	0.88 (0.74, 1.03)	0.94 (0.75, 1.17)	0.59 (0.37, 0.93)	1.04 (0.90, 1.20)
Apixaban 5 mg bid	0.79 (0.66, 0.95)	1.02 (0.81, 1.29)	0.51 (0.35, 0.75)	0.69 (0.60, 0.80)

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DRAFT POINTS TO CONSIDER (cont.)

Edoxaban has no proven advantages over any of the 3 direct-acting anticoagulants approved for stroke prevention in patients with atrial fibrillation. A new drug (1) with less effectiveness in preventing stroke in patients with normal renal function; (2) in a setting where 3 other therapies are available that have not been observed to be substantially less effective than warfarin in patients with normal renal function; and (3) without established advantages relative to the 3 other products, would usually lead to a complete response. However, several alternative approaches are proposed:

- Dose adjustment based on exposure-matching is routinely applied by the Agency for deriving recommended dosing in sub-populations, even when those that were not represented in the registration trials; accounting for exposure changes resulting from drug-drug interactions or mitigating safety concerns while maintaining acceptable efficacy. For example, for drugs that are excreted, we commonly recommend a reduced dose for patients with impaired renal function based on PK results, without requiring confirmation of efficacy. Conversely, in ENGAGE AF, patients with mild renal impairment had the most favorable balance of benefits and risks among renal function categories in ENGAGE AF, suggesting that they received effective concentrations that were not associated with unacceptable bleeding risk. Based on exposure-response analyses, dosing instructions for patients with normal renal function can be derived to match exposure to that observed in patients with mild renal impairment. Using this approach, the edoxaban dose required in patients with normal renal function will be more than the 60 mg studied in ENGAGE AF, but there is limited experience with doses higher than 60 mg in Phase 1. There are obvious concerns with recommending a higher dose than has been studied in long-term trials, although the increase in dose could be modest.
- Another option would be to retain 60 mg OD as the highest recommended dose, but with labeling intended to limit use of edoxaban to patients with impaired renal function.

There is also concern about the need for dose reduction in patients with weight ≤ 60 kg, those taking P-gp inhibitors, and patients with moderate renal impairment.

The advisory committee will be asked to consider the issues and options described above in its deliberations regarding the approval of edoxaban.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206316
Priority or Standard	Standard
Submit Date(s)	January 8, 2014
Received Date(s)	January 8, 2014
PDUFA Goal Date	January 8, 2015
Division / Office	DCaRP/ ODE I/ OND
Reviewer Name(s)	Melanie J. Blank, M.D. – efficacy Tzu-Yun McDowell, Ph.D. - safety
Review Completion Date	October 2, 2014
Established Name	Edoxaban
(Proposed) Trade Name	Savaysa
Therapeutic Class	Oral Anticoagulant
Applicant	Daiichi Sankyo
Formulation(s)	Tablet
Dosing Regimen	Once Daily
Indication(s)	Reduction in the risk of stroke and system embolism in patients with nonvalvular atrial fibrillation
Intended Population(s)	Adults with nonvalvular atrial fibrillation

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Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

After considering the overall trial data, subgroup analyses and exposure-outcomes relationships in the context of 3 other approved novel oral anticoagulants (NOACs) the primary clinical reviewers are currently recommending approval of edoxaban 60 mg QD in patients with NVAf, with a limitation of use to patients with abnormal renal function (CrCL by Cockcroft-Gault estimation < 80 mL/min).

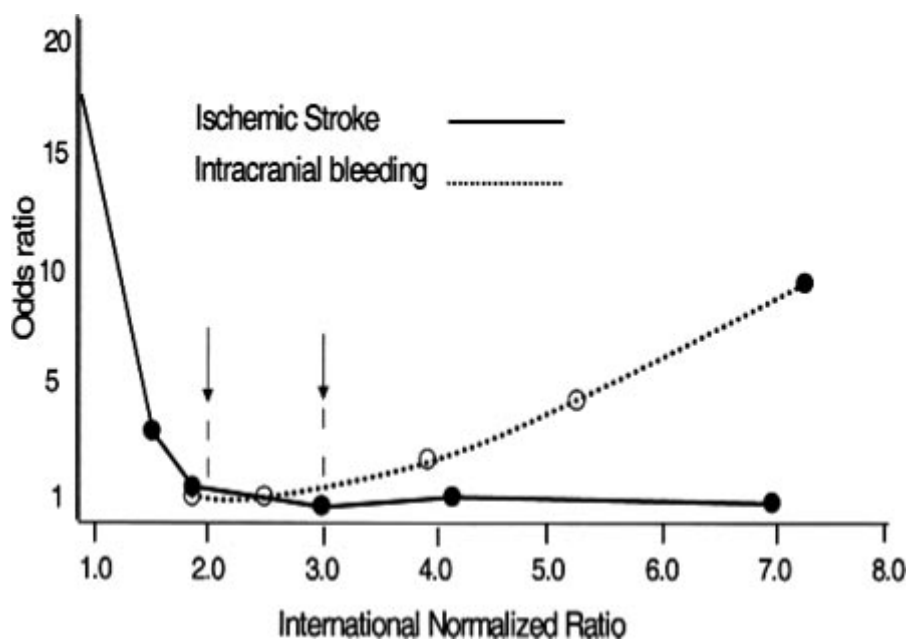
Edoxaban, if approved, will be the 4th approved NOAC and the 3rd approved Factor Xa inhibitor in the U.S for prevention of stroke and systemic embolic event (SEE) in patients with nonvalvular atrial fibrillation (NVAf) who qualify for anticoagulant therapy according to current ACC/AHA/ESC practice guidelines. The first NOAC approved on 10/19/2010 was dabigatran, a direct thrombin inhibitor, which was followed by rivaroxaban, a Factor Xa inhibitor (approved on 7/1/11) and apixaban, a Factor Xa inhibitor (approved on 12/28/12). As these products' labels show, dabigatran, the first NOAC to be approved met its prespecified criteria for superiority to warfarin for stroke/SEE prevention. It also was superior to warfarin on the 2 components of stroke: ischemic and hemorrhagic stroke. Rivaroxaban was found to be non-inferior to warfarin but superiority was not demonstrated. Apixaban was found to be superior to warfarin for stroke/SEE reduction as well as for major bleeding. It was superior on only hemorrhagic component of stroke. To put this in perspective, it should be remembered that warfarin is extremely effective at preventing stroke in NVAf. Warfarin was shown to reduce ischemic stroke by ~66% in the EAFT trial¹ with a targeted INR of 2.5 - 4.0 compared to placebo. Stroke reduction rate was even higher when INR was between 2 and 3. Refer to **Error! Reference source not found.** from the 2011 Update of ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation² which illustrates the efficacy of warfarin.

Edoxaban is also under review by another FDA division for the treatment of venous thromboembolism (VTE). The data to support the VTE indication was not considered in this review.

¹ "Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) study group". Lancet 1993;342:1255-62.

² "2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC2006 Guidelines for the Management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines". Circulation 2011; 123:e269-e367.

Figure 1: Odds ratio of ischemic stroke/ intracranial bleeding by INR; analysis of observational study in outpatients taking warfarin



*Data from Hylek et al, Ann Intern Med 1994; 120:897-902), Figure from ACC/AHA/ESC Practice Guidelines, Figure 10

There was one pivotal event-driven trial for edoxaban to support the indication of atrial fibrillation; “Effective aNticoagulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE AF-TIMI 48, referred to as ENGAGE AF throughout this review). It was a well conducted, large (21,105 subjects enrolled), double-blinded, double-dummy, randomized, parallel-group, multinational study. It was an active-controlled trial and warfarin (with a targeted INR of 2-3) was the comparator. To enroll, subjects had to have nonvalvular AF and be candidates for anticoagulation therapy according to current ACCF/AHA/HRS guidelines. Two edoxaban dosing were tested: 60 mg dose adjusted (DA) to 30 mg for subjects who met any of the following criteria: creatinine clearance (CrCL) \leq 50 mL/min, on P-gp inhibitors (verapamil, quinidine or dronedarone) or weight \leq 60 kg; or 30 mg DA to 15 mg using the same criteria.

There was a special protocol assessment, signed on October 15, 2008. ENGAGE AF was conducted between November 14, 2008 and May 24, 2013, inclusive. The protocol was amended several times. The only significant amendments were: 1) 2nd Amendment, April 12, 2010 – to increase sample size because of fewer events than anticipated; 2) 4th Amendment, August 26, 2010 – for safety purposes, the warfarin 5 mg tablet was removed; and 3) 7th Amendment, November 7, 2011, when the transition plan to other anticoagulants was added to decrease the risk of stroke/SEE when coming off treatment, a problem that has been seen in other NOAC trials. The finalized SAP was submitted on January 31, 2011.

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As one would expect from such a large trial, the treatment groups were well matched demographic and baseline disease-specific characteristics. The population was predominantly elderly (median age was 72 years), Caucasian (~80%), and male (~60%). There were very few Black subjects (~1%). Most subjects had hypertension and > 50% had a history of congestive heart failure. Approximately 30% had prior strokes or TIAs. Approximately 40% were VKA naïve. Approximately 30% were on aspirin at baseline. Much of the world (with the exception of Africa) was represented in the trial. Approximately 25% of subjects in the edoxaban arms had their dose adjusted at baseline. Most subjects who were dose reduced had low CrCL +/- other factors (~75% of the dose adjusted subjects). The rest of the dose adjusted subjects were dose adjusted because of weight alone (≤ 60 kg) or because of concomitant use of P-gp inhibitors (verapamil, quinidine or dronedarone).

Of 25,497 subjects screened who signed informed consent forms, 4,392 subjects (17%) were never randomized to receive study drug because protocol eligibility criteria were not met. Of the 21,105 subjects who were randomized and assigned to treatment, 79 never received treatment with study drug. Therefore, a total of 21,026 subjects were treated with study drug. Most subjects were followed to the end of the trial and the median study follow-up was 2.8 years, longer than the other pivotal trials for the approved NOACs.

The primary non-inferiority analysis was the time to first adjudicated stroke/SEE in the mITT population in the on treatment period. The mITT population included only subjects who received at least one dose of drug; and the on-treatment period was the period during which the subject took study drug unless the patient had early drug discontinuation(s) in which case the on-treatment period included the 3 days following drug discontinuation(s). The primary analysis was designed to demonstrate that at least one edoxaban treatment regimen was non-inferior to warfarin at a non-inferiority margin of 1.38, using a pairwise comparison significance level of $\alpha=0.05/2$ (where 2 = the number of comparisons for non-inferiority). The results were positive for both doses: edoxaban 30 mg: hazard ratio (HR): 1.07 (0.87-1.31), $p < 0.01$ and edoxaban 60 mg: HR: 0.79 (0.63-0.99), $p < 0.0001$. Therefore, both doses met the prespecified non-inferiority criteria compared to warfarin and could be considered for approval. The constancy assumption regarding the warfarin control was satisfied, making it possible to interpret the non-inferiority analyses (Table 119).

The superiority analysis was prespecified to be done in the high dose edoxaban group in the ITT population during the overall study period at a significance level of 0.01. The overall results for the 60 mg group were close to meeting the superiority criteria. Fewer subjects in the edoxaban 60 mg group experienced stroke or SEE than the warfarin group (1.57% and 1.80% per year, respectively), with a HR of 0.87 (95% CI: 0.74-1.02, $p=0.08$). However, the null hypothesis for superiority was not rejected.

In the mITT population, on treatment analysis, most of the adjudicated primary endpoint events were ischemic strokes (62% – 89% depending on the treatment group). There

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were very few SEEs (~5% of the adjudicated primary endpoint events). Of the adjudicated primary endpoint events, 7 - 33% were hemorrhagic strokes and 18 - 23% of the adjudicated primary endpoint events were disabling stroke (Modified Rankin score 3-5). It is notable that the subcomponent event that drove the primary efficacy analysis was hemorrhagic stroke [HR (95% CI): 0.23 (0.14-0.39), nominal $p < 0.01$ for edoxaban 30 mg (15 mg DA) and HR (95% CI): 0.53 (0.36-0.78), nominal $p < 0.01$ for edoxaban 60 mg (30 mg DA)]. The ischemic stroke and disabling stroke subcomponents of the primary efficacy analysis were consistent with non-inferior efficacy for the 60 mg edoxaban group. However, in the edoxaban 30 mg (15 mg DA) group, results were not favorable for ischemic stroke [HR (95% CI): 1.54 (1.25-1.9), nominal $p < 0.0001$] and disabling stroke [HR (95% CI): 1.36 (0.91-2.03)]. For this reason, the Applicant has proposed not to market the 30 mg (15 mg DA) edoxaban regimen. The reviewers concur with this choice.

It is useful to examine whether other relevant endpoints support the primary efficacy findings. Fewer subjects in the edoxaban 60 mg (30 mg DA) and edoxaban 30 mg (15 mg DA) groups experienced cardiovascular (CV) mortality than the warfarin group, with a HR of 0.86 (95% CI: 0.77-0.97) and 0.85 (95% CI: 0.76- 0.96), in the ITT population, overall study period, respectively. Fewer subjects in the edoxaban 60 mg (30 mg DA) and edoxaban 30 mg (15 mg DA) groups experienced all-cause mortality than the warfarin group, with a HR of 0.92 (95%CI: 0.83-1.01) and 0.87 (95% CI: 0.79-0.96), in the ITT population, overall study period, respectively.

The time in therapeutic range (TTR) and event rates in the warfarin arm were comparable to what has been seen in the previous pivotal NOAC trials. The mean TTR (2-3) was 65% (56 - 64% in other pivotal NOAC trials). The stroke/SEE event rate for the warfarin arm was 1.8 per 100 patient years (%/yr) in the ITT population, comparable to the ITT population warfarin event rate in the other NOAC trials (1.5 %/yr – 2.2%/yr).

A distinguishing aspect of ENGAGE AF was the transition program that provided a strategy to maintain anticoagulation when patients were transitioned from study drug to warfarin or other anticoagulants after the common study end date. In other pivotal NOAC trials, a transition program was lacking and this resulted in high stroke rates during transition off study drug.

All major subgroups performed well except for Western Europe and subjects with CrCL ≥ 80 mL/min measured by Cockcroft-Gault equation. The efficacy and safety in Blacks could not be evaluated because they represented only 1.3% of the enrolled population. Whereas the poorer performance in Western Europe was not considered to be a clinically relevant finding, the reduced relative efficacy (compared to warfarin) in the normal renal function subgroup became the issue of greatest focus during our review. For subjects with mild renal dysfunction (CrCL > 50 - < 80 mL/ min), the HR for the first stroke/SEE compared to warfarin in the edoxaban 60 mg (30 mg DA) group was 0.51 (95% CI: 0.38-0.69). For subjects with CrCL ≥ 80 mL/min, the HR for the first stroke/SEE relative to warfarin in the edoxaban 60 mg (30 mg DA) group showed harm

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at 1.41 (95% CI: 0.97-2.05). The nominal p value for this subgroup interaction was statistically significant ($p < 0.001$ for the 60 mg dose). There was also a statistically significant subgroup interaction between the mild renal dysfunction subgroup and the normal renal function subgroup in the 30 mg dose group ($p < 0.01$).

The results of the primary safety analysis showed that both edoxaban groups were superior to warfarin for modified International Society on Thrombosis and Hemostasis (ISTH) major bleeding³ [HR: 0.47 (0.41-0.55), 0.80 (0.71-0.91) for edoxaban 30 mg (15 mg DA) and 60 mg (30 mg DA), respectively]. The superiority of bleeding results in the edoxaban groups was robust across other major bleeding categories including intracranial hemorrhage (ICH), life threatening bleeds and fatal bleeds. However, edoxaban 60 mg (30 mg DA) increased the risk of major GI bleeding compared with warfarin (HR: 1.24, 95% CI: 1.02-1.50).

The opinion of the clinical reviewers is that there are two major efficacy issues that need to be considered when considering approval of edoxaban. No safety issues preclude approval:

- 1) Edoxaban will be the 4th NOAC to be approved. It was shown to be non-inferior to warfarin but not superior, whereas two other NOACs have superiority claims. The Food, Drug and Cosmetic Act requires that drugs be safe and effective to be approved regardless of comparisons to available therapy. However, it is undesirable to approve a therapy intended to reduce mortality or serious irreversible morbidity that is worse than available therapy because less effective therapy may displace more effective therapy resulting in worse health outcomes. This concept was codified in the Federal Register in 1995 in the 1995 Shultz Federal Register notice.⁴

Therefore, it is obvious to question whether edoxaban could be inferior to other approved therapies and whether this constitutes a reason not to approve. Because edoxaban came close to achieving superiority on its primary endpoint (HR: 0.87, 95% CI: 0.74-1.02), it is not reasonable to conclude that edoxaban is inferior to dabigatran or apixaban in the overall NVAf patient population. Therefore, an approval on the basis of the overall trial results would not be inconsistent with the 1995 Shultz Federal Register notice.

- 2) The second and more concerning issue is the renal function subgroup results. Often subgroup findings are dismissed because they are often not prespecified and subject to multiplicity. Thus, there is a high likelihood of finding an outlier subgroup with inferior efficacy just by chance. One can easily make false conclusions when it comes to subgroup findings. For this reason we looked for other supportive

³ Modified ISTH major bleeding used in ENGAGE AF: fatal bleeding, bleeding in a critical organ or any bleed leading to transfusion-adjusted drops in hemoglobin level of ≥ 2.0 g/dl (1 unit of packed RBC = 1 g/dl drop in hemoglobin). See [Appendix 7](#) for overview of all bleeding category definitions in ENGAGE AF.

⁴ "Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices," 60 Federal Register 147 (1 August 1995) pp.39180-39181.

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information before we reached our conclusion that the poor performance in the normal renal function subgroup most likely represents a consequence of under exposure and not a serendipitous finding.

1. The HRs (compared to warfarin) are worse (higher than 1) in both edoxaban groups for the primary endpoint, its components, and CV death in the normal renal function subgroup (CrCL ≥ 80 mL/min) compared to the mild renal impairment subgroup (CrCL $> 50 - < 80$ mL/min) (Table 1). Analyses of the primary efficacy endpoint by CrCL quintiles (Table 2) and continuous CrCL (Figure 2) also support these findings. As seen in Figure 2, the warfarin arm did exceptionally well in the normal renal function subgroup. It is notable that this excellent performance is typical of the warfarin performance in this subgroup in the other pivotal NOAC trials, presumably because patients with normal renal function are generally healthier.

Table 1: Summary results of HRs (compared to warfarin) by CrCL subgroup (mITT, on treatment)

Event	CrCL	Dose Group	HR (95% CI)	CrCL	Dose Group	HR (95% CI)
Stroke/SEE	>50- <80	E30/15 DA	0.82 (0.64-1.05)	≥ 80	E30/15 DA	1.61 (1.12, 2.32)
		E60/30 DA	0.51 (0.38-0.69)		E60 30 DA	1.41 (0.97, 2.05)
Ischemic Stroke	>50- <80	E30/15 DA	1.13 (0.85-1.51)	≥ 80	E30/15 DA	2.09 (1.38, 3.16)
		E60/30 DA	0.62 (0.43-0.87)		E60/30 DA	1.58 (1.02, 2.45)
Disabling Stroke	>50- <80	E30/15 DA	1.06 (0.66-1.70)	≥ 80	E30/15 DA	2.45 (1.13,5.32)
		E60/30 DA	0.39 (0.20-0.74)		E60/30 DA	2.45 (1.13,5.33)
CV Death	>50- <80	E30/15 DA	0.87 (0.72-1.04)	≥ 80	E30/15 DA	0.89 (0.69, 1.13)
		E60/30 DA	0.75 (0.62-0.9)		E60/30 DA	1.15 (0.91, 1.45)

E30/15 DA= Edoxaban 30 mg/ 15 mg Dose Adjustment

E60/ 30 DA= Edoxaban 60 mg/ 30 mg Dose Adjustment

Disabling Stroke is ModifiedRankin Score 3-5 (moderate to severely disabling and not fatal)

Dataset: ADJEFFCA.xpt, BASEGP.xpt; HRs calculated using modeling with Dose Adjustment, yes or no, CHADS2 $\leq 3=0$, or $>3=1$. (More details of this analysis are shown in Table 40, Table 42, Table 43, Table 45, and Table 46).

Reviewer's Table

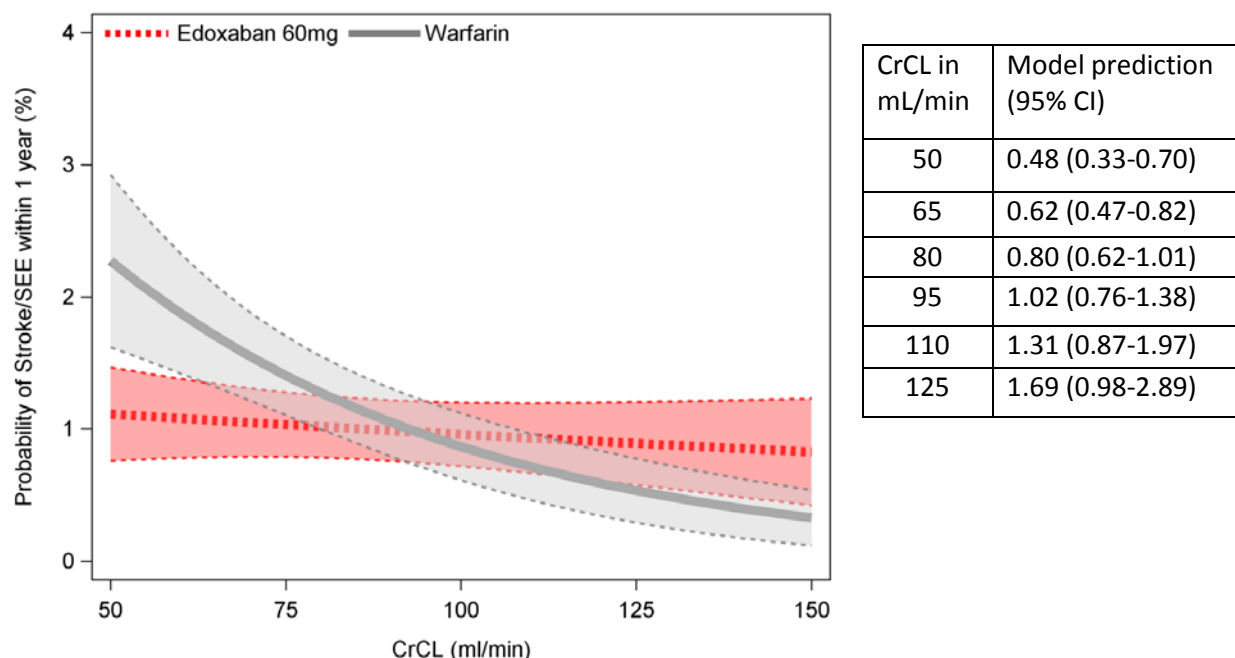
Table 2: Primary Efficacy Endpoint: Stroke/SEE by quintile of CrCL (mITT population, on treatment)

Quintile	CrCL (mL/min)	Edox 60mg (30mg DA) Event Rate (%/yr)/N	Warfarin Event Rate (%/yr)/N	HR (95% CI)
1	30 to ≤50.6	1.68/1344	2.04/1360	0.83 (0.56, 1.24)*
2	>50.6 - ≤63.6	1.13/1356	2.33/1381	0.48 (0.32, 0.72)
3	>63.6 - ≤ 77.9	0.93/1414	1.69/1409	0.55 (0.35, 0.85)
4	>77.9 - ≤ 98.1	1.12/1336	1.04/1415	1.08 (0.68, 1.74)
5	> 98.1	1.05/1434	0.61/1357	1.74 (1.01, 3.01)

%/yr = events/100 patient-years. Datasets: DM.xpt, ADJEFFCA.xpt, HR constructed using applicant's model [adjusted for DoseAdj (N, Y), and CHADS2 score (0, 1 for CHADS2 score <3 and ≥3, respectively)].

*Note that the HR relative to warfarin is higher in quintile 1 than in quintiles 2 and 3. Most of the subjects in quintile 1 were dose adjusted (reduced) and that dose reduction is now thought to have been excessive and probably accounted for the relatively higher HR.. Further discussion in Section 6.1.8.3. Reviewer's Table.

Figure 2: Effect of CrCL on risk of Stroke/SEE (mITT population, on treatment)



The risk of first Stroke/SEE was modeled as a function of history of stroke, CHADS₂ score, CrCL, treatment, and CrCL*treatment using a Cox proportional hazard model among subjects with no dose adjustment. Reviewer's Analysis, Datasets: ADJEFFCA, BASEGP and DM.

2. There is a mechanistic basis for the observed findings. Edoxaban is 50% renally excreted so it is expected that renal function would be a major determinant of edoxaban pharmacokinetics (PK) and pharmacodynamics

(PD). In fact, median trough edoxaban concentrations were ~1/3 lower and median changes from trough to peak anti-Factor Xa activity were ~1/4 lower in subjects with CrCL ≥ 80 mL/min than in subjects with mild renal impairment (CrCL >50 - <80 mL/min) .

3. The major bleeding results are in agreement with the observed lower exposure in the normal renal function subgroup. The HRs of major bleeding relative to warfarin were lower in subjects with CrCL ≥ 80 mL/min (HR: 0.70, 95%CI: 0.55-0.89) compared to subjects with mild renal impairment (CrCL >50 - <80 mL/min) (HR: 0.90, 95% CI: 0.74-1.08).

Can we be 100% sure that this subgroup issue is related to exposure and not a chance finding? No. If we need to be 100% sure before we can believe that the subgroup findings of decreased efficacy reflect reduced exposure in the normal renal function subgroup, the logical choice would be to approve edoxaban 60 mg with no restrictions. However, because there is no unmet medical need (with 3 NOACs on the market and no obvious advantage of edoxaban over these drugs), it is most reasonable to tolerate some uncertainty and err on the side of caution in this situation. These data strongly suggest that lower exposures in subjects with normal renal function resulted in an unacceptable reduction in efficacy. Therefore, our regulatory decision should be guided by these data.

In our view, there are three reasonable regulatory responses to this conclusion:

- 1) Issue a complete response (CR). A CR is reasonable because edoxaban failed to show consistency of efficacy across renal function subgroups with efficacy in the normal renal function subgroup, a substantial segment of the affected population, appearing to be inferior to warfarin. In the CR we would ask the applicant to perform another trial as a condition for approval in the normal renal function subgroup, preferably with a higher dose. This option is problematic because another trial would be resource intensive and hence, there is some probability that the trial would never be conducted. Edoxaban seems to have promise as an alternative to other anticoagulant therapies in most patients and it would be unfortunate to risk losing it as a therapeutic option.
- 2) Approve edoxaban only in the subpopulation of patients with abnormal renal function. The problem with this option is that the only way to be reasonably confident that this limitation of use would work as intended would be to implement a Risk Evaluation and Mitigation Strategy (REMS) with an ETASU (element to assure safe use, such as a restricted distribution system that incorporates a mandatory pre-use determination of creatinine clearance). Such a REMS would have a negative impact on use of the drug by making it difficult to prescribe. Also, it would be difficult to fashion an ETASU REMS for the atrial fibrillation indication if edoxaban is approved for treatment of deep vein thrombosis at a 60 mg dose without a REMS. A REMS with only a Medication Guide and communication plan for the NVA

indication (such as Dear Health Care Professional and professional society letters) would be easier to implement but probably not as effective at deterring use of edoxaban in patients with normal renal function.

- 3) Use a pharmacometric model to identify a dose that would match exposures of patients with normal renal function to the best performing subgroup (subjects with mild renal dysfunction: CrCL > 50 - < 80 mL/min). Of note, the sponsor proposes exposure matching to address the dose for patients with severe renal dysfunction (those with CrCL 15 to < 30 mL/min) who were not studied in the trial. Exposure matching also seems like a reasonable method for deciding upon whether to dose adjust for concomitant use of P-gp inhibitor or moderate renal dysfunction. If we can justify exposure matching in these circumstances, it becomes less of a leap to determine doses by exposure matching for patients with normal renal function.

Exposure-response relationships for various efficacy and safety endpoints were modeled by the Office of Clinical Pharmacology. Each efficacy and safety endpoint of interest was modeled using a Cox-proportional hazard model as a function of the individual's trough edoxaban exposure (derived from the post-hoc Bayesian population PK model), and selected covariates based on risk factors for the particular outcome.

The models illustrate that the risk of stroke/SEE as well as ischemic stroke decrease with increasing edoxaban trough exposure; while the risk of bleeding increases with increasing edoxaban trough exposure (see [Section 4.4.3.4](#)). The predicted event rates are generally in agreement with the observed findings in the trial. One could approach the decreased efficacy in subjects with normal renal function by increasing the dose based on exposure-outcome relationships. A 90 mg dose could be a reasonable choice for patients with CrCL ≥ 80 mL/min because it will achieve edoxaban exposures in the range observed in subjects with CrCL >50- <80 mL/min who received edoxaban 60 mg (the best performing subgroup for efficacy). The models predict that the 90 mg dose will decrease strokes/SEEs by ~ 2 per 1,000 patient-years but increase major bleeding events by about ~11 and increase life threatening bleeds by ~ 1 per 1,000 patient-years in patients with normal renal function over what would have occurred with the 60 mg dose. The models predict that compared with warfarin, edoxaban 90 mg will have similar effects on efficacy (model predicts ~0.4 more stroke/SEE per 1,000 patient-years than warfarin) at the expense of a worse bleeding profile [~ 5 more major bleeding events and ~ 8 more major GI bleeds per 1,000 patient-years, but still lower risk of life threatening bleeds (~1 less life threatening bleed per 1,000 patient-years) in subjects with normal renal function]. See Table 4.

Although exposure-matching provides a means to address the inferior efficacy in normal renal function, it is unclear if the models can accurately predict the net clinical benefit of a dose higher than ever tested in long term clinical trials when there is a potential for serious safety consequences. The clinical reviewers are concerned that

increasing the edoxaban dose (e.g. 90 mg) will lead to excessive major bleeding events; particularly GI bleeds in patients with normal renal function who have a relatively low risk for stroke (see [Section 1.2 Risk Benefit Assessment](#)). There is some concern among experts that local effects of NOACs may be responsible for the increased major GI bleeding relative to warfarin observed in the confirmatory studies of most of the NOACs.⁵ If this hypothesis is true, the pharmacometric models based on systemic edoxaban exposure may underestimate the risk of major GI bleeds. With other excellent drugs for the prevention of stroke/SEE in NVAf available, do we really need to embrace this much uncertainty?

After considering these three options, we are currently recommending the second option, approval of edoxaban 60 mg QD in patients with NVAf, with a limitation of use to patients with abnormal renal function (< 80 mL/min). We hope that another trial perhaps using a dose titration strategy to achieve a higher exposure level (on par with the exposure in the mild renal insufficiency subgroup) will be conducted in subjects with normal renal function. After considering the advice from the Cardiovascular Advisory Committee which will convene at the end of October, 2014, we may revise our recommendation.

As an aside, in all the pivotal NOAC trials, the point estimate for the HR for stroke/SEE was higher (worse) in the normal renal function subgroup compared to the mild renal impairment subgroup (but still less than 1). See Table 65 for event rates by renal function subgroup in the other NOAC trials. This pattern is probably related to reduced exposures in the normal renal function subgroups because all of these drugs are partially renally excreted [pattern less apparent in apixaban because the drug is only 27% renally excreted, dabigatran is 80% renally excreted and rivaroxaban (active metabolite) is 33% renally excreted]. The reason that worsening performance in higher renal function subgroups was not a review issue for the other NOACs is that the point estimates of the HRs for the event rates relative to warfarin in the normal renal function subgroups were less than 1. This is presumably because the doses of the other NOACs were high enough to provide adequate exposures even for patients with normal renal function. If edoxaban had been studied at a higher dose, it is possible that we would not be in this predicament.

⁵ Desai et al (2013) "Gastrointestinal Bleeding with the New Oral Anticoagulants – Defining the Issues and the Management Strategies", *Thromb and Haemo*: 110, p. 205-212.

1.2 Risk Benefit Assessment

The clinical reviewers assessed net clinical benefit of edoxaban compared with warfarin by evaluating absolute differences in event rate and hazard ratio for the non-bleeding aspect of the primary efficacy endpoint (ischemic stroke/SEE) and safety endpoints (life threatening bleeding as well as major bleeding) (see [APPENDIX 1](#)). The benefit-risk table shows that the edoxaban 60 mg (30 mg DA) reduced the ischemic stroke/SEE event rate by ~1 per 1,000 patient-years compared to warfarin. It also reduced the life threatening bleeding⁶ event rate by ~5 per 1,000 patient-years and the major bleeding event rate by ~ 6 per 1,000 patient-years compared to warfarin. Hence, the 60 mg dose of edoxaban has a favorable overall benefit-risk profile. Compared with the 60 mg (30 mg DA) group the benefit-risk analysis for the 30 mg (15mg DA) dose showed numerically less benefit but also less risk: there was an increase in the ischemic stroke/SEE event rate (by 5 per 1,000 patient-years) in the edoxaban 30 mg compared to warfarin. But it reduced the life threatening bleeding event rate by ~8 per 1,000 patient-years and the major bleeding event rate by ~ 17 per 1,000 patient-years compared to warfarin. Approximately 1/3 of life threatening bleeds were fatal in ENGAGE AF, whereas ~1/5 of the ischemic strokes in ENGAGE AF were disabling and ~1/5 of the ischemic strokes were fatal (~40% of ischemic strokes were disabling and/or fatal). Approximately 62% of hemorrhagic strokes in ENGAGE AF were disabling and/or fatal. Although edoxaban 30 mg had a significantly better bleeding profile compared with warfarin, the Applicant did not propose to market it due to its inferior effects on reduction of ischemic stroke and disabling stroke compared with warfarin.

Although we examined benefit-risk by comparing ischemic stroke event rate to life-threatening bleeding rate or major bleeding rate, it is not clear that weighting them equally is the fairest method. (see [APPENDIX 1](#) for the comprehensive table for benefit/risk using this method). When weighting ischemic stroke equally to life-threatening bleed, the pattern of favorable benefit- risk ratio for the 60 mg edoxaban dose is apparent across all subgroups except for the highest CrCL quintile (CrCL ≥98.1 mL/min) (Table 3). Among subjects with CrCL ≥ 98.1 mL/min, subjects treated with edoxaban 60 mg had 5 more ischemic stroke/SEE events and 2 fewer life threatening bleeds per 1,000 patient-years compared to subjects treated with warfarin. Hence, the net clinical benefit is negative in edoxaban 60 mg in this subgroup. Highest weight quartile also correlated with risk of diminishing benefit, but weight is used in the Cockcroft-Gault equation and the pharmacometric model showed that renal function was the better predictor of exposure.

⁶ Life threatening bleeds= Intracranial hemorrhage (ICH) or bleeds causing hemodynamic compromise requiring treatment (=GUSTO severe major bleed). This includes fatal bleeds.

Table 3 Benefit-Risk Assessment by CrCL

Benefit						Risk				
Efficacy (Ischemic Stroke/SEE)						Safety (Life Threatening Bleed†)				
		Edoxaban 60 mg	Warfarin	Delta ^{††}	HR	Edoxaban 60 mg	Warfarin	Delta ^{††}	HR	ΔΔ ^{††}
	N	(%/pt-yr)	(%/pt-yr)	(%/pt-yr)		(%/pt-yr)	(%/pt-yr)	(%/pt-yr)		(%/pt-yr)
All	14024	0.9	1.0	-0.1	0.92	0.6	1.1	-0.5	0.53	-0.6
CrCL	30 to <50.6	2704	1.3	1.3	-0.1	0.95*	0.7	1.6	-0.9	0.45
(ml/min)	>50.6 - ≤ 63.6	2737	0.9	1.6	-0.7	0.57	0.5	1.4	-0.9	0.37
	>63.6 - ≤ 77.9	2823	0.7	1.0	-0.3	0.68	0.7	1.1	-0.4	0.63
	>77.9 - ≤ 98.1	2751	0.9	0.8	0.1	1.14	0.6	0.9	-0.3	0.67
	>98.1	2791	0.9	0.5	0.5	2.00	0.3	0.5	-0.2	0.68

[†]Definition of life threatening bleeds (=GUSTO Severe bleeds): ICH or bleeds causing hemodynamic compromise requiring treatment, including fatal bleeds

^{††} A negative value indicates an absolute risk reduction (%/patient-years) of endpoint in the edoxaban group compared to warfarin. ΔΔ (the net clinical benefit) was assessed based on equal weight of the efficacy and safety endpoint.
%/patient year = # events per 100 patient years.

*Note that the HR relative to warfarin is higher in subjects with CrCL of 30-50.6 mL/min than in subjects with CrCL 50.6 -77.9 mL/min. Most of the subjects in the first quintile (CrCL of 30-50.6 mL/min) were dose adjusted (reduced) and that dose reduction is now thought to have been excessive and probably accounted for the relatively higher HR. Further discussion in Section 6.1.8.3. Reviewer's table.

Based on the efficacy results and benefit-risk assessment, the clinical reviewers do not think that edoxaban 60 mg is approvable for patients with normal renal function. The clinical pharmacology review also concludes that edoxaban 60 mg is not optimal for subjects with normal renal function based on their exposure-response analyses and states that increasing the edoxaban dose in patients with normal renal function is predicted to increase efficacy but also to increase bleeding.

One could approach the decreased efficacy in subjects with normal renal function by increasing the dose based on exposure-outcomes relationships. A 90 mg dose is one reasonable choice for patients with normal renal function because it should result in exposures similar to that achieved in the subjects with mild renal dysfunction who received edoxaban 60 mg.

Table 4 shows the observed and predicted event rates for outcomes of interest compared to warfarin in the normal renal function subgroup (≥ 80 mL/min). There were 3 more observed strokes or SEEs/1,000 patient-years in the edoxaban 60 mg arm than in the warfarin arm and 2 fewer observed life threatening bleeds/1,000 patient-years in

the trial. Model prediction of event rates in the 60 mg vs. warfarin groups expectedly shows some numerical differences from what was observed, but the predictions are in the same direction. If the dose in normal renal function were to be changed from 60 mg to 90 mg, the model-predicted event rate would be favorable for efficacy (1.4 fewer ischemic strokes/ 1,000 patient-years) but unfavorable for life-threatening bleeding, hemorrhagic stroke, major bleeding, and major GI bleeding. The models predict marked increase in major bleeding and major GI bleeding for normal renal function patients on 90 mg of edoxaban (10.7 more major bleeding and 8.6 more major GI bleeds/ 1,000 patient years compared to the 60 mg dose). It also would cause more life-threatening bleeds (0.9 more events/1,000 patient-years) and more hemorrhagic strokes (0.6 more events/1,000 patient-years). The models predict that compared with warfarin, edoxaban 90 mg has similar effects on ischemic stroke prevention (0.4 more events/1,000 patient-years) and would maintain lower life-threatening bleeds (1.4 fewer events/1,000 patient-years) in subjects with normal renal function. While the benefit-risk assessment for edoxaban 90 mg compared with warfarin seems acceptable, there are a few issues that should be considered when evaluating the net clinical benefit of edoxaban 90mg for this subgroup:

1. The reviewers are concerned that extrapolating bleeding outcomes solely on the basis of systemic edoxaban exposures may underestimate GI bleeding risk. Some have speculated that the increased risk of GI bleeds seen with the NOACs may be in part due to high concentrations of active drug in the GI tract. Whereas there was less bleeding with edoxaban than warfarin, there was more GI bleeding. All the models performed by the clinical pharmacology reviewers were assessed based on systemic edoxaban exposure. If local exposure indeed plays a significant role in the probability of developing GI bleeds, the impact of edoxaban 90 mg on the risk of major GI bleeds cannot be assessed adequately and could be underestimated.
2. Another problem with incurring more major bleeds is that cessation of drug is required which inevitably increases risk of consequent stroke. Additionally, patients and physicians may become less willing to reinitiate indicated anticoagulant therapy.

For these reasons, the clinical reviewers think that it is unclear if edoxaban 90 mg would provide a favorable net clinical benefit for patients with normal renal function. The choice of an appropriate edoxaban dose using the pharmacometric models depends on the benefit/risk that will be considered acceptable, a topic for discussion at the Cardiovascular Advisory Committee which will convene at the end of October. Understanding the clinical effects of an increased dose may require an additional trial.

If the decision is made to approve edoxaban, it will be important to address the risks and benefits of changing the dose adjustment strategy from what was studied in the

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trial. The clinical pharmacology review discusses the option of increasing the edoxaban dose from 30 mg to 45 mg for subjects with moderate renal impairment (30-50 mL/min) based on exposure-outcomes relationships.

Table 5 shows the analysis of observed and predicted events of interest compared with warfarin in the moderate renal dysfunction (CrCL= 30-50 mL/min) subgroup. There were 2.2 fewer observed strokes or SEEs/1,000 patient-years but 1 more observed ischemic strokes/1,000 patient-years in subjects with moderate renal impairment receiving edoxaban 60 mg (dose adjusted to 30 mg) than in the warfarin arm. Edoxaban had a significantly better bleeding profile in this subgroup compared with warfarin with 12.7 fewer major bleeds and 9.2 fewer observed life threatening bleeds/1,000 patient years. Model prediction of events in the dose adjusted subjects in the edoxaban 60 mg (30 mg DA) arm also shows some numerical differences from what was observed, but the predictions are in the same direction without exception. If the dose adjustment for patients with moderate renal dysfunction were changed to 45 mg instead of 30 mg, the model-predicted event rate would be favorable for efficacy (2.2 fewer stroke/SEEs and 2.4 fewer ischemic strokes/1,000 patient years) compared with the 30 mg dose but unfavorable for major bleeding (22.7 more major bleeds/1,000 patient-years), particularly major GI bleeding (17.7 more major GI bleeds/1,000 patient- years). The model also predicts 1.5 more life-threatening bleeds including 0.8 more hemorrhagic strokes/1,000 patient years if dose adjusted patients are treated with 45 mg instead of 30 mg.

Whether edoxaban 45 mg would produce a favorable net clinical profile for patients with moderate renal impairment requires careful examination.

One thing to keep in mind as we weigh our options is that edoxaban 30 mg (dose adjusted from the 60 mg dose) in this moderate renal failure subpopulation was tested in a well-controlled trial and demonstrated non-inferiority to warfarin for prevention of stroke/SEE [HR: 0.78 (0.450, 1.22)] with an overall acceptable benefit-risk profile whereas the 45 mg dose which is predicted by the model to result in ischemic stroke reduction, has not been tested in this group of patients.

Other decisions that need to be made are whether and how much to dose adjust in patients with low body weight (≤ 60 kg) or patients on P-gp inhibitors.

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Table 4 Observed and Predicted Absolute Difference* in Events per 1,000 patient-years in Subjects with Normal Renal Function (≥ 80 mL/min)

	Stroke/ SEE	Ischemic Stroke	Hemorrhagic Stroke	MACE	Major Bleed [†]	Life Threatening [†]	Major GI bleed [†]	CRNM + Major bleed [†]
Observed difference								
60 mg vs. warfarin	3.0	3.1	-3.0	2.9	-7.5	-2.0	-1.6	-12.0
Model predicted difference								
60 mg vs. warfarin	1.8	2.2	-0.5	0	-5.9	-2.3	-0.5	-16.2
90 mg vs. warfarin	0.4	0.8	0.1	-3.8	4.8	- 1.4	8.1	4.0
90 mg vs. 60 mg	-1.4	-1.4	0.6	-3.8	10.7	0.9	8.6	20.2

Reviewer's Table. Source: Clinical Pharmacology Review

*Model predicted event rates were derived from exposure-response analyses from Clinical Pharmacology Review. The differences were rounding to the nearest integer. A negative value indicates an absolute risk reduction (per 1,000 patient-years) of endpoint in the edoxaban group compared to warfarin. See 0for overview of all bleeding category definitions in ENGAGE AF

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Table 5 Observed and Predicted Absolute Difference* in Events per 1,000 patient-years in Subjects with Moderate Renal Impairment (30-50 mL/min)

	Stroke /SEE	Ischemic Stroke	Hemorrhagic Stroke	MACE	Major Bleed [†]	Life Threatening [†]	Major GI bleed [†]	CRNM + Major bleed [†]
Observed difference								
30 mg vs. warfarin	-2.2	1.0	-2.9	-3.4	-12.7	-9.2	-3.0	-53.9
Model predicted difference								
30 mg vs. warfarin	-3.4	1.6	-4.2	-6.0	-17.4	-9.9	-0.6	-66.4
45 mg vs. warfarin	-5.6	-0.8	-3.4	-12.9	5.3	-8.4	17.1	-28.5
45 mg vs. 30 mg	-2.2	-2.4	0.8	-6.8	22.7	1.5	17.7	37.9

Reviewer's Table. Source: Clinical Pharmacology Review

*Model predicted event rates were derived from exposure-response analyses from Clinical Pharmacology Review. The differences were rounding to the nearest integer. A negative value indicates an absolute risk reduction (per 1,000 patient-years) of endpoint in the edoxaban group compared to warfarin. See [Appendix 7](#) for overview of all bleeding category definitions in ENGAGE AF

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1.4 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

If approved only in patients with abnormal renal function, there will have to be a Risk Evaluation and Management Strategy (REMS) to prevent usage in the unintended population. Otherwise, a REMS will not be necessary.

1.5 Recommendations for Postmarket Requirements and Commitments

None. Note that we are not recommending approval of a dose higher than 60 mg. However, if a dose higher than 60 mg is recommended for patients with normal renal function, then a PMR to assess the effects of the approved higher dose on bleeding should be imposed. We expect this issue to be discussed at the AC meeting.

2 Introduction and Regulatory Background

2.1 Product Information

Edoxaban (DU 176) is a synthetic anticoagulant agent. It is an orally active, selective, direct and reversible inhibitor of the serine protease Factor Xa (FXa) located in the final common pathway of the coagulation cascade. FXa catalyzes the conversion of prothrombin to thrombin. FXa inhibition reduces thrombin generation, prolongs clotting time, and reduces the risk of thrombus formation. In human studies, edoxaban has a rapid onset of action with anticoagulant effects observed soon after the first dose administration.

(b) (4)



A bio-equivalence study demonstrated that edoxaban 60mg proposed commercial tablets was bio-equivalent to two edoxaban 30mg Phase 3 clinical tablets, with respect to exposure and C_{max}.

The chemical structure of edoxaban and additional product information is provided in Table 6.

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Table 6: Edoxaban Product Information

Attribute	Description
<div></div>	

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

2.2.1 Overview of Atrial Fibrillation (AF) and Stroke

AF is a common supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. An estimated 2.5 million Americans have the condition. Incidence of AF increases with age and approximately 8% of the population over 80 years of age have AF. Subjects with AF are at increased risk for stroke (~5% per year) and SEE, especially those with medium to high risk as determined by the risk assessment scheme, the CHADS₂ score⁷. The CHADS₂ score considers and weighs the following risk factors: congestive heart failure, hypertension, age > 75 years, diabetes mellitus (1 point each) and previous stroke or transient ischemic attack (2 points). Current American Heart Association (AHA) guidelines for subjects with documented AF recommend that life-long anticoagulant therapy for preventing stroke and systemic embolic events may be initiated when the CHADS₂ score is 1 (1 moderate risk factor which include age ≥ 75 years, hypertension, heart failure, LV EF ≤35% or diabetes mellitus) but aspirin 81 to 325 mg daily is also acceptable. However, when there are 2 moderate risk factors or 1 high-risk factor (previous stroke, TIA or embolism, mitral stenosis or prosthetic heart valve), vitamin K antagonists (warfarin almost exclusively in the U.S.) or a novel oral anticoagulant (NOAC) is recommended.^{8,9}

2.2.2 Current Available Treatments

Vitamin K antagonists (VKAs) are commonly used anticoagulants to reduce the risk of stroke and thromboembolic complications in subjects with AF. Five large randomized trials published between 1989 and 1992 evaluated oral anticoagulation mainly for primary prevention of thromboembolism in patients with nonvalvular AF.^{10,11,12,13} A sixth

7 CHADS₂ is an acronym for Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, and prior history of Stroke or TIA.

8 Fuster, V et al, (2006) ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation, *Circulation*: 114: e 257-e354.

9 (2011); 2011 ACCF/AHA/HRS Focused Updates Incorporated into the ACC/AHA/ESC2006 Guidelines for the Management of Patients With Atrial Fibrillation: A Report of the ACC/AHA task Force on Practice Guidelines, *Circulation*: 123: e269-e367.

10 Petersen, P et al, (1989) Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet*, 1: 175–9.

11 Connolly, SJ et al. (1991), Canadian Atrial Fibrillation Anticoagulation (CAFA) Study, *J Am Coll Cardiol*; 18: 349–55.

12 Ezekowitz, MD, et al. (1992) Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators [published erratum appears in *N Engl J Med*; 1993, 328:148]. *N Engl J Med*; 327: 1406–12.

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trial focused on secondary prevention among patients who had survived nondisabling stroke or cerebral TIA.¹⁴ Meta-analysis according to the principle of intention to treat showed that adjusted-dose oral anticoagulation is highly efficacious for prevention of all stroke (both ischemic and hemorrhagic), with a risk reduction of 61% (95% CI 47% to 71%) versus placebo¹⁵ (Figure 3). A separate meta-analysis done at the FDA which combined the same 6 studies using a random effects model gave similar results [risk reduction of 64% (95% CI 47% to 75%)]¹⁶. The limitation of these analyses to assess benefit/ risk is that the duration of follow-up in the clinical trials was generally between 1 and 2 years; whereas in clinical practice, the need for antithrombotic therapy in patients with AF typically extends over much longer periods. The recent warfarin-controlled trials of novel anticoagulants in patients with NVAF have shown no notable increase in thrombosis after approximately two and a half years of treatment in either the warfarin or experimental treatment arms. Efficacy after 2 ½ years of treatment is not known.

Use of warfarin is complicated by delayed onset of anticoagulant action, a narrow therapeutic index that requires close laboratory monitoring of the anticoagulant effect and frequent dosage adjustments, unpredictable and variable pharmacological response, and numerous drug- and food-interactions.¹⁷ Treatment with warfarin is also associated with serious side effects such as bleeding that could be fatal.

13 (1990), The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med.*; 323: 1505–11.

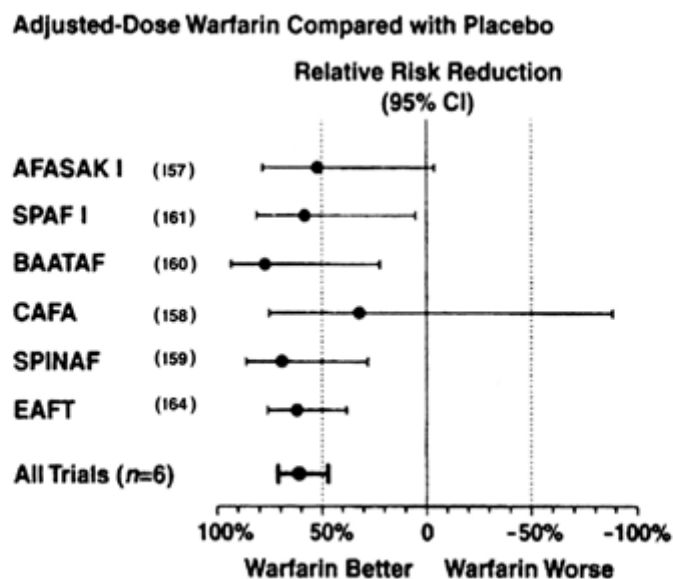
14 Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet.* 1993; 342: 1255–62.

15 Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med.* 1999; 131: 492–501.

16 Draft FDA Guidance for Industry; Non-Inferiority Clinical Trials, p.42,
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

17 Yeh, C. et al, (2014), Evolving use of new oral anticoagulants for treatment of venous thromboembolism. *Blood*, Jun 12. pii: blood-2014-03-563056. [Epub ahead of print]

Figure 3: Warfarin therapy for prevention of stroke (ischemic and hemorrhagic) in patients with nonvalvular atrial fibrillation



Fuster V et al. Circulation. 2006;114:700-752

There are currently 3 other NOACs (in addition to the drug under review) now available in the U.S. for prevention of stroke and systemic embolism; dabigatran (a direct thrombin inhibitor), rivaroxaban and apixaban (also Factor Xa inhibitors). Table 7 summarizes the trial design and main efficacy/safety results for each NOAC. Both dabigatran 150 mg and apixaban were shown in their pivotal trials to be superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (SEE) [HR was 0.66 (95% CI: 0.53-0.82, $p < 0.003$) and 0.79 (95% CI: 0.66-0.95, $p = 0.01$), respectively]. Rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint but superiority to warfarin was not demonstrated. Dabigatran 150 mg is the only NOAC demonstrated to decrease risk of ischemic stroke compared to warfarin.

The other main benefits of the approved NOACs are a significant reduction of hemorrhagic stroke compared to warfarin, absence of food interactions and absence of need for monitoring. In the dabigatran experience, the low dose which was not approved (110 mg BID) had similar risk of hemorrhagic stroke as the higher dose 150 mg BID). The three approved NOACs also had similar or less major bleeding compared with warfarin except an increased risk in major gastrointestinal bleeding seen in both dabigatran 150 mg and rivaroxaban. Apixaban had superior major bleeding risk at the dose that was tested compared to warfarin.

Table 7: Other Novel Anticoagulants approved for atrial fibrillation

	Dabigatran (approved dose)			Dabigatran (not approved dose)			Rivaroxaban			Apixaban		
Approved Dose	150 mg BID, with dose reduction to 75 mg BID when CrCl is between 15 and 30 mL/min			110 mg BID (not approved on the basis of decreased efficacy compared to 150 mg BID dose for ischemic stroke)			20 mg QD with evening meal, with dose reduction to 15 mg QD with evening meal when CrCl is between 15 and 50 mL/min			5 mg BID, or 2.5 mg BID if patients have any two of the following traits: age ≥ 80 years, BWt ≤ 60 kg, Serum Cr ≥ 1.5 mg/dL		
Pivotal Trial	RE-LY, FPFV = December 22, 2005 and LPLV=March 15, 2009			RE-LY, FPFV = December 22, 2005 and LPLV=March 15, 2009			ROCKET AF, FPFV = December 18, 2006 LPLV= June 17, 2009			ARISTOTLE, FPFV=December 19, 2006 LPLV=May 25, 2011		
Primary Efficacy Endpoint	Time to first adjudicated stroke or non-cerebral systemic embolic event in the ITT population (until event or until last time with vital status information). NI analysis with margin of 1.46 for the HR			Time to first adjudicated stroke or non-cerebral systemic embolic event in the ITT population (until event or until last time with vital status information). NI analysis with margin of 1.46 for the HR			Time to first adjudicated stroke or non-cerebral systemic embolic event in the ITT population. NI analysis with margin of 1.46 for the HR			Time to first adjudicated stroke or non-cerebral systemic embolic event in the ITT population during the intended treatment period (ITP, randomization to a January 30, 2011 projected end date) NI analysis with margin of 1.38 for the HR		
Results of Primary Efficacy Endpoint		Dabi 150 #/N (%/ y)	Warf #/N (%/ y)		Dabi 110 #/N (%/ y)	Warf #/N (%/ y)		Riva #/N (%/ y)	Warf #/N (%/ y)		Apix #/N (%/ y)	Warf #/N (%/ y)
	Str/SEE in ITT	134/6076 (1.1)	202/ 6022 (1.7)	Str/SEE in ITT	183/6015 (1.5)	202/6022 (1.7)	Str/SEE in ITT	269/7081 (2.1)	306/7090 (2.4)	Str/SEE in ITT/ITP	212/9120 (1.27)	265/9081 (1.60)
	HR (95%CI)	0.66 (0.53,0.83) ¹		HR (95% CI)	0.91 (0.74, 1.11) ⁷		HR (95%CI)	0.88 (0.74,1.03) ³		HR (95%CI)	0.79 (0.66, 0.95) ⁴	
Hemorrhagic Stroke		Dabi 150 #/N (%/ y)	Warf #/N (%/ y)		Dabi 110 #/N (%/ y)	Warf #/N (%/ y)		Riva #/N (%/ y)	Warf #/N (%/ y)		Apix #/N (%/ y)	Warf #/N (%/ y)
	Hem Str in ITT	12/ 6076 (0.1)	45/ 6022 (0.4)	Hem Str in ITT	14/6015 (0.1)	45/ 6022 (0.4)	Hem Str in ITT	33/7081 (0.3)	57/ 7090 (0.4)	Hem Str in ITT/ITP	40/9120 (0.44)	78/9081 (0.86)
	HR (95%CI)	0.26 (0.14,0.49)		HR (95%CI)	0.31 (0.17,0.56)		HR (95% CI)	Not reported in label		HR (95%CI)	0.51 (0.35, 0.75)	
Ischemic Stroke		Dabi 150 #/N (%/ y)	Warf #/N (%/ y)		Dabi 110 #/N (%/ y)	Warf #/N (%/ y)		Riva #/N (%/ y)	Warf #/N (%/ y)		Apix #/N (%/ y)	Warf #/N (%/ y)
	Isch Str in ITT	103/6076 (0.9)	134/6022 (1.1)	Isch Str in ITT	152/6015 (1.3)	134/6022 (1.1)	Isch. Str in SP on tx	206/7081 (1.6)	208/7090 (1.6)	Isch Str in ITT/ITP ⁵	140/9120 (0.83)	136/9081 (0.82)
	HR (95%CI)	0.75 (0.58,0.97)		HR (95%CI)	1.13 (0.89,1.42)		HR (95% CI)	0.94 (0.75 -1.17)		HR (95%CI)	1.02(0.81,1.29)	
Results of Major Bleeding Safety Endpoint		Dabi 150 #/N (%/ y)	Warf #/N (%/ y)		Dabi 110 #/N (%/ y)	Warf #/N (%/ y)		Riva #/N (%/ y)	Warf #/N (%/ y)		Apix #/N (%/ y)	Warf #/N (%/ y)
	Major Bleeding ^A	399/6076 (3.3)	421/6022 (3.6)	Major Bleeding ^A	342/6015 (2.9)	421/6022 (3.6)	Major Bleeding ^A	395 /7111 (3.6)	386/7125 (3.5)	Major Bleeding ^A	327/9088 (2.1)	462/9052 (3.1)
	HR (95%CI)	0.93(0.81, 1.07)		HR (95%CI)	0.80 (0.68, 0.90)		HR (95% CI)	1.04 (0.90-1.20)		HR (95% CI)	0.69 (0.60, 0.80)	

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(%/ y)= number of events per 100 patient years

SP=safety population (randomized patients who took at least one dose of study drug)

ITP=Intended treatment period

Dabi=dabigatran, Riva=rivaroxaban, Apix = apixaban, tx=treatment

A= Major Bleed definition: (ISTH definition) Satisfying at least one: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood or packed cells; symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding) or fatal bleeding

¹ p <.0001 for non-inferiority and p <.003 for superiority

² p <.0001 for non-inferiority and p = 0.3 for superiority

³ p < 0.001 for non-inferiority and p = 0.12 for superiority

⁴ p < 0.001 for non-inferiority and p = 0.01 for superiority

⁵ Ischemic stroke without hemorrhage

Reviewer's Table

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2.3 Availability of Proposed Active Ingredient in the United States

Edoxaban is not marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Bleeding is the most important safety issue with edoxaban and all anticoagulants. The bleeding risks may be potentiated by anti-platelet co-therapy and other concomitant medications. For further discussion, please see [Section 7.3.2.1.4](#)

(b) (4)
[REDACTED] Liver abnormalities are discussed in the
safety review in [Section 7.3.5.1](#).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Date	Regulatory Activity
May 14, 2007	Submission of IND 77,254
August 13, 2008	<p>EOP2 meeting:</p> <ul style="list-style-type: none"> FDA agreed that the target indication (to reduce the risk of stroke and SEE in patients with atrial fibrillation) "is potentially supportable with the proposed study, because the historical trials used to estimate the treatment effect of warfarin had a composite of stroke and SEE as their primary endpoints." The sponsor agreed that there would be a 60% cap on warfarin-experienced patients. FDA stated, "A single study may be sufficient if the results are compelling".
October 15, 2008	<p>SPA agreement with responses guiding the sponsor on various aspects of the protocol:</p> <ol style="list-style-type: none"> Advised that use of the CHADS₂ score for eligibility could result in a different study population than historical trials and in so doing, make the constancy assumption with the comparator invalid Advised that the superiority testing should be at a total type I error rate of 0.01 or less There were originally three expected dose groups but one was expected to be terminated possibly prior to study completion. FDA suggested that if one is terminated, the remaining regimens should be tested at the alpha/3 significance level. Agreed to count events in the mITT that occurred during treatment and during the 3 days after any dose interruption for the primary analysis. A randomization encryption code was requested at time of NDA study submission. We asked for a detailed justification of the proposed doses and dosing regimen which the sponsor stated was based on the phase 2 trial (PRT-018).
May 8, 2009	Submission of analysis of phase 2 study PRT-018 for dose justification.

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Date	Regulatory Activity
December 11, 2009	<p>Revised SAP:</p> <ul style="list-style-type: none"> • Instead of 3 edoxaban groups (low exposure, high exposure and 30 mg allocated), the statistical testing was changed to the high (60 mg with 30 mg dose adjustment for prespecified criteria¹⁸) and low (30 mg with 15 mg dose adjustment for the same prespecified criteria) exposure groups with the 30 mg allocated group to be analyzed in a prespecified exploratory analysis. • Changed superiority testing (as FDA recommended) so that only the high exposure group (ITT/ overall treatment period) would be tested and would be successful with a p value of ≤ 0.01 [for primary and the ordered secondary endpoints; (1) stroke/SEE/All-cause mortality and (2) MACE]. The FDA statistics team agreed with the changes. • The sponsor was advised that crossover rate (percentage of discontinued edoxaban patients switching to warfarin) needs to be reported and if not small may have serious implications on interpretability of NI results.
January 31, 2011	<p>A statistical analysis plan (SAP) was submitted to the Division with subsequent concurrence returned to the Sponsor on 3/16/2011. The following major agreements were established:</p> <ul style="list-style-type: none"> • Comparison of each edoxaban treatment group (High Dose, Low Dose) versus warfarin will be performed at $\alpha = 0.05/2$ for non-inferiority. • Information on how many randomized subjects (ITT set) did not receive at least one dose of the study drug (mITT set) will be reported in the clinical study report. • Superiority testing will be performed only for the High Exposure group with $\alpha=0.01$ (using the ITT population and the overall treatment period). • The non-inferiority (NI) margin will be performed at 1.38. • A modified Intent-To-Treat (mITT) population will be used for non-inferiority analyses for the primary efficacy endpoints and an Intent-To-Treat (ITT) population will be used for the subsequent superiority analyses.

¹⁸ At randomization, subjects with CrCL ≥ 30 and ≤ 50 mL/min, body weight ≤ 60 kg or on verapamil or quinidine were dose reduced (dronedarone was added to the list of concomitant medications requiring dose adjustment after the study randomization was complete in protocol amendment 5, December 22, 2010).

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Date	Regulatory Activity
October 19, 2011	Teleconference: The sponsor was informed that an increase in stroke rate in the 30 days following the end of the study would not be acceptable. They were also informed that a transition plan to warfarin had to be clinically tested so instructions for transitioning off edoxaban can be provided in the label.
July 19, 2012	The sponsor proposed to revise the overall α from 0.01 to $\alpha=0.05$ for superiority tests of edoxaban vs. warfarin.
September 19, 2012	The Division responded by recommending to keep the original $\alpha=0.01$ level. The Division stated the proposed statistical analysis ($\alpha=0.05$ for superiority) will be conducted as part of the review of the data.
February 28, 2012	Pre-NDA meeting: There was agreement on submission adequacy as currently planned. Request for a priority review and/or "rolling submission" was answered by FDA stating that this would not be decided until after the topline meeting.
September 10, 2013	Type C Meeting wherein Division agreed that The ENGAGE TIMI-AF 48 study should be sufficient to form the basis for a NDA. Agreed that REMS would probably not be needed.
December 5, 2013	Confirmation of submission of Agreed-Upon Pediatric Study Plan (with Division and PeRC agreement) for waiver of pediatric assessment in the AF indication on the basis that the necessary studies are impossible or highly impractical due to the low prevalence of AF in the pediatric population.

Reviewer's Table

2.6 Other Relevant Background Information

2.6.1 Foreign Approval

Edoxaban received marketing approval by the Japanese Ministry of Health, Labor and Welfare in April, 2011 for VTE prevention after total knee and hip arthroplasty and hip fracture surgery. It is sold as Lixiana. See [Section 8](#) for a more complete discussion on the post-marketing experience.

2.6.2 Other U.S. Activity

Edoxaban is under review also by the Division of Hematology for venous thromboembolism treatment, and pulmonary embolism treatment and prevention.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA for edoxaban was filed on January 8, 2014. During the filing review, the reviewers identified multiple issues related to submitted datasets and adjudication packages. Several IRs were issued which lead to multiple submissions. For example, in Sequence 0009 (dated February 18, 2014), the Applicant resubmitted five datasets that were originally submitted incorrectly (four that were submitted in Sequence 0003/ February 3, 2014 and one that was submitted in Sequence 0000/ January 8, 2014). In Sequences 10 (dated February 13, 2014), 11 (dated February 14, 2014), 12 (dated February 13, 2014), and 14 (dated February 19, 2014), the Applicant submitted 2,343 adjudication packages that were previously submitted as incomplete documents or not submitted at all. In the end some adjudication packages remained missing. Not all adjudication packages are needed to verify the integrity of the trial. However, the multiple submissions and incorrect submissions indicate the Applicant's lack of thorough quality control (QC) on preparation of the NDA contents prior to the submission. Following the unresolved issues about missing adjudication packages, the Applicant agreed to perform a QC of every adjudicated event in ENGAGE AF. The Applicant reported the outcomes of QC in Sequence 00059 (dated June 25, 2014) and submitted an additional 41 missing adjudication packages. They also found about 800 adjudication packages which required remediation and 9 cases where the final adjudication decision as captured in the dataset was not consistent with what was documented in the adjudication packages (Table 8).

Table 8: Adjudication data discrepancies between databases and documentations

Unique Subject Identifier	Event Identifier	Treatment Arm	Final Adjudication in Documentation	Final Adjudication in Database
13140029	SAE02	Edoxaban 60mg	Death (CV)	Death (Non-CV)
17100008	STR01	Edoxaban 60mg	Death (Non-CV)	Death (CV)
43350015	BLD07	Warfarin	Bleed (Major)	Bleed (CRNM)
61740009	BLD05	Warfarin	Bleed (CRNM)	Bleed (Major)
72500007	BLD03	Edoxaban 30mg	Bleed (Major)	Bleed (CRNM)
11060009	BLD01 Death	Edoxaban 30mg	Death (CV) Cardiovascular non-intracranial hemorrhage	Death (CV) Cardiovascular Atherosclerotic Vascular Disease
56090006	LIV01 Hepatic Specialist	Edoxaban 60mg	Two adjudications for the same event: 1) Hepatocellular Injury (First adjudication) 2) No liver injury (Second adjudication) The second adjudication should have been deleted	
73610063	BLD01	Edoxaban 60mg	No Bleed event	Minor bleed
73860025	BLD01	Warfarin	No Bleed event	Minor bleed
10400016	BLD01	Data entry error: Incorrect date of adjudication in the database		
30500001	STR02			
33040019	STR01			
	LIV02 Hepatic Specialist			
71220001				
51070031	STR01 Bleed			

Source: the Applicant's response in Sequence 00059 dated June 25, 2014

Reviewer's Comment(s): The Applicant did not identify any new events or major discrepancies during this QC checkout. None of the 9 cases with errors in the database involved the primary efficacy outcomes and had minimal impacts on the overall study results. The reviewers also sampled and reviewed several adjudication packages for primary efficacy and safety endpoints and generally agreed with the final adjudication results. After the Applicant's QC checkout and the independent review of the adjudication packages, the reviewers feel reassured about the quality of the adjudicated data in the trial.

3.2 Compliance with Good Clinical Practices

3.2.1 Ethical Conduct of the Study

According to the applicant, this study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (Committee on Human Medicinal Products (CPMP)/ICH/135/95), and applicable regulatory requirements including the following:

- European Commission (EC) Directive (2001/20/EC Apr 2001) and/or;
- European Commission Directive (2005/28/EC Apr 2005) and/or;
- United States (US) Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Other applicable local regulations

3.2.2 Subject Information and Consent

Subjects, after having the study explained to them by the investigator or designee, gave voluntary and signed informed consent before participating in any study-specific procedures. Also, a separate special consent was required for pharmacogenomic testing for this protocol.

For study sites in the US, an additional consent was required for the Health Insurance Portability and Accountability Act (HIPAA). For European Union (EU) sites, the Sponsor was to observe the rules from the European Data Protection Directive 95/46/EC on the protection of individuals with regard to the processing of personal data.

3.2.3 Medical/Scientific/ Clinical Trial Oversight

There was an elaborate system of organizational oversight to ensure a well conducted trial and safety of study subjects. See Table 9. One example of an intervention to protect study subjects and to ensure optimal management in the warfarin active control arm was Amendment 4, dated August 26, 2010, to remove the 5 mg warfarin tablet to minimize warfarin dosing errors.

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Table 9: Organizational Structure of ENGAGE AF

Organization	Responsibilities
(b) (4)	

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Organization	Responsibilities
Data Monitoring Committee (DMC)	Established to protect the safety and well-being of subjects who participated in this study. The DMC monitored the study data as per the pre-defined DMC Charter. Members were not Investigators in the study and not otherwise directly associated with the Sponsor. The Study Oversight committee (b) (4) selected the DMC chairperson and members with the approval of the Sponsor Senior Management Designee. An independent Data Analysis Group (DAG) within (b) (4) was responsible for providing the safety and other study-related data to the DMC. DAG was independent from the (b) (4) data management and biostatistics group involved with the design, conduct and management of the clinical study. The primary role for the DMC was to examine the unblinded safety data in an ongoing manner at prespecified timepoints and alert the Chairman of the Joint Management Team (JMT) in case of any clinically concerning safety issues, particularly if there was a need for a protocol modification.
Joint Management Team (JMT), otherwise known as the Study Oversight Committee	Comprised of senior representatives from (b) (4) and Daiichi-Sankyo and was chaired by (b) (4), MD from (b) (4) and was responsible for the overall design, execution, monitoring, and supervision of the study, including the development of any protocol amendments. The team was responsible for reviewing the progress of the study at regular intervals to ensure subject safety and study integrity. Any recommendations to the Sponsor Senior Management designee would come through the chairman of this team (b) (4)
Sponsor Senior Management designee	Responsible for making the final decision to accept or reject the DMC recommendations, including termination of the trial.

¹ Detailed explanation of event identification, event package handling, and adjudication process in [Sections 5.3.13](#), [5.3.14](#) and [5.3.15](#). Reviewer's Table.

3.2.4 Major Protocol Deviations

There were few major protocol deviations. Subjects with critical protocol deviations were identified by the applicant programmatically from the clinical trial database for inclusion/exclusion criteria violations, incorrect study drug dispensed (study drug kit errors), and the use of disallowed concomitant medications. In addition, data of subjects from the sites discontinued by the sponsor for GCP non-compliance were reviewed for evidence of fraud or fabrication of critical data.

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Cases with protocol deviations directly affecting the evaluation of the primary efficacy endpoint were identified. Prior to the database lock, the medical and statistical team ((b) (4) Daiichi Sankyo (b) (4)) reviewed such cases in a blinded manner and identified cases that should be excluded from the per protocol analysis based on the criteria described in the SAP.

Subjects in the ITT analysis set excluded from the PP analysis set are summarized in Table 10. The most common reason for exclusion in all 3 treatment groups was for subjects who did not take study drug after randomization.

Table 10: Major Protocol Deviations

	Edoxaban 30 mg (15mg DA) (N=7034) n (%)	Edoxaban 60 mg (30mg DA) (N=7035) n (%)	Warfarin (N=7036) n (%)
Subjects Excluded from the Per Protocol Analysis [a]	52 (0.7)	40 (0.6)	43 (0.6)
Reason for Exclusion			
Violated Critical Entry Criteria[b]	16 (0.2) [13 h/o IC bleed; 3 no AF/flut]	18 (0.3) [10 h/o IC bleed; 8 no AF/flut]	15 (0.2) [9 h/o IC bleed; 6 no AF/flut]
Subjects Who Received Wrong Study Drug[c]	1 (<0.1)	0 (0.0)	0 (0.0)
Subjects Who Did Not Take Study Drug After Randomization (noncompliance)	32 (0.5)	23 (0.3)	24 (0.3)
Disallowed Concomitant Medications with Major Impact on Primary Endpoint Evaluation[d]	3 (<0.1)	1 (<0.1)	5 (<0.1)
Fraud/Fabrication of Critical Data	0 (0.0)	0 (0.0)	0 (0.0)

DA=Dose Adjusted; h/o IC bleed= history of intracranial bleed; AF/flut=atrial fibrillation/ flutter

[a]: Subjects in the ITT Analysis Set with critical protocol violations directly affecting the evaluation of the primary endpoint are excluded from the Per Protocol Analysis Set.

[b]: Subjects violated critical entry criteria include those who did not have documentation of atrial fibrillation or atrial flutter at baseline or during study participation, or who had history of intracranial bleeding.

[c]: Subjects received wrong study drug include those who received incorrect study drug other than the randomized treatment for more than 104 consecutive days at any time during the study, or for the entire duration of the study participation if duration was 104 days or less.

[d]: Subjects received disallowed concomitant medications include those who received an oral or parenteral anticoagulant at a therapeutic dose, concomitantly with study drug for more than 30 consecutive days.

Note: Subjects could be counted in multiple categories.

Source: ENGAGE AF CSR, p. 105

3.2.5 Site-specific issues

A Division of Scientific Investigations (DSI) audit was requested to assess overall study conduct. None of the sites enrolled enough subjects to drive the results of the trial. However, to get a sense about overall study conduct, it was considered important to audit sites that were somewhat unusual, i.e., those that were the highest enrolling sites,

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had high treatment effects, and/or unusual death, serious adverse event or discontinuation rates. FDA also sent an investigator to the sponsor to examine the adjudication packages primarily to ensure that the adjudicators were properly blinded.

During the audit of Daiichi Sankyo, it was discovered that between 2009 and Sept 2011, the adjudication process was done by paper and the source documents were destroyed so it could not be determined if the adjudicators agreed or disagreed. After Sept 2011, the adjudication process was done electronically, and thus there is an auditable trail that records if the adjudicators agreed or disagreed. According to the FDA investigator, during the time prior to September 2011, there were ~ 8,000 events which included ~61% of all strokes/ SEE that were adjudicated during the entire study.

We compared the investigator reported first stroke/SEE to adjudicated first stroke/SEE to estimate the magnitude of disagreement that there might be between adjudicators (Table 11). We found that Investigator reported strokes hardly differed from the adjudicated first stroke (mITT/ on treatment period); [252 investigator reported/ 244 adjudicated for the edoxaban 30 mg (15 mg DA) group, 193 investigator reported/ 174 adjudicated for the edoxaban 60 mg (30 mg DA) group and 233 investigator reported/ 219 adjudicated for the warfarin group]. There was a much larger difference between the SEE event numbers [68 investigator reported/ 11 adjudicated for the edoxaban 30 mg (15 mg DA) group, 39 investigator reported/ 8 adjudicated for the edoxaban 60 mg (30 mg DA) group and 44 investigator reported/ 13 adjudicated for the warfarin group]. The small difference in stroke events between investigators and adjudicators suggests that it is unlikely that there was much disagreement between the adjudicators. The larger difference in the SEE events is not unusual for these types of trials and while large, it was consistent across treatment groups. SEEs also represented only ~5% of primary outcome events. For these reasons, while we think that the decision to destroy the original paper adjudication reports was a study conduct error, we do not think it affects the interpretability of the results.

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Table 11: Investigator/ Adjudicated Events Related to the Primary Endpoint in MITT population in on Treatment Period

Event	Edoxaban 30mg (15 mg DA) (N=7002)			Edoxaban 60mg (30 mg DA) (N=7012)			Warfarin (N=7012)		
	Investigator Reported	Adjudi- cated	Difference*	Investigator Reported	Adjudi- cated	Difference *	Investigator Reported	Adjudi- cated	Difference *
Stroke	252	244	8	193	174	19	233	219	14
Ischemic Stroke	230	226	4	146	135	11	139	144	5
Hemorrhagic Stroke	21	18	3	38	40	2	77	76	1
SEE	68	11	57	39	8	31	44	13	31

Difference= Investigator reported – adjudicated events
Source: Table 14.2.3.17 and 14.2.3.21: CSR, ENGAGE-AF

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The final results of the FDA audits are not available at this time.

3.3 Financial Disclosures

This study was conducted in 46 countries classified into 6 regions (North America, Latin America, Western Europe, Eastern Europe, Asia Pacific and South Africa, and Japan). A total of 1420 investigational study sites screened at least 1 subject and 1393 study sites randomized at least 1 subject in this study. There were 6 investigators who had disclosable financial interests. The presence of a CEC for adjudicating events, the small enrollment at each site and the absence of multiple investigators from any one site having disclosable financial interests makes it unlikely that the payments influenced the outcome of the trial. The financial disclosures are listed in Table 12.

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Table 12: Financial Disclosures

Name of Investigator or subinvestigator	Amount (\$USD)	Site Enrollment	Comments
(b) (6)	\$51,000	(b) (6)	(b) (6)
	\$71,528*		
	\$30,000		
	\$300,000		
	\$42,000		
	\$30,888.59		

*Paid over a 5-year period
 Reviewer's Table

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Active Pharmaceutical Ingredient (API) and selected (b) (4) ingredients are (b) (4)

The critical control points are identified in the process, (b) (4)

This in-process control is not considered as related to Real Time Release Testing and is not considered as being critical. The batch record information adequately documented the non-sterile manufacturing process.

All batches tested at release and on stability through 24 months met the compendial acceptance criteria in USP <1111> (b) (4)
(The proposed product expiry is 24 months.)

The applicant proposed to remove (b) (4) from the post approval stability protocol. Because the sponsor committed to maintain microbial limits testing for product release and stability protocol the removal of (b) (4) from the post-approval stability protocol was found to be acceptable by the FDA Quality reviewer.

No deficiencies in manufacturing or controls were identified by the FDA Quality reviewer.

See the Product Quality Microbiology Review (4/3/14) for more detailed information.

4.2 Clinical Microbiology

The internationally harmonized USP <61> Microbiological Examination of Nonsterile Products or JP <4.05> Microbial Limit Test was performed at release and as part of the registration/primary stability studies to monitor for microbial growth in the edoxaban tosylate drug substance. No microbial activity has been detected over the course of the ICH long-term stability studies.

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Microbial limits testing will be performed for every batch of product at release. No product quality microbiology deficiencies were identified by the FDA Quality reviewer.

4.3 Preclinical Pharmacology/Toxicology

This section provides a brief summary based on Dr. Baichun Yang's Pharmacology/toxicology (PT) review dated August 12, 2014. Please refer to her review for details. In general, the nonclinical studies were well designed and conducted except for few minor defects which do not have a major impact on the preclinical safety profile of edoxaban. Edoxaban is approvable from a PT perspective. The major preclinical safety findings and issues are summarized below:

Edoxaban is not considered to pose a risk to the cardiovascular system (negative findings for QTc and hERG), central nervous system, respiratory system, renal system or neuro-behavioral system in safety pharmacology studies and repeated-dose studies in rats and monkeys. Hemorrhage and anemia were found in monkeys at edoxaban doses of ≥ 15 mg/kg/day, in mice at 500 mg/kg/day, in rats at ≥ 200 mg/kg/day, and in rabbits at ≥ 30 mg/kg/day, leading to deteriorated animal condition or animal deaths. These doses with hemorrhagic findings and anemia in monkeys, mice, rats, and rabbits were 4.6, 4.5, 11, and 20 times, respectively, the human exposure (AUC) at the maximum recommended human dose (MRHD) of 60 mg/day. These findings were thought to be the exaggerated anticoagulant effect of edoxaban (its principal pharmacological action), which constitutes the dose-limiting toxicity for this compound. Safety margins for hemorrhagic risk were estimated by comparison of exposures between cynomolgus monkeys and humans. The mean exposure (AUC_{0-24h}) at no observed adverse event (NOAEL) in the 52-week repeated dose oral toxicity study in cynomolgus monkeys were approximately 1.5 times the exposures in human subjects given MRHD of 60 mg/day.

Among genotoxicity studies, numerical chromosome aberrations were observed in edoxaban or D21-2393 (active metabolite) treated CHL cells and human peripheral lymphocytes. These findings were associated with cell toxicity, which lessened the likelihood of genotoxic potential. There were no other positive findings among a battery tests for genotoxicity. Dr. Yang concluded that Edoxaban is not considered to pose a genotoxic risk based upon a weight evidence approach.

With respect to reproductive and developmental toxicology, edoxaban did not affect mating and fertility parameters in rats and was not teratogenic in rats and rabbits at doses up to 300 mg/kg/day and 600 mg/kg/day, respectively. However, edoxaban was toxic in maternal and embryo-fetal developmental studies at mid and/or high doses in both rats and rabbits. More post-implantation loss, fewer live fetuses, lower fetal weight, and increased variation in the gall bladder were found in rabbits at ≥ 200 mg/dg/day (~63 times the human exposure at MRHD of 60 mg/day). Increased skeletal variation was also found in rabbits at 600 mg/kg/day (~190 times at human MRHD of 60

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mg/day). In a postnatal development study, F1 female rates showed delayed avoidance response in a learning test at 30 mg/kg/day (~2.9 times the human exposure at human MRHD of 60 mg/day). Maternal toxicity including dam deaths and abortion, decreased food consumption and body weight, hemorrhage in uterus, or vaginal hemorrhage occurred at similar edoxaban doses to what led to embryo-fetal/developmental toxicity. Because maternal and embryo-fetal toxicities were observed at similar dose levels, Dr. Yang thought that edoxaban-associated embryo-fetal toxicity in rats and rabbits were considered to be secondary effects of maternal toxicity, rather than a direct edoxaban effect.

The carcinogenic studies showed no evidence of increased neoplasia at any given edoxaban dose in rats and mice. In a 2 year carcinogenicity study in rats, higher mortality was found in male rats at high dose (~ 8 times human MRHD of 60 mg/day) and the findings were associated with higher incidence and severity of centrilobular hepatocellular degeneration/necrosis. However, there were no differences in incidence and severity of centrilobular hepatocellular degeneration/necrosis among treated and control groups in mice (up to 3-6 times human exposure at 60 mg/day) and monkeys (up to 11 times human exposure at 60 mg/day). Although the potential liver toxicity for long-term use of high dose edoxaban cannot be ruled out because of the rat study findings, the absence of liver toxicity in the other tested species makes liver toxicity less of a concern.

The Pharmacology-Toxicology review stated that from their perspective, edoxaban is approvable. A few labeling changes that pertain to the reproductive and developmental studies and carcinogenicity studies are recommended.

4.4 Clinical Pharmacology

This section provides a brief summary primarily based on Clinical Pharmacology review by Drs. Menon-Anderson and Moon (Clinical Pharmacology) and Dr. Earp (Pharmacometrics) dated September 30, 2014. Please refer to their review for details.

4.4.1 Mechanism of Action

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. Inhibition of FXa in the coagulation cascade reduces thrombin generation and prolongs clotting time and reduces the risk of thrombus formation.

4.4.2 Pharmacodynamics

Single oral doses of edoxaban from 10 mg to 150 mg result in rapid (within 1-2 hours) increase in anti-FXa activity and rapid prolongation of PT and aPTT. For all dose levels, the maximum activity is observed between 1 to 3 hours post-dose which corresponds with peak edoxaban concentrations (C_{max}). Recovery to pre-dose values is dose-dependent with return to baseline by 24 to 36 hours post-dose in all subjects.

For once daily dosing, multiple-dose administration of edoxaban results in similar peak activity for PT, aPTT and anti-FXa activity on Day 10 as on Day 1. A direct linear correlation was observed between plasma concentrations and aPTT, PT, and anti-FXa activity, suggesting that single doses up to 150 mg (maximum dose administered) do not achieve maximum response. In summary, a concentration dependent effect of edoxaban was observed on all pharmacodynamic markers measured in the edoxaban development program. Figure 4 shows the relationship between plasma edoxaban concentration and anti-FXa/PT.

There is also an inhibition of thrombin generation. Repeat dose administration of edoxaban shows a rapid and sustained inhibition of biomarkers of thrombus formation and turnover (Thrombin anti-thrombin complexes [TAT], Prothrombin fragment 1 + 2 [F1+2], and D-dimer). It is not clear yet which biomarkers correlate best with clinical anticoagulation status and bleeding events. There is no evidence of a rebound effect following cessation of edoxaban.

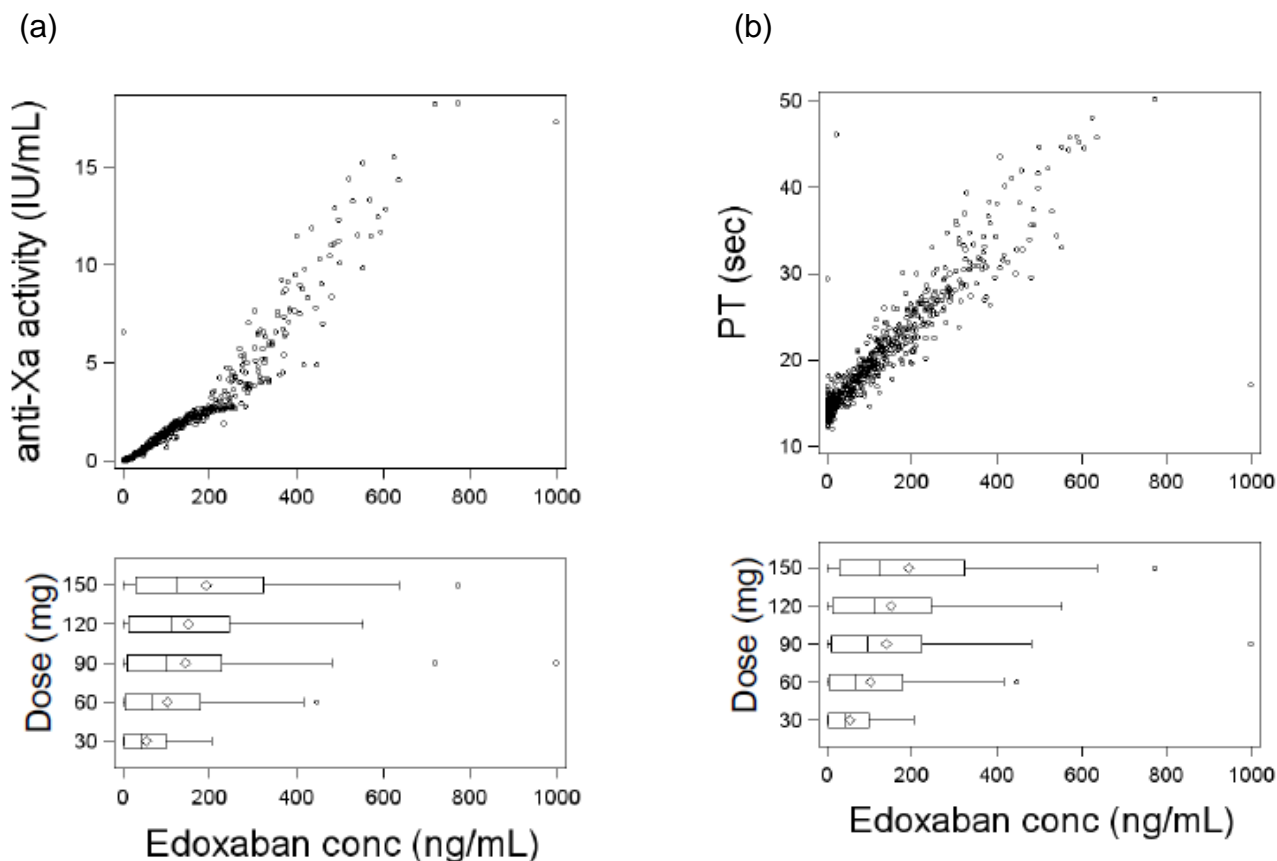
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Figure 4: Edoxaban concentration - (a) anti-Xa activity and (b) PT relationships in healthy subjects (n = 10/group) following a single dose of edoxaban tablet (Study PRT001)



Source: Clinical Pharmacology Review

4.4.3 Pharmacokinetics

4.4.3.1 PK parameters

Edoxaban is the active moiety and is the predominant circulating drug-related moiety. Following oral dosing, a 60 mg oral dose of edoxaban results in peak concentrations of 309 ± 97 ng/mL. Peak concentrations are achieved within 1-2 hours. The absolute bioavailability of edoxaban is approximately 62%. Edoxaban is predominantly absorbed in the upper GI tract with approximately 12% absorbed in the colon. The apparent terminal elimination half-life following oral administration is about 10 to 12 hours. The total clearance (arithmetic mean \pm SD) of edoxaban is estimated to be ~ 22 L/h with a steady-state volume of distribution of 107 ± 19.9 L. Edoxaban demonstrates linear PK;

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C_{max} and area under the concentration-time curve (AUC) values increase proportionally with dose (10 mg to 120 mg). Edoxaban follows biphasic disposition.

Edoxaban is eliminated mainly as an unchanged drug through multiple renal and non-renal pathways. Nonrenal elimination includes both metabolism and biliary excretion of unchanged drug. In healthy subjects with normal renal function, renal and non-renal clearances contribute equally (~ 50% each) to the total clearance of edoxaban. In healthy adult subjects, D21- 2393, an active metabolite formed by hydrolysis with similar activity to the parent compound, is the major metabolite, contributing less than 10% of total exposure in most studies.

Metabolism by CYP3A represents a minor pathway, accounting for approximately 4% of parent compound exposure. However, p-glycoprotein (P-gp), an efflux pump expressed in the apical membrane of the intestinal epithelial cells, plays an important role in the clearance of edoxaban. The inhibition of P-gp results in increased plasma edoxaban concentrations (see [Section 4.4.3.3](#)).

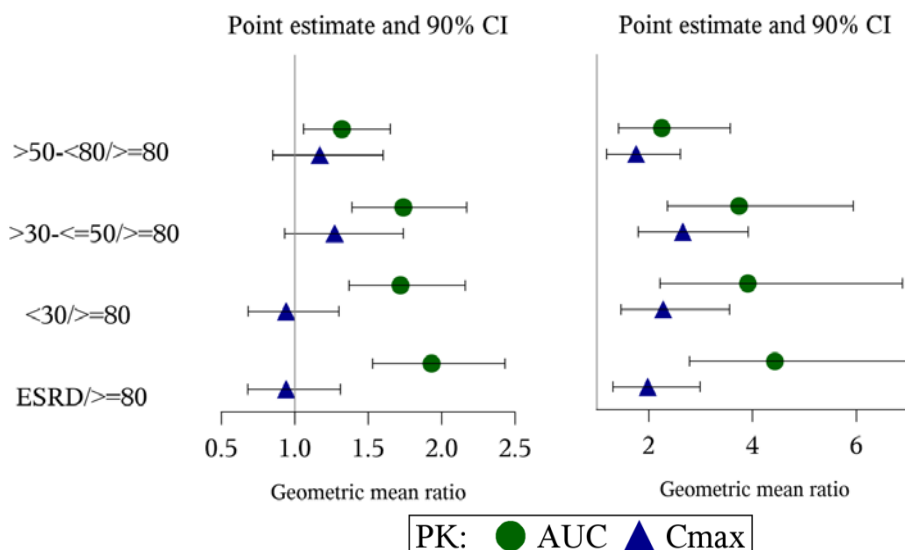
4.4.3.2 Intrinsic factors

Impaired renal or hepatic function are expected to impact edoxaban PK given that approximately 60% of a bioavailable dose of edoxaban is excreted in urine and the rest via biliary secretion. Total body weight was found to be a predictor of bleeding in a phase 2 trial. Gender, ethnicity and age (after accounting for renal function and body weight) did not have a significant effect on edoxaban PK. A brief summary of each relevant intrinsic factor is discussed below:

Renal function

The exposure of edoxaban increases with degree of renal impairment, but is similar for moderate and severe renal impairment subjects. Total systematic exposure to edoxaban increased 1.75x in subjects with moderate or severe renal impairment and close to 2X in subjects with ESRD in a phase 1 study (n = 8/group) (Figure 5). The apparent clearance values for healthy (CrCL > 80 mL/min), mild (50 ≤ CrCL ≤ 80 mL/min), moderate (30 < CrCL < 50 mL/min), severe (CrCL < 30 mL/min) and end stage renal disease patients undergoing peritoneal dialysis are ~35, ~25, ~19, ~18.5, ~17 mL/min, respectively. In end stage renal impairment subjects undergoing hemodialysis, apparent clearance values without dialysis are 22.5 ± 4.50 L/h and with dialysis are 24.1 ± 7.07 L/h. Renal impairment does not appear to affect total protein binding for edoxaban.

Figure 5: Total systemic exposure to edoxaban and D21-2393*



Source: Clinical Pharmacology Review
 *Considered exploratory because of bioanalytical problems

Hepatic function

In subjects with mild and moderate hepatic impairment, edoxaban total exposures (AUC_{0-∞}) are comparable to healthy controls, with only slight decreases of 6% and 5% in mild and moderate hepatic impairment. However, patients with moderate hepatic impairment (Child-Pugh B) may have intrinsic coagulation abnormalities. With limited data available for this subpopulation, clinical pharmacology reviewers state that dosing recommendations cannot be provided for this subgroup.

Weight

Total body weight (TBW) was identified as a risk factor for bleeding in a phase 2 AF study in Japan (12 week open label warfarin-controlled vs. blinded edoxaban groups: 30 mg QD, 45 mg QD and 60 mg QD). Subjects with a TBW ≤ 60 kg had approximately double the bleeding risk compared to subjects with a TBW > 60 kg. Thus, TBW ≤ 60 kg was a dose adjustment criterion in the Phase 3 trial.

Genetics

The Applicant evaluated the impact of genetic variants in *CYP2C9* and *VKORC1* on major and clinically relevant non-major bleeding in their Phase 2 and Phase 3 AF studies. They found that variants of the *VKORC1* and *CYP2C9* genes that are known to affect warfarin sensitivity had no effect on bleeding in patients treated with edoxaban.

4.4.3.3 Extrinsic factors

Concomitant administration of edoxaban with food does not significantly affect absorption. The concomitant administration of the proton pump inhibitor (PPI), esomeprazole, and digoxin also did not have a significant effect of the PK, PD, or safety of edoxaban. In clinical drug interaction studies with P-gp inhibitors (ketoconazole, quinidine, verapamil, erythromycin, cyclosporine, amiodarone and dronedarone), total exposure of edoxaban increases by 87%, 77%, 53%, 85%, 73%, 40% and 85%, respectively. In ENGAGE AF, subjects with concomitant use of quinidine, verapamil (and dronedarone after December 22, 2010) were required to receive dose adjustment (half dose). However, in ENGAGE AF these patients (~4%) had median trough concentrations that were about half of those who did not receive an adjusted dose.

P-gp inducer, rifampin reduced edoxaban oral exposure by about 34%. Co-administration with naproxen, low dose aspirin (100 mg) and enoxaparin do not have any effect on total exposure, however, high dose aspirin (325 mg) increases total edoxaban exposure by 32%. Co-administration with naproxen and aspirin results in prolongation of bleeding time, while co-administration with enoxaparin results in an increased effect on thrombin generation assay parameters.

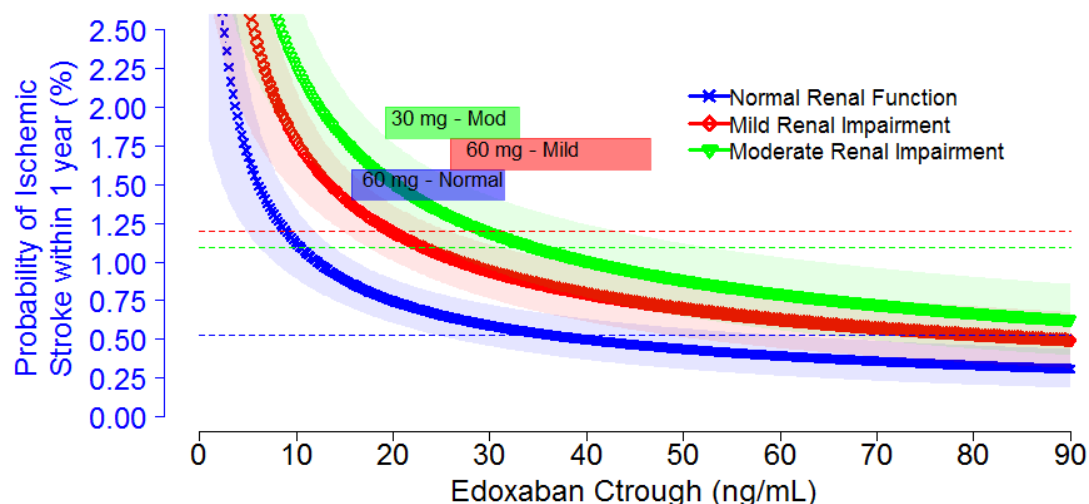
4.4.3.4 Exposure-Response Modeling

The pharmacometrics reviewers modeled the relationship between edoxaban systemic exposure [trough concentration (C_{trough}) derived from the post-hoc Bayesian population PK model estimates for each individual] and outcomes of interest (efficacy and safety endpoints) using a Cox-proportional hazard model. Model covariates were selected based on risk factors for the outcome of interest (stroke or bleeding) and were identified based on forward selection followed by backward elimination, retaining all covariates with a significance of at least 0.05 (See Clinical Pharmacology Review for detailed methodology).

Exposure-Response Relationships for Efficacy

Figure 6 shows that there is a significant reduction in the probability of ischemic stroke with increasing edoxaban C_{trough} across renal subgroups. However, comparing to the observed event rate in the warfarin group (horizontal dashed line), the two groups with lowest edoxaban exposures (normal renal function and moderate renal impairment) exhibit higher probability of ischemic stroke compared to warfarin across their range of exposures (5% to 95% exposure range showing in blue and green horizontal bands).

Figure 6 Exposure-Response for Ischemic Stroke by Renal Function



Source: Clinical Pharmacology Review

Predicted 1 year probability of ischemic stroke and 95% CI for a typical patient are shown for normal renal function (blue line), mild renal impairment (red line) and moderate renal impairment (green line). Horizontal bands indicate the exposure range (5th to 95th percentile) for edoxaban in each renal function group. Horizontal dashed reference lines indicate the observed rate of ischemic stroke for the warfarin group for the corresponding color coded renal function groups.

Reviewer's comment(s): Subjects with normal renal function had lower edoxaban concentrations due to higher renal clearance of the drug, which lead to worse efficacy compared to warfarin. The findings of exposure-ischemic stroke relationship are consistent with the observed efficacy results in the trial, which suggest that edoxaban 60 mg may not be an optimal dose (too low) for subjects with normal renal function.

Exposure-Response Relationships for Safety

The exposure-response relationship for bleeding events clearly illustrates that the risk of bleeding increases with edoxaban exposure (Figure 7 and Figure 8). The edoxaban exposures at the studied doses produce rates of bleeding that are similar or less than those for warfarin in each respective renal function subgroup. These predictions are in agreement with the observed results in ENGAGE AF.

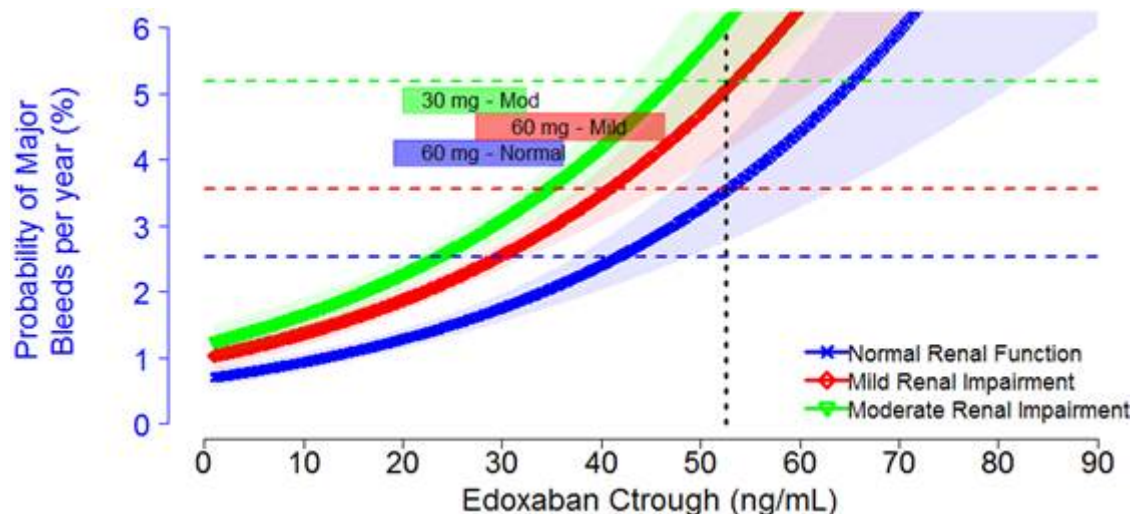
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Figure 7 Exposure-Response for Major Bleeds by Renal Function



Source: Clinical Pharmacology Review

Predicted 1 year probability of major bleeds and 95% CI for a typical patient are shown for normal renal function (blue line), mild renal impairment (red line) and moderate renal impairment (green line). Horizontal bands indicate the exposure range (5th to 95th percentile) for edoxaban in each renal function group. Horizontal dashed reference lines indicate the observed rate of major bleeds for the warfarin group for the corresponding color coded renal function groups

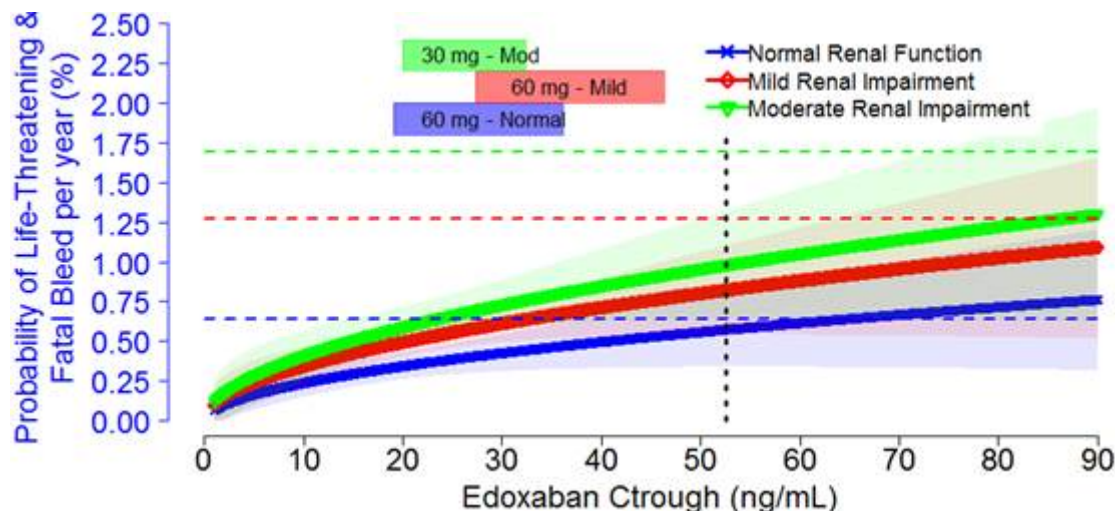
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Figure 8 Exposure-Response for Life-Threatening/Fatal Bleeds by Renal Function



Source: Clinical Pharmacology Review

Predicted 1 year probability of life threatening & fatal bleeds and 95% CI for a typical patient are shown for normal renal function (blue line), mild renal impairment (red line) and moderate renal impairment (green line). Horizontal bands indicate the exposure range (5th to 95th percentile) for edoxaban in each renal function group. Horizontal dashed reference lines indicate the observed rate of life threatening & fatal bleeds for the warfarin group for the corresponding color coded renal function groups

Definition of life-threatening/fatal bleeds: ICH and bleeds causing hemodynamic compromise requiring treatment (=GUSTO severe bleeding which includes fatal bleeds)

In the ENGAGE AF trial, edoxaban arms had superior bleeding results compared to warfarin except that there was an increased risk of major GI bleeding in the edoxaban 60 mg group compared to warfarin. By renal function subgroups, the worst major GI bleeding profile was seen in subjects with mild renal impairment (>50-<80 mL/min) with a HR of 1.61 (1.22-2.14). The exposure-response relationship for major GI bleeding is shown in Figure 9. The edoxaban exposures attained at the studied doses produce higher major GI bleeding event rate compared to the observed event rate in the warfarin group in subjects with mild or moderate renal impairment.

The clinical pharmacology reviewers also examined exposure-response relationships for various endpoints including hemorrhagic stroke, clinically relevant non-major bleeds and major bleeds, MACE and cardiovascular death (see Clinical pharmacology review for detail). In general, these relationships project a decrease in efficacy event rates with increasing edoxaban doses and a subsequent increase in safety event rates with increasing edoxaban doses.

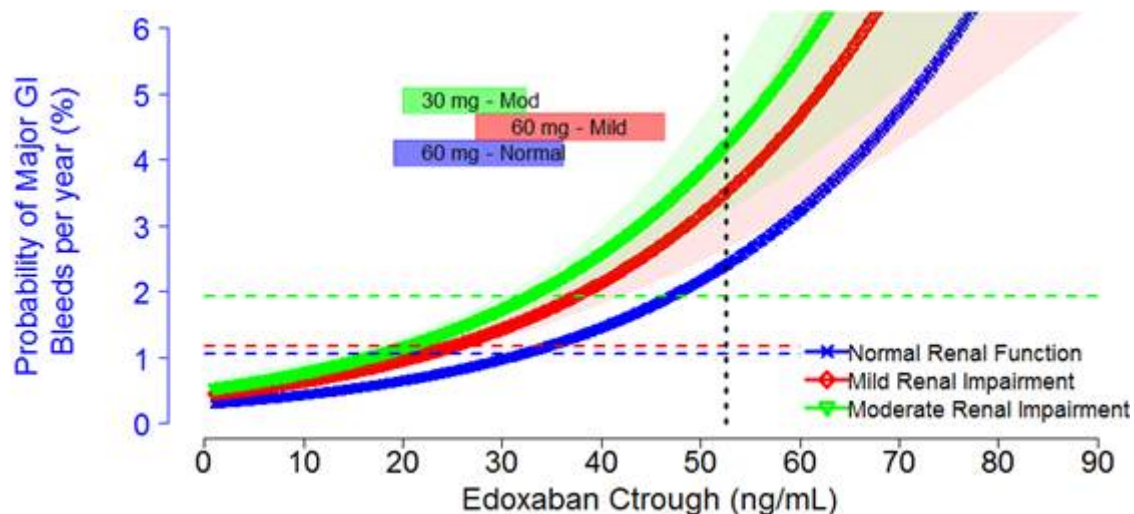
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Figure 9 Exposure-Response Relationship for Major GI Bleeds by Renal Function



Source: Clinical Pharmacology Review

Predicted 1 year probability of major GI bleeds and 95% CI for a typical patient are shown for normal renal function (blue line), mild renal impairment (red line) and moderate renal impairment (green line). Horizontal bands indicate the exposure range (5th to 95th percentile) for edoxaban in each renal function group. Horizontal dashed reference lines indicate the observed rate of major GI bleeds for the warfarin group for the corresponding color coded renal function groups

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The evidence for the efficacy and safety of edoxaban in the prevention of stroke and/or systemic embolic event (SEE) in subjects with atrial fibrillation (AF) comes primarily from the Applicant's global study DU-176b-C-301, "A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multi-Center, Multi-National Study for Evaluation of Efficacy and Safety of DU-176b (Edoxaban) Versus Warfarin in Subjects with Atrial Fibrillation (ENGAGE AF-TIMI 48, will refer to ENGAGE AF throughout the review)¹⁹. The description of the study DU-176b-C-301 is summarized in the sections that follow.

The dose-finding trial was a phase 2 trial, PRT-018. Because the dose that was chosen in ENGAGE AF is a significant review issue and because there was an SPA that agreed with the overall design of the trial, there is a summary of this trial in [Section 6.1.9](#) and [APPENDIX 9](#). See Table 13 for a list of the Phase 2 trials in subjects with NVAF.

Table 13: Phase 2 Studies in Subjects with NVAF

Number of Pooled Studies / Pooled Subjects	Subject Population	Protocol Numbers	Daily dose of Edoxaban	Duration of Treatment Planned	Number of Edoxaban Treated Subjects	Control Treatment/ Number of Subjects
Phase 2 AF Controlled Studies (Integrated) (3 studies / 1896 subjects)	Subjects with non-valvular AF	PRT018, C-J225, C-J226	30 to 120 mg (QD and BID regimens)	12 weeks	1446	Warfarin/ 450
Phase 2 AF Uncontrolled Studies (Nonintegrated) (2 studies / 56 subjects total)	Subjects with non-valvular AF	J-03	60 to 120 mg (BID regimens)	10 weeks	32	None
		J-05	5 to 30 mg (QD regimens)	6 weeks	24	None

Source: Summary of Clinical Safety, p. 21

¹⁹ Study Acronym: Effective aNticoagulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE AF-TIMI 48)

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5.2 Review Strategy

This is a joint review conducted by Melanie Blank, MD and Tzu-Yun McDowell, PhD. While this is a collaborative review, the main focus for Dr. Melanie Blank was on the data supporting efficacy and the main focus for Dr. Tzu-Yun McDowell's was on the data supporting safety. We reviewed the applicant's documents and also conducted many of our own analyses using the datasets provided in submission 0009.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Design of Study DU-176b-C-301(ENGAGE AF)

ENGAGE AF was an event-driven, Phase 3, multi-national, multi-center, randomized, double-blind, double-dummy, parallel-group study in subjects with documented AF within the preceding 12 months and in whom anticoagulation therapy is indicated and planned for the duration of the study. The sample size and the duration of treatment and follow-up of subjects in the study depended on the rate of accrual of events.

5.3.2 Study objectives:

The primary objective was to compare edoxaban to warfarin with regard to the composite primary efficacy endpoint of stroke and SEE in subjects with AF. Each edoxaban regimen (30 mg and 60 mg QD) was compared with warfarin separately for non-inferiority. If non-inferiority was established for the edoxaban High Exposure regimen, the edoxaban High Exposure regimen would be compared with warfarin for superiority.

The protocol specified four secondary objectives:

1. Compare edoxaban to warfarin for the composite clinical outcomes defined as stroke, SEE, and cardiovascular (CV) mortality, as well as each component separately
2. Compare edoxaban to warfarin for major adverse CV event (MACE) defined as a composite of non-fatal MI, non-fatal stroke, non-fatal SEE and death due to CV cause or bleeding, as well as each component separately
3. Compare edoxaban to warfarin for the composite clinical outcomes defined as stroke, SEE, and all-cause mortality, as well as each component separately.
4. Compare edoxaban to warfarin for major bleeding and a composite endpoint of major plus clinically relevant non-major (CRNM) bleeding.

5.3.3 Treatments, Dosage Form, Dose and Route of Administration:

This was a double-dummy trial such that both treatments were provided to each subject with the understanding that one would be placebo.

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There were three randomized treatment groups:

- Warfarin, the active control: (regimen: once daily with point-of-care (POC) dose adjusted to maintain INR between 2.0 and 3.0, inclusive);
- Edoxaban High Exposure (regimen: 60 mg QD with dosage adjustment to 30 mg qd for moderate renal impairment (creatinine clearance [CrCL] ≥ 30 and ≤ 50 mL/min), low body weight (≤ 60 kg), and/or use of specified concomitant medications (verapamil, quinidine, dronedarone);
- Edoxaban Low Exposure (regimen: 30 mg QD with dosage adjustment to 15 mg qd for same reasons as provided for the High Exposure above.

Edoxaban (15 and 30 mg and matching placebo) were supplied in PVC/foil blister packs. Blinded warfarin (1 and 2.5 mg tablets) and matching placebo were supplied in blister packs by the Sponsor. In addition, for China, Japan, Korea and Taiwan, 0.5 mg blinded warfarin and matching placebo were also supplied.

5.3.4 Study Scope and Population:

ENGAGE AF was conducted at a total of 1,420 sites in six regions (North America, Latin America, Western Europe, Eastern Europe, Asia Pacific, South Africa, and Japan) including 46 countries. The number of planned enrolled subjects was estimated to be approximately 20,500. The duration of the trial was dependent on primary efficacy event accrual.

5.3.5 Main Inclusion Criteria

1. Male or female subjects with age ≥ 21 years
2. History of AF documented by any electrical tracing within the prior 12 months and for which anticoagulation therapy is indicated and planned for the duration of the study (Subjects with AF includes subjects with paroxysmal, persistent, or permanent AF and subjects with or without previous VKA (including warfarin) experience)
3. CHADS₂ index score ≥ 2 . The CHADS₂ scoring is performed by assigning 1 point each for a history of Congestive heart failure, Hypertension, Age ≥ 75 years, or Diabetes mellitus; and by assigning 2 points for history of Stroke or TIA ([APPENDIX 2](#))

5.3.6 Main Exclusion Criteria

1. Transient AF secondary to other reversible disorders (e.g., thyrotoxicosis, cardiac or thoracic surgery, pneumonia, severe anemia)
2. Moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve (subjects with bioprosthetic heart valves and/or valve repair can be included). Mitral valve prolapse, mitral valve regurgitation, and aortic valve disease were allowed
3. History of left atrial appendage excision (either by surgery or by a procedure);

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4. Intracardiac mass or left ventricular thrombus
5. Discontinuation of chronic anticoagulation therapy is planned
6. Contraindication for anticoagulant agents
7. High risk of bleeding
8. On dual antiplatelet therapy (e.g., aspirin plus thienopyridine such as ticlopidine or clopidogrel)
9. On prohibited concomitant medications (fibrinolytics, non-study anticoagulants other than those used as a bridge to/from study drug, chronic oral or parenteral non-aspirin NSAID (≥ 4 days/week) and potent P-gp inhibitors (ritonavir, nelfinavir, indinavir, saquinavir, cyclosporin), GP IIb/IIIa inhibitors, PGY12 inhibitors or dextran
10. Acute MI, stroke, acute coronary syndrome (ACS), or percutaneous coronary intervention (PCI) within the previous 30 days
11. Chronic, active serious medical conditions

5.3.7 Stratification and Randomization

Eligible subjects were stratified by CHADS₂ risk score at randomization.

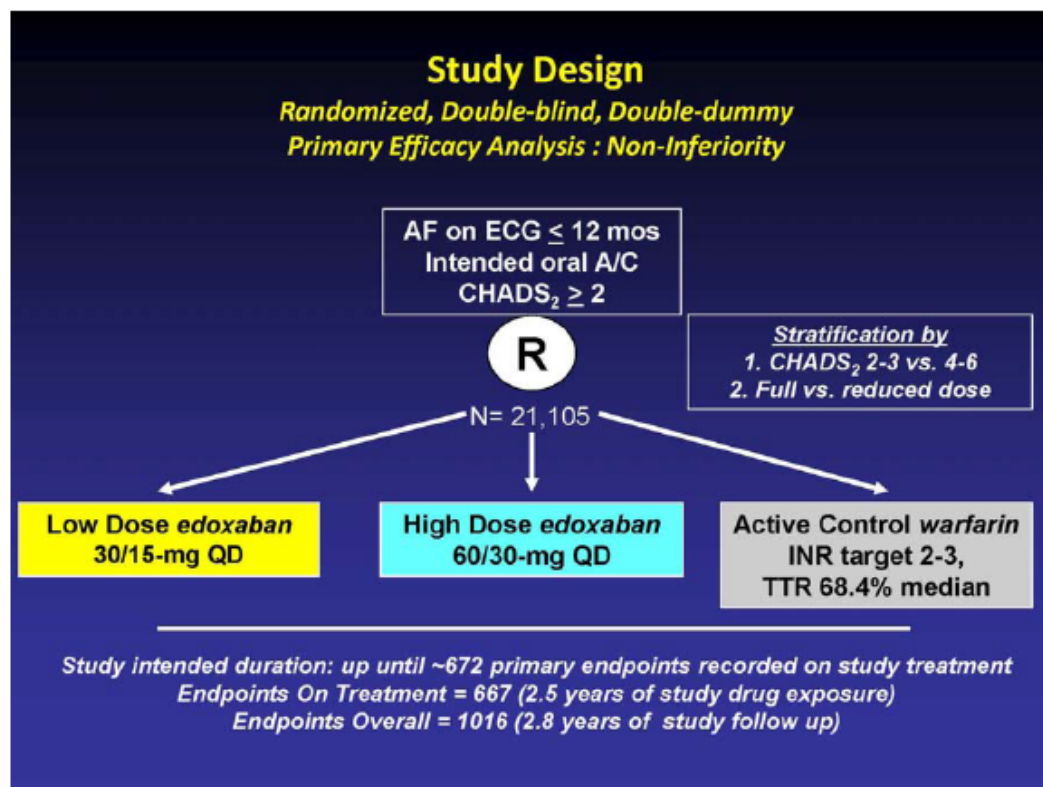
Stratum 1: CHADS₂ risk score 2 and 3

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

Subjects were then stratified further by whether they met the protocol-specified criteria for dose adjustment (yes or no).

After this second stratification, subjects were assigned randomly via interactive voice and web response system (IXRS) such that the study has a 1:1:1 ratio of subjects in the three treatment groups. See Figure 10.

Figure 10: Study Design in ENGAGE AF



Source: CSR, ENGAGE-AF, Figure 9.1

5.3.8 Edoxaban Dosage Modifications during Trial

As stated in [Section 5.3.3](#), subjects with one or more factors at screening requiring edoxaban dosage adjustment received the halved edoxaban dosage regimen. All dosage adjustments were implemented through the IXRS. The protocol specified that Investigators were required to use the appropriate IXRS option and provide the information on subject's body weight, CrCL, and concomitant medications. The IXRS provided the appropriate drug supply kit number based on the subject's information as provided by the Investigator.

For low body weight (\leq 60 kg) and moderate renal impairment (CrCL: 30-50 mL/min) present at randomization, the edoxaban dosage regimen was halved permanently even if the subject gained weight or experienced improved CrCL.

Edoxaban doses were halved *after* randomization in the following scenarios:

- if the subject's body weight dropped to \leq 60 kg (confirmed by repeat measurement at least one week apart) and the body weight change was $>$ 10%

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of the subject's baseline body weight (permanent reduction even if the subject subsequently gains weight)

- After randomization, if the subject's CrCL decreased to ≤ 50 mL/min and ≥ 30 mL/min (confirmed by repeat measurement at least one week apart) and the CrCL change was $> 20\%$ of the subject's baseline CrCL (permanent reduction even if the subject subsequently regains renal function)
- For specified concomitant medications (verapamil, quinidine, or dronedarone), dosage adjustment (increase or decrease) of edoxaban could occur at any time while on study drug. The doses would be halved if these medications were started during the protocol and returned to the regular dosage regimen at any time the subject was not taking these concomitant medications.

5.3.9 Study Procedures

5.3.9.1 Study Qualification:

Study qualification was done ≤ 60 days before randomization. The procedures included making sure that the subject signed the ICF and was eligible according to the inclusion/exclusion criteria.

5.3.9.2 Randomization (Day 1):

All baseline procedures were performed on this day. These included completing a worksheet that documented subject's age, body weight, eGFR, CHADS₂ score, vital signs, 12-lead ECG, laboratory tests, INR assessments and concomitant medications. Study drug was dispensed.

5.3.9.3 Monitoring:

In the first month of treatment, visits occurred at Days 8, 15, and 29. Subsequent visits occurred every month until the subject's last visit or study drug temporary interruption/permanent discontinuation. Subjects were contacted by telephone on Day 42 (Week 6) and Day 70 (Week 10) to confirm the current dosing of study medication. Subjects had a final follow-up telephone contact or visit 30-37 days after the final dose day except those subjects whose study drug was permanently discontinued for safety or other unanticipated reasons 30 days prior to or on the planned last visit (CSED Visit)²⁰. At this follow-up, all SAEs, endpoints and other events of interests were captured.

At the monthly visits, the INR assessments were to be done using the POC devices provided by the Sponsor for adjustment of warfarin (or placebo-to-match warfarin) doses. The subjects on edoxaban received a dummy placebo to match warfarin and

20 The common study end date (CSED) was the date on which the required number of primary endpoint events (stroke/systemic embolic events) was to be accrued. The CSED was not the end of study date or final dose day for subjects. The oversight committee informed the sites about the timing for the sites to schedule subjects for the CSED Visit which was the final dose day for subjects and followed the CSED by 90 days. On the CSED Visit, subjects were transitioned to open-label anticoagulant therapy.

Investigators received a “sham” INR value for these subjects based on an algorithm for shamming INR values. For subjects taking open-label VKA during study drug temporary interruption or permanent discontinuation, the protocol stated that it was preferred that they be followed at the site monthly for INR evaluations.

In addition, data as shown in [APPENDIX 3](#) was collected at visits. If subjects were away from the geographical location of the study site, they were allowed to go to other study sites. If no study site was available, remote management could occur. Blood samples for INR measurements were allowed to be drawn locally but had to be sent to the central laboratory for analysis.

See [APPENDIX 4](#) for detailed guidelines for INR-based dose adjustments for warfarin that were provided in the study protocol.

5.3.9.4 Special Considerations Regarding Aspirin Use

Investigators were strongly encouraged to restrict the dose of aspirin (if indicated) to \leq 100 mg daily, although higher doses were permitted for a strong clinical indication (e.g., development of an acute MI).

5.3.9.5 Treatment Interruptions or Discontinuations

Any subject who temporarily interrupted study drug treatment for more than three days for any reason had the reason recorded in the CRF. A subject could temporarily interrupt study drug for a number of reasons including those listed below:

1. AE (eg. major life-threatening bleeding or SAE, CrCL decreased to < 30 mL/min, confirmed by repeat testing at least one week later, or need for kidney dialysis); or liver abnormalities.
2. Marked liver enzyme elevation. Additional evaluations (i.e. hepatitis A, B, C, and E screening, abnormal ultrasound) were to be performed if the temporarily interruption of study drug was due to confirmed liver enzyme abnormalities or jaundice.
3. Other causes for study treatment interruption or discontinuation:
 - a. Withdrawal of Informed Consent
 - b. Initiation of fibrinolytic or additional anticoagulant therapy for MI or PE
 - c. Initiation of dual antiplatelet therapy
 - d. Initiation of strong P-gp inhibitors ritonavir, nelfinavir, indinavir, saquinavir and cyclosporine

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- e. Initiation of systemic use of the strong P-gp inhibitors ketoconazole, itraconazole, erythromycin, azithromycin, and clarithromycin required study drug treatment temporary interruption. These drugs are generally prescribed for short-term use (≤ 3 weeks). The subject was supposed to restart study drug after completing treatment with these medications. Topical use of these medications was allowed while taking study medication.
- f. Initiation of chronic use of NSAID other than aspirin by oral or parenteral administration (Use of NSAIDs via other routes (e.g., topical, inhaled, intranasal, intraocular, etc.) were not restricted
- g. Pregnancy
- h. Post-randomization changes in health status related to study exclusion criteria did not automatically lead to study drug interruption or permanent discontinuation unless continuing study drug placed the subject at undue hazard as determined by the Investigator. There was a (b) (4) HOTLINE number that was to be called so that difficult situations could be discussed and handled on a case-by-case basis.

A study drug temporary interruption was defined as being off both study drugs (warfarin/placebo or edoxaban/placebo). Individual subjects could temporarily interrupt or permanently discontinue study drug based on the rules specified in Table 14. There was no limit on either the number of study drug temporary interruptions or the maximum length of any study drug temporary interruption. Therefore, it was not possible in real time to distinguish a temporary interruption from a permanent discontinuation until the CSED Visit.

Subjects were identified as having discontinued study drug if they had not been on study drug within 30 days before the CSED visit (subjects with CSED visit) or had not been on study drug within 30 days before the CSED announcement if they did not have a CSED visit. All subjects were supposed to complete the Study Drug Discontinuation Visit procedures (Table 14).

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Table 14: Study Drug Discontinuation Rules

1. During a study drug temporary interruption or after a permanent study drug discontinuation, a subject was placed on open-label antithrombotic therapy per local guidelines and Investigator discretion. The open-label VKA therapy during study drug temporary interruptions also required INR monitoring as per local guidelines (however, no INR monitoring was allowed for the first 3 days after study drug interruption in order to maintain the blind).
2. The protocol emphasized the importance of maintaining subjects on anticoagulation therapy during study drug interruption to prevent stroke, unless anticoagulation therapy was contraindicated.
3. Following each interruption of study drug, subjects were evaluated within 7 days to determine whether the subject could resume the study drug or open-label anticoagulation therapy.
4. If a subject was switched to open-label VKA therapy, INR was measured as frequently as necessary to attain an INR in the target therapeutic range (INR 2.0 to 3.0) as quickly as possible.
5. All randomized subjects, including those who temporarily interrupted or prematurely permanently discontinued study drug, completed the CSED Visit. Those subjects who were receiving study drug on the day of the CSED Visit had their final dose at this visit. All randomized subjects who took their final dose within 30 days prior to the CSED Visit or on the day of the CSED Visit, had a post-final-dose follow-up visit or telephone contact 30 to 37 days after the CSED Visit to collect data on SAEs, endpoints and other events of interest. Subjects who permanently discontinued study drug at least 30 days prior to the CSED Visit were not required to have an additional follow-up telephone contact or visit.
6. Any study drug interruption of ≤ 3 consecutive days was recorded as missed doses rather than as a temporary interruption of study drug. The eCRF for study drug interruption was required only for temporary interruptions of > 3 consecutive days. The date/time of the last dose, the reason for the temporary interruption and other required details was recorded in the eCRF.
7. Transition kits (TK) containing warfarin were provided for use to allow subjects to transition to open-label VKA. These transition kits were not used for end-of-study transition, only for temporary stops. The end-of-study transition kits were different. The transition kits contained double-blind warfarin/placebo for the first 3 days of the transition period. Prior to transitioning, all study drug was retrieved from the subject to avoid drug administration errors. The transition kits contained warfarin (2 X 1-mg tablets) if the subject had been randomized to edoxaban or matching placebo if the subject had been randomized to warfarin. Using the TKs was optional. The investigator could determine the appropriateness of the use of the TKs on a case-by-case basis. The warfarin dose during the 3-day transition and after was modified at the discretion of the investigator. For the post-transition period, the Investigator determined the dosage of open-label VKA based on the clinical profile of the subject (age, body weight, CrCL, other clinical condition, and concomitant therapies), maintenance VKA dosage from before starting study drug if applicable, and local practice guidelines or an authoritative dosing algorithm such as the one available at www.warfarindosing.org. (For diagram of Temporary Stop plan, see [APPENDIX 5](#).)

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Special Cases of Transitioning:

The use of non-study parenteral (intravenous or subcutaneous) anticoagulant therapy (i.e., bridging anticoagulation) was permitted on a limited basis to ensure adequate anticoagulation at times when study drug had to be interrupted, such as just before/after invasive procedures or surgeries. Use of bridging anticoagulant during these occasions was not required and was left to the discretion of the Principal Investigator and treating physicians in accordance with local and international guidelines.

The Principal Investigator and treating physicians were supposed to evaluate the subject's risk of thrombosis versus bleeding to determine whether bridging anticoagulation was clinically indicated. For short interruptions of study drug (e.g., 3 days) in subjects with lower CHADS2 risk scores or high risk of bleeding, withholding bridging anticoagulation was considered to be a reasonable option. If however, the subject was at high risk of thrombotic events during interruption of anticoagulation, bridging strategies with open-label parenteral anticoagulants could be used. Investigators were instructed to hold study medications for 48 hours before initiating open-label "bridging" anticoagulation to avoid dual anticoagulation with study drug + open-label anticoagulant.

Bridging anticoagulation therapies that could be considered included:

1. Low-Molecular Weight Heparin. Weight adjusted dosing could begin no sooner than 48 hours after the last dose of blinded study medications. Monitoring of anticoagulant levels or anticoagulant effect (e.g., factor Xa levels, PT, aPTT, INR) was not recommended while administering LMWH. If LMWH was used after the procedure/surgery as a bridge back to blinded study drug, there was supposed to be a minimum of 12 hours between last dose of LMWH and the first dose of blinded study drug.
2. Unfractionated Heparin (UFH): Weight adjusted dosing of the bolus and infusion of UFH could begin no sooner than 48 hours after the last dose of blinded study medications. aPTT was to be monitored and the target was approximately twice the midpoint of the normal range of aPTT. If UFH was used after the procedure/surgery as a bridge back to blinded study drug, there was supposed to be a minimum of 2 hours between last dose of UFH and the first dose of blinded study drug.
3. Intravenous Direct Thrombin Inhibitors: These agents were preferred in patients with heparin-induced-thrombocytopenia (HIT) and the directions were the same as for UFH.

5.3.9.6 Subjects Undergoing Special Procedures

5.3.9.6.1 *Subjects Undergoing Cardioversion*

Subjects undergoing cardioversion were to stay on study drug and have their INRs tested (and kept within therapeutic range) every week for 3 weeks before and after cardioversion. In cases where subjects were not on study drug or not properly anticoagulated, a transesophageal echocardiogram was supposed to be done to exclude a left atrial thrombus. If excluded, cardioversion could proceed. Otherwise, the subject was supposed to be anticoagulated for 3-4 weeks before cardioversion.

5.3.9.6.2 *Subjects Undergoing Surgical/Invasive Procedures*

If the procedure did not carry an increased risk of bleeding (e.g., cataract surgery) in which warfarin could be safely continued, then both blinded study drugs before, during, and after the procedure were to be continued.

If the procedure carried an increased risk of bleeding (e.g., femoral bypass graft surgery), then the following steps were recommended:

1. Hold study drug for ≥ 3 days prior to surgery.
2. Draw an INR using the local hospital lab on Day 4 or after following the last dose of study drug without measuring an INR using the local laboratory until the 4th day after the last dose of study drug to avoid unblinding.
3. In subjects at high risk for thromboembolic complications (e.g., CHADS2 score of 5-6), consider bridging with low-molecular weight heparin prior to and after surgery in accordance with current guidelines and local standard of care. Proceed with elective surgery.
4. Follow the local standard of care with regard to prevention of thromboembolic phenomena (deep vein thrombosis [DVT] or pulmonary embolism [PE]).
5. Transition back to blinded study drug as if the subject was being newly entered into the study (i.e., first dose of blinded study drug could be given when INR was ≤ 2.5 if the subject was treated with an open-label vitamin K agonist [VKA] during study drug temporary interruption).
6. Check INR on or after the 4th day following resumption of study drugs.

5.3.9.7 Study Drug Discontinuation Visit procedures

The common study end date (CSED) was the date on which the required number of primary endpoint events (stroke/systemic embolic events or SEE) were accrued. The CSED was not the end of study date or final dose day for subjects. The oversight committee informed the sites about the timing for the sites to schedule subjects for the CSED Visit which was the final dose day for subjects and followed the CSED by 90 days. On the CSED Visit, subjects were transitioned to open-label anticoagulant therapy. All randomized subjects even those who temporarily or permanently discontinued study drug were to complete the CSED Visit.

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Final follow-up (telephone contact or visit): All subjects were to have a final follow-up telephone contact or visit 30-37 days after the final dose day or CSED Visit, except those subjects whose study drug was permanently discontinued for safety or other unanticipated reasons 30 days prior to or on the CSED Visit day. At this follow-up, all SAEs, endpoints and other events of interests were to be captured.

Before transitioning to open-label anticoagulant therapy, all unused double-blind study drug supplies were supposed to be retrieved from the subject to avoid drug administration errors. In order to maintain appropriate anticoagulation and blinding during the transition to the open-label anticoagulant at the end of the study, double-blind edoxaban /placebo transition kits (TK) were provided (see [APPENDIX 5](#)) to be used for subjects who received their final dose of double-blind study drug on the CSED Visit day. There was an INR/Sham INR done on the CSED Visit. INR was not to be checked again during the transition until Day 4 to preserve the blind. Following Day 4, the trough INR was to be tested once between day 4 and 7, once between day 7 and 10 and once between day 10 and 14 or until INR was controlled within the therapeutic (2-3) range. After the INR was in the therapeutic range, the transition kit could be stopped. Then an INR was supposed to be checked within a few days to make sure that the patient was still in the therapeutic range after stopping edoxaban/placebo.

Subjects transitioning to VKA therapies (warfarin, acenocoumarol, etc.) were supposed to receive the edoxaban /placebo TKs in addition to any Investigator prescribed dose of open-label VKA which was supposed to be the dose the patient was on prior to the study if the patient was VKA experienced, or if not, either warfarin dosing could be guided by “warfarindosing.org” or an algorithm was used [if age > 75 or weight < 60 kg, or CrCL < 50 mL/min, then warfarin 2.5 mg daily (or equivalent VKA), otherwise, warfarin 5 mg daily (or equivalent VKA dose)]. Each transition kit allowed for up to 14 days of treatment. The double-blind TK contained a prespecified dose of edoxaban (active drug) if they had been on edoxaban during the trial or matching placebo if they had been on a VKA during the trial. All subjects who had no dose adjustment, regardless of whether they were randomized to edoxaban 60 mg or 30 mg received 30mg of edoxaban in the transition kit and those who had dose adjustment in the trial whether they were randomized to the edoxaban 60/30 group or edoxaban 30/15 group received 15 mg of edoxaban in the transition kit). The TK for subjects transitioning from warfarin study drug to VKA therapy contained edoxaban matching placebo.

The edoxaban /placebo TK was given as additional therapy for the first 3-14 days after the CSED Visit until the INR target of ≥ 2.0 was attained. Once the INR was ≥ 2.0 , the transition kit was stopped and collected. A trough INR (at least 8 hours post-dose)/sham INR was done on the CSED visit. After the CSED visit, INRs were not to be assessed until the fourth day of transitioning to preserve the blind.

Subjects transitioning to Factor IIa inhibitor (dabigatran) or a Factor Xa inhibitor (rivaroxaban or apixaban) did not receive a TK and did not get a VKA. Investigators

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started the subjects on open-label Factor IIa or Xa inhibitor 24 hours after the last dose of study drug as long as the last INR (done on the CSED visit) was < 2.0. Otherwise, they would wait until day 4 when open INRs were allowed and dosing could commence when the INR was < 2.0.

5.3.9.8 Other Subject-Related Considerations

5.3.9.8.1 *Re-qualification procedures*

Subjects who failed to qualify for the study could not be randomized within the first 60 days of signing the informed consent but could be eligible for a second attempt at qualification. For the re-qualification or the second attempt at study qualification, the subject was to repeat study qualification in its entirety and be assigned a new subject identification number.

5.3.10 Committees

There were three independent committees by design:

- An independent Clinical Events Committee (CEC) that adjudicated key efficacy and safety endpoints in a blinded manner.
- An unblinded independent Data Monitoring Committee (DMC) responsible for monitoring safety during the study, and
- A blinded Study Oversight Committee that included (b) (4) and Sponsor's representatives.

5.3.11 Efficacy Endpoint Considerations

5.3.11.1 Primary Efficacy Endpoint

The primary efficacy endpoint was a composite of stroke and/or systemic embolic event (SEE). The stroke endpoint was to include any stroke including ischemic, hemorrhagic, and embolic stroke. SEE included non-central nervous system (non-CNS) arterial embolic events. The blinded CEC adjudicated these events. A pair of neurologists reviewed cerebrovascular events and a pair of cardiologists reviewed all other events of special interest.

If a subject had multiple strokes/SEEs, only the first event counted towards reaching the study's required number of primary endpoint events. (See [APPENDIX 6](#) for CEC definitions of endpoint events).

5.3.11.2 Secondary Efficacy Endpoints

- Composite of stroke, SEE, and CV mortality

-
- MACE: composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding
 - Composite of stroke, SEE, and all-cause mortality

5.3.12. Safety Endpoint and Safety Events of Special Interest

5.3.12.1 Primary Safety Endpoint.

The primary safety endpoint was adjudicated major bleeding. The definition of major bleeding was based on the International Society of Thrombosis and Haemostasis (ISTH) criteria with minor modifications for hemoglobin decrease and blood transfusion requirements

Major bleeding was defined as a clinically overt bleeding event that met at least one of the following criteria:

- Fatal bleeding
- Bleeding in a critical area or organ (e.g. retroperitoneal, intracranial, intraocular, intraspinal, intra-articular, pericardial, and intramuscular with compartment syndrome)
- Transfusion-adjusted drops in hemoglobin level of 2.0 g/dL or more. Each 1 unit of packed RBC or whole blood was counted as a 1.0 g/dL decrease in hemoglobin.

Major bleeding events were also further sub-classified as life-threatening or non-life-threatening.

A life-threatening major bleed is defined as a bleeding event that is either intracranial or is associated with hemodynamic compromise requiring intervention (see [APPENDIX 7](#) for overview of all bleeding category definitions).

5.3.12.2 Secondary Safety Endpoint

The secondary safety endpoint was adjudicated major or CRNM bleeding events.

CRNMs were defined as clinically overt bleeding events that require medical attention. Clinically overt bleeding requires visualization of bleeding by examination or radiologic imaging.

5.3.12.3 Evaluation of Liver abnormalities

Liver function assessment including alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBL) and alkaline phosphatase (ALP) was measured at screening, randomization, weekly in the first treatment month, monthly until

end of the treatment year one and then every three months until end of study (CSED visit or study drug discontinuation visit)(See [APPENDIX 3](#) for detailed visit schedule)

5.3.13 Adjudications

5.3.13.1 Investigator-Prompted Adjudications

Events were forwarded for review by the CEC when investigators indicated the presence of any of the following events in the eCRF (regardless of the relationship to study drug):

- Cerebrovascular events
- Systemic Embolic Event
- Death
- Myocardial Infarction / Myocardial Ischemia
- Non-Intracranial Bleeding events
- Hepatic cases of special interest

5.3.13.2 eCRF Event-Prompted Adjudications

In addition, the following events that were identified by review of the eCRF generated a query to the investigator for clarification. If the investigator confirmed the presence of a suspected clinical endpoint event or event of special interest, the CEC reviewed that event as well.

- Any single transfusion-adjusted hemoglobin drop greater than or equal to 2 g/dL during the course of the study in association with a bleeding event
- Any corrected hemoglobin drop between scheduled visits of greater than or equal to 2 g/dL
- Any corrected hemoglobin drop from the baseline value greater than or equal to 2 g/dL during the course of the study in the absence of a bleeding event
- Any case of a subject requiring transfusion of ≥ 2 units of PRBCs or whole blood between visits
- Any single CK-MB $> 3X$ ULN ($>10X$ ULN for peri-CABG)
- Any single AST or ALT $\geq 3x$ ULN
- Any single total bilirubin $\geq 2x$ ULN
- Any episode of jaundice or icterus
- Any case of an SAE due to an hepatic abnormality
- Any case of discontinuation of study drug due to hepatic abnormality
- Any new pathologic Q-waves on 12-lead electrocardiogram

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eCRF triggered events required the site to fill out the eCRF module related to the triggered event. Upon completion of the dossier, the event was submitted to the CEC for adjudication. These eCRF triggered events were kept track of separately but all events were included in the primary analyses.

The pair of independent CEC cardiologists reviewed all cases of special interest. A pair of independent CEC hepatic experts performed a 2nd (final) review of all hepatic events meeting prespecified categories:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X ULN
- ALT or AST \geq 3X ULN with total bilirubin (TBL) \geq 2X ULN
- ALT or AST \geq 2X ULN but not reaching the above limits in combination with clinical symptoms and signs suggestive of hepatitis
- Clinical jaundice
- Hepatic abnormalities or cases reported as SAEs or requiring discontinuation of study drug

5.3.14 Role of (b) (4) CRO

(b) (4), the CRO was responsible for compiling and sending completed endpoint packages to the (b) (4) CEC coordinator. The CEC coordinator distributed the packages to a pair of CEC reviewers who reviewed the packages independently. (b) (4) collected all supporting documentation, masked information that could identify the subject or unblind the CEC reviewer and prepared a complete package in English with supporting source documentation.

5.3.15 Adjudication Process

The CEC coordinator forwarded one copy of each endpoint package to two independent physician reviewers. The reviewers independently reviewed the cases and completed the appropriate adjudication endpoint form. The 2 reviewers met face-to-face to review the 2 forms. If they were in agreement, each reviewer signed and dated the form and it was given to the Chairman of the CEC for the meeting for his/her review. If in agreement and completed correctly, the form was ready for data entry and filing. If there was a discrepancy between the physician reviewers, or at the discretion of a physician reviewer, the case was presented for review by at least one additional CEC physician reviewer to establish a final adjudication. This third CEC reviewer also signed the final adjudication form. The final adjudication result was reviewed by the Chairman of the CEC and if correctly completed then entered into the electronic database.

Quality Control: At least 5% of adjudicated events were selected randomly to be re-submitted to two different independent CEC members for a second review throughout the review process. Discrepancies were to be broken down into “major” or “minor”

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disagreements as determined by the Chairman of the CEC. “Major” disagreements were those where the disagreement would impact whether or not the event would be counted toward the primary efficacy or safety endpoint. “Minor” disagreements were those where the disagreement would not impact whether or not the event would be counted toward the primary efficacy or safety endpoint. For all disagreements, the Chairman of the CEC made a determination regarding whether a major disagreement required that the event be reviewed by a third pair of CEC Adjudicators. If an event was re-submitted for re-adjudication, the CEC Adjudicators reviewed the case and provided the CEC Coordinator with the new adjudication result.

For ENGAGE AF, each event package consisted of the following:

- 1) A copy of the electronic adjudication page
- 2) Overall subject summary derived from the eCRF data specific to the endpoint being adjudicated including subject and event identification information, basic demographics, prior endpoint adjudication, prior hospitalizations, and targeted information regarding the event of interest identified from the relevant eCRF pages
- 3) Appropriate eCRF pages (or data summary), including narratives
- 4) Hospital admission note, consultant notes, operative reports, and discharge summary
- 5) Relevant source documents in English from the clinical site specific to the endpoint being adjudicated (admission/discharge notes, laboratory results, ECGs, angiography, CABG reports, brain imaging, consultant’s report, progress notes, autopsy reports, etc.).

5.3.16 Statistical Analysis

5.3.16.1 Sample Size

ENGAGE AF was an event-driven study. The study was to continue until at least 448 primary endpoint (composite of stroke and SEE) events occurred “on-treatment” for the modified Intent-to-Treat (mITT) Analysis Set in the edoxaban High Exposure and warfarin treatment groups combined and at least 448 primary endpoint events occurred “on-treatment” for the mITT Analysis Set in the edoxaban Low Exposure and warfarin treatment groups combined. This means that there had to be a total of 672 primary endpoint events for both arms combined. (The mITT Analysis Set included all randomized subjects who received at least one dose of study drug) and the analysis was to use an “on-treatment” (events that occurred after any “first” dose up to and including 3 days following the date of the corresponding “last” dose) approach. A “first” dose could be a restart dose after an interruption of dosing.

It was hypothesized that at least one edoxaban dosage regimen would be non-inferior to warfarin in reducing the risk of the composite primary endpoint of stroke and SEE in subjects with AF. The planned sample size of approximately 20,500 subjects (6,833 in each of the three treatment groups, at least 488 primary endpoint events for each pairwise combination of treatment regimens) was derived based on the assumptions and parameters listed as follows:

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- Non-inferiority margin for the risk ratio: 1.38 (this ensures preservation of 50% of the warfarin effect over placebo)
- Power for testing non-inferiority: 87% for a single comparison and >90% power to reject at least one of the two null hypotheses of inferiority
- Test of Significance Level (pairwise comparison): 0.05/2
- A projected, blinded, aggregate event rate of the primary endpoint of approximately 1.7% per subject year
- Median follow-up time of 24 months

5.3.16.2 Efficacy analyses:

5.3.16.2.1 Primary statistical analyses

The primary statistical analyses and summaries were the following two comparisons:

- Edoxaban High Exposure (60 mg) regimen vs. warfarin, and
- Edoxaban Low Exposure (30 mg) regimen vs. warfarin.

The primary analysis was designed to demonstrate that at least one edoxaban treatment regimen was non-inferior to warfarin at a non-inferiority margin of 1.38. This ratio supported the concept of preserving 50% of the observed warfarin efficacy and was agreed upon by FDA. Each of the two dose-group comparisons for non-inferiority against warfarin was to be performed at a significance level of 0.05/2 (2-sided) to control the study-wise type-I error rate of two-sided $\alpha=0.05$ for non-inferiority.

The primary analysis was designed to compare treatment efficacy for the first occurrence of a primary efficacy endpoint event (stroke or SEE) that occurred during the “on-treatment” period for all subjects in the mITT Analysis Set. For those subjects who had an efficacy endpoint event the “On-Treatment” period was defined as starting when the subject took study drug and ended at the date of the first event. If the patient had an event, however, after the CSED visit at which time the patient would have been off treatment, this would not be considered “on treatment” and would not count in the primary efficacy analysis. For subjects who did not have an endpoint event, the censoring period for the “On-Treatment” period began at the first dose and continued until the earlier of the last dose +3 days or the Common Study End Date (CSED) announcement +90 days, the CSED visit, death date, withdrawal of consent date, or last assessment date. The rationale for the 3 days following the last dose was based on 3 days being approximately 5 times the $t_{1/2}$ of edoxaban. The Cox proportional hazards model included treatments and the following two stratification factors as covariates:

1. The dichotomized CHADS2 score (1 if CHADS2 ≥ 4 ; 0 otherwise)
2. The dichotomized calculated CrCL, body weight, or specific concomitant medication at randomization (1 if CrCL ≤ 50 mL/min, or body weight ≤ 60 kg, or taking verapamil or quinidine; 0 otherwise)

The statistical analysis plan stipulated that the edoxaban High Exposure regimen would be compared for the overall study period in the ITT population with warfarin for superiority only if non-inferiority of the edoxaban High Exposure regimen was established at a significance level of 0.025. The “Overall Study Period” was defined as starting at randomization and ending at first event or if there was no event, the earliest date of Common Study End Date (CSED) announcement +90 days, the CSED visit, death date, withdrawal of consent date, or last assessment date. The time to first event was to be estimated by a KM estimate and compared between each edoxaban treatment group and warfarin using a log-rank test, at a pairwise comparison significance level of $\alpha=0.01$.

All of the non-inferiority and superiority analyses were to be performed on observed endpoints only. No missing endpoints were to be imputed. Data on subjects who did not reach the primary endpoint were to be censored.

Additional non-inferiority analyses were to be performed using the following datasets:

1. mITT population including events occurring during on-treatment study period only
2. mITT population including events occurring throughout the overall study period from the first dose to CSED Visit
3. Per Protocol (PP)²¹ Population including events occurring during on-treatment study period only
4. PP Population including events occurring throughout the overall study period from the first dose to CSED Visit

5.3.16.2.2 Secondary efficacy analyses:

The statistical plan stipulated that the hierarchy of secondary efficacy analyses would be testable only if the edoxaban 60 mg group was judged to be superior with respect to the primary efficacy endpoint.

There were 3 hierarchically sequenced secondary time-to-event efficacy endpoints. For all 3, the time to first event was to be estimated by a KM estimate and was to be compared between the edoxaban 60 mg group and the warfarin group using a log-rank test at a pairwise comparison significance level of $\alpha=0.01$. Success on the first secondary endpoint was necessary to proceed to the second secondary endpoint and so forth. The secondary efficacy analyses were to be conducted in the ITT population – overall study period.

The secondary endpoints were as follows:

²¹ All randomized subjects who received at least 1 dose of randomized study drug and did not have any major protocol violations. Subjects excluded from the PP analysis set because of major protocol violations were identified by a documented process prior to unblinding.

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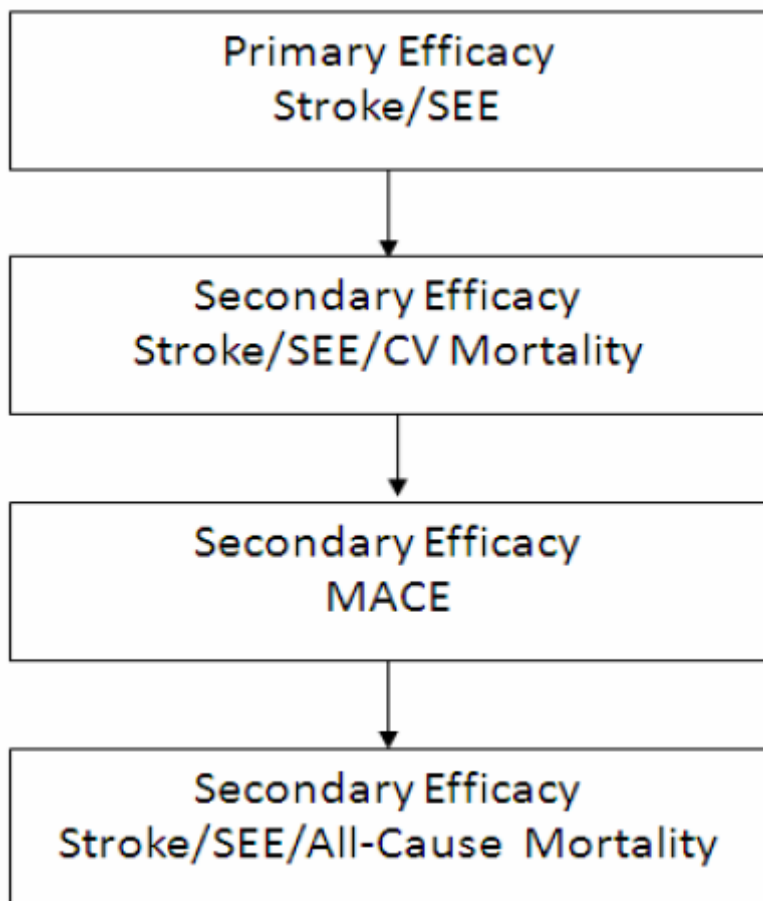
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1. The composite of stroke, SEE, and CV mortality. The time to first event was defined as the time (years) from the day of randomization to the first event experienced by a subject.
2. MACE: a composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding. The time to first MACE event was to be assessed as follows:
 - For non-fatal (MI, stroke or SEE) events, the time to event was the time to the onset date of the non-fatal event.
 - For fatal, MIs, fatal strokes, or fatal SEEs, the time to event was to be based on time to onset date of the originating event.
 - For any other CV death (eg, death due to CHF or dysrhythmia) or death due to bleeding, the time to event was to be based on time to the date of death.
3. Composite of stroke, SEE, and all-cause mortality. The time to first event was defined as the time (years) from the day of randomization to the first event experienced by a subject.

Figure 11: Planned Hierarchical Sequence for Superiority Testing



Source: CSR, ENGAGE-AF

5.3.16.3 Safety Analyses

The primary analysis was to examine the first occurrence of a primary safety endpoint (ISTH major bleeding) that occurred during the “on-treatment” period in the safety analysis set (all randomized subjects who received at least one study drug, i.e. subjects who actually received study drug were used for the analysis). In ENGAGE AF-TIMI 48 the safety analysis set is identical to the mITT analysis set. The hazard ratio and 95% CI were estimated using the Cox proportional hazard model including treatment group and two covariates as described in the efficacy analysis. Subjects were censored at 3 days after the final dose, the CSED visit, the subject’s last assessment, or death, whichever came first.

The same analysis was used to examine the secondary safety endpoint: the combination of major bleeding and CRNM bleeding events.

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5.3.17 Protocol Amendments

All of the protocol amendments except for the April 12, 2010 amendment clarified the protocol or improved safety. The increase in sample size on April 12, 2010 was reasonable because less than 10% of the total events in the trial were collected by then and the rationale was sound. See below.

Original Protocol: September 15, 2008

- 1st amendment, Version 2, February 3, 2009 (0 overall first strokes or SEEs in mITT population). Description of changes:
 1. Edoxaban dosage adjustment rules were changed after new data from study C-J225 and questions from Investigators.
 - Low body weight (≤ 60 kg) added as a factor requiring dosage adjustment
 - Dosage adjustment allowed to occur multiple times during study drug treatment as a subject goes on/off verapamil and/or quinidine
 - Dosage reduction allowed if CrCL or body weight decreased below specified thresholds while on study drug
 - Added assessments of body weight and serum creatinine at more visits so that the factors requiring dosage adjustment could be better monitored
 2. Study qualification procedures modified/clarified based on Investigator comments.
 - Study qualification period changed from 30 days to 60 days
 - ALP removed from list of labs required during study qualification
 - Study re-qualification rules clarified
 3. Removed requirement for in-clinic study drug administration on the day of randomization. Explicitly stated that study drug could be taken in AM or PM.
 4. Transition from blinded study drug to open-label warfarin clarified and added explanation/instruction for use of transition study drug kit.
 5. Modified study drug supply sections to accommodate the different regions (Added 0.5 mg warfarin tablet for specified Asian countries).
 6. Added a second sensitivity analysis for non-inferiority analysis of primary efficacy endpoint (count all strokes/SEEs in the mITT while in the study). [The first sensitivity analysis was all events “on-treatment” in the mITT subjects who do not have major protocol violations]. Superiority testing limited to edoxaban High Dosage regimen vs. warfarin. Removed superiority testing for lower edoxaban regimens vs. warfarin.
 7. Added analysis for new neoplasms.
 8. Added $\geq 8 \times \text{ULN}$ to categories of liver enzyme abnormalities.
- 2nd amendment, Version 3, April 12, 2010. Number of overall first stroke/SEEs in mITT population: (38 edoxaban 30mg (15 mg DA), 29 edoxaban 60 mg (30 mg DA), 26 warfarin, 93 total (~ 9% of overall events in mITT population)).

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Description of Change:

1. Sample size adjustment from 16.5 K subjects to 20.5 K subjects because following enrollment of > 50% of the originally planned subjects, the rate was lower for primary endpoint event rates (~1.7% per subject year).

- 3rd amendment, Version 4, July 29, 2010. Number of overall first strokes/SEEs in mITT population: 67 edoxaban 30 mg (15 mg DA), 45 edoxaban 60 mg (30 mg DA), 56 warfarin, 168 total (~ 17% of overall events in mITT population).

Description of Changes:

1. Protocol clarifications
2. Added telephone calls at Week 6 and Week 10 to review study medication dosing with subject and confirm subject's understanding.

- 4th amendment, Version 5, August 26, 2010. Number of overall first strokes/SEEs in mITT population: 72 edoxaban 30mg (15 mg DA), 51 edoxaban 60 mg (30 mg DA), 70 warfarin, 193 total (~ 20% of overall events in mITT population).

Description of Change:

Removal of all mention of the 5-mg warfarin and placebo-to-match tablets because the 5 mg dose of warfarin was no longer to be used in the study because there were warfarin overdoses.

- 5th amendment, Version 6, December 22, 2010. Number of overall first strokes/SEEs in mITT population: 115 edoxaban 30 mg (15 mg DA), 83 edoxaban 60 mg (30 mg DA), 114 warfarin, 312 total (~ 30% of overall events in mITT population).

Description of Change:

The purpose of this amendment was to include dronedarone as a concomitant medication that needed edoxaban dose adjustment. Results of a completed Phase 1 dronedarone drug-drug interaction study showed that the plasma levels (PK exposure) of edoxaban (C_{max}, AUC, and C_{24h}) increased significantly.

- 6th amendment, Version 7, January 12, 2011, Number of overall first strokes/SEEs in mITT population: 124 edoxaban 30 mg (15 mg DA), 93 edoxaban 60 mg (30 mg DA), 118 warfarin, 335 total (~33% of overall events in mITT population).

Description of Change:

Administrative change that deleted the following text: "Future knowledge of additional concomitant drugs requiring dosage adjustments for edoxaban will not result in a protocol amendment. These changes will be communicated to the sites via a memo."

- 7th amendment, Version 8, November 7, 2011, Number of overall first strokes/SEEs in mITT population: 222 edoxaban 30 mg (15 mg DA), 168 edoxaban 60 mg (30 mg DA), 214 warfarin, 604 total (~ 60% of events in mITT population).

Description of Changes:

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Update of the statistical section and secondary objectives and endpoints to make them consistent with the revised Statistical Analysis Plan (SAP).

The main change in the SAP was the change from 3 to 2 treatment regimens to be compared to warfarin for primary non-inferiority testing:

- Edoxaban High Exposure vs. warfarin
- Edoxaban Low Exposure vs. warfarin

(The third comparison, Edoxaban 30 mg QD allocated vs. warfarin was removed).

An additional secondary efficacy endpoint was added: composite of stroke/systemic embolic event and CV mortality. The sequence of secondary endpoints was rearranged.

Clarification regarding the CSED and timing schedule for CSED Visits (clarified that it could be up to 90 days following the CSED and that efficacy events that occurred after the CSED visit would not be counted toward the primary efficacy endpoint), and an updated guidance for transitioning subjects from the double-blind study drug to other locally available anticoagulant therapies. See APPENDIX 4 for graphic representations of the transition plan.

6 Review of Efficacy

Efficacy Summary

ENGAGE AF was a well conducted, large (21,105 subjects enrolled), double-blinded, double-dummy, randomized, parallel-group, multinational study. It was an active-control trial. To enroll, subjects had to have nonvalvular AF and be candidates for anticoagulation therapy according to current ACC/AHA guidelines. Two edoxaban doses were tested: [60 mg dose adjusted (DA) to 30 mg for subjects who met any of the following criteria: CrCL \leq 50 mL/min, on P-gp inhibitors (verapamil, quinidine or dronedarone) or weight \leq 60 kg and 30 mg dose adjusted (DA) to 15 mg for the same criteria] against warfarin.

There was a special protocol assessment signed on October 15, 2008. ENGAGE AF was conducted between November 14, 2008 and May 24, 2013, inclusive. The protocol was amended several times. The only significant amendments were 1) 2nd Amendment, April 12, 2010 – to increase sample size because of fewer events than anticipated, 2) 4th Amendment, August 26, 2010 – for safety purposes, removed warfarin 5 mg tablet, and 3) 7th Amendment, November 7, 2011 when the transition plan to other anticoagulants was added to decrease the risk of stroke/ SEE when coming off treatment that has been seen in other NOAC trials. The finalized SAP was submitted on January 31, 2011.

As one would expect from such a large trial, the treatment groups were well matched demographically and baseline medical conditions. The population was predominantly elderly (median age was 72), Caucasian (~80%), and male (~60%). There were very few Black subjects (~1%). Much of the world (with the exception of Africa) was represented in the trial. Most subjects had hypertension and > 50% had a history of congestive heart failure. Approximately 30% had prior strokes or TIAs. Approximately 40% were VKA naïve. Approximately 30% were on aspirin at baseline. Approximately 25% of subjects in the edoxaban arms had their dose adjusted at baseline. Note that most subjects who were dose reduced had low CrCL +/- other factors (~75% of the dose adjusted subjects). The rest of the dose adjusted subjects were dose adjusted because of weight alone (\leq 60 kg) or because of concomitant use of P-gp inhibitors (verapamil, quinidine or dronedarone).

Of 25,497 subjects screened who signed informed consent forms, 4,392 subjects were never randomized to receive study drug because protocol eligibility criteria for randomization were not met. Of the subjects screened, 21,105 subjects (83%) were randomized and assigned to treatment. Of these, 79 never received treatment with study drug. Therefore, a total of 21,026 subjects were treated with study drug. Most subjects were followed to the end of the trial and the median study follow-up was 2.8 years, longer than the other studies that have supported drug NOAC approvals.

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~70% of subjects who were dose adjusted (including warfarin subjects whose edoxaban placebo was “dose adjusted”) and ~60% of subjects who were not dose adjusted had their study drug interrupted at least once. ~45 % of subjects who were dose adjusted and ~30 % of subjects who were not dose adjusted had their study drug discontinued. The most common reasons for study drug interruptions and discontinuations were AEs or suspected endpoint events. A larger percentage of subjects interrupted or discontinued study drug prematurely in the subset that had their dose reduced. This is probably because subjects with dose reductions tended to have renal insufficiency and therefore were at higher risk for endpoint events and AEs.

The results of the primary efficacy analysis on first adjudicated stroke/SEE (mITT population, on treatment period) were positive for both doses: edoxaban 30 mg: HR: 1.07 (0.87, 1.31), $p = 0.0055$ and edoxaban 60 mg: HR: 0.79 (0.63, 0.99), $p < 0.0001$. Strictly speaking, both doses met the prespecified noninferiority criteria and could be considered for approval. The sensitivity analysis (mITT analysis set, overall study period which started at randomization and ended at first event or if there was no event, the earliest date of Common Study End Date (CSED) announcement +90 days, the CSED visit, death date, withdrawal of consent date, or last assessment date) also was successful for both doses. The constancy assumption of the warfarin control was satisfied, making it possible to interpret the non-inferiority analyses (Table 119).

In the mITT population, on treatment analysis, most of the adjudicated primary endpoint events were ischemic strokes (62% – 89% depending on the treatment group). There were very few SEEs (~5% of the adjudicated primary endpoint events). 7-33% of the adjudicated primary endpoint events were hemorrhagic strokes and 18 -23% of the adjudicated primary endpoint events were disabling stroke. It is notable, that the sub-component event that drove the primary analysis was hemorrhagic stroke [HR (95% CI): 0.23 (0.14, 0.39), $p < 0.0001$ for edoxaban 30 mg (15 mg DA) and HR (95% CI): 0.53 (0.36, 0.78), $p = 0.001$ for edoxaban 60 mg (30 mg DA). The ischemic stroke and disabling stroke subcomponents of the primary efficacy analysis were consistent with non-inferior efficacy for the 60 mg edoxaban group. However, in the edoxaban 30 mg treatment group, results were not favorable for ischemic stroke [HR (95% CI): 1.54 (1.25, 1.9), nominal $p < 0.0001$] and disabling stroke [HR (95% CI): 1.36 (0.91, 2.03). For this reason, the applicant has proposed not to carry forth the 30 mg (15 mg DA) edoxaban regimen to market.

The results of the superiority analysis were almost statistically significant. The superiority analysis was prespecified to be done in the high dose edoxaban group in the ITT population during the overall treatment period. Fewer subjects in the edoxaban 60 mg group experienced stroke or SEE than the warfarin group (1.57% and 1.80% per year, respectively), with a hazard ratio of 0.87 (99% CI: 0.709, 1.068, 95% CI: 0.744, 1.017, $p=0.08$).

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As prespecified in the hierarchical plan for secondary efficacy endpoint testing, further statistical testing would not occur unless there was success on superiority testing for the primary endpoint in the ITT set – overall study period. Since there was no success on the superiority testing of the primary endpoint in the ITT set, there was no alpha left for secondary endpoint testing.

Nevertheless, it is useful to know if the other tested endpoints support the primary efficacy findings. Edoxaban-treated subjects had a numerically lower CV and all-cause mortality than those treated with warfarin. Fewer subjects in the edoxaban 60 mg (30 mg DA) and edoxaban 30 mg (15 mg DA) groups experienced CV mortality than the warfarin group, with a hazard ratio of 0.86 (95% CI: 0.77, 0.97) and 0.85 (95% CI: 0.76, 0.96), in the ITT population, overall treatment period, respectively. Fewer subjects in the edoxaban 60 mg (30 mg DA) and edoxaban 30 mg (15 mg DA) groups experienced all-cause mortality than the warfarin group, with a hazard ratio of 0.92 (95% CI: 0.83, 1.01) and 0.87 (95% CI: 0.79, 0.96), in the ITT population, overall treatment period, respectively.

The TTR and event rates in the warfarin arm were comparable to what has been seen in previous NOAC trials. The mean time in therapeutic range (2-3) was 65% (56-64% in other NOAC trials). The stroke/SEE event rate for the warfarin arm was 1.8 per 100 patient years (%/yr) in the ITT population, comparable to the ITT population warfarin event rates in the other NOAC trials. On treatment stroke/SEE event rate in the warfarin treatment group was 2.16 %/yr in ROCKET (last dose + 2 days), 1.49 %/yr in ARISTOTLE (last dose + 2 days), and 1.5%/yr in ENGAGE AF (last dose + 3 days).

A distinguishing aspect of ENGAGE AF was the transition program which maintained the stroke rate during transition at the same rate as during the rest of the trial. In other NOAC programs, a transition program was lacking and this resulted in high stroke rates during transition off study drug.

All subgroups that were large enough to evaluate performed well except for Western Europe and subjects with CrCL ≥ 80 mL/min measured by Cockcroft-Gault equation. While the poorer performance in Western Europe was not considered to be a clinically relevant finding, the reduced relative efficacy (compared to warfarin) in the normal renal function subgroup became the issue of greatest focus during our review. For subjects with CrCL > 50 mL/min and < 80 mL/min (mild renal dysfunction) the HR for first stroke/SEE compared to warfarin in the edoxaban 60 mg (30 mg DA) group was 0.51 (0.38, 0.69). For subjects with CrCL ≥ 80 mL/min, the HR for first stroke/SEE compared to warfarin in the edoxaban 60 mg (30 mg DA) group was 1.41 (0.97, 2.05). There were not enough enrolled Black patients to evaluate efficacy. All pivotal efficacy trials for NOACs enrolled very low percentages of Blacks. There is no reason to suspect that there would be a difference in the performance of these drugs in Blacks, but their underrepresentation in these huge clinical trials is concerning. In the pivotal VTE trial, approximately 3.5% of the enrolled population was Black. The point estimate for the HR

for edoxaban 60 mg compared to warfarin in Blacks in the VTE trial was <1 which is modestly reassuring.

Subgroup analyses are often not prespecified and are subject to multiplicity. Thus, there is a high likelihood of finding an outlier subgroup with inferior efficacy just by chance. One can easily make false conclusions when it comes to subgroup findings. For this reason we looked for other supportive information before we reached our conclusion that the poor performance in the normal renal function subgroup likely represents a consequence of reduced exposure and not a serendipitous finding. The information we used to arrive at our conclusion was the following:

1. The HRs (compared to warfarin) were worse (higher) in both edoxaban groups for sub-components of the primary efficacy endpoint and CV death in the normal renal function subgroup (CrCL ≥ 80 mL/min) compared to the mild renal impairment subgroup (CrCL $> 50 - < 80$ mL/min) (Table 15). Analyses of efficacy by CrCL quintiles (Table 16) and continuous CrCL level (Figure 17) also supported this finding.
2. There is a mechanistic basis for the observed findings. Edoxaban is 50% renally excreted so it is expected that renal function would be a major determinant of edoxaban pharmacokinetics (PK) and pharmacodynamics (PD). In fact, median trough edoxaban concentrations were $\sim 1/3$ lower (see Table 47) and median changes from trough to peak anti-Factor Xa activity were $\sim 1/4$ lower in subjects with CrCL ≥ 80 mL/min than in subjects with mild renal impairment (CrCL $> 50 - < 80$ mL/min, see Table 48) .
3. While not an efficacy endpoint, the major bleeding results are useful to discuss here because the major bleeding event rates in the normal renal function subgroup (relative to warfarin) are consistent with what would be expected in the setting of lower exposures. The HRs of major bleeding relative to warfarin were lower in subjects with CrCL ≥ 80 mL/min (HR: 0.70, 95%CI: 0.55-0.89) compared to subjects with mild renal impairment (CrCL $> 50 - < 80$ mL/min) (HR: 0.90, 95% CI: 0.74-1.08). See Table 15.

Table 15: Summary Results of HRs (compared to warfarin) by CrCL subgroup (mITT, on Treatment)

Event	CrCL	Dose Group	HR (95% CI)	CrCL	Dose Group	HR (95% CI)
Stroke/SEE	>50- <80	E30/15 DA	0.82 (0.64, 1.05)	≥80	E30/15 DA	1.61 (1.12, 2.32)
		E60/ 30 DA	0.51 (0.38, 0.69)		E60/ 30 DA	1.41 (0.97, 2.05)
Isch. Str.	>50- <80	E30/15 DA	1.13 (0.85, 1.51)	≥80	E30/15 DA	2.09 (1.38, 3.16)
		E60/ 30 DA	0.62 (0.43, 0.87)		E60/ 30 DA	1.58 (1.02, 2.45)
Hem. Str.	>50- <80	E30/15 DA	0.24 (0.12, 0.46)	≥80	E30/15 DA	0.53 (0.21, 1.34)
		E60/ 30 DA	0.36 (0.20, 0.64)		E60/ 30 DA	0.85 (0.38, 1.9)
Dis. Str.	>50- <80	E30/15 DA	1.06 (0.66, 1.70)	≥80	E30/15 DA	2.45 (1.13,5.32)
		E60/ 30 DA	0.39 (0.20, 0.74)		E60/ 30 DA	2.45 (1.13,5.33)
Major Bleed	>50- <80	E30/15 DA	0.55 (0.45, 0.68)	≥80	E30/15 DA	0.44(0.33, 0.58)
		E60/ 30 DA	0.75 (0.58, 0.98)		E60/ 30 DA	0.70 (0.55, 0.89)
CV Death (Overall Treatment Period)	>50- <80	E30/15 DA	0.87 (0.72, 1.04)	≥80	E30/15 DA	0.89 (0.69, 1.13)
		E60/ 30 DA	0.75(0.62, 0.9)		E60/ 30 DA	1.15 (0.91, 1.45)

E30/15 DA= Edoxaban 30 mg/ 15 mg Dose Adjustment

E60/ 30 DA= Edoxaban 60 mg/ 30 mg Dose Adjustment

Isch. Str. = Ischemic Stroke, Hem. Str. = Hemorrhagic Stroke, Dis. Str. = Disabling Stroke (Modified Rankin score 3-5)

Dataset: ADJEFFCA.xpt, BASEGP.xpt; HRs calculated using modeling with Dose Adjustment, yes or no, CHADS2≤3=0, or >3=1.

Major Bleed rates were not an efficacy endpoint. The data are placed in this section because the lower HR for major bleed compared to warfarin in the normal renal function subgroup relative to the mild renal dysfunction subgroup provides evidence that the decreased efficacy in the normal renal function subgroup is based on lower exposure and is real.

(More details of this analysis are shown in Table 40, Table 42, Table 43, Table 45, and Table 46).

Reviewer's Table.

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Table 16: Stroke/SEE, mITT population, on treatment by quintile of CrCL

CrCL	Edox 60mg (30mg DA)	Warfarin		
	Event Rate (%/yr)/N	Event Rate (%/yr)/N	HR (95% CI)	
30 to <=50.6	1.68/1344	2.04/1360	0.83	(0.56, 1.24)
50.6< to 63.6	1.13/1356	2.33/1381	0.48	(0.32, 0.72)
63.6< to 77.9	0.93/1414	1.69/1409	0.55	(0.35, 0.85)
77.9 < to 98.1	1.12/1336	1.04/1415	1.08	(0.68, 1.74)
>= 98.1	1.05/1434	0.61/1357	1.74	(1.01, 3.01)

%/yr = events/100 patient years. Datasets: DM.xpt, ADJEFFCA.xpt, HR constructed using applicant's model [adjusted for DoseAdj(N,Y), and CHADS2 score (0,1 for CHADS2 score <3 and ≥3, respectively (More details of this analysis are shown in section 6.1.7.2.

Reviewer's Table.

One cannot be 100% sure that these findings are reflective of reduced exposures in subjects with normal renal function. However, the evidence points strongly in that direction. Given that there are 3 other NOACs available in the U.S. and given that the 30 mg (15 mg DA) and 60 mg (30 mg DA) doses of edoxaban are arguably inferior to warfarin in the subpopulation of subjects with normal renal function, one could question the approvability of either one of these doses in this subpopulation.

Exposure-response relationships for various efficacy and safety endpoints were modeled by the Office of Clinical Pharmacology. Each efficacy and safety endpoint of interest was modeled using a Cox-proportional hazard model as a function of the individual's trough edoxaban exposure (derived from the post-hoc Bayesian population PK model), and selected covariates based on risk factors for the particular outcome. The models clearly illustrate that the risk of stroke/SEE as well as ischemic stroke decrease with increasing edoxaban trough exposure; while the risk of bleeding increases with increasing edoxaban trough exposure. The predicted event rates are generally in agreement with the observed findings in the trial. The models predict that an increased dose in the subjects with CrCL ≥ 80 mL/min from 60 mg to 90 mg would match the exposure to the best performing subgroup: CrCL >50-<80 mL/min. The models predict that the 90 mg dose will decrease ~ 2 strokes/SEEs per 1,000 patient-years compared to the edoxaban 60 mg in the normal renal function group and will result in an increase in stroke/SEE by 0.4 per 1,000 patient-years when compared to warfarin instead of 1.8 more stroke/SEE per 1,000 patient-years expected with edoxaban 60 mg. The predicted benefits of having a higher dose available for normal renal function patients must be weighed against the predicted risk of increased bleeding including increased hemorrhagic stroke. The models predict that 90 mg would cause 0.6 more hemorrhagic strokes/1,000 patient-years compared to a 60 mg dose (0.1/1,000 patient-years more than warfarin).

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The other area of focus in the efficacy section of the edoxaban review was the appropriateness of dose adjustment. The overall performance of both dose adjusted and non-dose adjusted groups appeared comparable but when dividing subjects by renal function it becomes apparent that subjects who had mild renal insufficiency or normal renal function and were not dose adjusted had a lower HR compared to warfarin for first stroke/SEE (mITT, on Treatment) compared to the dose adjusted cohorts (Table 17). This could mean that the dose adjustment was not necessary or too extreme in those subjects. The same analysis done only for ischemic stroke confirmed the findings. These clinical study findings suggest that dose adjustment for weight or P-gp inhibitors may not be necessary or the amount of dose adjustment should not be as great. The pharmacometric models support no need for dose adjustment in patients with low body weight and concomitant P-gp inhibitors. See the pharmacometrics review for a detailed explanation of the models and derived conclusions.

Table 17: Summary Results (compared to warfarin) by CrCL subgroup and Dose-Adjustment (DA vs. NOT DA), (mITT, on Treatment)

Event	CrCL	Dose Group	HR (95% CI)	CrCL	Dose Group	HR (95% CI)
Stroke/SEE	>50- <80	E 60 NOT DA	0.45 (0.32, 0.64)	≥80	E 60 NOT DA	1.38 (0.97, 2.03)
		E 60, DA	0.73 (0.42,1.27)		E 60, DA	2.1 (0.38, 11.49)
Isch. Str.	>50- <80	E 60 NOT DA	0.58 (0.39, 0.87)	≥80	E 60 NOT DA	1.54 (0.98, 2.40)
		E 60, DA	0.75 (0.37, 1.51)		E 60, DA	3.26 (0.34, 31.46)

E 60 NOT DA = Edoxaban 60 mg NOT Dose Adjusted

E 60, DA = Edoxaban 60 mg, Dose Adjusted (i.e., administered 30 mg edoxaban QD)

Dataset: ADJEFFCA.xpt, BASEGP.xpt; HRs calculated using modeling with Dose Adjustment, yes or no, CHADS₂≤3=0, or >3=1.

(More details of this analysis are shown in Table 58 and Table 59).

Reviewer's Table.

Because there were so few subjects in the moderate renal dysfunction group who did not get dose adjusted, it is difficult to evaluate the appropriateness of dose adjustment in this subgroup on the basis of clinical data. The HR for ischemic stroke compared to warfarin for the dose adjusted segment of the moderate renal dysfunction subgroup in the 60 mg (30 mg DA) treatment arm was 1.03 (95% CI: 0.59, 1.80) compared to 2.08 (95% CI: 0.40, 10.75) for the small segment of that subgroup (mITT, on treatment) who did not get dose adjusted. The HR for stroke/SEE in the dose adjusted moderate renal function group also trended better than the non-dose adjusted group. However, the 32% decrease in median trough edoxaban exposure and 42% decrease in median trough to peak in anti-Factor Xa levels in the subgroup of subjects with moderate renal dysfunction who had dose adjustment (compared to the non-dose adjusted subjects with mild renal dysfunction who were the best performers relative to warfarin) suggest that the magnitude of dose reduction was overzealous. See Table 18. The pharmacometric models support a dose adjustment of 45 mg for patients with moderate renal insufficiency (CrCL= 30 - ≤ 50 mL/min) if the goal is to match the exposures to the

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subjects who had mild renal insufficiency. The predicted benefits of having a higher dose available for patients with moderate renal dysfunction must be weighed against the predicted risk of increased bleeding including increased hemorrhagic stroke. The models predict that 45 mg would cause 2.4 fewer ischemic strokes and 0.8 more hemorrhagic strokes/1000 patient-years compared to a 30 mg dose (0.1 fewer ischemic strokes and 3.4 fewer hemorrhagic strokes/1000 patient-years than warfarin). See the pharmacometrics review for a detailed explanation of these models.

Table 18: Biomarker Levels by CrCL, dose adjustment (Y/N) day 29 in some subjects

Biomarker	CrCL= 30-≤50 mL/min		CrCL > 50-< 80 mL/min	
	Dose Group	Median	Dose Group	Median
Trough Edoxaban Levels	E 60 NOT DA	48.6	E 60 NOT DA	42.9
	E 60, DA	28.8	E 60, DA	23
Anti- Factor Xa change from trough to peak	E 60 NOT DA	4.2	E 60 NOT DA	3.6
	E 60, DA	2.1	E 60, DA	2.3

E 60 NOT DA = Edoxaban 60 mg NOT Dose Adjusted

E 60, DA = Edoxaban 60 mg, Dose Adjusted (i.e., administered 30 mg edoxaban QD)

Datasets: XB.xpt, PCANAL.xpt, BASEGP.xpt

(More details of this analysis are shown in Table 47 and Table 48).

Reviewer's Table.

6.1 Indication

6.1.1 Methods

6.1.1.1 Important Study Dates:

- July 21, 2008: First SAP
- August 13, 2008: End of Phase 2 (EOP2) Meeting
- September 15, 2008: Protocol version 1
- October 15, 2008: SPA Agreement
- November 14, 2008: First Subject Screened
- November 19, 2008: First Subject Randomized
- December 11, 2009: Revised SAP; the sponsor was originally planning on comparing 3 dose regimens to warfarin for efficacy: High, Low and 30 mg. The sponsor originally proposed controlling the study-wise type I error rate of 0.05 by performing each analysis at an alpha of 0.05/3. This revision proposed that only the High Dose and Low Dose would be compared to warfarin at an alpha= 0.05/2

level and the 30 mg would be analyzed in an exploratory analysis. The test for superiority was also proposed in this revision: “The test for superiority will be performed only for the DU-176b High Exposure regimen and warfarin at a significance level of 0.01. This test will be performed only if noninferiority for this regimen is shown first.”

- April 12, 2010: Protocol Version 3,— to increase sample size because of fewer events than anticipated after prospectively planned (Blinded Pooled Event Rate) interim analysis to assess sample size;
- August 26, 2010: Protocol Version 5,— for safety purposes, removed warfarin 5 mg tablet
- January 31, 2011: Final SAP
- November 7, 2011: Protocol version 8 (Final):— transition plan to other anticoagulants added
- May 24, 2013: Last subject completed (according to protocol)*
- August 6, 2013: Data base lock

*During our review we noticed that there were subjects in the database with visits after August 6, 2013. The applicant clarified that all dates after the August 6, 2013 database lock date were data entry errors and could not be deleted due to system functionality. The applicant stated that these visits did not alter the time to event analyses in any way. The applicant confirmed that no data was entered or changed after database lock.

6.1.2 Demographics

Table 19, Table 20, and Table 21 are tabular summaries of the demographic data. The treatment groups were well matched demographically. The population was predominantly elderly (median age of 72), Caucasian (~80%) and male (~60%). ~25% of subjects in the edoxaban arms had their doses adjusted at baseline because of reduced renal function (~ 18% of all edoxaban subjects), weight ≤ 60 kg (~10% of the edoxaban subjects) or concomitant P-gp inhibitors that required dose adjustment (~3.5% of edoxaban subjects). Approximately half of the subjects were CHADS₂ score 2 and most of the other half had CHADS₂ scores between 3 and 5. There were a few subjects with CHADS₂ scores of 1 and 6. Most subjects had hypertension and > 50% had a history of congestive heart failure. Approximately 30% had prior strokes or TIAs. Approximately 40% were VKA naïve. Approximately 30% were on aspirin at baseline.

Refer to [APPENDIX 10](#) for a comparison between demographics in ENGAGE AF and studies of other NOACs.

Table 19: Demographics and Other Baseline Characteristics

	Edoxaban (15mg DA)	Edoxaban (30mg DA)	Warfarin
Age (years), n	7002	7012	7012
Mean (SD)	70.6 (9.31)	70.6 (9.51)	70.5(9.44)
Median	72.0	72.0	72.0
Minimum, Maximum	27, 95	25, 96	27, 95
>= 65 years n(%)	5218 (74.5)	5182 (73.9)	5143 (73.3)
>= 75 years n(%)	2789 (39.8)	2838 (40.5)	2805 (40.0)
>= 80 years n(%)	1197 (17.1)	1177 (16.8)	1195 (17.0)
Gender, n (%)	7002	7012	7012
Male	4284 (61.2)	4353 (62.1)	4383 (62.5)
Race, n (%)^[a]	7001	7012	7012
Caucasian	5650 (80.7)	5679 (81.0)	5679 (81.0)
Black	94 (1.3)	96 (1.4)	88 (1.3)
Asian	975 (13.9)	956 (13.6)	963 (13.7)
Other	282 (4.0)	281 (4.0)	282 (4.0)
Edoxaban/Placebo Dose Adjusted at	7002	7012	7012
Yes	1774 (25.3)	1776 (25.3)	1780 (25.4)
No	5228 (74.7)	5236 (74.7)	5232 (74.6)
CrCL (mL/min), n (%)²²	6961	6954	6973
< 30	42 (0.6)	70 (1.0)	51 (0.7)
30 - <= 50	1274 (18.2)	1287 (18.4)	1297 (18.5)
> 50 - < 80	3034 (43.3)	2985 (42.6)	3030 (43.2)
>= 80	2611 (37.3)	2612 (37.3)	2595 (37.0)
Weight (kg), n (%)²³	6996	7007	7007
<= 50	148 (2.1)	158 (2.3)	172 (2.5)
<= 60	692 (9.9)	681 (9.7)	697 (9.9)
> 60	6304 (90.0)	6326 (90.2)	6310 (90.0)
Mean (SD)	83.9 (20.11)	84.2 (20.40)	83.7 (20.09)

²² n is less than MITT because data not reported for all subjects

²³ n is less than MITT because data not reported for all subjects

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

	Edoxaban (15mg DA)	Edoxaban (30mg DA)	Warfarin
Verapamil or Quinidine Use at Randomization, n (%)	7002	7012	7012
Yes	259 (3.7)	257 (3.7)	241 (3.4)
No	6743 (96.3)	6755 (96.3)	6771 (96.6)
CHADS2, n (%)	7002	7012	7012
2 - 3	5437 (77.6)	5401 (77.0)	5422 (77.3)
4 - 6	1559 (22.3)	1606 (22.9)	1585 (22.6)
≥ 3	3705 (52.9)	3784 (54.0)	3686 (52.6)
0	0 (0.0)	0 (0.0)	1 (<0.1)
1	6 (<0.1)	5 (<0.1)	4 (<0.1)
2	3291 (47.0)	3223 (46.0)	3321 (47.4)
3	2146 (30.6)	2178 (31.1)	2101 (30.0)
4	1077 (15.4)	1123 (16.0)	1072 (15.3)
5	399 (5.7)	397 (5.7)	424 (6.0)
6	83 (1.2)	86 (1.2)	89 (1.3)
VKA Use, n (%)	7002	7012	7012
Naive	2857 (40.8)	2879 (41.1)	2888 (41.2)
Experienced	4144 (59.2)	4133 (58.9)	4124 (58.8)
Type of Atrial Fibrillation, n (%)	7002	7012	7010
Paroxysmal	1827 (26.1)	1747 (24.9)	1774 (25.3)
Persistent	1581 (22.6)	1645 (23.5)	1624 (23.2)
Permanent	3593 (51.3)	3620 (51.6)	3612 (51.5)
Region, n (%)	7002	7012	7012
North America	1550 (22.1)	1559 (22.2)	1556 (22.2)
USA	1308 (18.7)	1288 (18.4)	1297 (18.5)
Latin America	882 (12.6)	884 (12.6)	885 (12.6)
Western Europe	1075 (15.4)	1075 (15.3)	1070 (15.3)
Eastern Europe	2369 (33.8)	2374 (33.9)	2378 (33.9)
Asia/Pacific and South Africa (Excluding Japan)	789 (11.3)	784 (11.2)	786 (11.2)
Japan	337 (4.8)	336 (4.8)	337 (4.8)

Source: ENGAGE-AF CSR, p.108

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Table 20: Baseline Cardiovascular Status

	Edoxaban 30 mg (15mg DA) (N=7002) n (%)	Edoxaban 60 mg (30mg DA) (N=7012) n (%)	Warfarin (N=7012) n (%)
Prior Stroke or TIA	1999 (28.5)	1968 (28.1)	1983 (28.3)
Prior Stroke	1309 (18.7)	1291 (18.4)	1321 (18.8)
Prior TIA	820 (11.7)	836 (11.9)	793 (11.3)
Prior Congestive Heart Failure	3962 (56.6)	4086 (58.3)	4038 (57.6)
Prior Hypertension	6545 (93.5)	6568 (93.7)	6566 (93.6)
Prior Diabetes	2533 (36.2)	2550 (36.4)	2516 (35.9)
Prior MI, CAD, or CABG	2358 (33.7)	2327 (33.2)	2310 (32.9)

DA= Dose Adjustment

Source: ENGAGE-AF CSR,p.130

Table 21: Medication at Baseline

Medication at Randomization	Edoxaban 30 mg (15mg DA) (N=7002) n (%)	Edoxaban 60 mg (30mg DA) (N=7012) n (%)	Warfarin (N=7012) n (%)
VKA experienced	4144 (59.2)	4133 (58.9)	4124 (58.8)
VKA naïve	2857 (40.8)	2879 (41.1)	2888 (41.2)
Aspirin	2009 (28.7)	2060 (29.4)	2083 (29.7)
Thienopyridine	146 (2.1)	172 (2.5)	163 (2.3)
Anti-platelet Drug Excluding Aspirin/Thienopyridines	54 (0.8)	54 (0.8)	59 (0.8)
NSAIDs	85 (1.2)	68 (1.0)	77 (1.1)
Lipid Lowering Agents (Statins, Others)	3388 (48.4)	3290 (46.9)	3365 (48.0)
Verapamil	239 (3.4)	235 (3.4)	221 (3.2)
Quinidine	2 (<0.1)	6 (<0.1)	1 (<0.1)
Amiodarone	796 (11.4)	862 (12.3)	826 (11.8)
Dronedarone	42 (0.6)	42 (0.6)	48 (0.7)
ACE Inhibitors or ARBs	4618 (66.0)	4617 (65.8)	4615 (65.8)
Beta Blocker	4649 (66.4)	4592 (65.5)	4693 (66.9)
Calcium Channel Blocker[c]	2218 (31.7)	2181 (31.1)	2153 (30.7)
Diuretics	4182 (59.7)	4245 (60.5)	4184 (59.7)

Source: ENGAGE-AF CSR, p.108

The frequency of dose adjusted subjects in each group was nearly identical and the reasons for dose adjustment were also similar (Table 22). The “dose adjusted” warfarin subjects were not really dose adjusted; their edoxaban placebo was dose adjusted. Note that most subjects who were dose reduced had low CrCL +/- other factors.

Table 22: Dose Adjustment at randomization

	Edoxaban 30 mg (15mg DA) (N=7002) n (%)	Edoxaban 60 mg (30mg DA) (N=7012) n (%)	Warfarin (N=7012) n (%)
Dose Adjustment at Randomization	1774 (25.3)	1776 (25.3)	1780 (25.4)
Reasons for Dose Adjustment			
Low CrCl only	871 (12.4)	894 (12.7)	892 (12.7)
Low CrCl and Low weight	381 (5.4)	364 (5.2)	414 (5.9)
Low CrCl and P-gp inhibitor	28 (0.4)	31 (0.4)	31 (0.4)
Low CrCl, P-gp inhibitor and low weight	16 (0.2)	17 (0.2)	15 (0.2)
Low weight only	294 (4.2)	291 (4.2)	259 (3.7)
P-gp inhibitor only	169 (2.4)	167 (2.4)	156 (2.2)
Low weight and P-gp inhibitor only	15 (0.2)	12 (0.2)	13 (0.2)

Reviewer's Table.

6.1.3 Subject Disposition

Of 25,497 subjects screened who signed informed consent forms, 4,392 subjects were never randomized to receive study drug because protocol eligibility criteria for randomization were not met (n = 2,523), the Investigator's decision (n=619) subjects, the subject's decision (n=1,245), or because the reason was not available (n=5). For a tabular listing of the specific reasons for screening failure see [APPENDIX 8](#). Of the subjects screened, 21,105 subjects (83%) were randomized and assigned to treatment. Of these, 79 never received treatment with study drug. Therefore, a total of 21,026 subjects were treated with study drug. This group of 21,026 subjects comprises the mITT and safety analysis set. There were only 135 (0.6%) randomized subjects excluded from the Per Protocol analysis set (N=20,970). The most common reasons were that they either violated a critical entry criteria such as no documentation of atrial fibrillation or atrial flutter at baseline or during study participation or had a history of intracranial bleeding [49 (36.3%)] or they did not take study drug after randomization [79 (58.5%)]. One subject (0.7%) received the wrong study drug and 9 subjects (6.7%) were on disallowed concomitant medication (such as an oral or parenteral anticoagulant at therapeutic dose) that would have a major impact on the primary endpoint. Major protocol violations were evenly distributed among treatment groups.

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

See Table 23 for a tabular listing of subject disposition categories by treatment.

Importantly, most subjects were followed to the end of the trial and median study follow-up was 2.8 years, longer than the other studies that have supported NOAC approvals.

Clinical Review
 Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
 NDA 206316
 Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Table 23: Subject Disposition

	Edoxaban 30mg (15 mg DA)	Edoxaban 60mg (30mg DA)	Warfarin	Total
Total Screened				25,497
ITT/ Randomized and Assigned Treatments	7034	7035	7036	21, 105
mITT/ Safety set (received at least one dose of treatment)	7002	7012	7012	21,026
PP analysis set	6982	6995	6993	20,970
Median Study Drug Exposure	916 days (2.5 yr)	904 days (2.5 yr)	904 days (2.5 yr)	
Subject-year Exposure	15,840	15,471	15,569	
Median Study Follow-up	1023 days (2.8 yr)	1023 days (2.8 yr)	1021 days (2.8 yr)	
Mean Percentage of Exposed Days (SD)	82.2 (30.6)	80.3 (32.5)	81.4 (31.3)	
Completed Study	6956 (98.9%)	6956 (98.9%)	6946 (98.7%)	
Completed CSED Visit (Did not die before CSED visit, withdraw consent or get lost to follow-up)	6250 (88.9%)	6228 (88.5%)	6157 (87.5%)	
<u>Reasons for Not Completing</u>				
Withdrew Consent (some still followed for morbidity/vital status)	77(1.1%)	77(1.1%)	90(1.3%)	
Lost to follow-up for morbid events	44 (0.6%)	53 (0.8%)	50 (0.7%)	
Lost to follow-up for vital status	12 (0.2%)	17 (0.2%)	12 (0.2%)	

Source: ENGAGE-AF CSR, Figure 10.1 (p.101), Figure 10.2 (p. 102) and other communications pre- and post-submission with the applicant

6.1.4 Treatment Interruptions and Discontinuations

Treatment interruptions occurred commonly with ~63% of the subjects having at least one occurrence of treatment interruption. The most common reason for treatment interruption (~36%) was because of an AE or suspected endpoint event, followed by investigator decision (~27%), surgery (~16%) and subject decision (~13%). The number of treatment interruptions and reasons for treatment interruptions were generally comparable among treatment groups. See Table 24.

Table 24: Treatment Interruptions

	Edoxaban 30 mg (15mg DA) (N=7002) n (%)	Edoxaban 60 mg (30mg DA) (N=7012) n (%)	Warfarin (N=7012) n (%)
Subjects Interrupting Study Drug at Least Once[a]	4326 (61.8)	4386 (62.5)	4590 (65.5)
Reason for Interruption[b]			
AE or Suspected Endpoint Event[c]	2454 (35.0)	2527 (36.0)	2737 (39.0)
Investigator Decision	1876 (26.8)	1825 (26.0)	1941 (27.7)
Missed Visit	90 (1.3)	93 (1.3)	92 (1.3)
Non-compliance	68 (1.0)	57 (0.8)	78 (1.1)
Prohibited Medication	73 (1.0)	51 (0.7)	62 (0.9)
Surgery	1112 (15.9)	1110 (15.8)	1110 (15.8)
Other	774 (11.1)	781 (11.1)	896 (12.8)
Subject Decision	917 (13.1)	870 (12.4)	951 (13.6)
Subject Refused Routine Follow-Up	156 (2.2)	199 (2.8)	196 (2.8)
Number of Occurrences[d]			
≥1	4326 (61.8)	4386 (62.5)	4590 (65.5)
≥2	1701 (24.3)	1701 (24.3)	1896 (27.0)
≥3	685 (9.8)	690 (9.8)	785 (11.2)
≥4	333 (4.8)	313 (4.5)	347 (4.9)

Source: ENGAGE-AF CSR, p.165

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

The subjects who had their dose reduced (subjects with CrCL ≥ 30 mL/min and ≤ 50 mL/min, body weight ≤ 60 kg, or concomitant P-gp inhibitors) had a higher incidence of efficacy endpoints and bleeding and non-bleeding AEs and required more interruptions compared to subjects who were not dose-reduced, for each of the 3 randomized treatment groups (Table 25).

Table 25: Study Drug Interruptions by Treatment Regimen, Safety Analysis Set

	Edoxaban 30mg		Edoxaban 60mg		Warfarin	
	15mg DA (N=1774) n (%)	30mg NoDA (N=5228) n (%)	30mg DA (N=1776) n (%)	60mg NoDA (N=5236) n (%)	Warfarin/Plb Edo DA (N=1780) n (%)	Warfarin/Plb Edo NoDA (N=5232) n (%)
Subjects Interrupting Study Drug at Least Once[a]	1228 (69.2)	3098 (59.3)	1257 (70.8)	3129 (59.8)	1325 (74.4)	3265 (62.4)
Reason for Interruption						
AE or Suspected Endpoint Event[d]	762 (43.0)	1692 (32.4)	759 (42.7)	1768 (33.8)	890 (50.0)	1847 (35.3)
Investigator Decision	472 (26.6)	1404 (26.9)	474 (26.7)	1351 (25.8)	485 (27.2)	1456 (27.8)
Missed Visit	24 (1.4)	66 (1.3)	18 (1.0)	75 (1.4)	22 (1.2)	70 (1.3)
Non-compliance	21 (1.2)	47 (0.9)	13 (0.7)	44 (0.8)	27 (1.5)	51 (1.0)
Prohibited Medication	16 (0.9)	57 (1.1)	16 (0.9)	35 (0.7)	21 (1.2)	41 (0.8)
Surgery	237 (13.4)	875 (16.7)	248 (14.0)	862 (16.5)	234 (13.1)	876 (16.7)
Other	236 (13.3)	538 (10.3)	249 (14.0)	532 (10.2)	261 (14.7)	635 (12.1)
Subject Decision	241 (13.6)	676 (12.9)	226 (12.7)	644 (12.3)	247 (13.9)	704 (13.5)
Subject Refused Routine Follow-up	50 (2.8)	106 (2.0)	62 (3.5)	137 (2.6)	58 (3.3)	138 (2.6)
Number of Occurrences						
>=1	1228(69.2)	3098 (59.3)	1257 (70.8)	3129 (59.8)	1325 (74.4)	3265(62.4)
>=2	482 (27.2)	1219 (23.3)	453 (25.5)	1248 (23.8)	544 (30.6)	1352 (25.8)
>=3	192 (10.8)	493 (9.4)	172 (9.7)	518 (9.9)	228 (12.8)	557 (10.6)
>=4	95 (5.4)	238 (4.6)	75 (4.2)	238 (4.5)	103 (5.8)	244 (4.7)

Source: ENGAGE-AF CSR, p. 166

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

At the end of the study, subjects who were not on study drug within 30 days of the CSED Visit (subjects with CSED Visit) or within 30 days of CSED announcement (subjects with no CSED Visit) were identified as subjects discontinuing study drug prior to study end. Thus, the number of subjects that discontinued study drug was derived at the end of the study based on those subjects who never resumed study drug after their last interruption. For the subjects who were identified at the end of the study as having discontinued study drug, the reasons for discontinuation are summarized in Table 26. The percentage of subjects who discontinued study drug was comparable among the edoxaban 60 mg, edoxaban 30 mg, and the warfarin treatment groups (34.4%, 33.0%, and 34.5%, respectively). The most common reason for discontinuation of study drug in the edoxaban 60 mg, edoxaban 30 mg, and the warfarin treatment groups was AE or suspected endpoint event (19.9%, 18.4%, and 19.7%, respectively)(see Table 91 and Table 92).

Table 26: Study Drug Discontinuation

	Edoxaban 30 mg (15mg DA) (N=7002) n (%)	Edoxaban 60 mg (30mg DA) (N=7012) n (%)	Warfarin (N=7012) n (%)
Subjects that Discontinued Study Drug	2309 (33.0)	2415 (34.4)	2417 (34.5)
Reason for Discontinuation			
AE or Suspected Endpoint Event	1285 (18.4)	1398 (19.9)	1382 (19.7)
Investigator Decision	349 (5.0)	317 (4.5)	318 (4.5)
Missed Visit	22 (0.3)	15 (0.2)	28 (0.4)
Non-compliance	50 (0.7)	45 (0.6)	43 (0.6)
Prohibited Medications	13 (0.2)	15 (0.2)	20 (0.3)
Surgery	77 (1.1)	70 (1.0)	85 (1.2)
Other	187 (2.7)	172 (2.5)	142 (2.0)
Subject Decision	539 (7.7)	522 (7.4)	551 (7.9)
Subject Refused Routine Follow-up	128 (1.8)	169 (2.4)	161 (2.3)

Source: ENGAGE-AF CSR, p. 168

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Data on study drug discontinuations and the reasons for discontinuation are presented by treatment regimen in Table 27. In all 3 treatment groups, a larger percentage of subjects discontinued study drug prematurely in the subset that had their dose reduced. This is the same pattern seen in the subjects who had dose interruptions and is likely because subjects with dose reductions tended to have renal insufficiency and therefore were at higher risk for endpoint events and AEs. The proportion of subjects discontinuing study drug prematurely was comparable among the treatment groups for the subjects who had their dose reduced.

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Table 27: Study Drug Discontinuations by Treatment Regimen, Safety Analysis Set

	Edoxaban 30mg		Edoxaban 60mg		Warfarin	
	15mg DA (N=1774) n (%)	30mg NoDA (N=5228) n (%)	30mg DA (N=1776) n (%)	60mg NoDA (N=5236) n (%)	Warfarin/Plb Edo DA (N=1780) n (%)	Warfarin/Plb Edo NoDA (N=5232) n (%)
Subjects with Study Drug Discontinuations[a]	774 (43.6)	1535 (29.4)	817 (46.0)	1598 (30.5)	837 (47.0)	1580 (30.2)
Reason for Discontinuation						
AE or Suspected Endpoint Event	467 (26.3)	818 (15.7)	484 (27.3)	914 (17.5)	541 (30.4)	841 (16.1)
Investigator Decision	120 (6.8)	229 (4.4)	127 (7.2)	190 (3.6)	96 (5.4)	222 (4.2)
Missed Visit	5 (0.3)	17 (0.3)	4 (0.2)	11 (0.2)	4 (0.2)	24 (0.5)
Non-compliance	16 (0.9)	34 (0.7)	11 (0.6)	34 (0.6)	13 (0.7)	30 (0.6)
Prohibited Medication	4 (0.2)	9 (0.2)	3 (0.2)	12 (0.2)	5 (0.3)	15 (0.3)
Surgery	20 (1.1)	57 (1.1)	22 (1.2)	48 (0.9)	15 (0.8)	70 (1.3)
Other	75 (4.2)	112 (2.1)	87 (4.9)	85 (1.6)	59 (3.3)	83 (1.6)
Subject Decision	139 (7.8)	400 (7.7)	147 (8.3)	375 (7.2)	143 (8.0)	408 (7.8)
Subject Refused Routine Follow-up	45 (2.5)	83 (1.6)	55 (3.1)	114 (2.2)	54 (3.0)	107 (2.0)

DA=dose adjustment

noDA=no dose adjustment

Source: ENGAGE-AF CSR, p. 170

Study Drug Compliance

Edoxaban (or matching edoxaban placebo for the warfarin group) compliance was assessed by percentage of doses taken ($\geq 80\%$ versus $< 80\%$) at each compliance visit (Day 29, Month 2, Month 3 and then every 3 months). At least 98% of subjects in the edoxaban 30 mg and 60 mg groups were more than 80% compliant at all compliance visits, with the exception of Month 45 (98% and 93%, respectively). In the warfarin group, at least 97.8% of subjects were more than 80% compliant at all compliance visits. Not all subjects, however, were present at all compliance visits. The amount of missing data at each compliance visit ranged from 5% to 20.8% but there was little difference among treatment groups. This degree of compliance probably mimics the real world, or is better than what occurs in the real world.

Warfarin compliance was also assessed by the percentage of time subjects INR was within the range of 2.0 – 3.0. See [Section 6.1.4.5](#).

6.1.5 Analysis of Primary Endpoint(s)

6.1.5.1 Prespecified Primary Endpoint Results:

Both the edoxaban 30 mg and 60 mg groups were non-inferior to warfarin on time to adjudicated first stroke or SEE in the mITT analysis set on-treatment (primary endpoint) and overall study periods (sensitivity analysis), using the upper boundary of the 97.5% confidence interval. The per protocol analysis were also consistent. Therefore, the trial met its primary endpoint. Results are shown in Table 28 and Figure 12. See Figure 18 for the Kaplan-Meier curve of time to first occurrence of stroke or SEE, ITT analysis set-overall study period.

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Table 28: Adjudicated Primary Endpoint (Stroke or SEE), mITT Analysis Set - On-Treatment and Overall Study Period (Non-Inferiority)

Primary Endpoint	Edoxaban 30 mg (15mg DA) (N=7002)		Edoxaban 60 mg (30mg DA) (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg (15mg DA) vs Warfarin		Edoxaban 60 mg (30mg DA) vs Warfarin	
First Stroke or SEE	# of events	Event Rate (%/yr) [a]	# of events	Event Rate (%/yr) [a]	# of events	Event Rate (%/yr) [a]	HR (97.5% CI)	p-value[b]	HR (97.5% CI)	p-value[b]
mITT Analysis Set On Treatment Period	253	1.61	182	1.18	232	1.50	1.07 (0.87, 1.31)	0.0055	0.79 (0.63, 0.99)	<0.0001
mITT Analysis Set Overall Study Period	382	2.04	292	1.55	336	1.80	1.13 (0.96, 1.34)	0.0074	0.86 (0.72, 1.03)	<0.0001

Abbreviations: DA = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, mITT = Modified Intent-to-Treat, SEE = Systemic Embolic Event, yr = year.

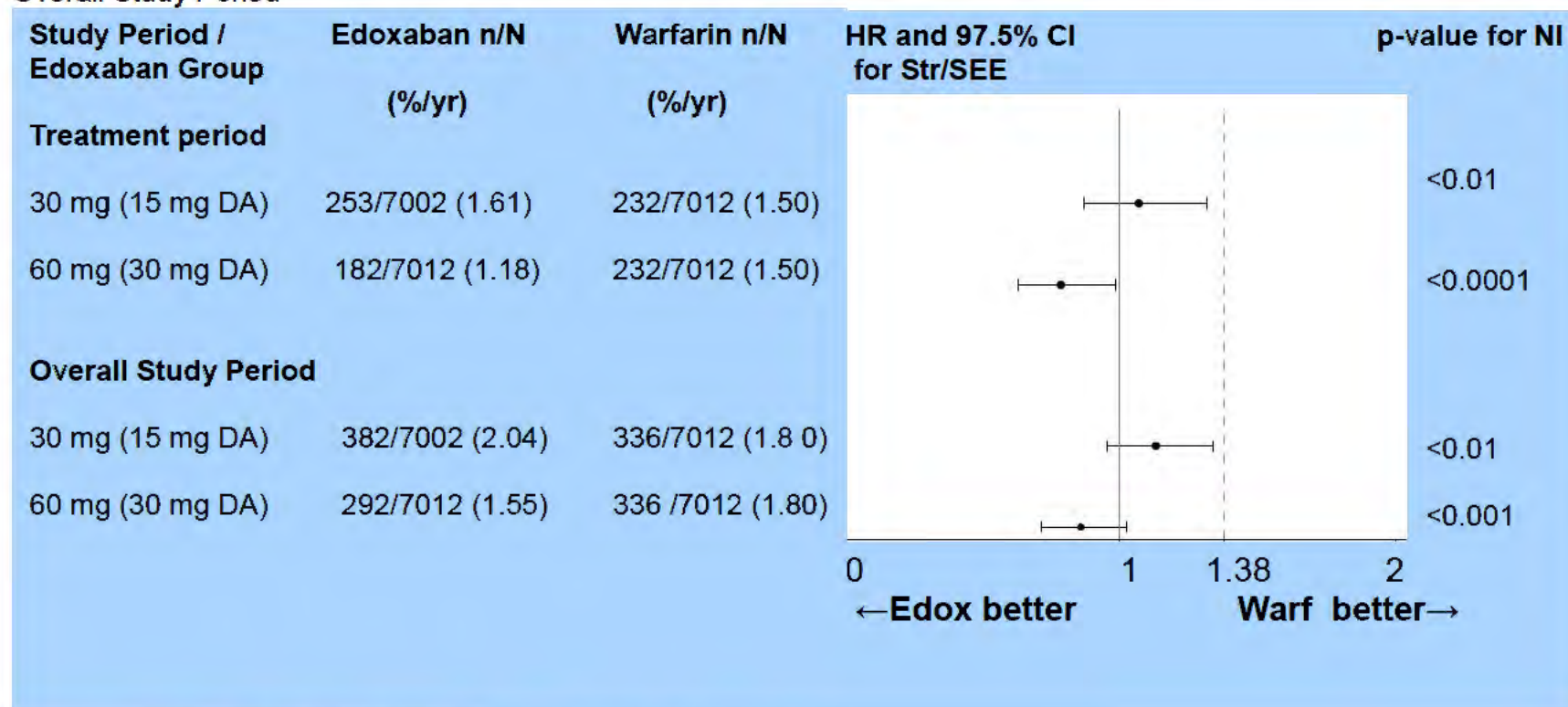
[a]: The event rate (%/yr) is calculated as # of events/subject-year exposure (%/yr = events/100 patient-years).

[b]: The two-sided p-value is based on the non-inferiority margin of 1.38

Source data: Tables 14.2.1.1 and 14.2.1.2

ENGAGE-AF CSR p. 121

Figure 12: Forest Plot of the Primary Efficacy Analysis, mITT Analysis Set - On-Treatment (primary efficacy analysis) and Overall Study Period



Source: Tables 14.2.1.1 and 14.2.1.2. (ENGAGE AF CSR p. 122)

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6.1.5.2 Superiority Testing (ITT Overall Study Period)

It was prespecified in the statistical analysis plan that if ENGAGE AF was successful on its primary endpoint, the High Dose Edoxaban 60 mg group would be tested for superiority compared to warfarin. This superiority analysis compared edoxaban 60 mg to warfarin for the adjudicated first occurrence of stroke or SEE in the ITT analysis set during the overall study period. The results are shown in Table 29. Fewer subjects in the edoxaban 60 mg group experienced stroke or SEE than the warfarin group (1.57% and 1.80% per year, respectively), with a hazard ratio of 0.87 (99% CI: 0.709, 1.068, 95% CI: 0.744, 1.017, $p=0.0807$). While the results leaned in the direction of superiority they were not statistically significant. Thus, the null hypothesis for superiority was not rejected.

Table 29: Adjudicated Primary Endpoint (Stroke or SEE), ITT Analysis Set - Overall Study Period (Superiority)

First Stroke/SEE	Edoxaban 30 mg (15mg DA) (N=7034)	Edoxaban 60 mg (30mg DA) (N=7035)	Warfarin (N=7036)
# of Events	383	296	337
Subject Year Exposure	18779.79	18874.84	18690.95
Event Rate (%/yr)	2.04	1.57	1.80
HR (99% CI)	1.13 (0.93, 1.37)	0.87 (0.71, 1.07)	
(97.5% CI)	(0.96, 1.34)	(0.73, 1.04)	
(95% CI)	(0.98, 1.31)	(0.74, 1.02)	
Log rank p-value	0.10	0.08	

Abbreviations: DA = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, ITT = Intent-to-Treat, SEE = Systemic Embolic Event, yr =year.

(%/yr) is # of events/ 100 subject-year exposure.

Source data: Table 14.2.1.7, ENGAGE AF CSR p.125

While not a prespecified analysis, it is useful to look at the time to the first occurrence of the composite of stroke and SEE in the mITT population during the on-treatment period for superiority. Nominally fewer subjects in the edoxaban 60 mg group experienced stroke or SEE than the warfarin group (1.18% and 1.5% per year, respectively), with a HR of 0.79 [95% CI (0.650, 0.958); $p=0.0167$]. The results are displayed in Table 30.

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Table 30: Adjudicated Primary Endpoint (Stroke or SEE), mITT Analysis Set – On-Treatment Period (Superiority)

First Stroke/SEE	Edoxaban 30 mg (15mg DA) (N=7002)	Edoxaban 60 mg (30mg DA) (N=7012)	Warfarin (N=7012)
# of Events	253	182	232
Subject Year Exposure	15755.57	15438.26	15512.32
Event Rate (%/yr)	1.61	1.18	1.50
HR (99% CI)	1.07 (0.85, 1.36)	0.79 (0.61, 1.02)	
(95% CI)	(0.90, 1.28)	(0.65, 0.96)	
p-value*	0.44	0.02	

HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, SEE = Systemic Embolic Event,
DA= Dose Adjusted

(%/yr) is # of events/ 100 subject-year exposure.

Source: Table 14.2.1.10, ENGAGE AF CSR p.127

* p value for analyses with 95% confidence interval

6.1.5.3 Analysis of Components and Select Subcomponents of the Primary Endpoint

Table 31 provides the breakdown of results of ENGAGE AF by type of stroke in the ITT analysis, overall study period. This table reveals that the favorable results in the edoxaban 60 mg (30mg DA) treatment group were driven by a reduction in first hemorrhagic stroke compared to warfarin (almost half in the edoxaban 60 mg (30 mg DA) arm compared to the warfarin arm). The event rate for first ischemic stroke was the same for these treatment groups. Few first events were SEEs and therefore, differences in event rates of SEEs are hard to interpret. There were 1/3 fewer fatal hemorrhagic strokes in the edoxaban 60 mg (30 mg DA) treatment group compared to the warfarin treatment group. However, the event rates for first disabling stroke and for fatal stroke were similar between the edoxaban 60 (30mg DA) treatment group and the warfarin treatment group. There were (~16%) more fatal ischemic strokes in the edoxaban 60 mg (30 mg DA) treatment group compared to warfarin. There was a similar pattern seen in the event rates of the components and subcomponents of the primary endpoint in the mITT population on treatment (Table 32).

The results of the edoxaban 30 mg group showed an even further reduction in first hemorrhagic stroke compared to the warfarin group (approximately 1/3 the rate, a difference that was nominally statistically significant) but there were relatively more first ischemic strokes (~41% more). In fact, the event rate for first ischemic stroke was nominally statistically significantly worse in the edoxaban 30 mg (15 mg DA) treatment group compared to warfarin in the ITT population, overall study period. The 30 mg (15 mg DA) group was also associated with a 42% higher rate of disabling stroke than

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warfarin. First SEE/Ischemic stroke rates were also ~ 40% higher in the 30 mg edoxaban group than in the warfarin group.

The Per Protocol analysis of the on-treatment and overall treatment periods were similar to the mITT on-treatment analysis, and ITT overall treatment period, respectively (not shown in this review).

Table 31: Components and Select Subcomponents of the Primary Endpoint, ITT Analysis, Overall Study Period

Event	Edoxaban 30mg (15mg DA) (N=7002)		Edoxaban 60mg (30mg DA) (N=7012)		Warfarin (N=7012)		Edoxaban 30mg (15mg DA) vs Warfarin		Edoxaban 60mg (30mg DA) vs Warfarin	
	# of events	Event Rate (%/yr)	# of events	Event Rate (%/yr)	# of events	Event Rate (%/yr)[a]	HR (95% CI)	p-value	HR (95% CI)	p-value
First Stroke	360	1.91	281	1.49	317	1.69	1.13 (0.97, 1.31)	0.12	0.88 (0.75, 1.03)	0.11
First Ischemic Stroke	333	1.77	236	1.25	235	1.25	1.41 (1.19, 1.67)	<0.0001	1.00 (0.83, 1.19)	0.97
First Hemorrhagic Stroke	30	0.16	49	0.26	90	0.47	0.33 (0.22, 0.50)	<0.0001	0.54 (0.38, 0.77)	0.0005
Fatal Stroke	73	0.38	80	0.42	86	0.45	0.84 (0.61, 1.15)	0.27	0.92 (0.68, 1.25)	0.62
Fatal Ischemic Stroke	63	0.33	53	0.28	46	0.24	1.35 (0.93, 1.98)	0.12	1.15 (0.78, 1.7)	0.50
Fatal Hemorrhagic Stroke	10	0.05	27	0.14	40	0.21	0.25 (0.12, 0.50)	<0.0001	0.67 (0.41, 1.09)	0.21
First Disabling Stroke[a]	82	0.43	54	0.28	57	0.30	1.42 (1.02, 1.99)	0.04	0.94 (0.65, 1.36)	0.75
First SEE	29	0.15	15	0.08	23	0.12	1.24 (0.72, 2.15)	0.43	0.65 (0.34, 1.24)	0.19
First SEE/Ischemic Stroke	356	1.89	251	1.33	255	1.36	1.39 (1.18, 1.63)	<0.0001	0.98 (0.82, 1.16)	0.79

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, MITT = Modified Intent-to-Treat, SEE = Systemic Embolic Event, yr = year, n = number of events.

(%/yr) is calculated as # of events/subject-year exposure and = events/100 patient-years.

[a]: Disabling is based on the Rankin score (3 to 5) supplied by the Investigator as well as taking into account if the stroke event was adjudicated as fatal. Rankin score 3 = Moderate disability requiring some help, but able to walk without assistance; 4 = Moderately severe disability, unable to

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walk without assistance and unable to attend to own bodily needs without assistance; 5 = Severe disability, bedridden, incontinent, and requiring constant nursing care and attention.

Source data: Tables 14.2.1.14 and 14.2.1.19

Source: ENGAGE AF CSR p. 132

Table 32: Components and Select Subcomponents of the Primary Endpoint, mITT Analysis, On-Treatment Period

Event	Edoxaban 30 mg (15mg DA) (N=7002)		Edoxaban 60 mg (30mg DA) (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg (15mg DA) vs Warfarin		Edoxaban 60 mg (30mg DA) vs Warfarin	
	# of events	Event Rate (%/yr)[a]	# of events	Event Rate (%/yr)[a]	# of events	Event Rate (%/yr)[a]	HR (95% CI)	p-value	HR (95% CI)	p-value
First Stroke	244	1.61	174	1.13	219	1.41	1.1 (0.91, 1.32)	0.32	0.80 (0.66, 0.98)	0.027
First Ischemic Stroke	226	1.43	135	0.87	144	0.93	1.54 (1.25, 1.9)	<0.0001	0.94 (0.75, 1.19)	0.63
First Hemorrhagic Stroke	18	0.11	40	0.26	76	0.49	0.23 (0.14, 0.39)	<0.0001	0.53 (0.36, 0.78)	0.001
Fatal Stroke	40	0.25	45	0.29	43	0.28	0.91 (0.59, 1.40)	0.67	1.05 (0.69, 1.60)	0.80
Fatal Ischemic Stroke	35	0.22	22	0.14	13	0.08	2.63 (1.39, 4.97)	<0.01	1.70 (0.86, 3.38)	0.13
Fatal Hemorrhagic Stroke	5	0.03	23	0.15	30	0.019	0.16 (0.06, 0.42)	<0.001	0.77 (0.45, 1.33)	0.35
First Disabling Stroke[b]	57	0.36	35	0.23	41	0.26	1.36 (0.91, 2.03)	0.13	0.86 (0.55, 1.35)	0.51
First SEE	11	0.07	8	0.05	13	0.08	0.83 (0.37, 1.85)	0.6453	0.62 (0.26, 1.50)	0.29
First SEE/Ischemic Stroke	235	1.49	143	0.93	157	1.01	1.47 (1.2, 1.8)	<0.001	0.92 (0.73, 1.15)	0.45

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Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, MITT = Modified Intent-to-Treat, SEE = Systemic Embolic Event, yr = year, n = number of events.

[a]: The event rate (%/yr) is calculated as # of events/subject-year exposure.

[b]: Disabling is based on the Rankin score (3 to 5) supplied by the Investigator as well as taking into account if the stroke event was adjudicated as fatal. Rankin score 3 = Moderate disability requiring some help, but able to walk without assistance; 4 = Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = Severe disability, bedridden, incontinent, and requiring constant nursing care and attention.

Source data: Tables 14.2.1.10 and 14.2.1.15

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Table 33 shows that the HR for the primary endpoint for edoxaban 60 mg subjects who had their dose adjusted (lowered) for factors such as moderate renal impairment (CrCL 30-50 mL/min), low body weight (≤ 60 kg), or a need for concomitant treatment with P-gp inhibitors was similar to that of the subjects who received the full dose; 0.81 and 0.78, respectively. This indicates the presence of a similar risk reduction in both dose adjusted and full dose subjects. The HR for the primary endpoint for subjects who had their dose reduced and for subjects who received the full dose were both 1.07 for the edoxaban 30 mg (15 mg DA) group compared to the warfarin group, indicating a similar risk reduction in both dose reduced and full dose subjects.

It should be noted that the event rate in both arms of the dose adjusted groups was higher overall, probably because these are mostly higher risk subjects (renal insufficiency and low body weight).

Table 34 shows the HRs for the primary endpoint by quartiles of site-average INR TTR for the warfarin treatment group in the mITT analysis set-on treatment period. It is shown that edoxaban 60 mg (30 mg Dose Adjustment) has a HR < 1.0 for the lowest three quartiles, but for the highest quartile (TTR > 73.9%), the HR for edoxaban 60 mg (30 mg DA) vs. warfarin was 1.07 (0.65, 1.75) suggesting a loss of relative efficacy of edoxaban at centers where warfarin control is excellent.

Table 35 shows the HRs for CV death by quartiles of site-average INR TTR for the mITT population during the overall period. There was no difference in the HRs of edoxaban vs. warfarin for overall CV death based on site-average TTR and the point estimates consistently favored both doses of edoxaban.

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Table 33: Adjudicated Primary Endpoint (Stroke or SEE), mITT Analysis Set, On-Treatment and Overall Study Period

	Edoxaban 30mg		Edoxaban 60mg		Warfarin	
Primary Endpoint	(1) 15mg DA (N=1774)	(2) 30mg No DA (N=5228)	(3) 30mg DA (N=1776)	(4) 60mg No DA (N=5236)	(5)Warfarin/ Plb Edo DA (N=1780)	(6)Warfarin/ Plb Edo No DA (N=5232)
On-Treatment Period						
First Stroke/SEE						
# of Events	85	168	62	120	77	155
Event Rate (%/yr)	2.36	1.38	1.79	1.00	2.21	1.29
HR (95% CI)[a]	1.07 (0.79, 1.46)	1.07 (0.86, 1.34)	0.81 (0.58, 1.13)	0.78 (0.61, 0.90)		
Overall Study Period						
First Stroke/SEE						
# of Events	143	239	104	188	119	217
Event Rate (%/yr)[b]	3.15	1.69	2.28	1.32	2.67	1.53
HR (95% CI)[a]	1.18 (0.92, 1.50)	1.10 (0.92, 1.33)	0.86 (0.66, 1.12)	0.86 (0.71, 1.05)		

Abbreviations: DA = Dose Adjusted, NoDA = Not Dose Adjusted, Plb Edo = Placebo Edoxaban, CI = Confidence Interval, HR = Hazard Ratio versus Warfarin, mITT = Modified Intent-to-Treat, SEE = Systemic Embolic Event, yr = year.

The dose adjustment for the warfarin group represents edoxaban-placebo dose adjustment

(%/yr) is # of events/ 100 subject-year exposure

[a]: The pairwise comparisons include Column (1) versus (5), (2) versus (6), (3) versus (5), and (4) versus (6).

Source Data: Tables 14.2.4.1 and 14.2.4.2

Source: ENGAGE AF CSR, p. 139

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Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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Table 34: Primary Endpoint (Stroke or SEE) by center-level quartiles of INR TTR, mITT analysis set- on-treatment period

Primary Endpoint	Edoxaban 30 mg (15mg DA) (N=7002)		Edoxaban 60 mg (30mg DA) (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg (15mg DA) vs Warfarin	Edoxaban 60 mg (30mg DA) vs Warfarin
Quartiles of INR TTR	n/M	Event Rate (%/yr)	n/M	Event Rate (%/yr)	n/M	Event Rate (%/yr)	HR (95% CI)	HR (95% CI)
1st Quartile ($\leq 57.7\%$)	54/1406	1.78	51/1413	1.68	57/1406	2.07	0.82 (0.56, 1.18)	0.80 (0.55, 1.16)
2nd Quartile ($>57.7\%$ to $\leq 66.4\%$)	80/2103	1.69	56/2104	1.21	81/2196	1.68	1.02 (0.75, 1.38)	0.73 (0.52, 1.02)
3rd Quartile ($>66.4\%$ to $\leq 73.9\%$)	71/1906	1.63	42/1908	0.99	63/2038	1.35	1.22 (0.87, 1.72)	0.74 (0.50, 1.09)
4th Quartile ($>73.9\%$)	39/1367	1.23	31/1369	1.02	31/1364	0.95	1.30 (0.81, 2.09)	1.07 (0.65, 1.75)

Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.

Source: ENGAGE AF CSR, p. 142

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Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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Table 35: CV death by center-level quartiles of INR TTR, mITT analysis set- overall period

Primary Endpoint	Edoxaban 30 mg (15mg DA) (N=7002)		Edoxaban 60 mg (30mg DA) (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg (15mg DA) vs Warfarin	Edoxaban 60 mg (30mg DA) vs Warfarin
Quartiles of INR TTR	n/M	Event Rate (%/yr)	n/M	Event Rate (%/yr)	n/M	Event Rate (%/yr)	HR (95% CI)	HR (95% CI)
1st Quartile ($\leq 57.7\%$)	139/1330	3.81	122/1365	3.27	151/1358	4.12	0.89 (0.70, 1.1)	0.79 (0.62, 1.00)
2nd Quartile ($>57.7\%$ to $\leq 66.4\%$)	172/2079	3.03	173/2089	3.02	210/2140	3.59	0.85 (0.70, 1.04)	0.84 (0.69, 1.03)
3rd Quartile ($>66.4\%$ to $\leq 73.9\%$)	118/2009	2.13	140/1965	2.6	153/2144	2.60	0.82 (0.65, 1.04)	1.01 (0.80, 1.27)
4th Quartile ($>73.9\%$)	75/1382	1.93	79/1394	2.03	94/1380	2.45	0.80 (0.59, 1.08)	0.82 (0.61, 1.11)

Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.

Reviewer's Table: Datasets: DM, CENTTTR, BASEGRP, ADJEFFCA

6.1.5.4 Analysis of Warfarin Active Control Arm

An important aspect of study conduct in a NOAC trial is the time in therapeutic range (TTR) achieved in the warfarin arm as well as time above and below therapeutic range. If the TTR is subpar, one might erroneously conclude that a comparator treatment is non-inferior.

The percentage of time within the therapeutic range (TTR), INR = 2-3, as well as the percentage of time outside of therapeutic range for the mITT analysis set on-treatment period is summarized in Table 36. The overall warfarin group had a median TTR of 68.4%, a median time below therapeutic range of 17.7% and a median time above therapeutic range of 10.8%.

Overall, all regions had good TTR control in line with the overall median of 68.4%. North America, Western Europe and Japan had a median TTR of 72 to 73%, Latin America and Eastern Europe had a median TTR of 66%, and Asia/Pacific and South Africa (excluding Japan) had a median TTR of 63%.

The INR control in the warfarin arm is adequate for comparison and in line with that achieved in other pivotal NOAC trials.

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Table 36: Time in Various INR Ranges for Subjects Randomized to Warfarin, Safety Analysis Set – On Treatment Period, Excluding Initial 7 Days

	Percent Time in INR								
	<1.5	1.5-2.0	<2	2-3 (TTR)	>3	>=4	>5	>=8	1.8-3.2
Overall (N=6897)									
Mean (SD)	6.10(13.8)	22.70(13.3)	22.80(18.9)	64.90(18.7)	12.40(10.3)	1.80(4.5)	0.30(2.3)	0.00(0.8)	78.40(18.1)
Median	1.90	21.00	17.70	68.40	10.80	0.40	0.00	0.00	83.10

Abbreviations: INR = International Normalized Ratio, SD = Standard Deviation, TTR = Time in Therapeutic Range.

[a]: Percent Time in INR range is defined by the percentage of days the subjects have been within the specified range. Percent Time in Therapeutic Range (TTR) is calculated as the mean percentage in the range 2-3.

Note: N = Number of subjects with at least 1 INR recorded beyond Day 7.

Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.

Note: Analyses of INR use a linear interpolation method to impute INR for study days that do not have an actual INR value.

Source data: Table 14.3.4.1

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6.1.6 Analysis of Secondary Endpoints(s)

As prespecified in the hierarchical plan for secondary efficacy endpoint testing, further statistical testing would not occur unless there was success on superiority testing for the primary endpoint in the ITT set – overall study period.

However, it is interesting to examine the results to see if they support the primary efficacy findings. Results of superiority testing for the secondary efficacy endpoints (ITT population – overall study period) demonstrated that subjects in the edoxaban 60 mg group had a reduced risk of experiencing the composite secondary efficacy endpoints that included one or more of the following components: stroke, SEE, CV mortality, all-cause mortality and MACE compared with subjects in the warfarin group (see Table 37). The HRs for the comparison of the edoxaban 60 mg (30mg DA) group to the warfarin group for the 3 secondary efficacy endpoints were between 0.87 and 0.90 (all nominally statistically significant). The HRs for the comparison of the edoxaban 30 mg (15mg DA) group to the warfarin group for the 3 secondary efficacy endpoints was between 0.94 and 0.98.

Breaking down the secondary endpoints further, edoxaban-treated subjects had a lower CV and all-cause mortality than those treated with warfarin. Fewer subjects in the edoxaban 60 mg and edoxaban 30 mg groups experienced CV mortality than the warfarin group, with a hazard ratio of 0.86 and 0.85, respectively (Table 38). Fewer subjects in the edoxaban 60 mg and edoxaban 30 mg groups experienced all-cause mortality than the warfarin group, with a hazard ratio of 0.92 and 0.87, respectively. As expected for the study population (median age 72 years, average CHADS₂ score 2.8), approximately 70% of deaths were due to CV causes. Fatal bleeds were included in the category of CV deaths, and edoxaban-treated subjects experienced fewer deaths due to bleed events. MI also trended favorably for edoxaban 60 mg except for fatal MI in the ITT population, overall study period (Table 38). Table 39 shows the CV mortality, all-cause mortality and MI results in the mITT population, on-treatment period.

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Table 37: Secondary Endpoint Results (ITT/overall treatment period)

First Event	Edoxaban 30 mg (15mg DA) (N=7034)		Edoxaban 60 mg (30mg DA) (N=7035)		Warfarin (N=7036)		Edoxaban 30 mg (15mg DA) vs Warfarin		Edoxaban 60 mg (30mg DA) vs Warfarin	
	# of events	Event Rate (%/yr)	# of events	Event Rate (%/yr)	# of event s	Event Rate (%/yr)	HR (95% CI)	Log- rank p- value	HR (95% CI)	Log- rank p- value
Stroke, SEE, or CV Mortality	796	4.23	728	3.85	831	4.43	0.95 (0.87, 1.05)	0.34	0.87 (0.79, 0.96)	< 0.01
MACE	913	4.90	827	4.41	926	4.98	0.98 (0.90, 1.08)	0.72	0.89 (0.81, 0.97)	0.01
Stroke, SEE, or All-Cause Mortality	985	5.23	949	5.01	1046	5.57	0.94 (0.86, 1.02)	0.15	0.90 (0.82, 0.98)	0.02

Abbreviations: DA = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, ITT = Intent-to-Treat, yr = year, SEE = Systemic Embolic Event, CV = cardiovascular, MACE = MI, Stroke, SEE, and Death due to Cardiovascular Cause or Bleeding.

The event rate (%/yr) is # of events/ 100 subject-year exposure.

Source data: Table 14.2.2.1

Source: ENGAGE AF CRF, p. 129

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Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Table 38: Key Components of the Secondary Efficacy Endpoints, ITT Analysis Set – Overall Study Period

First Event	Edoxaban 30 mg (15mg DA) (N=7034)		Edoxaban 60 mg (30mg DA) (N=7035)		Warfarin (N=7036)		Edoxaban 30 mg (15mg DA) vs Warfarin		Edoxaban 60 mg (30mg DA) vs Warfarin	
	# of events	Event Rate (%/yr)	# of events	Event Rate (%/yr)	# of events	Event Rate (%/yr)	HR (95% CI)	p-value	HR (95% CI)	p-value
MI	169	0.89	133	0.70	141	0.75	1.19 (0.95, 1.49)	0.13	0.94 (0.74, 1.19)	0.60
Fatal	22	0.11	18	0.09	17	0.09	1.28 (0.68, 2.41)	0.44	1.05 (0.54, 2.05)	0.88
Non-fatal	148	0.78	117	0.62	125	0.66	1.18 (0.93, 1.49)	0.18	0.93 (0.72, 1.20)	0.58
CV Mortality	527	2.71	530	2.74	611	3.17	0.85 (0.76, 0.96)	<0.01	0.86 (0.77, 0.97)	0.013
All-Cause Mortality	737	3.80	773	3.99	839	4.35	0.87 (0.79, 0.96)	<0.01	0.92 (0.83, 1.01)	0.08

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, ITT = Intent-to-Treat, yr = year, CV = cardiovascular, MI = Myocardial Infarction. %/yr = n events/ 100 years patient exposure

Note: A subject can appear in multiple rows of this table (eg, MI and death).

Source data: Table 11.10, p. 136 of ENGAGE AF CSR, and Table 14.2.2.6

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Table 39: Key Components of the Secondary Efficacy Endpoints, mITT Analysis Set – On-Treatment Period
 First Event

First Event	Edoxaban 30 mg (15mg DA) (N=7002)		Edoxaban 60 mg (30mg DA) (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg (15mg DA) vs Warfarin		Edoxaban 60 mg (30mg DA) vs Warfarin	
	# of events	Event Rate (%/yr)	# of events	Event Rate (%/yr)	# of events	Event Rate (%/yr)	HR (95% CI)	p- value	HR (95% CI)	p- value
MI	120	0.76	88	0.57	105	0.68	1.12 (0.86, 1.46)	0.38	0.84 (0.64, 1.120)	0.24
Fatal	14	0.09	10	0.06	11	0.07	1.25 (0.57, 2.75)	0.58	0.92 (0.39, 2.16)	0.84
Non-Fatal	106	0.67	78	0.50	94	0.60	1.11 (0.84, 1.46)	0.47	0.84 (0.62, 1.13)	0.24
CV Mortality	195	1.23	208	1.34	236	1.51	0.81 (0.67, 0.98)	0.03	0.89 (0.74, 1.07)	0.21
All-Cause Mortality	221	1.39	234	1.51	258	1.65	0.84 (0.70, 1.01)	0.06	0.91 (0.77, 1.09)	0.32

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, MITT = Modified Intent-to-Treat, yr = year, CV = cardiovascular, MI = Myocardial Infarction. %/yr = n events/ 100 years patient exposure

Note: A subject can appear in multiple rows of this table (eg, MI and death).

Source data: Table 11.11, p.137 of ENGAGE AF CSR, and Table 14.2.2.8

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6.1.7 Other Endpoints

Not applicable.

6.1.8 Subpopulations

6.1.8.1 Efficacy by Subgroup

The subgroups that showed worse outcomes in the edoxaban 60 mg and 30 mg treatment groups than the warfarin group were subjects with CrCl \geq 80 mL/min and Western Europeans (Figure 13, Figure 14, Figure 15, and Figure 16). Generally speaking, subgroups are not a major focus of a clinical review because of multiplicity and the high chance of finding a subgroup that performs unlike the others when one does multiple comparisons. For this reason, the Western European performance is probably not a concern. The poor performance in the CrCl \geq 80 mL/min subgroup is a different issue, however, because it is reflective of the PK of the drug and reflects a dosing/ exposure deficiency in that subpopulation. This issue is the pivotal issue of this review and will be discussed in detail in [Section 6.1.8.2](#).

There were too few enrolled Blacks (1.3%) to assess performance in this subpopulation.

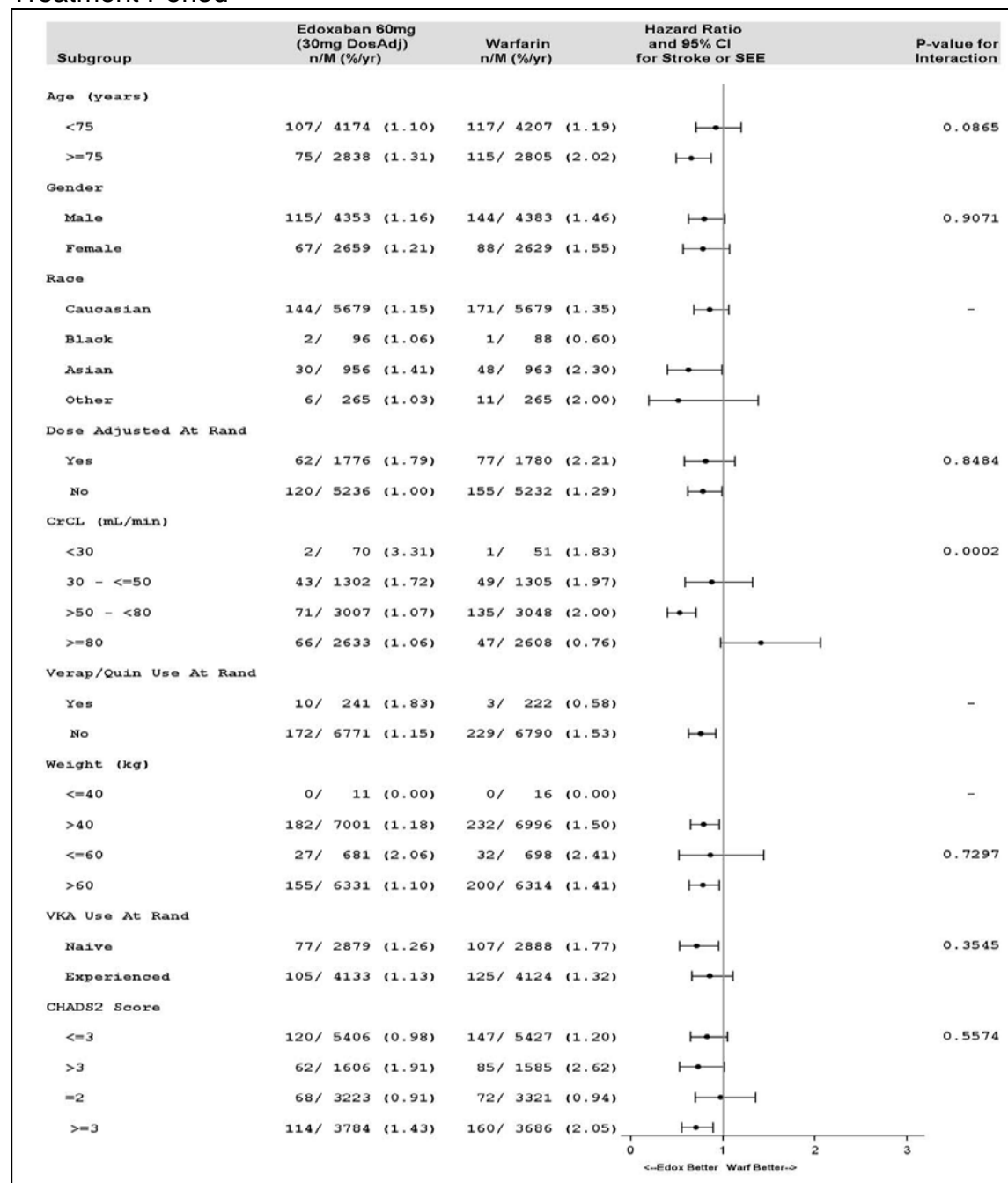
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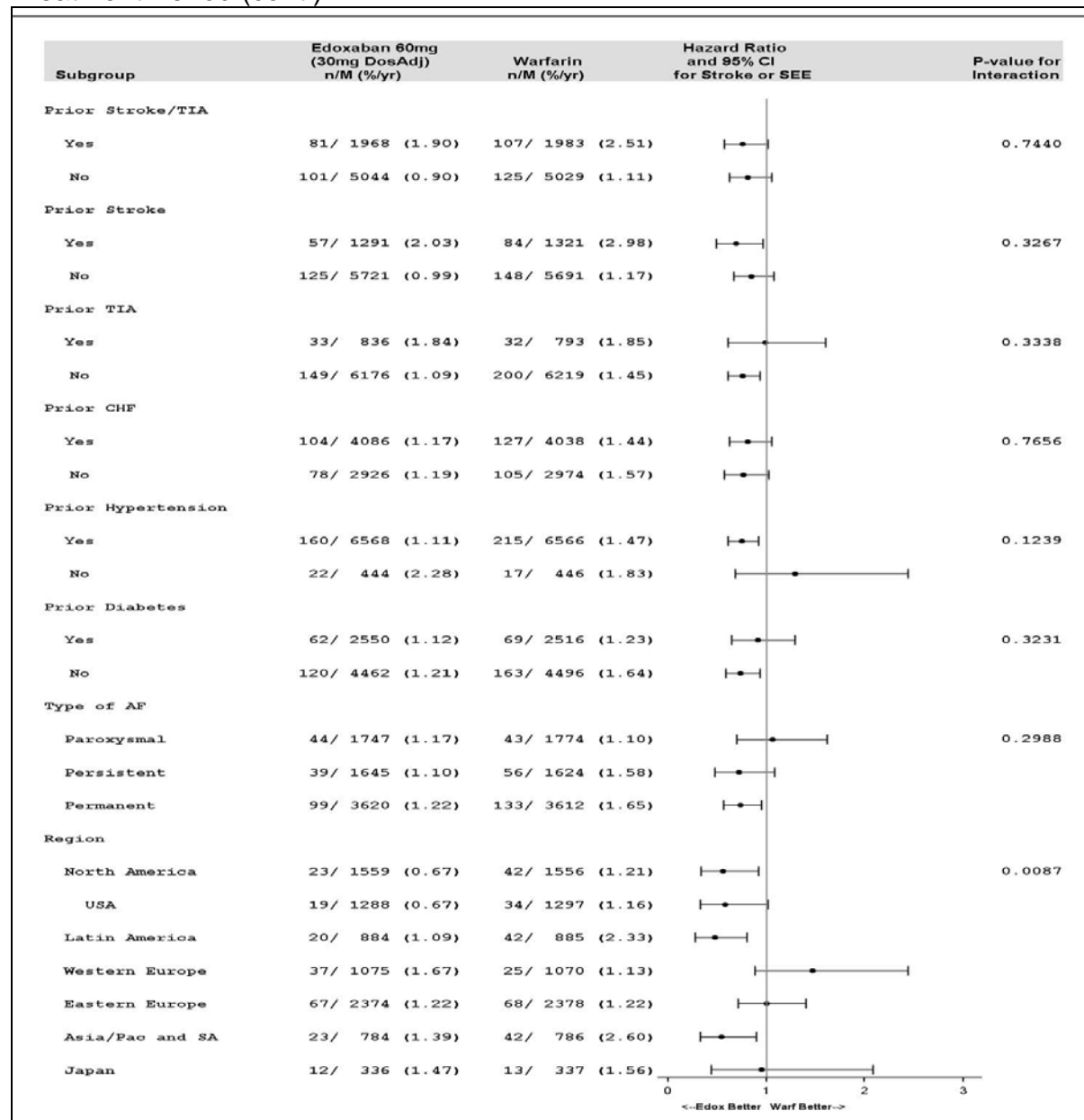
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Figure 13: Forest Plot of Primary Endpoint (Stroke or SEE) by Baseline Characteristics for Edoxaban 60 mg Group Versus Warfarin, mITT Analysis Set - On-Treatment Period



Source: ENGAGE AF CSR, p. 145

Figure 14: Forest Plot of Primary Endpoint (Stroke or SEE) by Baseline Characteristics for Edoxaban 60 mg Group Versus Warfarin, mITT Analysis Set - On-Treatment Period (cont.)



Source: ENGAGE AF CSR, p. 146

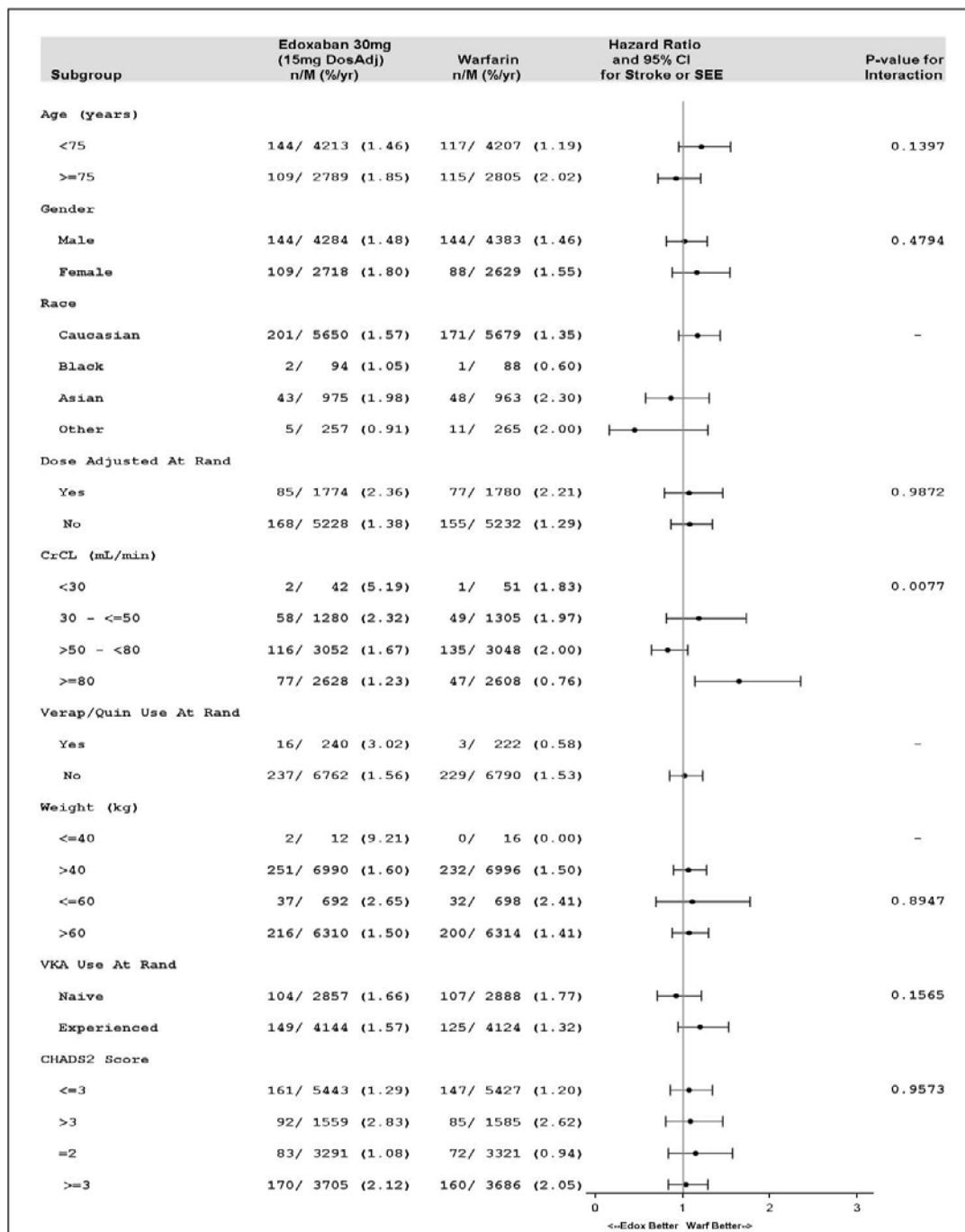
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Figure 15: Forest Plot of Primary Endpoint (Stroke or SEE) by Baseline Characteristics for Edoxaban 30 mg (15mg DA) Group Versus Warfarin, mITT Analysis Set - On-Treatment Period



Source: ENGAGE AF CSR p. 147

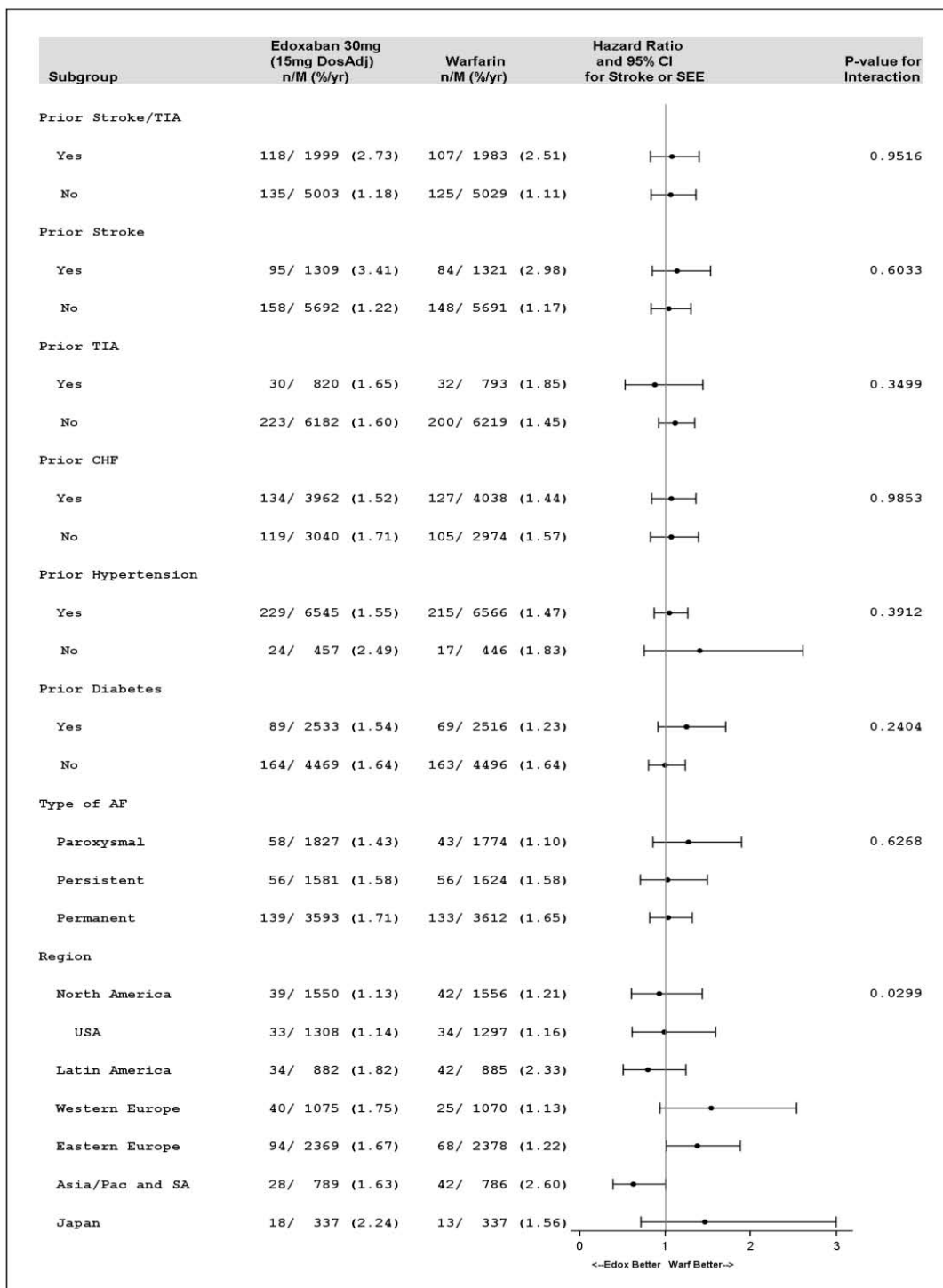
Clinical Review

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Figure 16: Forest Plot of Primary Endpoint (Stroke or SEE) by Baseline Characteristics for Edoxaban 30 mg (15 mg DA) Group Versus Warfarin, mITT Analysis Set - On-Treatment Period (cont.)



Source: p. 148, CSR

6.1.8.2 Efficacy by Renal Function

For the purpose of conducting renal function subgroup analysis, the applicant divided the subjects into three renal function categories [moderate renal insufficiency (CrCl 30-50 mL/min), mild renal insufficiency (CrCl >50 and < 80 mL/min) and normal (CrCl ≥ 80 mL/min). As discussed previously, the hazard ratio for Stroke/SEE (mITT, on treatment) in the 60 mg edoxaban (30mg DA) group compared to warfarin was 0.79 (95% CI=0.65, 0.96). However, the hazard ratio for Stroke/SEE in the subgroup with normal renal function was 1.41 (0.98, 2.06). See Table 40. The same pattern is seen in the other randomized edoxaban group, 30 mg (15 mg DA). Here the Stroke/SEE (mITT, on treatment) hazard ratio was 1.07 (0.90, 1.28), whereas, the hazard ratio in normal renal function subgroup was particularly dismal, 1.61 (1.12, 2.33). The nominal p values for these subgroup interactions were highly statistically significant (< 0.001 for the 60 mg dose and < 0.01 for the 30 mg dose).

When looking only at ischemic stroke (Table 42), hemorrhagic stroke (Table 43), fatal stroke (Table 44), disabling stroke (Table 45) and also overall cardiovascular death (will put in), the pattern of worse HRs in the normal renal function subgroup compared to the mild renal dysfunction subgroup persists.

Note that the event rate (%/yr) in subjects treated with warfarin decreased markedly in subjects with normal renal function. This might be expected because normal renal function is associated with overall lower morbidity. However, one cannot dismiss the possibility that it was a chance finding and is an underrepresentation of stroke/SEE rate in real-world patients with normal renal function who are on warfarin. It should be noted, however, that in the other NOAC trials, event rates in patients with normal renal function on warfarin were ~1.0 per 100 patient-years (except ROCKET-AF which enrolled a higher-risk population). See Table 65.

Table 40: Stroke/SEE on treatment/ mITT population by CrCl subgroup

Stroke/SEE		n(N)	Event Rate %/yr	HR vs. W
overall	W	232(7012)	1.5	
	E30	253 (7002)	1.61	1.07 (0.90, 1.28)
	E60	182(7012)	1.18	0.79 (0.65, 0.96)
30 -<=50	W	49(1297)	1.98	
	E30	58 (1274)	2.33	1.19 (0.81, 1.74)
	E60	43 (1287)	1.73	0.88 (0.59,1.33)
>50- <80	W	135 (3030)	2.01	
	E30	115 (3034)	1.66	0.82 (0.64, 1.05)
	E60	69 (2985)	1.04	0.51 (0.38, 0.69)
≥80	W	47 (2595)	0.76	
	E30	76 (2611)	1.22	1.61 (1.12, 2.32)
	E60	66 (2612)	1.07	1.41 (0.97, 2.05)

Reviewer's Table: Source Data: BASEGP.xpt, ADJEFFCA.xpt, modeling with Dose Adjustment, yes or no. CHADS2≤3=0, or >3=1.

Table 41: Stroke on treatment/ mITT population by CrCl subgroup

Stroke		n(N)	Event Rate %/yr	HR vs. W
overall	W	(7012)	1.41	
	E30	(7002)	1.61	1.1 (0.91, 1.32)
	E60	(7012)	1.13	0.80 (0.66, 0.98)
30-<=50	W	45 (1297)	1.81	
	E30	55 (1274)	2.21	1.23 (0.83, 1.82)
	E60	41 (1287)	1.65	0.92 (0.60, 1.40)
>50- <80	W	128 (3030)	1.90	
	E30	109 (3034)	1.58	0.82 (0.63, 1.06)
	E60	66 (2985)	1.00	0.52 (0.38, 0.70)
≥80	W	45(2595)	0.73	
	E30	76 (2611)	1.22	1.68 (1.16, 2.43)
	E60	63(2612)	1.02	1.41 (0.96, 2.06)

Reviewer's Table: Source Data: BASEGP.xpt, ADJEFFCA.xpt, modeling with Dose Adjustment, yes or no. CHADS2≤3=0, or >3=1.

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Table 42: Ischemic Stroke on treatment/ mITT population by CrCl subgroup

Ischemic Stroke		n(N)	%/yr	HR vs. W
overall	W	144(7012)	0.93	
	E30	226(7002)	1.43	1.55 (1.26, 1.91)
	E60	135(7012)	0.87	0.94 (0.75, 1.19)
30-<=50	W	28 (1348)	1.09	
	E30	55 (1274)	2.21	2.04 (1.29, 3.24)
	E60	30 (1287)	1.29	1.12 (0.67, 1.89)
>50- <80	W	83 (3030)	1.23	
	E30	98 (3034)	1.42	1.13 (0.85, 1.51)
	E60	51 (2985)	0.77	0.62 (0.43, 0.87)
≥80	W	33 (2595)	0.53	
	E30	69 (2611)	1.11	2.09 (1.38, 3.16)
	E60	52(2612)	0.84	1.58 (1.02, 2.45)

Reviewer's Table: Source Data: BASEGP.xpt, ADJEFFCA.xpt, modeling with Dose Adjustment, yes or no. CHADS2≤3=0, or >3=1.

Table 43: Hemorrhagic Stroke on treatment/ mITT population by CrCl subgroup

Hem. Stroke		n(N)	%/yr	HR vs. W
overall	W	76(7012)	0.49	
	E30	18(7002)	0.11	0.23 (0.13, 0.38)
	E60	40(7012)	0.26	0.53 (0.36, 0.77)
30-<=50	W	18 (1297)	0.72	
	E30	0 (1274)	0	---
	E60	11 (1287)	0.44	0.61 (0.29, 1.28)
>50- <80	W	45 (3030)	0.66	
	E30	11 (3034)	0.16	0.24 (0.12, 0.46)
	E60	16 (2985)	0.24	0.36 (0.20, 0.64)
≥80	W	13 (2595)	0.21	
	E30	7 (2611)	0.11	0.53 (0.21, 1.34)
	E60	11(2612)	0.18	0.85 (0.38, 1.9)

Reviewer's Table: Source Data: BASEGP.xpt, ADJEFFCA.xpt, modeling with Dose Adjustment, yes or no. CHADS2≤3=0, or >3=1.

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Table 44: Fatal Stroke on treatment/ mITT population by CrCl subgroup

Fatal Stroke		n(N)	%/yr	HR vs. W
overall	W	43(7012)	0.28	
	E30	40(7002)	0.25	0.91 (0.59, 1.40)
	E60	45(7012)	0.29	1.05 (0.69, 1.61)
30-<=50	W	11 (1297)	0.47	
	E30	13 (1274)	0.52	1.18 (0.53, 2.62)
	E60	10 (1287)	0.40	0.95 (0.40, 2.23)
>50- <80	W	20 (3030)	0.29	
	E30	19 (3034)	0.27	0.92 (0.49, 1.73)
	E60	22 (2985)	0.33	1.11 (0.61, 2.03)
≥80	W	11 (2595)	0.18	
	E30	8 (2611)	0.13	0.73 (0.29, 1.81)
	E60	13(2612)	0.21	1.19 (0.53, 2.66)

Reviewer's Table: Source Data: BASEGP.xpt, ADJEFFCA.xpt, modeling with Dose Adjustment, yes or no. CHADS2≤3=0, or >3=1.

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Table 45: Disabling Stroke overall study period, mITT population, by CrCl subgroup

Dis. Stroke		n(N)	%/yr	HR vs. W
overall	W	57(7012)	0.30	
	E30	81(7002)	0.43	1.41 (1.00, 1.97)
	E60	85(7012)	0.28	0.92(0.63, 1.34)
30- <=50	W	15 (1297)	0.46	
	E30	23 (1274)	0.70	1.53 (0.80, 2.93)
	E60	17 (1287)	0.51	1.11 (0.56, 2.23)
>50- <80	W	33 (3030)	0.40	
	E30	36 (3034)	0.44	1.06 (0.66, 1.70)
	E60	13 (2985)	0.16	0.39 (0.20, 0.74)
≥80	W	9 (2595)	0.12	
	E30	22 (2611)	0.30	2.45 (1.13,5.32)
	E60	22(2612)	0.31	2.45 (1.13,5.33)

Reviewer's Table: Source Data: BASEGP.xpt, ADJEFFCA.xpt, modeling with Dose Adjustment, yes or no. CHADS2≤3=0, or >3=1. Modified Rankin Score's 3-5 define disabling stroke. 3 = Moderate disability requiring some help, but able to walk without assistance; 4 = Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = Severe disability, bedridden, incontinent, and requiring constant nursing care and attention.

Table 46: CV death, overall study period, mITT population by CrCl subgroup

Overall CV death		n(N)	%/yr	HR vs. W
overall	W	234(7012)	1.51	
	E30	195(7002)	1.23	0.85 (0.76, 0.96)
	E60	205(7012)	1.34	0.86(0.77, 0.97)
30-<=50	W	201 (1297)	5.96	
	E30	160 (1274)	4.75	0.80 (0.65, 0.98)
	E60	162 (1287)	4.74	0.80 (0.65, 0.99)
>50- <80	W	257(3030)	3.09	
	E30	227 (3034)	2.70	0.87 (0.72, 1.04)
	E60	192 (2985)	2.33	0.75(0.62, 0.9)
≥80	W	134 (2595)	1.83	
	E30	119 (2611)	1.62	0.89 (0.69, 1.13)
	E60	154 (2612)	2.11	1.15 (0.91, 1.45)

Reviewer's Table: Source Data: BASEGP.xpt, ADJEFFCA.xpt, modeling with Dose Adjustment, yes or no. CHADS2≤3=0, or >3=1.

The decreased efficacy in the higher creatinine clearance subgroup corresponds to a decrease in serum trough edoxaban levels and anti-Factor Xa increase from trough to peak. See Table 47 and Table 48.

The differences in PK and PD which are expected because the drug is 50% renally excreted provide a physiological explanation for the observation of poorer performance in the subjects with normal renal function.

INR by treatment is shown in Table 49 and Table 50. Median trough INR is not helpful but median peak INR seems to track with level of exposure (edoxaban levels) as expected.

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Table 47: Serum Trough Edoxaban Levels (C-Min) Day 29, by treatment group/Dose Adjustment (Y/N) and CrCL

CrCL	Dose Adjust: YES			Dose Adjust: NO			
	n(N)	median ng/mL	Min/max ng/mL	n(N)	median ng/mL	Min/max ng/mL	
30- ≤ 50 mL/min							
	E30 (15mgDA)	948	13.6	0.4/203	212	23.9	0.4/207
	E60 (30 mg DA)	971	28.8	0.4/320	211	48.6	0.4/491
>50-<80 mL/min							
	E30 (15mgDA)	526	10.9	0.4/183	2314	21.5	0.4/312
	E60 (30 mg DA)	480	23.0	0.4/357	2254	42.9	0.4/704
≥80 mL/min							
	E30 (15mgDA)	104	6.5	0.4/109	2336	14.3	0.4/436
	E60 (30 mg DA)	104	14.2	0.4/81.1	2347	28.5	0.4/522

Reviewer's Table: Source Data: PCANAL.xpt and BASEGP.xpt

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Table 48: Anti-Factor Xa (IU/mL) change from trough to peak on day 29 (from immediately pre-dose to 1-3 hours post-dose)

CrCL	Dose Adjust: YES				Dose Adjust: NO		
		n(N)	median IU/mL	Min/max ng/mL	n(N)	median IU/mL	Min/max ng/mL
30- ≤ 50 mL/min	E30 (15mgDA)	217	1.1	-6.6/2.8	55	2.0	-1.1/7.7
	E60 (30 mg DA)	228	2.1	-4.4/6.9	54	4.2	-4.4/7.7
>50-<80 mL/min	E30 (15mgDA)	119	1.0	-1.8/7.8	555	1.8	-6.4/7.9
	E60 (30 mg DA)	106	2.3	-7.4/7.5	588	3.6	-7.1/7.9
≥80 mL/min	E30 (15mgDA)	18	0.7	-1.1/1.8	654	1.5	-2.5/7.8
	E60 (30 mg DA)	19	2.3	0/4.5	636	2.8	-5.0/7.7

Reviewer's Table: Source Data:XB.xpt, BASEGP.xpt

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Table 49: Trough INR at Day 29 by CrCL and dose adjustment (Y/N)

Dose Adjust: YES						Dose Adjust: NO			
CrCL		n(N)	median	Mean (SD)	Min/max	n(N)	median	Mean (SD)	Min/max
30- ≤ 50 mL/min	W	233	2.6	3.0 (2.1)	0.9/17.5	49	2.6	2.6 (0.9)	1.2/5.5
	E30 (15mgDA)	223	1.2	1.6 (2.2)	0.8/17.5	56	1.2	1.3 (0.6)	0.9/4.9
	E60 (30 mg DA)	236	1.2	1.4 (1.2)	0.9/17.5	54	1.3	1.5 (1.2)	1.0/9.9
>50-<80 mL/min	W	87	2.4	2.9 (2.5)	1.1/17.5	616	2.3	2.7 (1.9)	1.0/17.5
	E30 (15mgDA)	122	1.1	1.3 (1.5)	0.9/17.5	570	1.2	1.5 (1.8)	0.9/17.5
	E60 (30 mg DA)	108	1.2	1.5 (2.2)	1.0/17.5	597	1.3	1.5 (1.1)	0.9/17.5
≥80 mL/min	W	27	2.6	3.6 (3.6)	1.1/17.5	639	2.2	2.5(1.6)	0.9/17.5
	E30 (15mgDA)	18	1.1	1.1 (0.1)	0.9/1.5	671	1.1	1.3 (1.0)	0.8/17.5
	E60 (30 mg DA)	19	1.1	1.4 (0.8)	1.0/4.8	650	1.2	1.3 (0.9)	0.9/17.5

Reviewer's Table: Source Data: XB.xpt, BASEGP.xpt

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Table 50: Peak INR at Day 29 by CrCL and dose adjustment (Y/N)

Dose Adjust: YES						Dose Adjust: NO			
CrCL		n(N)	median	Mean (SD)	Min/max	n(N)	median	Mean (SD)	Min/max
30- ≤ 50 mL/min	W	229	2.7	2.9 (1.4)	0.9/8.9	49	2.5	2.6 (1.1)	1.2/5.9
	E30 (15mgDA)	219	1.4	1.7 (1.3)	0.9/17.5	56	1.7	2.6 (3.5)	1.1/17.5
	E60 (30 mg DA)	232	1.8	2.2 (2.1)	0.9/17.5	54	2.2	2.3 (0.8)	1.1/4.7
>50-<80 mL/min	W	87	2.4	3.1 (2.7)	1.1/17.5	615	2.4	2.7 (1.7)	1.0/17.5
	E30 (15mgDA)	121	1.4	1.8 (2.4)	1.0/17.5	565	1.6	1.9 (1.8)	1.0/17.5
	E60 (30 mg DA)	107	1.7	2.1 (2.2)	1.0/17.5	594	2.2	2.4 (1.8)	1.0/17.5
≥80 mL/min	W	27	2.6	3.5 (3.1)	1.0/15.6	642	2.3	2.6(1.7)	0.9/17.5
	E30 (15mgDA)	18	1.2	1.2 (0.1)	1.0/1.5	667	1.5	1.7 (1.4)	0.9/17.5
	E60 (30 mg DA)	19	1.7	1.9 (0.8)	1.3/5.1	644	1.9	2.1 (1.7)	0.9/17.5

Reviewer's Table: Source Data: XB.xpt, BASEGP.xpt

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An analysis of the data by quintiles of renal function continues to show the same pattern. The hazard ratio for first stroke/SEE (mITT, on treatment) in the edoxaban 60 mg (30mg DA) group compared to warfarin was 0.79 (95% CI=0.65, 0.96). However, the hazard ratio for the highest quintile of renal function (CrCl at randomization of ≥ 98.1 mL/min) was 1.74 (95%CI= 1.01, 3.01). See Table 52 (also see Table 51 for the key to the numbers of subjects in each quintile). The general pattern persists across sub-components of the primary endpoint and CV death (Table 53, Table 54, Table 55, Table 56, and Table 57).

Table 51: Number of subjects in each quintile/ treatment group

	Quintile 1 30 to ≤ 50.6	Quintile 2 50.6 < to 63.6	Quintile 3 63.6 < to 77.9	Quintile 4 77.9 < to 98.1	Quintile 5 ≥ 98.1
	N	N	N	N	N
E30 (15)	1340	1413	1385	1407	1374
E60 (30)	1344	1356	1414	1336	1434
Warfarin	1360	1381	1409	1415	1357

Reviewer's Table

Table 52: Stroke/ SEE, mITT population, on Treatment by quintile of CrCL

Quintile	Event Rate			Hazard Ratio (95% CI)			
	E30 (15DA)	E60 (30 DA)	Warfarin	E60 (30 DA) vs. W		E30 (15 DA) vs. W	
	(%/yr)	(%/yr)	(%/yr)				
30 to ≤ 50.6	2.36	1.68	2.04	0.83	(0.56, 1.24)	1.16	(0.80, 1.67)
>50.6 - ≤ 63.6	1.93	1.13	2.33	0.48	(0.32, 0.72)	0.81	(0.58, 1.14)
>63.6 - ≤ 77.9	1.45	0.93	1.69	0.55	(0.35, 0.85)	0.86	(0.58, 1.27)
>77.9 - ≤ 98.1	1.33	1.12	1.04	1.08	(0.68, 1.74)	1.29	(0.82, 2.01)
> 98.1	1.06	1.05	0.61	1.74	(1.01, 3.01)	1.72	(0.99, 2.98)

W=warfarin, %/yr = events/100 patient years. Datasets: DM.xpt, ADJEFFCA.xpt, HR constructed using applicant's model [adjusted for DoseAdj (N, Y), and CHADS2 score (0, 1 for CHADS2 score <3 and ≥ 3 , respectively)] Reviewer's Table.

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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Table 53: Stroke, mITT population, on Treatment by quintile of CrCL

Quintile	Event Rate			Hazard Ratio (95% CI)			
	E30 (15DA) (%/yr)	E60 (30 DA) (%/yr)	Warfarin (%/yr)	E60 (30 DA) vs. W		E30 (15 DA) vs. W	
30 to ≤50.6	2.24	1.61	1.84	0.88	(0.58, 1.33)	1.22	(0.83, 1.79)
>50.6 - ≤63.6	1.90	1.06	2.19	0.48	(0.31, 0.73)	0.85	(0.60, 1.20)
>63.6 - ≤77.9	1.32	0.90	1.63	0.55	(0.35, 0.86)	0.81	(0.54, 1.22)
>77.9 - ≤98.1	1.30	1.05	1.01	1.05	(0.65, 1.70)	1.30	(0.82, 2.04)
> 98.1	1.06	1.03	0.58	1.78	(1.02, 3.12)	1.81	(1.04, 3.16)

W=warfarin, %/yr = events/100 patient years. Datasets: DM.xpt, ADJEFFCA.xpt, HR constructed using applicant's model [adjusted for DoseAdj (N, Y), and CHADS2 score (0, 1 for CHADS2 score <3 and ≥3, respectively)] Reviewer's Table.

Table 54: Event: Ischemic Stroke, mITT population, on Treatment by quintile of CrCL

Quintile	Event Rate			Hazard Ratio (95% CI)			
	E30 (15DA) (%/yr)	E60 (30 DA) (%/yr)	Warfarin (%/yr)	E60 (30 DA) vs. W		E30 (15 DA) vs. W	
30 to ≤50.6	2.24	1.19	1.15	1.04	(0.63, 1.72)	1.94	(1.25, 3.02)
>50.6 - ≤63.6	1.68	0.86	1.46	0.58	(0.35, 0.95)	1.12	(0.76, 1.68)
>63.6 - ≤77.9	1.20	0.68	0.97	0.69	(0.40, 1.19)	1.23	(0.76, 1.97)
>77.9 - ≤98.1	1.18	0.80	0.73	1.10	(0.63, 1.92)	1.62	(0.97, 2.69)
> 98.1	0.96	0.88	0.43	2.07	(1.10, 3.91)	2.25	(1.20, 4.21)

W=warfarin, %/yr = events/100 patient years. Datasets: DM.xpt, ADJEFFCA.xpt, HR constructed using applicant's model [adjusted for DoseAdj (N, Y), and CHADS2 score (0, 1 for CHADS2 score <3 and ≥3, respectively)] Reviewer's Table.

Table 55: Event: Hemorrhagic Stroke, mITT population, on Treatment by quintile of CrCL

Quintile	Event Rate			Hazard Ratio (95% CI)			
	E30 (15DA) (%/yr)	E60 (30 DA) (%/yr)	Warfarin (%/yr)	E60 (30 DA) vs. W		E30 (15 DA) vs. W	
30 to ≤50.6	0.00	0.42	0.69	0.61	(0.29, 1.29)	.	.
>50.6 - ≤63.6	0.22	0.24	0.72	0.32	(0.14, 0.76)	0.30	(0.13, 0.69)
>63.6 - ≤77.9	0.13	0.22	0.65	0.33	(0.14, 0.78)	0.20	(0.07, 0.57)
>77.9 - ≤98.1	0.12	0.25	0.27	0.93	(0.36, 2.42)	0.44	(0.13, 1.42)
> 98.1	0.09	0.15	0.18	0.82	(0.25, 2.67)	0.49	(0.12, 1.96)

W=warfarin, %/yr = events/100 patient years. Datasets: DM.xpt, ADJEFFCA.xpt, HR constructed using applicant's model [adjusted for DoseAdj (N, Y), and CHADS2 score (0, 1 for CHADS2 score <3 and ≥3, respectively)] Reviewer's Table.

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Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

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Table 56: Overall Disabling Stroke, mITT population, Overall Study Period by CrCL quintile

Quintile	Event Rate			Hazard Ratio (95% CI)			
	E30 (15DA) (%/yr)	E60 (30 DA) (%/yr)	Warfarin (%/yr)	E60 (30 DA) vs. W		E30 (15 DA) vs. W	
30 to ≤50.6	0.72	0.49	0.43	1.12	(0.56, 2.24)	1.66	(0.88, 3.15)
>50.6 - ≤63.6	0.58	0.24	0.40	0.59	(0.26, 1.34)	1.36	(0.71, 2.62)
>63.6 - ≤77.9	0.32	0.08	0.42	0.18	(0.05, 0.62)	0.75	(0.36, 1.59)
>77.9 - ≤98.1	0.31	0.33	0.18	1.84	(0.73, 4.68)	1.74	(0.69, 4.43)
>98.1	0.26	0.28	0.11	2.65	(0.84, 8.32)	2.52	(0.79, 8.03)

W=warfarin, %/yr = events/100 patient years. Datasets: DM.xpt, ADJEFFCA.xpt, HR constructed using applicant's model [adjusted for DoseAdj (N, Y), and CHADS2 score (0, 1 for CHADS2 score <3 and ≥3, respectively)] Disabling Stroke = Modified Rankin Score 3-5. Reviewer's Table.

Table 57: CV Death, mITT population, Overall Study Period by CrCL quintile

Quintile	Event Rate			Hazard Ratio (95% CI)			
	E30 (15DA) (%/yr)	E60 (30 DA) (%/yr)	Warfarin (%/yr)	E60 (30 DA) vs. W		E30 (15 DA) vs. W	
30 to ≤50.6	4.68	4.76	5.82	0.82	(0.67, 1.01)	0.81	(0.66, 0.99)
>50.6 - ≤63.6	3.24	2.55	3.63	0.70	(0.54, 0.91)	0.88	(0.69, 1.13)
>63.6 - ≤77.9	2.23	2.05	2.65	0.77	(0.57, 1.03)	0.83	(0.62, 1.11)
>77.9 - ≤98.1	1.80	2.10	2.02	1.04	(0.76, 1.42)	0.90	(0.65, 1.23)
>98.1	1.47	2.09	1.72	1.22	(0.88, 1.68)	0.86	(0.60, 1.22)

W=warfarin, %/yr = events/100 patient years. Datasets: DM.xpt, ADJEFFCA.xpt, HR constructed using applicant's model [adjusted for DoseAdj (N, Y), and CHADS2 score (0, 1 for CHADS2 score <3 and ≥3, respectively)] Reviewer's Table.

The risk of stroke/SEE was also examined as a function of continuous CrCL level and other covariates using a Cox Proportional Hazard Model. Figure 17 shows the derived probability of stroke/SEE within 1 year by CrCL for edoxaban 60 mg and warfarin. The predicted hazard ratio for first stroke/SEE (edoxaban 60 mg compared to warfarin) increases (worse) as renal function improves. The hazard ratio crosses over 1 at a CrCL of ~95 mL/min. Note that the probability of stroke/SEE stays about the same regardless of renal function in the edoxaban 60 mg group but decreases in the warfarin group as renal function improves and that it is this discrepancy that results in the change in HR with renal function.

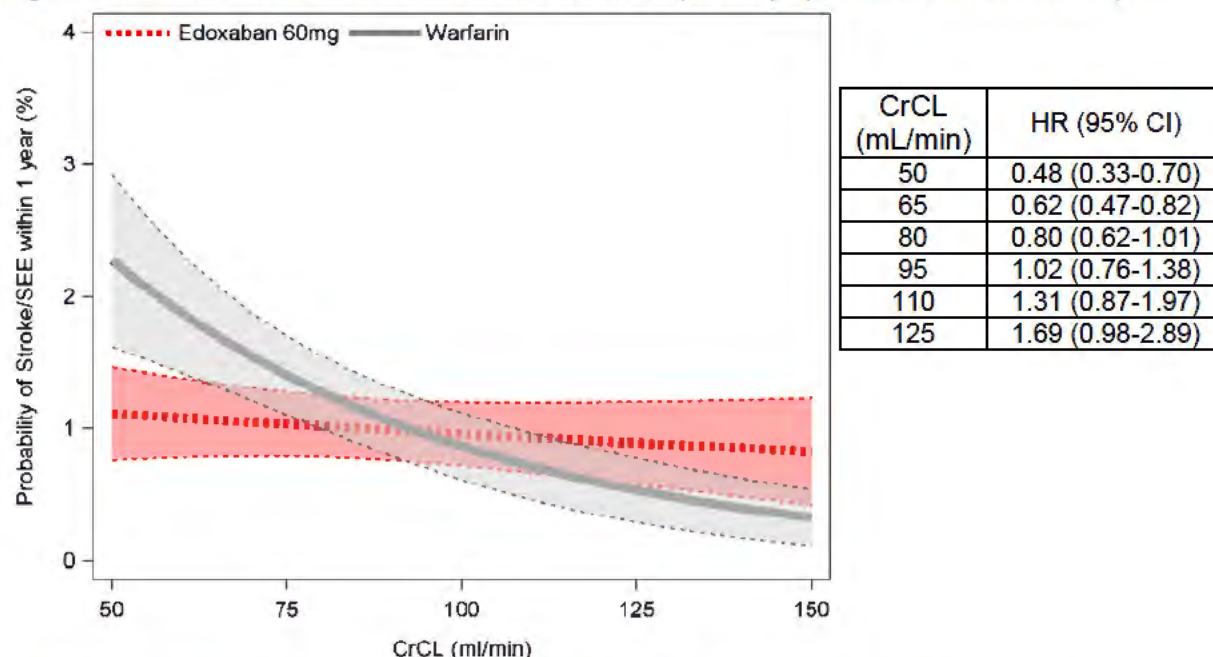
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Figure 17: Effect of CrCL on risk of Stroke/SEE (mITT population, on treatment)



The risk of first Stroke/SEE was modeled as a function of history of stroke, CHADS₂ score, CrCL, treatment, and CrCL*treatment using a Cox proportional hazard model among subjects with no dose adjustment

Dr. McDowell's analysis and figure, Dataset: ADJEFFCA, BASEGP and DM

6.1.8.3 Efficacy by Dose Adjustment

Dose adjustment occurred if the subject at screening had a CrCL of ≤ 50 mL/min or was ≤ 60 kg or was on verapamil, quinidine or dronedarone. 572 of 14069 (4.1%) subjects randomized to edoxaban did not get dose adjusted upon study entry even though they met the criteria for dose adjustment at baseline. Six were underweight at baseline on the eCRF, 469 had CrCL ≤ 50 mL/min at baseline on the eCRF, and 108 were on verapamil, quinidine or dronedarone at baseline on the eCRF) but there was some overlap. These subjects were analyzed as non-dose adjusted patients because the analyses were done based on the randomized treatment which was based on screening criteria, not baseline criteria.

The efficacy on the primary endpoint (first stroke/SEE, mITT, on Treatment) in the cohort of subjects who had a dose adjustment at baseline looks very similar to the cohort without dose adjustment at baseline as shown in Table 58 (see OVERALL row). The event rates were higher in subjects with dose adjustment as might be expected. Most of the subjects with dose adjustments had renal dysfunction and were therefore not as healthy as the non-dose adjusted cohort.

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The numbers of subjects are small in each subgroup when comparing subjects by categories of CrCL who had dose adjustments to those who didn't, so interpretation is limited.

The subjects who were dose adjusted for moderate renal insufficiency seemed to benefit from the dose adjustment if one just looks at the hazard ratios for events. However, as shown in Table 59, the first ischemic stroke rates in the edoxaban 60 mg group are lower in the moderate renal insufficiency group that did not get dose adjusted than in the moderate renal insufficiency group that got dose adjusted (1.06 %/yr and 1.24 %/yr, respectively). The reason that the HR favors dose adjustment is the low first ischemic stroke rate for warfarin in the group who did not get their edoxaban placebo dose adjusted (0.5 %/yr which is much lower than the event rate in the warfarin subjects who got their edoxaban placebo doses adjusted (1.2 %/yr). Because there were so few subjects in the subgroup of moderate renal dysfunction subjects without dose adjustment, it is difficult to evaluate the wisdom of dose reduction in this lowest renal function subgroup by this type of subgroup analysis.

Another way to analyze the dose adjustment is to examine exposures and pharmacodynamic biomarkers by renal function subgroup. If you refer to Table 47 and Table 48 you can see that the dose adjustments may have been overzealous. For instance, the trough edoxaban median exposure was 28.8 ng/mL in the dose-adjusted edoxaban 60 mg (30 mg) subgroup of subjects with moderate renal dysfunction and 48.6 ng/mL in the same subgroup of subjects who did not get dose adjusted. The dose adjustment overshot what it was intended to do (i.e., match the pharmacodynamic effect of the non-dose adjusted subjects). The PK/PD data might suggest that the dose adjustment for moderate renal dysfunction was too extreme. However, the outcomes data, as stated above do not support that. However, the small numbers of subjects who did not get dose adjusted in the moderate renal dysfunction subgroups limits the reliability of the clinical outcomes analyses.

Subjects who had mild renal insufficiency or normal renal function and were not dose adjusted had a lower HR (compared to warfarin) for first stroke/SEE (mITT, on Treatment) compared to the dose adjusted cohorts (see Table 58). This could mean that the dose adjustment based on factors other than moderate renal dysfunction was not necessary or too extreme in those subjects. The same analysis done only for ischemic stroke confirmed the findings (see Table 59), suggesting that dose adjustment for weight or P-gp inhibitors may not be necessary or the amount of dose adjustment may not need to be as great. This differences in PK and PD between the dose adjusted and non-dose adjusted subjects mimic what was seen for the moderate renal insufficiency cohorts. This adds support to the conclusion that the dose reduction for low weight and P-gp inhibitors was too extreme and may not be needed.

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Table 58: First Stroke/SEE by Dose Adjustment/ No Dose Adjustment, mITT, on Treatment

First Stroke/SEE	Dose Adjust (Str/SEE)				No dose Adjust (Str/SEE)		
		n(N)	event rate %/yr	HR vs. W	n(N)	event rate %/yr	HR vs. W
OVERALL	W	77 (1780)	2.21		155 (5232)	1.29	
	E30 (15mgDA)	85 (1774)	2.36	1.07 (0.79, 1.46)	168 (5228)	1.38	1.07 (0.86, 1.34)
	E60 (30 mg DA)	62 (1776)	1.79	0.81 (0.58, 1.13)	120 (5236)	1	0.78 (0.61, 0.99)
30- ≤ 50 mL/min	W	45 (1106)	2.17		4 (191)	0.99	
	E30 (15mgDA)	49 (1081)	2.33	1.09 (0.72, 1.64)	11 (233)	2.31	2.20(0.70, 6.93)
	E60 (30 mg DA)	34 (1058)	1.68	0.78 (0.50, 1.22)	9 (229)	1.90	1.88 (0.58, 6.12)
>50-<80 mL/min	W	29 (510)	2.68		106 (2520)	1.88	
	E30 (15mgDA)	31 (569)	2.45	0.92 (0.56, 1.53)	84 (2465)	1.49	0.79 (0.59, 1.05)
	E60 (30 mg DA)	22(526)	1.94	0.73 (0.42, 1.27)	47 (2459)	0.86	0.45 (0.32, 0.64)
≥80 mL/min	W	2(108)	0.77		45 (2487)	0.76	
	E30 (15mgDA)	5 (115)	1.86	2.38 (0.46, 16.92)	71 (2496)	1.19	1.57 (1.08, 2.29)
	E60 (30 mg DA)	4 (111)	1.6	2.10 (0.38, 11.49)	62 (2501)	1.05	1.38 (0.94, 2.03)

Reviewer's Table: Model: by ARM and CHADS cut 0 (≤ 3), 1 (≥ 3), BASEGP, ADJEFFCA datasets

Table 59: First Ischemic Stroke by Dose Adjustment/ No Dose Adjustment, mITT, on Treatment

First Isch. Stroke	Dose Adj (Isch Str)	Dose Adj (Isch Str)			Not Dose Adj (Isch Str)		
		n(N)	event rate %/yr	HR vs. W	n(N)	event rate %/yr	HR vs. W
OVERALL	W	45 (1780)	1.29		155 (5232)	0.82	
	E30 (15mgDA)	83 (1774)	2.3	1.80 (1.25, 2.58)	143(5228)	1.18	1.43 (1.11, 1.85)
	E60 (30 mg DA)	120 (1776)	1.24	0.96 (0.63, 1.46)	92 (5236)	0.77	0.94 (0.70, 1.24)
30- ≤ 50 mL/min	W	26 (1106)	1.20		2 (191)	0.50	
	E30 (15mgDA)	45 (1041)	2.23	1.88 (1.15, 3.07)	10 (233)	2.07	4.05 (1.07, 26.36)
	E60 (30 mg DA)	25 (1058)	1.24	1.03 (0.59, 1.80)	5 (229)	1.06	2.08 (0.40, 10.75)
>50-<80 mL/min	W	18 (510)	1.66		65 (2520)	1.15	
	E30 (15mgDA)	31 (569)	2.45	1.49 (0.84, 2.67)	67 (2465)	1.19	1.02 (0.73, 1.44)
	E60 (30 mg DA)	14 (526)	1.23	0.75 (0.37, 1.51)	37 (2459)	0.86	0.58 (0.39, 0.87)
≥80 mL/min	W	1 (108)	0.38		32 (2487)	0.54	
	E30 (15mgDA)	5 (115)	1.86	4.66 (0.54, 40.04)	64 (2496)	1.07	2.0 (1.31, 3.05)
	E60 (30 mg DA)	3 (111)	1.2	3.26 (0.34, 31.46)	49 (2501)	0.83	1.54 (0.98, 2.40)

Reviewer's Table: Model: by ARM and CHADS cut 0 (≤3), 1 (≥3), BASEGP, ADJEFFCA datasets

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Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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6.1.8.4 Efficacy by Multiple Stokes/SEEs

Table 60 shows that few subjects in ENGAGE AF had multiple strokes/SEEs. Subjects in the edoxaban 30 mg group had a higher risk of multiple events than warfarin (about 3 times as many). The risk for multiple events in the edoxaban 60 mg dosing group was somewhat less than warfarin.

Table 60: Multiple Stroke/SEE Events in ENGAGE AF

		Edox 30 mg (15 mg DA) N=7002	Edox 60 mg (30 mg DA) N=7012	Warfarin N=7012
<u>Occurrences of Stroke/SEE</u>				
≥1	n(%)	253 (3.6)	182 (2.6)	232 (3.3)
≥2	n(%)	21 (0.3)	5 (< 0.1)	8 (0.1)
≥3	n(%)	0(0)	1(< 0.1)	0(0)

Source: Table 14.2.1.10: Components of Primary Efficacy Endpoint Events MITT Analysis Set - On-Treatment Period (CSR: ENGAGE AF)

6.1.8.5 Efficacy by CHADS₂ score

For the edoxaban 60 mg dose cohort there was little difference in HR compared to warfarin for Stroke/SEE among the subgroups of subjects with different CHADS₂ scores (Table 61). In the three CHADS₂ score groups (2, 3 and > 3), edoxaban 60 mg always had a HR < 1 compared to warfarin. The edoxaban 30 mg dose HR compared to warfarin became slightly worse with increasing CHADS₂ score.

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Table 61: Stroke/SEE by CHADS2 score

	n(N)	n(N)	event rate %/yr	HR vs. Warfarin
OVERALL	Warfarin	232 (7012)	1.5	
	Edoxaban 30mg (15mg DA)	253 (7002)	1.61	1.07 (0.9, 1.28)
	Edoxaban 60mg (30mg DA)	182 (7012)	1.18	0.79 (0.64, 0.96)
CHADS2=2	Warfarin	80 (3409)	1.01	
	Edoxaban 30mg (15mg DA)	84 (3372)	1.06	1.03 (0.76, 1.41)
	Edoxaban 60mg (30mg DA)	71 (3349)	0.92	0.90 (0.66, 1.24)
CHADS2=3	Warfarin	72 (2090)	1.59	
	Edoxaban 30mg (15mg DA)	76 (2117)	1.63	1.03 (0.75, 1.43)
	Edoxaban 60mg (30mg DA)	53 (2151)	1.14	0.72 (0.50, 1.03)
CHADS2>3	Warfarin	80 (1513)	2.59	
	Edoxaban 30mg (15mg DA)	93 (1513)	2.97	1.15 (0.85, 1.55)
	Edoxaban 60mg (30mg DA)	58 (1512)	1.9	0.73 (0.52, 1.02)

Reviewer's Table: Source Data: BASEGRP.xpt, ADJEFFCA.xpt, modeled with ARM and DOSEADJ
(Y/N) only for time to event analysis/HR.

For overall, used the model of ARM, DOSEADJ and CHADS score cut ($\leq 3=0$, $>3=1$)

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6.1.7.6 Efficacy by Proton Pump Inhibitor (PPI) at baseline

Because a gel forms when edoxaban tosylate is exposed to high pH, we were concerned that absorption might be decreased at increased pH. For this reason we were concerned that PPIs could impair absorption and decrease efficacy. We did an analysis of the event rate of stroke/SEE (the primary endpoint) in the mITT population on treatment and ischemic stroke (mITT, on treatment) by PPI use during the trial (≥ 3 month consecutive PPI use, Yes/No) (Table 62 and Table 63). The event rate was stable irrespective of whether the subject was on a PPI for at least 3 months in the edoxaban 60 mg (30 mg DA) group, but the warfarin subjects on a PPI for at least 3 months had an increase in event rate by ~50%. This resulted in a decreased HR for edoxaban 60 mg (30 mg DA) for first stroke/SEE and first ischemic stroke (mITT, on treatment). The subjects on PPIs for at least 3 months who were randomized to the edoxaban 30 mg (15 mg DA) dose had a higher event rate than edoxaban 30 mg (15 mg DA) subjects who were not on PPIs for at least 3 months [also ~50% increase which resulted in stable HR for first stroke/SEE and first ischemic stroke relative to warfarin (mITT, on treatment)]. PPI use does not appear to reduce efficacy of drug in the edoxaban 60 mg group and therefore, the concern regarding gel formation that might occur at higher pH does not appear to be clinically relevant.

Table 62: PPI effect on Stroke/SEE on Treatment, mITT

Subgroup		n(N)	event rate %/yr	HR vs. Warfarin
< 3 mo. consecutive PPI use	Warfarin	189 (6136)	1.39	
	Edoxaban 30mg (15mg DA)	209 (6163)	1.50	1.07 (0.88, 1.31)
	Edoxaban 60mg (30mg DA)	159 (6156)	1.17	0.84 (0.68, 1.04)
≥ 3 mo. consecutive PPI use	Warfarin	43 (876)	2.27	
	Edoxaban 30mg (15mg DA)	44 (839)	2.36	1.07 (0.70, 1.63)
	Edoxaban 60mg (30mg DA)	23 (856)	1.23	0.55 (0.33, 0.91)

Reviewer's Table: Datasets used: CM.xpt, DM.xpt, BASEGP.xpt, ADJEFFCA.xpt

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Table 63: PPI effect on Ischemic Stroke on Treatment, mITT population

Subgroup		n(N)	event rate %/yr	HR vs. Warfarin
< 3 mo. consecutive PPI use	Warfarin	117 (6136)	0.86	
	Edoxaban 30mg (15mg DA)	188 (6163)	1.35	1.56 (1.24, 1.97)
	Edoxaban 60mg (30mg DA)	118 (6156)	0.87	1.01 (0.78, 1.31)
≥ 3 mo. consecutive PPI use	Warfarin	27 (876)	1.42	
	Edoxaban 30mg (15mg DA)	38 (839)	2.04	1.49 (0.91, 2.45)
	Edoxaban 60mg (30mg DA)	17 (856)	0.91	0.65 (0.35, 1.18)

Reviewer's Table: Datasets used: CM.xpt, DM.xpt, BASEGP.xpt, ADJEFFCA.xpt

6.1.8.6 Investigator Reported Efficacy Events

The investigator reported strokes were similar in number to the adjudicated strokes. However, SEEs were much less frequent in the adjudicated reports. Nevertheless, there were fewer investigator reported SEEs in the edoxaban 60 mg group than in the warfarin group, so if the investigator results were used, this discrepancy would not change the direction of the results.

Table 64: Investigator Reported Efficacy Events

	Edoxaban 30mg (15mg DosAdj) (N=7002)	Edoxaban 60mg 30mg DosAdj (N=7012)	Warfarin (N=7012)
Subjects with Stroke	252 (3.6)	193 (2.8)	233 (3.3)
Ischemic Stroke	230 (3.3)	146 (2.1)	139 (2.0)
Hemorrhagic Stroke	21 (0.3)	38 (0.5)	77(1.1)
SEE	68 (1.0)	39 (0.6)	44 (0.6)

Source: ENGAGE AF CSR, Table 14.2.3.17: Investigator Reported Suspected Cerebrovascular Ever MITT Analysis Set - On-Treatment Period

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6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Study PRT018 was the three month phase 2 dose ranging study that helped guide the applicant's dose choice for the pivotal trial. It was a multinational, randomized, parallel group, double blind study (DB to dose of edoxaban) but open label to whether subjects were on warfarin or edoxaban conducted mostly in Eastern Europe. Subjects had NVAf with a CHADS₂ index score of at least 2 and were equally randomized to 4 dose regimens of edoxaban (30 mg QD, 60 mg QD, 30 mg BID, 60 mg BID) or warfarin. The study was designed to evaluate safety and was underpowered for an efficacy assessment. D-dimer levels and prothrombin fragment 1 and 2 (F12) levels were used to evaluate efficacy. The safety assessments were focused on hepatic enzymes and bleeding. Analysis of bleeding events was based on blinded adjudication provided by the CEC.

The trial enrolled between 180 and 250 subjects per arm. The conduct of the trial was good with adequate subject retention and completion. Exposure (both time exposure and number of subjects exposed) was equally matched among treatment groups except for the 60 mg BID arm. The 60 mg BID arm stopped enrollment early and enrolled subjects were discontinued early at the request of the DMC because of excessive bleeding in that dosing group. Compared to ENGAGE AF, subjects were more likely to be younger (mean of ~65 years old compared to mean of ~70 years old in ENGAGE AF), warfarin naïve (~60% vs. 40% in ENGAGE AF), and with a history of congestive heart failure (~87% vs. ~57% in ENGAGE AF). They were less likely to have had a prior stroke or TIA (~20% vs. ~28% in ENGAGE AF).

The number of MACE events during the treatment period was low. No dose relationship was apparent. Because of the low number events, conclusions regarding the dose of edoxaban could not be made based on this endpoint. The edoxaban 30 and 60 mg QD groups were comparable in bleeding rates to warfarin (~3% clinically relevant or major bleeds). The BID regimens had higher bleeding rates than warfarin (~7-10% clinically relevant or major bleeds) and for this reason these regimens were not brought forward to the phase 3 study.

The sponsor explored the relationship of exposure on D-dimer change from baseline at day 28. They estimated that the maximum effect was a 35-40% reduction in D-dimer levels from baseline for warfarin and all edoxaban doses tested in PRT-018. There was very high intersubject variability making the interpretation of these data difficult.

There was also high inter-subject variability for F12 change from baseline. The warfarin treatment group had a slight mean elevation in F12 change from baseline at day 28 whereas all edoxaban treatment groups had a slight mean reduction. Both D-dimer and F12 levels generally increase in states of thrombosis and so would be expected to decrease when on anticoagulants. The unexpected effect of warfarin on the F12 levels made interpretation of these data difficult.

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PT, INR and Factor Xa activity were predictive of all categories of bleeding. Increased F12 levels were predictive of bleeding, but this was contrary to expectations (bleeding is expected to decrease with increasing F12). However, multiple analyses and explorations revealed that steady state trough edoxaban plasma concentration was the best predictor of bleeding events because the subjects who received the BID doses (and had the highest trough edoxaban levels) had the highest bleeding rates. In the end, the 60 mg and 30 mg QD doses were chosen in an attempt to match and possibly lower bleeding relative to warfarin. The analyses and rationale for dose selection were requested by FDA at the time of signing the SPA agreement on October 15, 2008 because it was not clear to us that the doses were optimal. DS submitted the analyses and rationale for choosing the 30 mg and 60 mg QD doses on May 8, 2009. No further discussion between FDA and DS occurred regarding this issue.

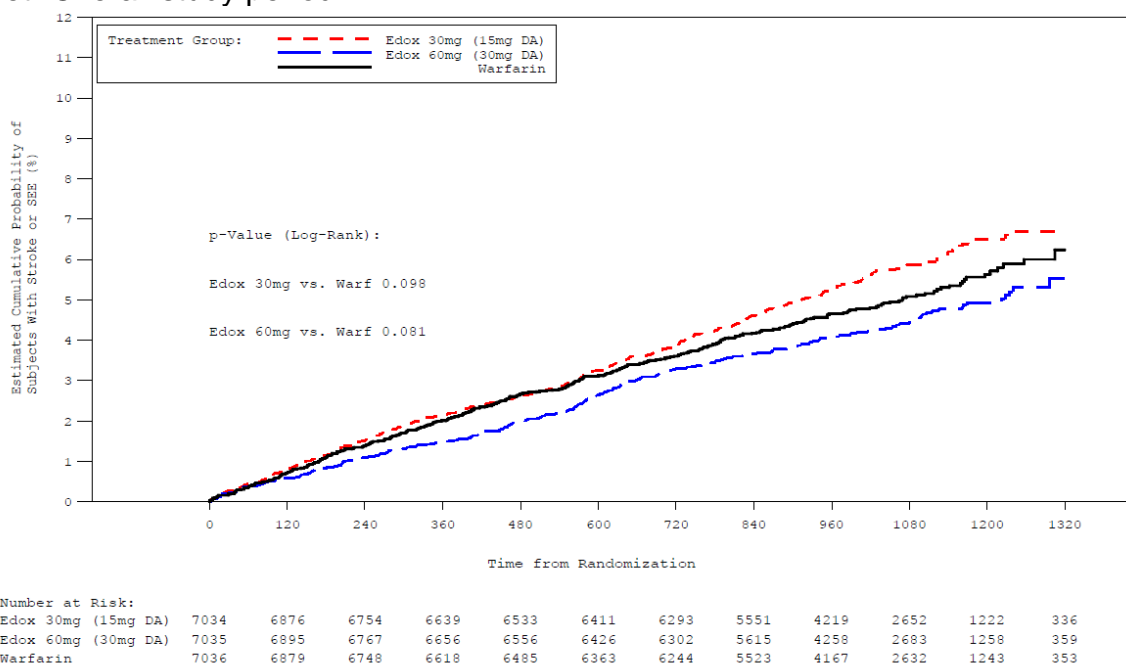
One might wonder what the bleeding rates would have been for a somewhat higher daily dose. Unfortunately, this was not tested.

Refer to [Appendix 9](#) for a detailed summary of the protocol and clinical results.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Kaplan-Meier curve in Figure 18 demonstrates that the relative probabilities of a first stroke/SEE and first major bleed stays consistent over time from randomization. This is evidence of persistence of efficacy.

Figure 18: Kaplan-Meier Curve Time to First Occurrence of Stroke or SEE, ITT analysis set- Overall study period



Source: p. 126, CSR ENGAGE AF

6.1.11 Additional Efficacy Issues/Analyses

6.1.11.1 Decreased Efficacy in Patients with Normal Renal Function in other NOAC trials

The review issue identified is the observation that there was decreased efficacy in the subgroup of subjects with normal renal function. Decreased efficacy in normal renal function subgroups was also observed in other NOAC pivotal trials as shown in Table 65.

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Table 65: Effect of Baseline Creatinine on Event Rates in Warfarin-Controlled Trials of Novel Anticoagulants

Study and Cr Cl subgroups	Primary Event (first stroke/SEE) Rates in %/year			Hazard Ratio	
	ExD Low Dose	ExD High Dose	Warfarin	High dose v. Warfarin	Low dose vs. Warfarin
Edoxaban - ENGAGE AF					
Overall	1.61	1.18	1.5	0.79	1.07
30 - <= 50	2.33	1.73	1.98	0.99	1.19
>50 - <80	1.66	1.04	2.05	0.51	0.82
>=80	1.22	1.07	0.76	1.41	1.61
% decrease in event rate from >50 - <80 cohort to >= 80 cohort	26.51	2.8	62.93		
% increase in HR (compared to warfarin) from >50 - <80 cohort to >= 80 cohort				176.47	96.34
Dabigatran - RE-LY					
Overall	1.5	1.1	1.7	0.65	0.88
<= 50	2.40	1.27	2.69	0.47	0.89
>50 - <80	1.69	1.21	1.87	0.65	0.90
>=80	0.86	0.73	1.03	0.71	0.84
% decrease in event rate from >50 - <80 cohort to >= 80 cohort	49.11	39.67	44.92		
% increase in HR (compared to warfarin) from >50 - <80 cohort to >= 80 cohort				9.2%	-6.7% (not approved)
Rivaroxaban - ROCKET AF*					
Overall	NA	1.71	2.16	0.79.	
<= 50	NA	2.38	2.77	0.86	
>50 - <80	NA	1.75	2.41	0.73	
>=80	NA	1.27	1.42	0.89	
% decrease in event rate from >50 - <80 cohort to >= 80 cohort	NA	27.43	41.08		
% increase in HR (compared to warfarin) from >50 - <80 cohort to >= 80 cohort				18.0	

ExD: Experimental Drug, Event rates are #/100 patient years, * ROCKET rates are from per-protocol, on treatment analysis; ENGAGE AF rates are from mITT, overall study period analysis, RE-LY rates are from ITT, overall study period analysis

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Study and Cr CI subgroups	Primary Event (first stroke/SEE) Rates in %/year			Hazard Ratio	
	ExD Low Dose	ExD High Dose	Warfarin	High dose v. Warfarin	Low dose vs. Warfarin
Apixaban - ARISTOTLE					
Overall	NA	1.27	1.60	0.79	
<= 50	NA	2.11	2.67	0.79	
>50 - <80	NA	1.24	1.69	0.73	
>=80	NA	0.99	1.12	0.88	
% decrease in event rate from >50 - <80 cohort to >= 80 cohort	NA	20.16	33.73		
% increase in HR (compared to warfarin) from >50 - <80 cohort to >= 80 cohort				20.5	

ExD: Experimental Drug, Event rates are #/100 patient years, ARISTOTLE rates are from ITT, overall study period analysis

Reviewer Table

One might ask why FDA didn't suggest an increased dose for the normal renal clearance subgroups for the other NOACs. The reason is that the HRs observed in the normal renal function subgroups in the other trials, while not as good as in the lesser renal function subgroups were still < 1 relative to warfarin. In ENGAGE AF, the HR for edoxaban 60 mg vs. warfarin for the primary endpoint in the normal renal function group was 1.41 and the lower bound of the CI barely crossed 1. Furthermore, there was a 176.5%% increase in HR (compared to warfarin) from the >50 - <80 cohort to the ≥ 80 cohort in the edoxaban 60 mg normal renal function subgroup. The percentage increase in HR (compared to warfarin) from the >50 - <80 cohort to the ≥ 80 cohort for the other approved NOACs ranged between 9.2% and 20.5%. In all pivotal NOAC trials, except for ROCKET AF (which enrolled a higher risk study population), the event rates in the warfarin arm in the normal renal function subgroup were low (near 1/ 100 patient-years), albeit not as low as the warfarin event rate in ENGAGE AF (0.76/ 100 patient-years).

6.1.11.2 Efficacy during the Transition Period

The applicant performed an analysis of the Stroke/SEE event rate that occurred during the transition period at study end to validate the success of the transition program that they instituted to avoid a period where patients would be on no stroke prophylaxis. See Table 66. There were 13,651 subjects who completed the CSED Visit and were on study drug within 3 days of CSED Visit. Of these subjects, 9,282 (68.0%) received a

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transition kit and were transitioned to a VKA, 4258 (31.2%) transitioned to an open-label FIIa/FXa inhibitor [2,140 (15.7%) transitioned to open-label FIIa inhibitor therapy, 2,118 (15.5%) transitioned to open-label FXa inhibitor therapy], 33 (0.2%) transitioned to other antiplatelet drugs, 62 (0.5%) transitioned to other or no therapy, and data were not available for 16 subjects (0.1%). In general, results were similar among treatment groups. Major bleeding was more common in the subjects transitioning from edoxaban 30 mg (15 mg DA).

This analysis examines the subjects who didn't have early discontinuation which accounts for 2/3 of the randomized population. Therefore, the analysis is limited by the fact that the groups of subjects can no longer be considered a randomized set. If one multiplies the number of transition days evaluated (30/ subject) by the number of subjects, one is looking at ~ 380 subject years per treatment group. The event number (7/ treatment group) divided by subject years gives an event rate of 1.8%/year/ treatment group, same as the warfarin group during the trial. Even though this is imprecise and not randomized, it is still a reassuring assessment of the transition period plan. That the event rate was similar to the event rate during the trial informs us that the transition plan was successful.

Table 66: Adjudicated Events Occurring During the Transition Period at the End of the Study by Type of Therapy, Subjects Who Completed the Common Study End Date (CSED) Visit and Were On Study Drug Within 3 Days of the CSED Visit

Subjects with Adjudicated Events during the Transition Period[a]	Edoxaban 30mg (15mg DA) (N=4616) n (%)	Edoxaban 60mg (30mg DA) (N=4529) n (%)	Warfarin (N=4506) n (%)
Subjects with Stroke/SEE	7 (0.2)	7 (0.2)	7 (0.2)
Subjects with All-cause Mortality	10 (0.2)	8 (0.2)	7 (0.2)
Subjects with Adjudicated Major Bleeding	18 (0.4)	10 (0.2)	11 (0.2)
Transitioned to VKA Using a Transition	3103	3041	3138
Strokes/SEEs	4 (0.1)	4 (0.1)	5 (0.2)
All-cause Mortality	7 (0.2)	5 (0.2)	5 (0.2)
Major Bleeds	10 (0.3)	7 (0.2)	7 (0.2)
Transitioned to IIa or Xa Inhibitor	1485	1445	1328
Strokes/SEEs	3 (0.2)	2 (0.1)	2 (0.2)
All-cause Mortality	2 (0.1)	2 (0.1)	2 (0.2)
Major Bleeds	8 (0.5)	2 (0.1)	4 (0.3)
Transitioned to Other or No Therapy	24	35	36
Strokes/SEEs	0 (0.0)	0 (0.0)	0 (0.0)
All-cause Mortality	1 (5.3)	1(3.8)	0 (0.0)
Major Bleeds	0 (0.0)	1(3.8)	0 (0.0)

[a]The 'Transition Period' is defined as the time from CSED Visit + 1 to CSED Visit + 30. Source: ENGAGE AF CSR, p. 233,234.

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Adjudicated events occurring during the 30 days following the final dose of study drug in subjects who were not on study drug within 3 days of the CSED Visit or did not complete the CSED Visit are summarized in Table 67. The majority of these subjects had their study drug prematurely discontinued because of an efficacy endpoint, bleeding event, or non-bleeding adverse event, and consequently did not qualify for the end of study transition scheme. Since the on-treatment analysis includes events during the first 3 days of study drug interruption, the table provides events from Day 4 to 30. The adjudicated events are generally comparable among the treatment groups. However, subjects who prematurely discontinued had higher event rates (similar among treatment groups). The percentage of subjects that reported adjudicated stroke in the edoxaban 60 mg group, edoxaban 30 mg group, and the warfarin group is 1.3%, 1.8%, and 1.4%, respectively. But the %/year rate is high; 25.3%/year for edoxaban 30mg / 15 mg DA, 18.6%/year for edoxaban 60mg /30 mg DA and 19.6%/year for warfarin.

Table 67: Adjudicated Events Occurring During the 30 Days Following the Final Dose of Study Drug, Subjects Who Were Not On Study Drug Within 3 Days of the Common Study End Date (CSED) Visit or Did **Not** Complete the CSED Visit

Day 4-30 of Transition Period	Edoxaban 30mg (15mg DA) (N=2386) n (%)	Edoxaban 60mg (30mg DA) (N=2483) n (%)	Warfarin (N=2506) n (%)
Stroke	43 (1.8)	33 (1.3)	35 (1.4)
Ischemic Stroke	38 (1.6)	29 (1.2)	31 (1.2)
Hemorrhagic Stroke	5 (0.2)	4 (0.2)	4 (0.2)
Systemic Embolic Event	9 (0.4)	2 (<0.1)	2 (<0.1)
Myocardial Infarction	11 (0.5)	9 (0.4)	7 (0.3)
All-Cause Mortality	168 (7.0)	145 (5.8)	174 (6.9)
Cardiovascular Mortality	114 (4.8)	88 (3.5)	112 (4.5)
Malignant Mortality	17 (0.7)	19 (0.8)	19 (0.8)
Non-Cardiovascular/Non-Malignant Mortality	37 (1.6)	38 (1.5)	43 (1.7)
Transient Ischemic Attack	7 (0.3)	5 (0.2)	4 (0.2)
ICH	8 (0.3)	8 (0.3)	12 (0.5)
Non-ICH Bleed	65 (2.7)	66 (2.7)	68 (2.7)

Source: ENGAGE AF CSR, p. 233,235

6.1.11.3 VKA-naïve vs. VKA experienced subjects and effect on efficacy

There was a significant ($p < 0.05$) interaction between VKA-naïve versus VKA experienced for the mITT during the overall study period results but not for the mITT on-

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treatment period. For the mITT overall study period, the HR [edoxaban 60 mg (30 mg DA)/ warfarin] was 0.70 for VKA naïve subjects and 1.0 for VKA experienced subjects. For the mITT on-treatment period, the HR [edoxaban 60 mg (30 mg DA)/ warfarin] was similar for both the VKA naïve and VKA experienced subjects (0.71 and 0.86, respectively). The mITT, on treatment analysis is shown in Table 68. One might expect lower hazard ratios when comparing edoxaban treated subjects to warfarin treated subjects who were not on VKA before study start because of the time it takes for naïve subjects VKA to achieve therapeutic range.

Table 68: First Stroke/SEE by VKA Naïve vs. Not Naïve Subgroups, mITT, On-treatment period

Subgroup		n(N)	event rate %/yr	HR vs. Warfarin
VKA	Warfarin	107 (2888)	1.77	
Naïve AT	Edoxaban 30mg (15mg DA)	104 (2857)	1.66	0.92 (0.71, 1.21)
Randomization	Edoxaban 60mg (30mg DA)	77 (2879)	1.26	0.71 (0.59, 0.95)
VKAs				
NOT Naïve At	Warfarin	2125 (4124)	1.32	
Randomization	Edoxaban 30mg (15mg DA)	149(4144)	1.57	1.20 (0.95, 1.52)
VKA	Edoxaban 60mg (30mg DA)	105 (4133)	1.13	0.86 (0.66, 1.11)

Source: Table 14.2.5.1, ENGAGE AF CSR, p.15/31 of tables

An amendment was written to remove the warfarin 5 mg tablet from the study because it was noticed that there was excessive bleeding in the w arm because of drug errors. The dose wasn't changed but the strength of the tablets was reduced to be a maximum of 2.5 mg. This change occurred on 12/1/10. The event rate before and after the change is shown in Table 69. The event rate in the warfarin group was reduced after the change in the warfarin group was reduced. Therefore, there is no concern that the change favored the experimental arms.

Table 69: Adjudicated Stroke/SEE on treatment period, mITT before and after removal of warfarin 5.0 mg tablet

Data cutoff		n(N)	Event Rate %/yr
Before 12/1/10	Warfarin	84(7009)	2.0
	Edoxaban 30mg (15mg DA)	74 (7001)	1.74
	Edoxaban 60mg (30mg DA)	52 (7011)	1.24
12/1/10 Or after	Warfarin	149(6041)	1.31
	Edoxaban 30mg (15mg DA)	180(6142)	1.56
	Edoxaban 60mg (30mg DA)	131 (5998)	1.16

7 Review of Safety

Safety Summary

Clinical safety of edoxaban in AF population was primarily evaluated based on the safety data from ENGAGE AF. This pivotal trial was the largest randomized trial with the longest follow-up time (median: 2.8 years) to study the risk of stroke/SEE in AF population to date. As described in [Section 5](#), a total of 21,105 AF patients were randomized to three treatment groups: edoxaban 30 mg, edoxaban 60 mg and warfarin with 1:1:1 ratio. Edoxaban was administered once daily with required dose adjustment (50% dose reduction: 15 mg or 30 mg) for subjects with moderate renal impairment (CrCL 30-50 ml/min), low body weight (≤ 60 kg) and concomitant use of P-gp inhibitors. The safety dataset contains a total of 21,026 subjects who received at least one dose of study drug [$n = 7002$, 7012 and 7012 for edoxaban 30 mg²⁴, edoxaban 60 mg²⁵ and warfarin, respectively]. The size of the dataset should provide sufficient information to evaluate the safety of edoxaban in AF population. The three treatment groups in general had comparable duration of drug exposure and similar patterns in terms of dropouts and discontinuation.

The primary adjudicated safety endpoint was modified ISTH major bleeding²⁶. Although ISTH major bleeding could include some clinically insignificant and readily reversible bleeds, it was the primary safety endpoint in the AF trials for the other three NOACs and has been historically used in studies of long-term anticoagulation. The Applicant also categorized major bleeding events using TIMI Major²⁷ and GUSTO Severe²⁸ definitions which allow an evaluation of more serious major bleeding events. The primary safety analysis was to compare on-treatment ISTH major bleeding events (last dose + 3 days) between each group of edoxaban and warfarin using a Cox-proportional Hazard Model controlled for dose adjustment and CHADS₂ covariates.

Both edoxaban groups were superior to warfarin for ISTH major bleeding [HR: 0.47 (0.41-0.55), 0.80 (0.71-0.91) for edoxaban 30 mg and 60 mg, respectively]. The superiority of bleeding results in the edoxaban groups were consistent across other major bleeding categories including ISTH major bleeding without hemorrhagic stroke,

²⁴ Edoxaban 30 mg refers to subjects receiving edoxaban 30 mg /15 mg dose adjusted.

²⁵ Edoxaban 60 mg refers to subjects receiving edoxaban 60 mg /30 mg dose adjusted

²⁶ Definition of modified ISTH major bleeding used in ENGAGE AF: fatal bleeding, bleeding in a critical organ or any bleed leading to transfusion-adjusted drops in hemoglobin level of ≥ 2.0 g/dl (1 unit of packed RBC = 1 g/dl drop in hemoglobin). See [APPENDIX 7](#) for details.

²⁷ Definition of TIMI Major bleeding: : ICH, or clinical overt bleeding with a ≥ 5 mg/dL fall in hemoglobin or a 15% fall in hematocrit

²⁸ Definition of GUSTO Severe bleeding: ICH or bleeding resulting in hemodynamic compromise requiring treatment

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Intracranial hemorrhage (ICH), Fatal bleeding, TIMI Major and GUSTO Severe bleeding (Table 70).

Table 70 Primary Major Bleeding Results[†] in ENGAGE AF - on treatment, safety set

	E 30 mg N = 7002 n (%/pt-yr)	E 60 mg N = 7012 n (%/pt-yr)	Warfarin N = 7012 n (%/pt-yr)	E30 mg vs. W HR (95% CI)	E60 mg vs. W HR (95% CI)
Major Bleeding (MB)	254 (1.57)	418 (2.68)	524 (3.34)	0.47 (0.41-0.55)	0.80 (0.71-0.91)
-Intracranial (ICH)	41 (0.25)	61 (0.38)	132 (0.82)	0.31 (0.22-0.43)	0.47 (0.34-0.63)
-Gastrointestinal(GI)	129 (0.80)	232 (1.48)	190 (1.20)	0.67 (0.53-0.84)	1.24 (1.02-1.50)
-Fatal Bleeding (FB)	20 (0.12)	32 (0.20)	59 (0.37)	0.33 (0.20-0.55)	0.55 (0.36-0.84)
MB without HS*	223 (1.38)	376 (2.41)	445 (2.84)	0.49 (0.42-0.57)	0.85 (0.74-0.98)
-ICH without HS	10 (0.06)	17 (0.11)	51 (0.32)	0.19 (0.10-0.38)	0.34 (0.20-0.58)
TIMI Major	106 (0.65)	165 (1.04)	259 (1.63)	0.40 (0.32-0.50)	0.64 (0.53-0.78)
GUSTO Severe	56 (0.34)	92 (0.58)	175 (1.09)	0.31 (0.23-0.42)	0.53 (0.41-0.68)

*ISTH major bleeding without hemorrhagic stroke (HS)

Reviewer's Table. Source: Table 76 and Table 79 See [APPENDIX 7](#) for overview of all bleeding category definitions.

However, edoxaban 60 mg significantly increased the risk of major gastrointestinal (GI) bleeding compared with warfarin (HR: 1.24, 95% CI: 1.02-1.50). About 60% of these major GI bleeding occurred in the upper GI tract. The risk of more severe GI major bleeding using TIMI Major and GUSTO Severe definitions was similar between edoxaban 60 mg and warfarin (Table 71). These findings were similar to our experience with the other three approved NOACs, where each of them had a significant reduction in ICH and similar or superior ISTH major bleeding compared with warfarin. The increased risk of major GI bleeding was also observed in two out of the three approved NOACs. The secondary safety endpoint is combination of major bleeding and clinically relevant non-major bleeding (CRNMB) (see [APPENDIX 7](#) for definitions). Consistent with the findings for major bleeding events, both edoxaban groups had favorable outcomes with lower event rates for CRNMB alone or the combination of major bleeding events and CRNMB (Table 78).

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Table 71 Major GI Bleeding Results in ENGAGE AF - on treatment, safety set

	E 30 mg N = 7002 n (%/pt-yr)	E 60 mg N = 7012 n (%/pt-yr)	Warfarin N = 7012 n (%/pt-yr)	E30 mg vs. W HR (95% CI)	E60 mg vs. W HR (95% CI)
Major GI Bleeding	129 (0.80)	232 (1.48)	190 (1.20)	0.67 (0.53-0.84)	1.24 (1.02-1.50)
-Upper GI	88 (0.54)	140 (0.89)	111 (0.70)	0.78 (0.59-1.03)	1.24 (0.99-1.64)
-Lower GI	44 (0.27)	96 (0.61)	81 (0.51)	0.54 (0.37-0.77)	1.20 (0.89-1.61)
TIMI Major -GI	47 (0.29)	80 (0.50)	83 (0.52)	0.56 (0.39-0.80)	0.97 (0.71-1.32)
GUSTO Severe -GI	9 (0.06)	21 (0.13)	25 (0.16)	0.36 (0.17-0.76)	0.85 (0.47-1.51)

Reviewer's Table. Source: Table 76

ISTH major bleeding results by center level INR controlled were evaluated using time in therapeutic range (TTR) and time above therapeutic range (TATR) (Table 80 and Table 81). In general, the findings of these analyses were in agreement with the primary major bleeding result. The only exception is the highest quartile of TTR, where the result was numerically in favor of warfarin over the edoxaban 60 mg group (HR: 1.10, 95% CI: 0.9-1.4). This result was primarily driven by a particularly high event rate in the edoxaban 60 mg group in the centers with the highest quartile of TTR. The centers with high TTR could represent good warfarin control as well as overall better quality of care. It is possible that the investigators/nurses in these centers more thoroughly and actively reported potential bleeding events.

Subgroup analyses of ISTH major bleeding by baseline characteristics and medical conditions were generally consistent with the primary major bleeding findings (Figure 22 and Figure 23). Unlike the significant interaction effect of renal function seen in the efficacy results, major bleeding results were consistent across CrCL subgroups and numerically better in both edoxaban groups compared with warfarin (Figure 22 and Figure 23). A few subgroups in the edoxaban arms had noticeably less bleeding compared with warfarin including dose adjustment subgroups in both high and low edoxaban dose groups and the subgroup of subjects with weight \leq 60 kg in edoxaban 30 mg. These results are in support of the efficacy findings which suggest that the Applicant's criteria for dose adjustment were not optimal and these subjects were likely under-dosed.

Edoxaban is metabolized by CYP3A and is a substrate of the efflux transporter P-gp and an inhibitor of P-gp. Co-administration with a strong P-gp inducer (rifampin) decreased edoxaban exposure by ~40%. Co-administration with P-gp inhibitors generally increases edoxaban exposure by > 50% -< 90% and was dose adjusted (50% reduction) in ENGAGE AF. The clinical pharmacology reviewers recommend, and I agree, to avoid concomitant use with rifampin. No dose adjustment is recommended for co-administration of P-gp inhibitors given that the need for dose adjustment is not evident in ENGAGE AF (see [Section 4.4.3.3](#)).

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In ENGAGE AF, both edoxaban groups generally had less major bleeding than the warfarin group regardless of the use of concomitant medication (Figure 24). Concurrent use of aspirin or other antiplatelet increased the risk of having major bleeding events in all treatment groups but did not change the relative risk. Subjects taking aspirin at any time on or after the first dose of study drug in the edoxaban 60 mg group had a lower major bleeding event rate compared to those treated with warfarin [HR: 0.79 (0.66-0.94)].

There were a total of 2,336 deaths in ENGAGE AF during the overall study period [731 (10.4%) for edoxaban 30 mg, 769 (11.0%) for edoxaban 60 mg and 836 (12.0%) for warfarin)]. As expected, approximately 70% of deaths were due to CV related conditions. In general, the percentage of subjects was similar across categories of causes of death among the three treatment groups (Table 74).

Similar percentages of subjects in the edoxaban 30 mg, edoxaban 60 mg and warfarin groups reported at least one non-bleeding SAE during the on treatment period (34.5%, 33.0% and 35.9%, respectively). The most common non-bleeding SAEs were CV conditions in all three treatment groups (~13%). Overall, the type and incidence of SAEs were similar between treatment groups with few notable imbalances. Subjects in the edoxaban 60 mg group had a higher incidence of anemia-related SAEs compared with the warfarin group (1.3% vs. 0.6%). There were two fatal cases (one secondary to the lung cancer and the other possibly related to anemia) and one hemolytic anemia case (with a resolved outcome) in the edoxaban 60 mg group. Although the frequency was very low, we cannot rule out the possibility that some subjects may have experienced severe anemia due to chronic clinically silent bleeds in the edoxaban groups.

The reviewer also evaluated deaths and SAEs using MedDRA SMQs of interest (Table 75 and Table 87). There was no clinically meaningful imbalance between the edoxaban and warfarin groups for the majority of SMQs of interest including acute renal failure (SMQ) and drug related hepatic disorders (SMQ). However, interstitial lung disease (ILD) SAEs (n = 17 vs. 9) and ILD-related deaths (n = 8 vs. 0) were reported more frequently in the edoxaban 60 mg group compared with the warfarin group. There was no imbalance with regard to ILD-related conditions at baseline between edoxaban 60 mg and warfarin. Although the incidence of ILD was very low, the reviewer has some concerns given that early this year PMDA requested an “important precaution” to be added to the Japanese prescribing information for rivaroxaban relating to the potential risk of ILD. These unbalanced findings were still present after review of individual case by excluding those who were likely not true ILD or were confounded by amiodarone use. Additionally, the incidence of ILD SAE in the edoxaban groups was much higher among subjects with ILD related conditions at baseline (5%) compared to those without ILD at baseline (0.1%). Considering the similar post-marketing findings in a member of the same class of drug in Japan, the potential that edoxaban could exacerbate ILD among those with an existing condition cannot be ruled out. The reviewer recommends adding these unbalanced findings to the label.

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The frequency and type of non-bleeding AEs were generally similar among the treatment groups except anemia, which was reported more frequently in the edoxaban 60 mg group than the warfarin group (8.2% vs. 5.6%). However, the majority of anemia AEs were mild to moderate and with very few leading to discontinuation of study drug. These imbalanced findings in anemia-related AEs are likely partly due to higher incidence of GI bleeds or potentially non-apparent bleed in the edoxaban 60 mg group compared with the warfarin group. The reviewer also performed AE analyses searching for MedDRA SMQs of interest (Table 102). The only notable imbalance ($\geq 0.5\%$ more frequently in the edoxaban arm) was that both edoxaban groups had slightly higher frequency of acute renal failure (SMQ) AEs compared with warfarin (10.5%, 10.6% vs. 9.5%). Further evaluation of the reported PTs for acute renal failure SMQ found that the imbalanced results were largely driven by PTs such as creatinine renal clearance decreased and renal impairment.

Evaluation of all laboratory data revealed only noteworthy changes in renal parameters and hemoglobin. Both edoxaban groups on average had slightly greater CrCL decrease as well as greater serum creatinine increases during the study compared with the warfarin group (Figure 32 and Figure 33). The reviewer does not have sufficient data to evaluate if this phenomenon is reversible given that the laboratory data were not systematically collected after discontinuation of study drug. The category shift table also shows slightly higher percent of subjects in the edoxaban groups changed to worse renal profile compared with warfarin (Table 103 and Table 104). These small changes in renal parameters are aligned with our AE findings. Because there were no imbalanced findings with regard to SAEs for acute renal failure and no pre-clinical evidence for renal toxicity, the reviewer does not think these renal findings represent a significant safety concern and could be due to a PD effect of the drug. The reviewer recommends including the information about small changes in creatinine clearance and serum creatinine in the label. The edoxaban 60 mg group also had greater decreases in hemoglobin compared with the warfarin group during the study period. A higher percent of subjects in the edoxaban 60 mg group had hemoglobin drops ≥ 2 g/dL (23.9% vs. 19.5%) or ≥ 4 g/dL (5.9% vs. 3.8%) compared with the warfarin group. These results are in agreement with the findings of anemia AEs. Review of vital signs and ECGs revealed no safety concerns. The Thorough QT study was negative. .

Edoxaban does not appear to cause drug induced liver injury (DILI). The OSE liver consult review did not identify a clear-cut case of edoxaban-induced serious and probably drug-caused hepatocellular jaundice in ENGAGE AF (See [Section 7.3.5.1.3](#)). The available data suggest that edoxaban is not different from warfarin and other NOACs in the market with regard to liver toxicity. The fairly frequent elevation of liver transaminases is likely associated with underlying cardiac condition in the AF population.

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7.1 Methods

The Applicant's summary of clinical safety (SCS) primarily focused on data from 2 pivotal Phase 3 studies: Study DU176b-C-U301 (ENGAGE AF, n = 21,026 treated and Study DU176b-D-U305 (Hokusai VTE, n = 8240 treated). Other supportive data included safety information from subjects treated in five Phase 2 AF studies and 7 phase 2/3 VTE Prophylaxis studies as well as phase 1 clinical pharmacology studies and other studies (Table 72).

Table 72. Studies for Summary of Clinical Safety for Edoxaban

Type of Study	Planned Duration of Treatment	Number of Subjects Treated		
		Edoxaban	Control Group	Total
AF: Phase 3, C-U301 (ENGAGE AF-TIMI 48)	2.5 years	14,014	7012 (warfarin)	21,026
VTE Treatment and Secondary Prevention: Phase 3, D-U305 (Hokusai VTE)	3 to 12 months	4118	4122 (warfarin)	8240
AF: Phase 2 studies	6 to 12 weeks	1502	450 (warfarin)	1952
VTE-Prophylaxis: Subjects undergoing orthopedic surgeries (Phase 2/3)	7 to 14 days (post-operative; in-hospital)	2638	1040 (enoxaparin, dalteparin or placebo)	3678
Phase 1 PK/PD/DDI Studies (Integrated): Healthy volunteers or special populations	Single or multiple dose	1250 ^a	159 ^b	1409
Phase 1 PK/PD Studies (Non-Integrated): Healthy volunteers or subjects with end-stage renal disease undergoing hemodialysis	Single or multiple dose	218	0	218
Phase 3 Severe Renal Impairment studies in Japanese Subjects	2 or 12 weeks	152	20 (fondaparinux)	172
Other Ongoing Studies: (eTRIS, ePAD)	12 weeks	34 (160 planned)	21 (130 planned) (LMWH/warfarin or clopidogrel)	55 (290 planned)
Post-Marketing Experience (Japan)	NA	134,875	NA	134,875

Source: The Applicant's Summary of Clinical Safety Table A-1.1

AEs of special interest in all phase 2 and phase 3 studies include bleeding events, liver enzyme and total bilirubin (TBL) abnormalities and liver-related treatment-emergent adverse events (AEs). Malignancy and bone fractures were also AEs of special interest in ENGAGE AF and Hokusai VTE. Although there is no evidence that anticoagulant therapy increases the risk of cancer, evaluation of bleeding locations/sources is likely to lead to identification and diagnosis of malignancy. The Applicant's rationale for selecting

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bone fractures as an additional event of interest is because some evidence has suggested that chronic therapy with warfarin may increase the risk of bone fracture, especially in men.

In ENGAGE AF and Hokusai VTE, bleeding events were addressed and adjudicated blindly by Clinical Event Adjudication Committees (CECs), independent of investigators' assessments. The CECs designated each event as falling into one of the protocol-defined categories: major bleeding, clinically relevant non-major bleeding (CRNM) or minor bleeding (ENGAGE AF) or nuisance bleeding (Hokusai VTE) (See [APPENDIX 7](#) for overview of all bleeding category definitions in ENGAGE AF).

In ENGAGE AF, the Applicant's primary analysis for bleeding events evaluated on-treatment events in the safety population set (subjects who received at least one dose of study treatment). The definition of "on treatment" was the period between first dose and 3 days after study drug discontinuation (temporary or permanent) unless the subject completed the CSED visit. For subjects who completed the CSED visit the "on treatment" period was the period between first dose and the CSED visit. Time to the first major bleeding event was examined using a Cox-proportional hazard model to estimate HR and 95% CI while adjusting two covariates: dichotomized CHADS₂ (1 if CHADS₂ ≥ 4, 0 otherwise) and dichotomized dose-adjustment factor (1 if dose adjustment, 0 otherwise). The Applicant also conducted safety analysis during the overall study period, which is defined as the time from the initial dose of study drug date to the CSED visit²⁹.

In addition to the bleeding events, hepatic abnormalities reported as SAEs or requiring discontinuation of study drug, or pre-defined liver laboratory abnormalities were also evaluated and adjudicated by two external hepatic specialists in a blinded manner. Any hepatic abnormalities with the criteria listed below were adjudicated:

- ALT or AST ≥ 8 x ULN
- ALT or AST ≥ 3 x ULN with TBL ≥ 2 x ULN
- ALT or AST ≥ 2 x ULN with clinical symptoms and signs suggestive of hepatitis
- Clinical jaundice
- Hepatic abnormalities or cases reported as SAEs
- Hepatic abnormalities requiring discontinuation of study drug

Two hepatic specialists reviewed cases to determine the nature of liver injury, the clinical severity of liver injury, and the causal relationship to study drug.

²⁹ The Common Study End Date (CSED) was announced on 22 Jan 2013 for ENGAGE AF based on the accrual rate of primary endpoint events. The CSED visit was a mandatory visit within 90 days after the CSED, and the final dose day for all subjects.

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7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant's primary safety data are from the two phase 3 trials: ENGAGE AF (see [Section 5](#) for detailed description of the trial) and Hokusai VTE. The database lock date for ENGAGE AF was 06 Aug 2013 and 27 Jun 2013 for HOKUSAI VTE. The reviewer's safety analysis focused on data in ENGAGE AF, which should allow substantive assessment of the safety of edoxaban in an AF population. The OSE liver consult evaluated liver data from both ENGAGE AF and HOKUSAI VTE.

ENGAGE AF was conducted worldwide at 1393 sites in 46 countries in the following 6 regions: North America, Latin America, Western Europe, Eastern Europe, Asia Pacific and South Africa, and Japan. A total of 21,105 subjects were randomized with 21,026 subjects having at least one study drug treatment (N = 7002, 7012, and 7012 for the edoxaban 30 mg, edoxaban 60 mg and warfarin groups, respectively).

7.1.2 Categorization of Adverse Events

AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. The Applicant defined treatment-emergent adverse events (AEs) as any untoward medical occurrence which started on or after any first dose of study drug or started prior to but worsened after any first dose of study drug. Because a subject could have multiple study drug interruptions, "first dose" refers to the first dose of study drug during the study and the first dose of study drug when the drug was restarted after a temporary study drug interruption. SAEs included event that results in death; was life-threatening; required or prolonged hospitalization; resulted in a persistent or significant disability; was a congenital anomaly/birth defect; or was a medically important event. All deaths were adjudicated.

The Applicant also conducted addition searches using Standard MedDRA Query (SMQs). The investigated SMQ terms are as follows: acute renal failure, acute pancreatitis, interstitial lung disease, hypersensitivity reactions, Torsade de pointes/QT prolongation, hematopoietic events and hemolytic disorders.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant did not combine Phase 2 AF studies with data from ENGAGE AF primarily because of smaller sample size and shorter treatment duration in the Phase 2 studies.

Reviewer comment: The Applicant's decision of not pooling the data was reasonable.

7.2 Adequacy of Safety Assessments

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

The median duration of study drug exposure, accounting for drug interruptions, in ENGAGE AF was ~ 2.5 years in all three groups. Figure 19 shows the distribution of study drug exposure by treatment arm. Table 73 summarizes study drug exposure by treatment arm and by different subsets (e.g. VKA naïve). Overall, the exposure was similar among the three treatment groups. VKA naïve subjects had less study drug exposure compared with VKA experienced subjects, and the trend was similar in each of the three treatment groups.

Table 73 Study Drug Exposure in ENGAGE AF

Population	Exposure (days)	Edoxaban 30mg	Edoxaban 60mg	Warfarin
Safety set (As treated)	n	7002	7012	7012
	Mean	826.3	805.9	811.0
	SD	374.2	390.8	383.1
	Median	916.0	904.0	904.0
	Min	1.0	1.0	1.0
	Max	1530	1530	1540
	Subject-Years	15839.85	15470.96	15569.23
VKA naïve	Mean	803.3	779.4	767.7
VKA experienced	Mean	842.1	824.3	841.3
Dose Adjustment	Mean	746.4	715.0	716.0
No Dose Adjustment	Mean	853.4	836.7	843.3

Reviewer's Table. Source: The Applicant's datasets- DM, BASEGRP, DRUGPER.
Similar findings were observed using ITT, per-protocol analysis sets

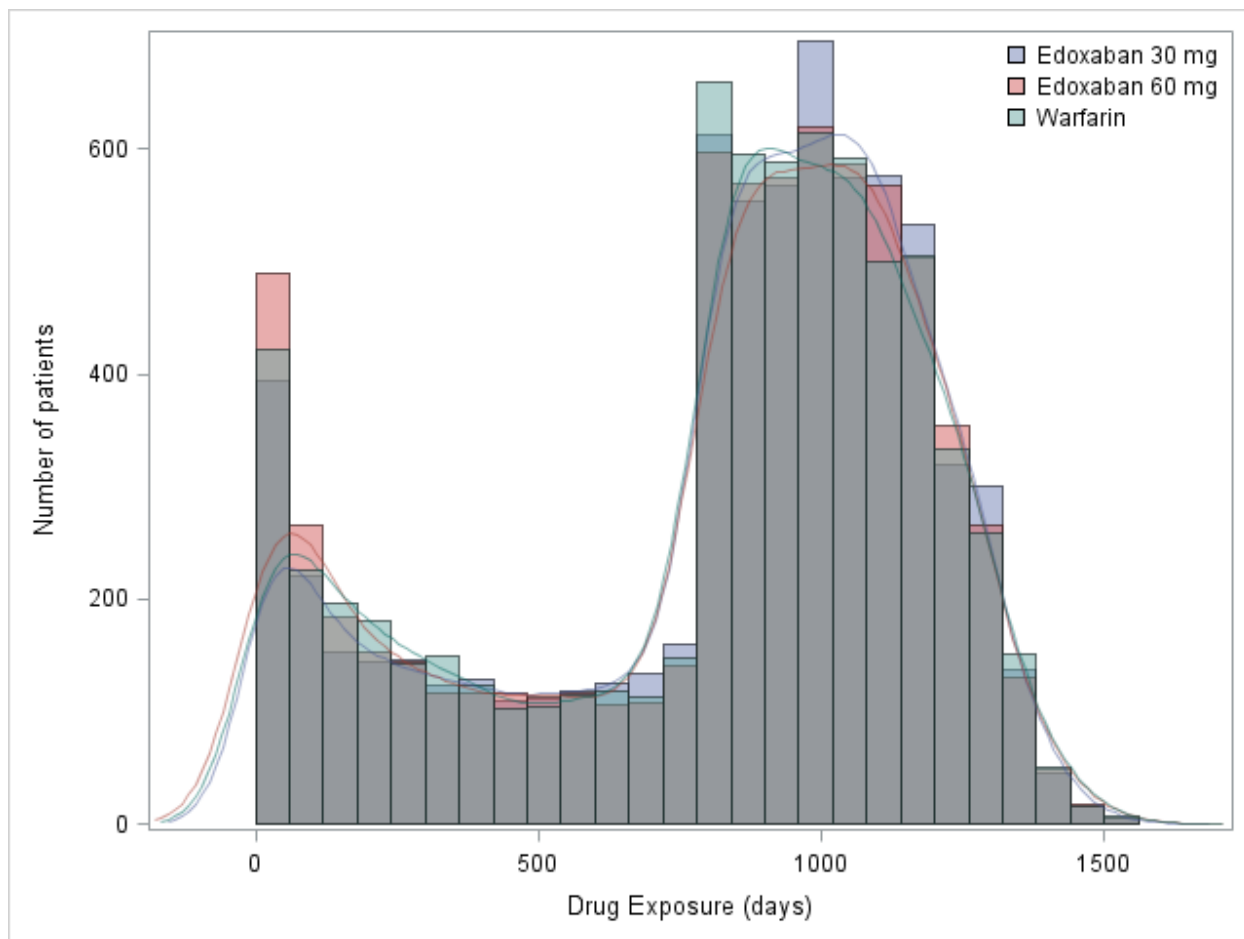
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Figure 19 Drug Exposure by Treatment group



Reviewer's Figure. Source: the Applicant's dataset DM & DRUGPER

7.2.2 Explorations for Dose Response

See [Section 6.1.9](#)

7.2.3 Special Animal and/or In Vitro Testing

Non-clinical testing was adequate to investigate potential adverse reactions. See brief summary in [Section 4.3](#).

7.2.4 Routine Clinical Testing

See [Section 5](#) and [Appendix 3](#) for detailed visit schedule in ENGAGE AF. The safety assessments were appropriate. Liver function assessment was measured as frequent as INR (weekly in the first month and monthly thereafter) up to end of year one. After year one, the assessment was done every three months. Laboratory chemistries were measured monthly in the year one and every six months after year one.

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7.2.5 Metabolic, Clearance, and Interaction Workup

See [Section 4.4 Clinical Pharmacology](#)

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

The major safety concern of anticoagulant drugs is pathological bleeding.

(b) (4)
Both bleeding event and liver-related AEs/liver chemistries abnormalities were adjudicated in ENGAGE AF.

In addition to these known or potential SAEs specific to this drug class, the Applicant also identified malignancy and bone fractures as special event of interest. All the safety events of special interest were captured on the separated pre-designed e-CRF pages. To minimize the possible errors of not reporting those events on the event specific e-CRF pages, the Applicant has implemented a process with trigger terms to detect and handle these errors.

REVIEWER'S COMMENT(S): The methodologies and identification of AEs of interest were appropriate and aligned with reported AEs for similar drugs in the drug class. Selecting new bone fractures as an event of interest is not directly related to edoxaban.

7.3 Major Safety Results

7.3.1 Deaths

There were a total of 2336 deaths in ENGAGE AF during the overall study period (731 for edoxaban 30 mg, 769 for edoxaban 60 mg and 836 for warfarin). All deaths were adjudicated as CV or non-CV deaths by the CEC and were a component of the secondary efficacy endpoint in ENGAGE AF. The CEC also adjudicated the relationship of death to a malignancy or to bleeding. Table 74 shows the causes of all adjudicated deaths during the overall study period. As expected, approximately 70% of deaths were due to CV related conditions. In general, the percentage of subjects was similar across categories of causes of death among the three treatment groups.

Deaths were considered to be related to bleeding in fewer subjects in the edoxaban groups [n = 54 (0.8%) and 59(0.8%) for edoxaban 30 mg and 60 mg, respectively] compared with the warfarin group [n = 101 (1.4%)]. Deaths were considered to be directly related to malignancy in slightly higher number of subjects in the edoxaban groups [n =93 (1.3%) and 94 (1.3%) for edoxaban 30 mg and 60 mg, respectively] compared with the warfarin group [n =84 (1.2%)]. It is noted that death due to pancreatic malignancies was slightly higher in the edoxaban treated patients compared to the warfarin treated subjects.

The reviewer also evaluated AEs with an outcome reported as fatal during the overall study periods. The number of subjects with at least one non-bleeding AE leading to fatal outcome was similar among the treatment groups (568 for edoxaban 30 mg, 632 for edoxaban 60 mg and 662 for warfarin).

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Table 74 Summary of Adjudicated Deaths- overall study period

	Edoxaban 30mg (15mg Dos.Adj) (N=7002)	Edoxaban 60mg (30mg Dos.Adj) (N=7012)	Warfarin (N=7012)
Total	731 (10.4)	769 (11.0)	836 (11.9)
Primary Cause			
Cardiovascular	522 (7.5)	527 (7.5)	608 (8.7)
Sudden/Unwitnessed Death	229 (3.3)	246 (3.5)	269 (3.8)
Congestive Heart Failure/Cardiogenic Shock	117 (1.7)	129 (1.8)	142 (2.0)
Other Cardiovascular	48 (0.7)	45 (0.6)	50 (0.7)
Ischemic Stroke	55 (0.8)	43 (0.6)	47 (0.7)
Intracranial Hemorrhage	16 (0.2)	30 (0.4)	53 (0.8)
Dysrhythmia	20 (0.3)	16 (0.2)	15 (0.2)
Atherosclerotic Vascular Disease	11 (0.2)	5 (<0.1)	8 (0.1)
Directly Related to CABG or PCI	3 (<0.1)	5 (<0.1)	4 (<0.1)
Non-Intracranial Hemorrhage	9 (0.1)	5 (<0.1)	12 (0.2)
Pulmonary Embolism	9 (0.1)	3 (<0.1)	5 (<0.1)
Systemic Arterial Embolic Event	5 (<0.1)	0 (0.0)	3 (<0.1)
Malignancies	93 (1.3)	94 (1.3)	84 (1.2)
Lung	25 (0.4)	29 (0.4)	18 (0.3)
Pancreatic	13 (0.2)	14 (0.2)	5 (<0.1)
Non-CV/Non-Malignancy	116 (1.7)	148 (2.1)	144 (2.1)
Infection	69 (1.0)	94 (1.3)	92 (1.3)
Other Non-Cardiovascular/Non-Malignancy	30 (0.4)	36 (0.5)	30 (0.4)
Accidental/Trauma	5 (<0.1)	10 (0.1)	10 (0.1)
Renal	9 (0.1)	4 (<0.1)	8 (0.1)
Suicide	1 (<0.1)	3 (<0.1)	1 (<0.1)
Hepatobiliary	2 (<0.1)	1 (<0.1)	3 (<0.1)

Data source: The Applicant's CSR Table 12.18

Table 75 shows incidence of death using the MedDRA SMQs of interest. There was no imbalance among the treatment groups for most of conditions, including malignancies SMQ, acute renal failure SMQ and drug related hepatic disorders SMQ. The only notable imbalance is that 13 subjects died from interstitial lung disease (ILD) (SMQ) in the edoxaban groups compared with 0 in the warfarin group.

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Table 75 Summary of incidence of death by MedDRA SMQs during the overall study period

	Edoxaban 30mg N = 568	Edoxaban 60mg N = 632	Warfarin N = 662
Malignancies (SMQ)	89 (1.3%)	89 (1.3%)	87 (1.2%)
Acute central respiratory depression (SMQ)	52 (0.7%)	67 (1.0%)	60 (0.9%)
Interstitial lung disease (SMQ)	5 (0.1%)	8 (0.1%)	0 (0.0%)
Acute Renal Failure (SMQ)	13 (0.2%)	7 (0.1%)	12 (0.2%)
Drug related hepatic disorders - comprehensive search (SMQ)	9 (0.1%)	6 (0.1%)	11 (0.2%)
Hypersensitivity reactions*	48 (0.7%)	63 (0.9%)	60 (0.9%)
Torsade de pointes/QT prolongations (SMQ)	100 (1.4%)	105 (1.5%)	121 (1.7%)
Hemodynamic edema, effusions and fluid overload (SMQ)	7 (0.1%)	6 (0.1%)	3 (<0.1%)

Reviewer's analysis, Source: the Applicant's dataset: AEEV1, DM. Analyses were based on MedDRA broad SMQ.

*Hypersensitivity reactions include three SMQs: anaphylactic reaction, angioedema and severe cutaneous adverse reaction

The reviewers evaluated patient profile and narratives for the 13 fatal cases due to ILD (SMQ). We excluded seven cases from the 13 deaths, whose cause of death was considered to be due to other medical conditions instead of true ILD. Six deaths due to ILD included 5 in the edoxaban 60 mg group and 1 in the edoxaban 30mg group. The median age for the 6 death cases was 77 years (range 73-85 years). All were male and the majority (5/6) had former smoking history. Four out of the 6 death cases had reported ILD or pulmonary fibrosis at baseline.

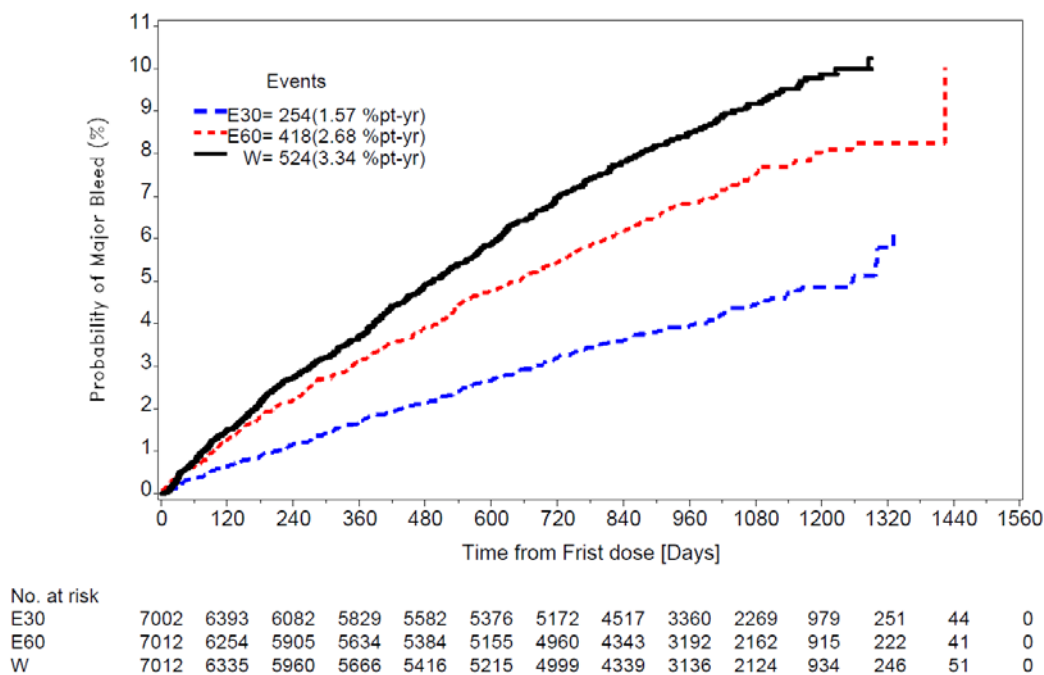
Reviewer's Comment: The imbalanced finding between edoxaban and warfarin in ILD-related death was still present after further evaluation of each individual fatal case. Higher frequency of ILD SAEs was also reported in the edoxaban groups compared with warfarin (See [Section 7.3.2.2](#)). There was no imbalance observed with regard to ILD-related conditions at baseline between edoxaban 60 mg and warfarin. Although the frequency of death due to ILD is very low, the consistently imbalanced findings among ILD-related SAEs and deaths are hard to ignore. We cannot rule out the possibility that edoxaban may induce ILD or worsen the disease among subjects with pre-existing ILD. The information about these imbalanced findings should be added to the label.

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Major Bleeding Events

The primary safety outcome for ENGAGE AF is adjudicated major bleeding events that occurred during the on-treatment period in the safety analysis set. Figure 20 shows the K-M estimate of time to the first adjudicated major bleeding event. The K-M curves show an early separation between two edoxaban groups and warfarin that appears to separate further throughout the study. Table 76 summarizes the event rates and hazard ratios (warfarin as the reference group) by main categories of major bleeding events. The event rate was lower in all categories of major bleeding for edoxaban 30 mg and was lower in all categories but gastrointestinal (GI) bleeding for edoxaban 60 mg compared with warfarin. Both edoxaban 30 mg and 60 mg groups were superior to warfarin in major bleeding, intracranial hemorrhage (ICH), fatal bleeding, GUSTO Severe and TIMI Major bleeding. On the contrary, edoxaban 60 mg significantly increased the risk of GI major bleeding compared with warfarin (HR: 1.24, 95% CI: 1.02-1.50). About 60% of these major GI bleeding occurred in the upper GI tract. The risk of GI major bleeding using GUSTO severe and TIMI major definitions (more serious GI bleeding) was similar between edoxaban 60 mg and warfarin. Figure 21 shows the K-M curves for GI major bleeding. The K-M curves seemed to diverge early after about 6 month of treatment and keep diverging throughout the study.

Figure 20 Time to First ISTH Major Bleeding event – on treatment, safety analysis set



Reviewer's Analysis, Source: the Applicant's dataset: BLDDATA, DM,

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Table 76 Adjudicated Major Bleeding Results[†]- on treatment, safety analysis set

Name	Edoxaban 30 mg N = 7002	Edoxaban 60 mg N = 7012	Warfarin N = 7012	Edoxaban 30mg vs. W		Edoxaban 60 mg vs. W	
	<i>n</i> (per 100 pt-year)	<i>n</i> (per 100 pt-year)	<i>n</i> (per 100 pt-year)	HR (95% CI)	<i>p</i> value	HR (95% CI) value	<i>p</i>
Major Bleeding	254 (1.57)	418 (2.68)	524 (3.34)	0.47 (0.41-0.55)	<.0001	0.80 (0.71-0.91)	0.0009
Gastrointestinal (GI)	129 (0.80)	232 (1.48)	190 (1.20)	0.67 (0.53-0.84)	0.0004	1.24 (1.02-1.50)	0.0309
-Upper GI	88 (0.54)	140 (0.89)	111 (0.70)	0.78 (0.59-1.03)	0.08	1.28 (0.99-1.64)	0.06
-Lower GI	44 (0.27)	96 (0.61)	81 (0.51)	0.54 (0.37-0.77)	0.0009	1.20 (0.89-1.61)	0.2301
Intracranial (ICH)	41 (0.25)	61 (0.38)	132 (0.82)	0.31 (0.22-0.43)	<.0001	0.47 (0.34-0.63)	<.0001
Non-ICH	213 (1.32)	359 (2.30)	396 (2.52)	0.52 (0.44-0.62)	<.0001	0.91 (0.79-1.05)	0.2177
Fatal Bleeding	20 (0.12)	32 (0.20)	59 (0.37)	0.33 (0.20-0.55)	<.0001	0.55 (0.36-0.84)	0.0061
-ICH	12 (0.07)	24 (0.15)	42 (0.26)	0.28 (0.15-0.53)	0.0001	0.58 (0.35-0.95)	0.0319
-Non ICH	8 (0.05)	8 (0.05)	17 (0.11)	0.46 (0.20-1.07)	0.0708	0.48 (0.21-1.10)	0.0822
GUSTO Severe	56 (0.34)	92 (0.58)	175 (1.09)	0.31 (0.23-0.42)	<.0001	0.53 (0.41-0.68)	<.0001
-Non ICH	15 (0.09)	31 (0.20)	44 (0.27)	0.34 (0.19-0.60)	0.0003	0.71(0.45-1.12)	0.1443
-GI	9 (0.06)	21 (0.13)	25 (0.16)	0.36 (0.17-0.76)	0.0077	0.85 (0.47-1.51)	0.58
TIMI Major	106 (0.65)	165 (1.04)	259 (1.63)	0.40 (0.32-0.50)	<.0001	0.64 (0.53-0.78)	<.0001
-Non ICH	65 (0.40)	104 (0.66)	127 (0.80)	0.50 (0.37-0.68)	<.0001	0.83 (0.64-1.07)	0.1475
-GI	47 (0.29)	80 (0.50)	83 (0.52)	0.56 (0.39-0.80)	0.0013	0.97 (0.71-1.32)	0.8520

[†]See [APPENDIX 7](#) for overview of all bleeding category definitions in ENGAGE AF

Reviewer's analysis, Source: Applicant's dataset: BLDDATA, BASEGRP and DM. First major bleeding event for each category was used. Subjects without a major bleeding event were censored at the earliest day of death, last dose +3 days, withdrawal of consent, or last known information about the event of interest.

Definition of GUSTO Severe Bleeds: ICH or bleeding resulting in hemodynamic compromise requiring treatment. Definition of TIMI Major Bleeds: ICH, or clinical overt bleeding with a ≥ 5 mg/dL fall in hemoglobin or a 15% fall in hematocrit.

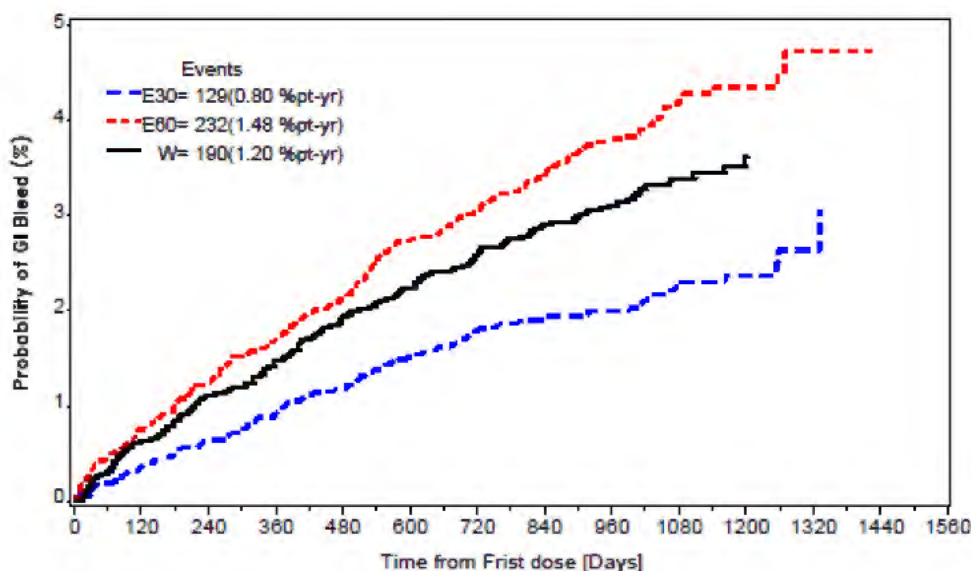
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Figure 21 Time to First GI Major Bleeding event – on treatment, safety analysis set



No. at risk															
E30	7002	6398	6097	5850	5608	5404	5201	4548	3383	2284	986	254	45	0	
E60	7012	6272	5938	5675	5431	5209	5021	4408	3241	2193	936	230	43	0	
W	7012	6355	6001	5723	5492	5297	5099	4442	3219	2182	958	255	54	0	

Reviewer's Analysis, Source: the Applicant's dataset: BLDDATA, DM

Considering that subjects might have multiple bleeds during the study, the reviewer also compared total number of major bleeding among the treatment groups (Table 77). The number of re-bleeds on treatment was similar between edoxaban 60 mg and warfarin. About 70% of re-bleeds in the edoxaban 60 mg group were GI bleeds.

Table 77 Total number of major bleeds-on treatment, safety analysis set

	Edoxaban 30 mg N = 7002	Edoxaban 60 mg N = 7012	Warfarin N = 7012
First Major Bleeding	254	418	524
Total Major Bleeding	265 (+11)*	451 (+33)	558 (+34)
First Non-ICH Bleeding	213	359	396
Total Non-ICH Bleeding	223 (+10)	390 (+31)	425 (+29)
First Major GI Bleeding	129	232	190
Total Major GI Bleeding	133 (+4)	255 (+23)	203 (+13)

For total bleed, if multiple major bleeds occurred in a day, only one bleed event was counted.

*(+n) = the difference between total bleeds compared to the first bleed

Reviewer's Analysis, Source: the Applicant's dataset: BLDDATA, DM

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The secondary safety endpoint is combination of major bleeds and clinically relevant non-major bleeds (CRNMB). Consistent with the findings for major bleeding events, both edoxaban groups had favorable outcomes with lower event rates for CRNMB alone or the combination of major bleeding events and CRNMB (Table 78). However, edoxaban 60 mg also had an increased risk of CRNMB in the GI tract compared with warfarin (HR: 1.65, 95% CI: 1.38-1.97). Moreover, the event rate of vaginal CRNMB was slightly higher in the edoxaban groups compared with warfarin (0.58 % per patient-year for both edoxaban groups and 0.44 % per year for the warfarin group).

Table 78 Adjudicated Major Bleeding and Clinically Relevant Non-Major Bleeding events† - on treatment, safety analysis set

Name	Edoxaban 30 mg N = 7002	Edoxaban 60 mg N = 7012	Warfarin N = 7012	Edoxaban 30mg vs. W		Edoxaban 60 mg vs. W	
	n (per 100 pt-year)	n (per 100 pt-year)	n (per 100 pt-year)	HR (95% CI)	p value	HR (95% CI)	p value
Major Bleeding + CRNMB	1161 (7.68)	1528 (10.64)	1761 (12.39)	0.62 (0.58-0.67)	<.0001	0.86 (0.80-0.92)	<.0001
-GI Bleeding	349 (2.19)	528 (3.43)	369 (2.36)	0.93 (0.80-1.10)	0.3341	1.46 (1.28-1.66)	<.0001
CRNMB	965 (6.34)	1210 (8.32)	1390 (9.65)	0.66 (0.61-0.71)	<.0001	0.86 (0.80-0.93)	0.0002
-GI Bleeding	231 (1.44)	326 (2.10)	201 (1.27)	1.13 (0.94-1.37)	0.1981	1.65 (1.38-1.97)	<.0001

†See [APPENDIX 7](#) for overview of all bleeding category definitions in ENGAGE AF

Reviewer's analysis, Source: Applicant's dataset: BLDDATA and BASEGRP. First bleeding event was used. Subjects without a bleeding event were censored at the earliest day of death, last dose +3 days, withdrawal of consent, or last known information about the event of interest.

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7.3.2.1.1 Major Bleeding without Hemorrhagic Stroke

Table 79 provides primary major bleeding results excluding hemorrhagic stroke (HS) to address the issue of double-counting HS in the primary safety endpoint as well as in the primary efficacy endpoint. Both edoxaban groups were still superior to warfarin in major bleeding, ICH, fatal bleeding, GUSTO Severe and TIMI Major bleeding.

Table 79 Major Bleeding Results without Hemorrhagic stroke- on treatment, safety analysis set

Name	Edoxaban 30 mg N = 7002 <i>n (per 100 pt-year)</i>	Edoxaban 60 mg N = 7012 <i>n (per 100 pt-year)</i>	Warfarin N = 7012 <i>n (per 100 pt-year)</i>	Edoxaban 30mg vs. W <i>HR (95% CI)</i>	Edoxaban 60 mg vs. W <i>HR (95% CI)</i>
Major Bleeding without HS	223 (1.38)	376 (2.41)	445 (2.84)	0.49 (0.42-0.57)	0.85 (0.74-0.98)
ICH without HS	10 (0.06)	17 (0.11)	51 (0.32)	0.19 (0.10-0.38)	0.34 (0.20-0.58)
Fatal without HS	10 (0.06)	8 (0.05)	28 (0.17)	0.35 (0.17-0.72)	0.29 (0.13-0.63)
-ICH	2 (0.01)	0	11 (0.07)	0.18 (0.04-0.80)	--
-Non ICH	8 (0.05)	8 (0.05)	17 (0.11)	0.46 (0.20-1.07)	0.48 (0.21-1.1)
GUSTO Severe without HS	25 (0.15)	48 (0.30)	94 (0.59)	0.26 (0.17-0.41)	0.52 (0.36-0.73)
TIMI Major without HS	75 (0.46)	121 (0.76)	178 (1.12)	0.41 (0.32-0.54)	0.69 (0.54-0.86)

Reviewer's analysis, Source: Applicant's dataset: BLDDATA, BASEGRP and DM. This analysis excluded MB due to hemorrhagic stroke (HS) which included both adjudicated HS and ischemic stroke with hemorrhagic conversion
 First major bleeding event for each category was used. Subjects without a major bleeding event were censored at the earliest day of death, last dose +3 days, withdrawal of consent, or last known information about the event of interest.

7.3.2.1.2 Major bleeding by level of INR control

To evaluate major bleeding results by level of INR control in warfarin, the reviewer conducted subgroup analyses by center-level time in therapeutic range (TTR) and time above therapeutic range (TATR). Table 80 shows the major bleeding events by center-level TTR. For all the INR quartiles, both edoxaban 60 mg and edoxaban 30 groups had lower major bleeding event rate compared with the warfarin group except for the highest quartile, where the result was numerically in favor of warfarin over the edoxaban 60 mg group (HR: 1.10, 95% CI: 0.9-1.4). It is noted that the event rate for the edoxaban 60 mg group was particularly high in the centers with the highest quartile of TTR. The centers with high TTR could represent good warfarin control as well as overall better quality of care. It is possible that the investigators/nurses in these centers more thoroughly and actively checked and reported potential bleeding events.

Table 80 Adjudicated Major Bleeds by Quartiles of Center Time in Therapeutic Range – on treatment, safety analysis set

Center TTR	Edoxaban 30 mg N = 7002		Edoxaban 60 mg N = 7012		Warfarin N = 7012		Edoxaban 30mg vs. W		Edoxaban 60 mg vs. W	
	<i>n (per 100 pt-year)</i>		<i>n (per 100 pt-year)</i>		<i>n (per 100 pt-year)</i>		<i>HR (95% CI)</i>		<i>HR (95% CI)</i>	
Q1: ≤59.8%	51 / 1700	1.34	92 / 1750	2.39	127 / 1722	3.63	0.37	(0.27, 0.51)	0.67	(0.51, 0.87)
Q2: >59.8%	57 / 1685	1.46	83 / 1664	2.23	114 / 1741	2.90	0.50	(0.36, 0.69)	0.76	(0.58, 1.01)
Q3: >66.3%	58 / 1681	1.47	86 / 1641	2.31	145 / 1780	3.53	0.42	(0.31, 0.57)	0.66	(0.51, 0.86)
Q4: >72.4%	72 / 1716	1.80	141 / 1739	3.68	138 / 1761	3.33	0.54	(0.41, 0.72)	1.10	(0.87, 1.39)

Reviewer's analysis, Source: the Applicant's dataset: DM, BLDDATA and ODFLGTTT. Time in therapeutic range (TTR) was averaged time in INR range of 2-3 for warfarin-treated subjects while on study drug excluding the first seven days of therapy. Center TTR was averaged TTR of warfarin-treated subject at each site.

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Table 81 shows the major bleeding results by TATR. One would expect that subjects treated with warfarin who spent more time above therapeutic range may bleed more. However, such relationship was not consistently observed here. It is likely that some risk factors for bleeding such as age could be related to how well warfarin was controlled thus confounded the observed relationship. The bottom line for these subgroup analyses was that we did not observe obvious deviation from the primary major bleeding result that could warrant our attention.

Table 81 Adjudicated Major Bleeds by Quartiles of Center Time above Therapeutic Range – on treatment, safety set

Center TATR	Edoxaban 30 mg N = 7002		Edoxaban 60 mg N = 7012		Warfarin N = 7012		Edoxaban 30mg vs. W		Edoxaban 60 mg vs. W	
	n (per 100 pt-year)		n (per 100 pt-year)		n (per 100 pt-year)		HR (95% CI)		HR (95% CI)	
Q1: ≤8.9%	62 / 1614	1.66	115 / 1734	2.98	128 / 1720	3.35	0.49	(0.36, 0.66)	0.89	(0.69, 1.14)
Q2: >8.9%	56 / 1676	1.44	97 / 1692	2.56	147 / 1780	3.63	0.40	(0.29, 0.54)	0.71	(0.55, 0.92)
Q3: >11.8%	52 / 1720	1.30	92 / 1735	2.36	115 / 1745	2.86	0.46	(0.33, 0.64)	0.83	(0.63, 1.09)
Q4: >14.7%	68 / 1772	1.68	98 / 1633	2.74	134 / 1759	3.54	0.47	(0.35, 0.63)	0.78	(0.60, 1.01)

Reviewer's analysis, Source: the Applicant's dataset: DM, BLDDATA and ODFLGTTT. Time above therapeutic range (TATR) was averaged time in INR range of > 3 for warfarin-treated subjects while on study drug excluding the first seven days of therapy. Center TATR was averaged TATR of warfarin-treated subject at each site.

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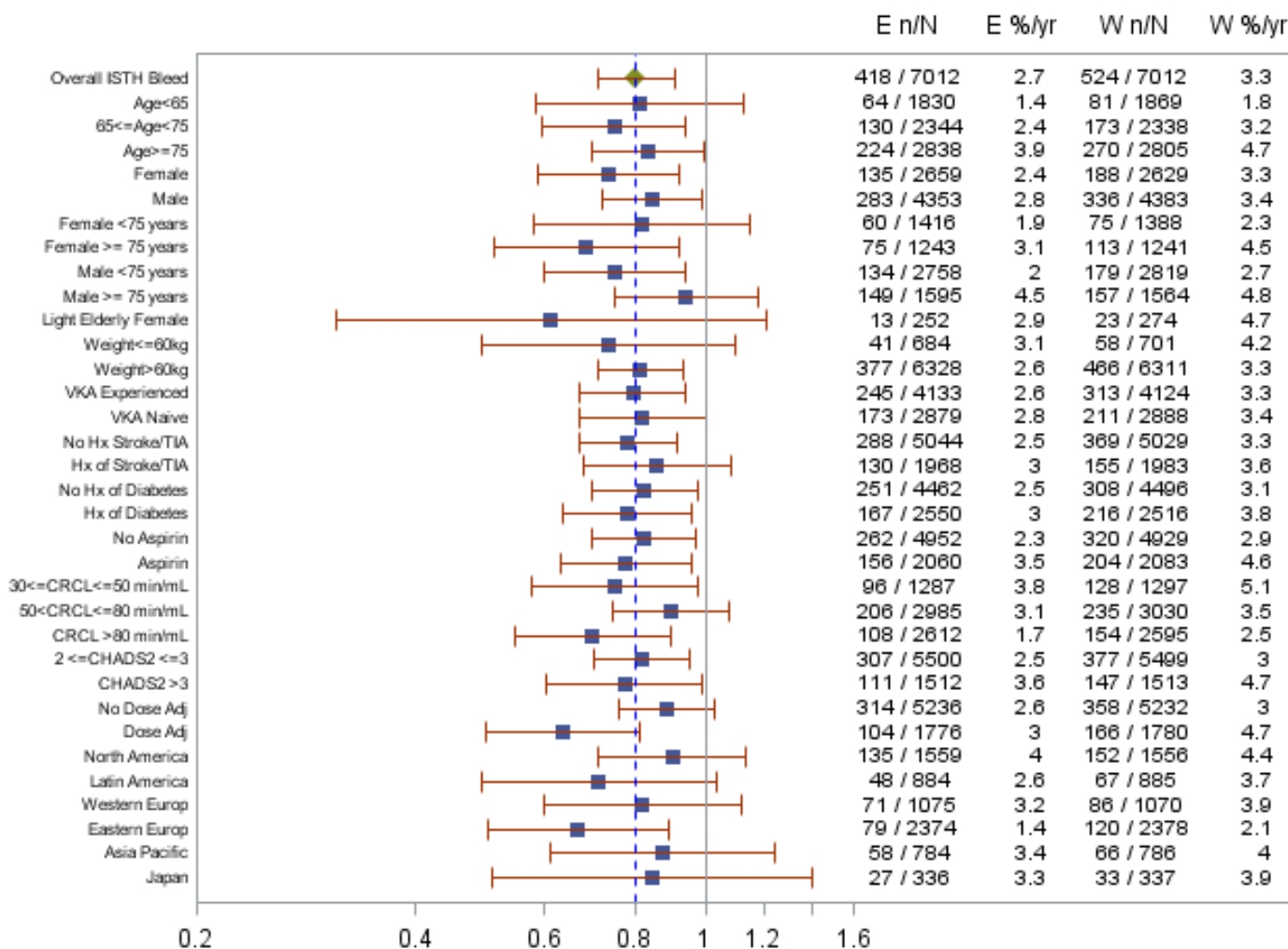
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7.3.2.1.3 Subgroup analysis –Demographics/Medical Conditions at Baseline

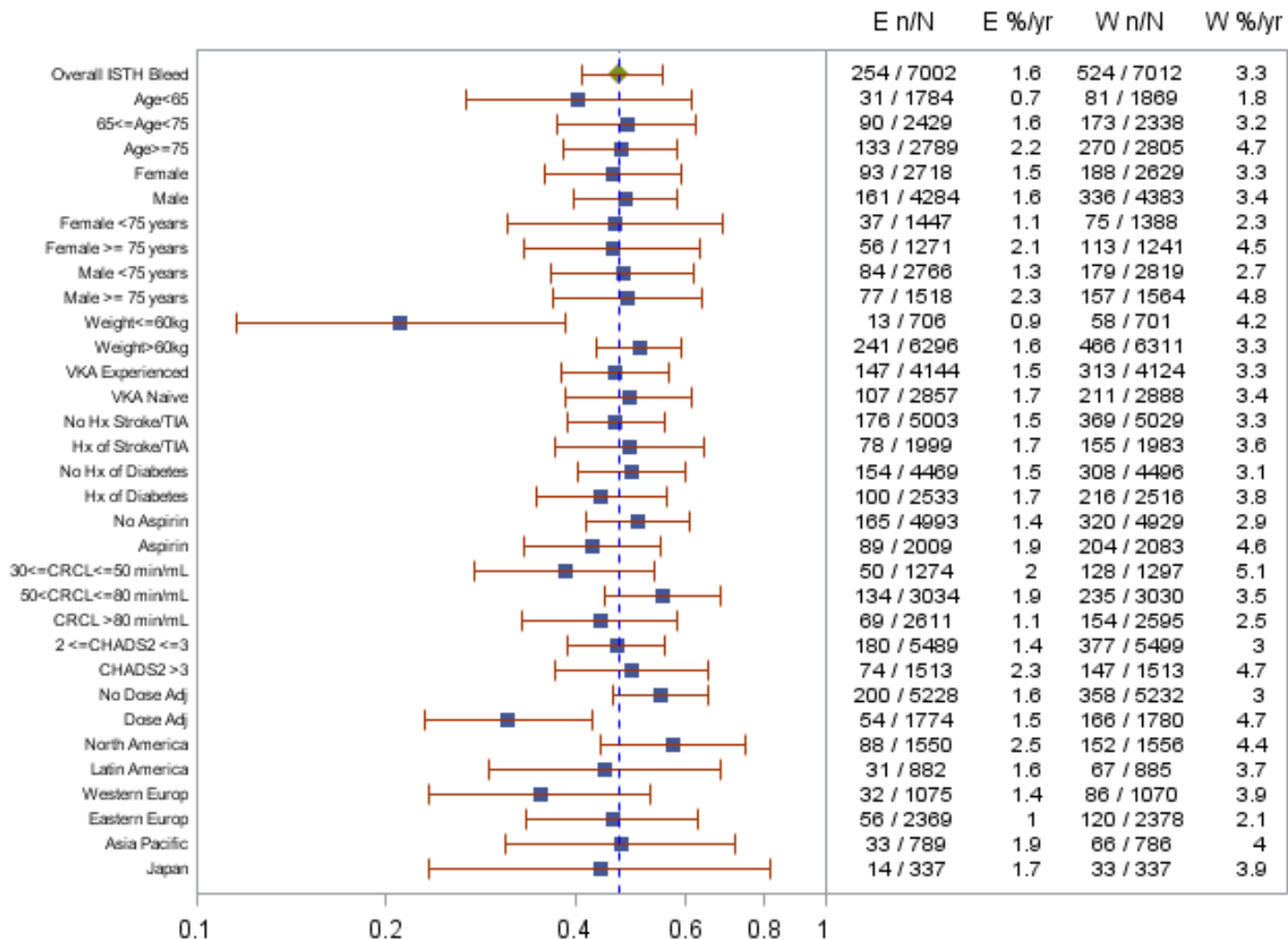
The major bleeding results were in general consistent across subgroups and regions with the point estimates favoring both edoxaban groups (Figure 22 and Figure 23). A few subgroups in the edoxaban arms had considerably less bleeding compared with warfarin including dose adjustment subgroups in both high and low edoxaban dose groups and the subgroup of subjects with weight ≤ 60 kg in edoxaban 30 mg. These results support the efficacy findings that the dose adjustment strategy might not be optimal and these patients were likely under-dosed. In addition, the HRs of major bleeding relative to warfarin were lower in subjects with $\text{CrCL} \geq 80$ mL/min (HR: 0.70, 95%CI: 0.55-0.89) compared to subjects with mild renal impairment ($\text{CrCL} > 50 - < 80$ mL/min) (HR: 0.90, 95% CI: 0.74-1.08). These results were in agreement with the observed lower exposure and poor efficacy in subjects with normal renal function.

Figure 22 Major Bleeding by Subgroups for Edoxaban 60 mg – on treatment, safety set



Reviewer's Analysis, Source: the Applicant's datasets: BLDDATA, DM and BASEGRP. X axis is in log scale *Light elderly female were female subjects with weight < 60 kg and age ≥ 75 year old.

Figure 23 Major Bleeding by Subgroups for Edoxaban 30 mg – on treatment, safety set



Reviewer's Analysis, Source: the Applicant's datasets: blddata, DM, basegrp. X axis is in log scale

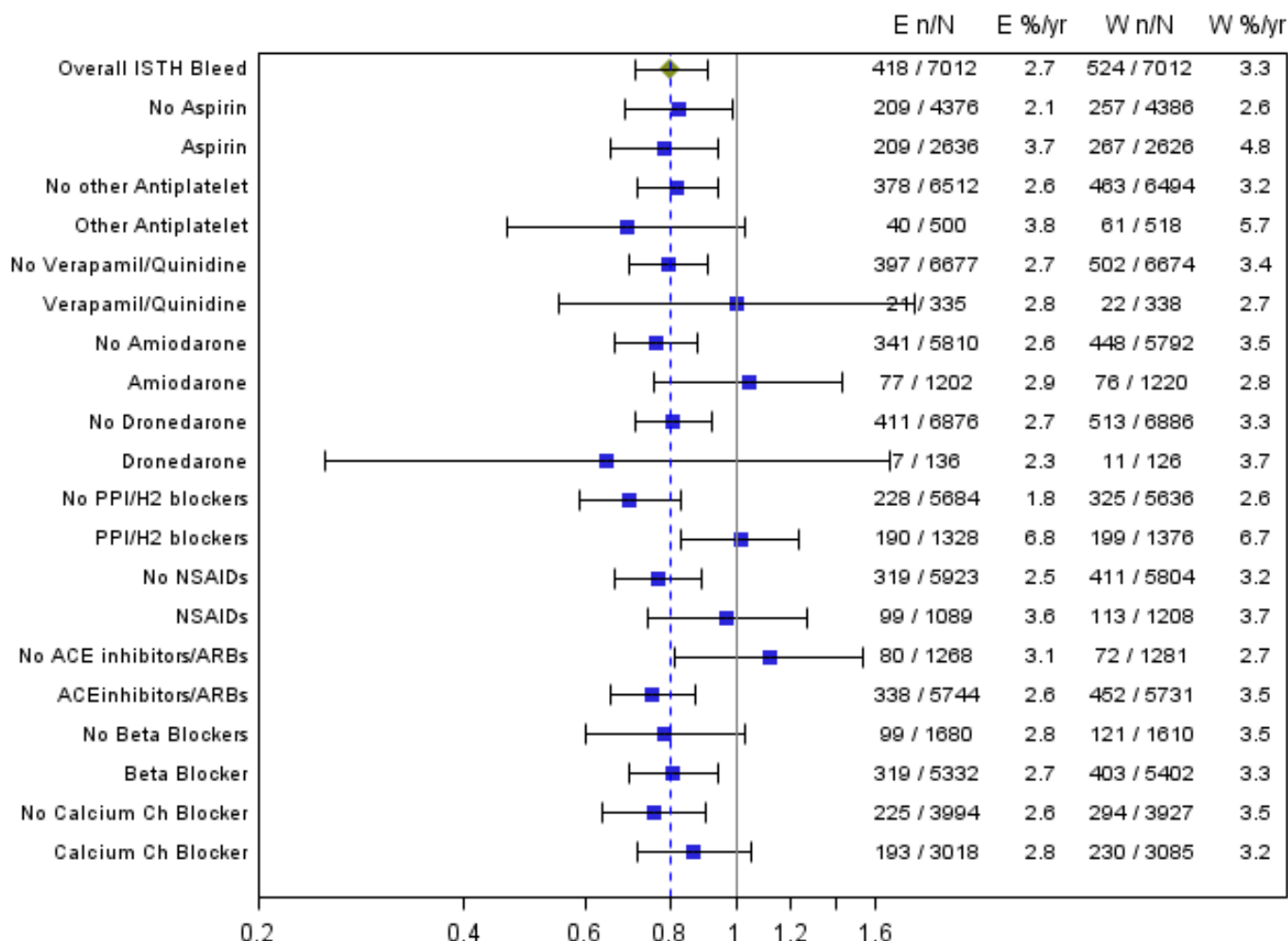
7.3.2.1.4 Subgroup analysis –Concomitant Medication

Figure 24 shows the major bleeding events by concomitant medication use during the study. Concomitant medication is defined as the medication taken at any time on or after the first dose through the last dose. Overall, the annual rate of major bleeding events in the edoxaban 60 mg group was either less or very similar to that in the warfarin group across all concomitant medication of interest.

Although concurrent use of aspirin or other antiplatelet drugs increased the risk of having major bleeding events, it did so in both groups. HR was less than 1 and consistent with the overall major bleeding results. Use of P-gp inhibitors such as dronedarone, quinidine or verapamil required dose adjustment in the trial. There were very few subjects who used these medications during the study. The major bleeding event rate was very similar among subjects who did or did not receive these drugs in the edoxaban 60 mg group. Concomitant use of amiodarone, a P-gp inhibitor was not dose adjusted during the study but did not seem to increase the bleeding risk in the edoxaban 60 mg group compared with warfarin.

It should be noted that the major bleeding event rates were very high among subjects receiving PPIs or histamine 2 (h2) blockers in both groups and the HR was higher in those taking these acid blocking drugs than in those not taking them. The observed pattern of the hazard ratios is the opposite of what one might expect because of the concern that antacid therapy might reduce the solubility and thus the absorption of edoxaban (see Table 6 and accompanying text for a discussion of the effect of pH on the solubility of edoxaban). These results were likely confounded given that use of PPI or h2 blockers was probably related to an individual's bleeding risk and likely followed a bleeding event. The reviewer conducted further analysis and defined concomitant use of PPIs or h2 blockers as medication taken prior to a major bleeding event. The major bleeding event rate was 3.73 %/patient-year (79/946) in the edoxaban 60 mg group comparing to 4.1 %/patient-year (91/969) in the warfarin group among subjects who received PPIs or h2 blocker. This event rate was more reasonable but probably still confounded by other major bleeding risk factors. For example, clinicians might be more likely to prescribe PPIs or h2 blockers to subjects who had higher bleeding risk. The bottom line is the use of PPI or h2 blocker seemed not affect the relative bleeding risk in the edoxaban 60 mg group compared with warfarin.

Figure 24 Forest Plot of Major Bleeding Events by Concomitant Medication Use for Edoxaban 60 mg vs. Warfarin



Reviewer's Analysis, The Applicant datasets: BLDDATA, POSTGRP, DM and CM. X-axis is in log scale
Concomitant medication is defined as the medication taken at any time on or after the first dose through the last dose.

7.3.2.1.5 Sensitivity analysis - Overdose/Dosing Error

The Applicant submitted the protocol amendment 4, dated 26 August 2012 to remove all mention of the 5 mg warfarin and placebo-to-match tablets to avoid warfarin dosing errors (see [Section 5.3.17](#)). An eCRF for warfarin dosing error was introduced after 4th Amendment and the investigators were asked to fill out the form retroactively for prior events since the start of the study. The Applicant stated that all sites had implemented the amendment by 01 December 2010.

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There were 205 subjects in the warfarin group with a VKA dose error, 25 subjects had a major bleeding event; 6 of these were ICH and 4 were fatal bleeding events (Table 82).

Table 82 Bleeding events associated with warfarin/placebo-to-match dosing error

	Edoxaban 30mg (15mg DosAdj) (N=7002)	Edoxaban 60mg (30mg DosAdj) (N=7012)	Warfarin (N=7012)
Subjects with At Least 1 VKA Overdose/Dose Error, M (%) [a]	105(1.5)	114(1.6)	205(2.9)
Any Confirmed Bleeding, m(%)	10(9.5)	9(7.9)	54(26.3)
Major, m (%)	1(1.0)	1(0.9)	25(12.2)
ICH, m (%)	0(0.0)	0(0.0)	6(2.9)
Fatal, m (%)	0(0.0)	0(0.0)	4(2.0)
Clinically Relevant Non-Major, m (%)	4(3.8)	7(6.1)	30(14.6)
Minor, m (%)	5(4.8)	1(0.9)	7(3.4)

Source: CSR Table 12.31

To evaluate the potential impact of dosing error on major bleeding results, the reviewer conducted a sensitivity analysis to evaluate the major bleeding event rate before and after the implementation of the protocol amendment 4 (Table 83). The bleeding event rates were notably higher in all treatment groups before Amendment 4, however, the major bleeding results before or after Amendment 4 were overall consistent with the primary major bleeding results. It is noted that the fatal bleeding rate in the edoxaban 60 mg group was more than doubled before 12/01/2010 compared with that after 12/01/2010. Further review did not reveal any significant reason associated with this finding. The study was fully enrolled by the cutoff date. It is known that bleeding is often higher early in treatment with an anticoagulant agent compared to later, which could likely account for the observed findings. .

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Table 83 Major Bleeding Events before and after implementation of the protocol amendment 4 (12/01/2010)

<i>Name</i>	<i>Edoxaban 30 mg N = 7002 n (per 100 pt-year)</i>	<i>Edoxaban 60 mg N = 7012 n (per 100 pt-year)</i>	<i>Warfarin N = 7012 n (per 100 pt-year)</i>	<i>Edoxaban 30mg vs. W HR (95% CI)</i>	<i>Edoxaban 60 mg vs. W HR (95% CI)</i>
<i>Before 12/01/2010*</i>					
Major Bleeding	74 (1.70)	146 (3.42)	179 (4.17)	0.41 (0.31-0.54)	0.82 (0.66-1.02)
GI	41 (0.94)	82 (1.91)	65 (1.51)	0.62 (0.42-0.92)	1.27 (0.92-1.76)
Intracranial (ICH)	9 (0.21)	20 (0.46)	43 (0.99)	0.21 (0.10-0.43)	0.47 (0.28-0.80)
Fatal Bleeding	5 (0.11)	14 (0.32)	20 (0.46)	0.25(0.09-0.66)	0.71 (0.36-1.40)
<i>On or After 12 /01/2010**</i>					
Major Bleeding	180 (1.14)	272 (1.79)	345 (2.25)	0.50 (0.42-0.60)	0.79 (0.68-0.93)
GI	88 (0.55)	150 (0.98)	125 (0.80)	0.69 (0.52-0.90)	1.22 (0.96-1.54)
Intracranial (ICH)	32 (0.20)	41 (0.26)	89 (0.57)	0.35 (0.23-0.53)	0.47 (0.32-0.67)
Fatal Bleeding	15 (0.09)	18 (0.12)	39 (0.25)	0.38 (0.21-0.68)	0.47 (0.27-0.81)

Reviewer's analysis, Source: the Applicant's datasets: Blddata, DM and Basegrp.

*Subjects with the first dose after 12/01/2010 were excluded in the analysis

** Subjects with the event or was censored before 12/01/2010 were excluded in the analysis

7.3.2.2 Other Non-major bleeding SAEs

The percentages of subjects in the edoxaban 30 mg, edoxaban 60 mg and the warfarin groups with non-bleeding SAEs were similar during the on-treatment (34.5% 33.0% and 35.9%) and overall study period (43.3%, 42.5% and 44.5%). The most common non-bleeding SAEs were CV diseases in all three treatment groups (~13%).

The reviewer evaluated incidence of SAEs during the on-treatment and overall study period by the MedDRA SOC and PT terms. For the most part, the frequency of SAEs and type of SAEs were similar between the edoxaban and warfarin groups with few exceptions. Table 84 lists the on-treatment SAEs by SOC and related PT terms with a notable difference among the treatment groups ($\geq 0.5\%$ more frequently in either edoxaban group compared to the warfarin group). The notable differences during the overall study period are listed in the [Appendix 11](#).

Subjects in the edoxaban 60 mg group had a higher incidence of anemia-related SAEs compared to the warfarin group (1.3% vs. 0.6%). There were two fatal cases and one hemolytic anemia case (with a resolved outcome) in the edoxaban 60 mg group. One fatal case died of lung neoplasm malignant and anemia, ongoing at the time of death, was considered to be secondary to the lung cancer. The cause of death for the other fatal case was not as clear. The anemia had been ongoing for most of the subject's study participation since about 2.5-months on edoxaban 60 mg. The subject was diagnosed with erosive gastritis and experienced a minor lower GI bleed about 3 months prior to the death. Two weeks before the death, the subject presented with palpitations, malaise, and pallor with dyspnea and anemia was reported to be of moderate severity. Anemia subsequently became severe and the subject was admitted to the hospital. Two days later, the subject died. No autopsy was performed. The cause of death, per the death certificate, was cardiopulmonary arrest with unsuccessful resuscitation, cardiogenic shock, heart failure, anemia and melena. Whether or not anemia was due to bleeding was not confirmed but cannot be ruled out.

It is not clear why higher frequency of anemia-related SAEs was reported in the edoxaban 60 mg group compared with the warfarin group. The Applicant asserted that the imbalance may be due to higher frequency of major or CRNM GI bleeding in the edoxaban 60 mg group compared with the warfarin group. However, the reviewer found that the imbalance in anemia-related SAEs was still present among subjects who never reported any bleeding event in the trial (Table 85). Although the frequency was very low, we cannot rule out the possibility that some subjects may experience severe anemia due to chronic clinically silent bleeds in the edoxaban groups.

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Table 84 Incidence of SAEs by SOC ($\geq 0.5\%$ more frequently in the edoxaban groups) and related PT terms during the on-treatment period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Subjects with at least one SAE	2418 (34.5%)	2315 (33.0%)	2516 (35.9%)
Blood And Lymphatic System Disorders	62 (0.9%)	94 (1.3%)	49 (0.7%)
Anemia	39 (0.6%)	49 (0.7%)	24 (0.3%)
Iron Deficiency Anemia	12 (0.2%)	24 (0.3%)	9 (0.1%)
Any Anemia-related PT*	57 (0.8%)	89 (1.3%)	40 (0.6%)

Reviewer's analysis. Applicant's dataset: AEEV1 and DM.

*Anemia-related PT include hematocrit abnormal, hematocrit decreased, hemoglobin decreased, red blood cell count decreased, and any PT term containing anemia

Table 85 Incidence of Anemia-related SAEs among subjects who did not report any bleed during the on-treatment period

	Edoxaban 30 mg N= 4468	Edoxaban 60 mg N = 4163	Warfarin N=3925
Any Anemia-related PT*	17 (0.4%)	29 (0.7%)	9 (0.2%)

Reviewer's analysis. Applicant's dataset: AEEV1 and DM

*Anemia-related PT include hematocrit abnormal, hematocrit decreased, hemoglobin decreased, red blood cell count decreased, and any PT term containing anemia

Considering the possibility that use of multiple of MedDRA PTs for identifying the same event might obscure a safety signal, the reviewer also checked higher level terms (HLT) for any pattern or imbalance in the reported SAEs. Overall, the three groups were very similar with regard to type and frequency of reported SAEs but a few respiratory-related HLTs disfavored the edoxaban groups, particularly the high dose group (Table 86). The frequency was low and could be a chance finding considering few respiratory-related HLTs were also reported more frequently in warfarin. However, these observations did raise a flag for further evaluation of safety of edoxaban in this area.

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Table 86 Incidence of SAEs by Pulmonary related HLTs during the on-treatment period

MedDRA SOC/HLT	Edoxaban 30mg (15mg DosAdj) N = 7002	Edoxaban 60mg (30mg DosAdj) N = 7012	Warfarin N = 7012
Respiratory, Thoracic and Mediastinal Disorders (SOC)	197 (2.8%)	199 (2.8%)	175 (2.5%)
Breathing Abnormalities	23 (0.3%)	27 (0.4%)	17 (0.2%)
Bronchial Conditions Nec	0 (0.0%)	2 (0.0%)	2 (0.0%)
Bronchospasm And Obstruction	102 (1.5%)	86 (1.2%)	83 (1.2%)
Conditions Associated With Abnormal Gas Exchange	1 (0.0%)	1 (0.0%)	2 (0.0%)
Coughing And Associated Symptoms	0 (0.0%)	1 (0.0%)	0 (0.0%)
Laryngeal And Adjacent Sites Disorders Nec (Excl Infections And Neoplasms)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Lower Respiratory Tract Inflammatory And Immunologic Conditions	11 (0.2%)	7 (0.1%)	10 (0.1%)
Lower Respiratory Tract Signs And Symptoms	1 (0.0%)	0 (0.0%)	0 (0.0%)
Nasal Disorders Nec	0 (0.0%)	0 (0.0%)	1 (0.0%)
Paranasal Sinus Disorders (Excl Infections And Neoplasms)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Parenchymal Lung Disorders Nec	12 (0.2%)	14 (0.2%)	4 (0.1%)
Pharyngeal Disorders (Excl Infections And Neoplasms)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Pleural Infections And Inflammations	0 (0.0%)	0 (0.0%)	2 (0.0%)
Pneumothorax And Pleural Effusions Nec	12 (0.2%)	9 (0.1%)	19 (0.3%)
Pulmonary Hypertensions	3 (0.0%)	3 (0.0%)	7 (0.1%)
Pulmonary edema	17 (0.2%)	18 (0.3%)	13 (0.2%)
Pulmonary Thrombotic And Embolic Conditions	10 (0.1%)	9 (0.1%)	7 (0.1%)
Respiratory Failures (Excl Neonatal)	16 (0.2%)	27 (0.4%)	18 (0.3%)
Respiratory Tract Disorders Nec	3 (0.0%)	4 (0.1%)	2 (0.0%)
Upper Respiratory Tract Signs And Symptoms	0 (0.0%)	0 (0.0%)	1 (0.0%)

Reviewer's Table, Source: the Applicant dataset: AEEV1 and DM

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To evaluate further any potential imbalance in SAEs among the treatment groups, the reviewer examined the MedDRA SMQs of interest and clinical event groups during the on-treatment (Table 87) and overall study period ([Appendix 11](#)). There was no clinically meaningful imbalance between the edoxaban and warfarin groups for the majority of SMQs of interest. Hematopoietic erythropenia (SMQ) SAEs, hypersensitivity reactions SAEs, acute central respiratory depression (SMQ) SAEs and the SMQ for interstitial lung disease (ILD) SAEs were reported more frequently in the edoxaban 60 mg group compared with the warfarin group.

The imbalanced finding of hematopoietic erythropenia (SMQ) was consistent with the findings of anemia SAEs. The reviewer evaluated reported MedDRA PTs for hypersensitivity reaction SAEs and found that the imbalance was due to slightly higher numbers of reported respiratory-related SAEs in the edoxaban 60 mg group (Table 88). This imbalance was also captured in acute central respiratory depress (SMQ) (Table 89). Of note, there were 3 cases of Stevens-Johnson syndrome in the edoxaban groups. Review of each individual case revealed that the primary trigger of Stevens-Johnson syndrome was likely due to other drugs such as penicillin and levofloxacin.

The reviewer has some concerns about the imbalanced data seen in ILD (SMQ) given that early this year PMDA requested an “important precaution” to be added to the Japanese prescribing information for rivaroxaban relating to the potential risk of ILD. This safety signal from the same class drug prompted our review on the cases with ILD (SMQ) SAEs. We evaluated the ILD status at baseline and found that there was a slightly higher percent of subjects in the edoxaban 30 mg group who reported ILD-related conditions at baseline; but no imbalance was found between the edoxaban 60 mg and warfarin groups (Table 90). We further reviewed patient profiles and narratives of individual cases with ILD SAEs. We excluded 28 out of 40 ILD cases who were likely not true ILD (e.g. respiratory distress syndrome due to other medical condition) or were confounded by amiodarone use. The final 12 cases with ILD SAE included 8 subjects in the edoxaban 60 mg group and 4 in the edoxaban 30 mg group. The median time for the onset of the event since treatment was about 292 days (range 59 to 744 days). Six cases reported having ILD-related conditions at baseline. The incidence of ILD SAE in the edoxaban groups was higher, about 5% (6/124), among subjects who reported prior history of ILD at baseline compared to those who did not (6/13890, 0.04%).

Reviewer’s Comment(s): The imbalanced findings in ILD SAEs between the edoxaban groups and the warfarin group were consistent with the finding for ILD-related deaths. It was challenging to identify ILD cases solely based on the narratives. However, it was clear that all the warfarin cases were due to other medical conditions (n= 6) or confounded by amiodarone use (n = 3). There were more cases in the edoxaban arms with complex clinical presentations or with insufficient information that require subjective judgments. In general, if the verbatim term for the SAE was ILD, pulmonary fibrosis or exacerbation of ILD/pulmonary fibrosis, the reviewer would count it as an ILD case unless there was a strong confounding factor(s) such as concurrent use of amiodarone.

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After reviewing the individual cases, 12 vs. 0 ILD SAEs were observed in the edoxaban groups compared with the warfarin group. Additionally, the incidence of ILD SAEs in the edoxaban groups was much higher among subjects with prior history of ILD.

Considering the findings in ENGAGE AF in light of the similar post-marketing findings seen in Japanese patients who received rivaroxaban, the potential that edoxaban could cause or exacerbate ILD among those with an existing condition cannot be ruled out. As discussed in [Section 7.3.1](#), the reviewer recommends adding these imbalanced findings to the label.

Table 87 Incidence of SAEs by SMQ of interest[†] during the on-treatment study period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Hematopoietic erythropenia (SMQ)	41 (0.6%)	54 (0.8%)	28 (0.4%)
Acute central respiratory depression (SMQ)	59 (0.8%)	79 (1.1%)	56 (0.8%)
Interstitial lung disease (SMQ)	14 (0.2%)	17 (0.2%)	9 (0.1%)
Acute Renal Failure (SMQ)	59 (0.8%)	59 (0.8%)	53 (0.8%)
Hypersensitivity reactions ^a	104 (1.5%)	119 (1.7%)	107 (1.5%)
Torsade de pointes/QT prolongations (SMQ)	151 (2.2%)	131 (1.9%)	164 (2.3%)
Hepatic Disorder			
Liver function test elevation PTs ^b	9 (0.1%)	21 (0.3%)	14 (0.2%)
Drug related hepatic disorders-comprehensive search (SMQ)	47 (0.7%)	48 (0.7%)	104 (1.5%)
Drug related hepatic disorders-comprehensive search (SMQ), excluding INR increased PT	41 (0.6%)	43 (0.6%)	44 (0.6%)
Drug related hepatic disorders-severe events only— (SMQ)	26 (0.4%)	22 (0.3%)	20 (0.3%)
Hepatitis, non-infectious (SMQ)	7 (0.1%)	7 (0.1%)	2 (0.0%)

Reviewer's Table. Applicant's dataset: AEEV1 & DM.

[†] SMQ broad terms were used for the analysis

^a. Hypersensitivity reactions include three SMQs: anaphylactic reaction, angioedema and severe cutaneous adverse reaction

^b. PTs include alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, blood bilirubin unconjugated increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, liver function test abnormal and transaminases increased.

Clinical Review
 Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
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Table 88 MedDRA Prefer Terms associated with Hypersensitivity Reaction SAEs

MedDRAM 14.1 SMQ	Prefer Term	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Hypersensitivity Reaction SAEs		104 (1.5%)	119 (1.7%)	107 (1.5%)
Anaphylactic reaction (SMQ)	Acute Respiratory Failure	9	11	10
	Anaphylactic Reaction	0	1	1
	Angioedema	0	2	0
	Asthma	15	11	17
	Blood Pressure Decreased	0	0	1
	Bronchospasm	2	1	1
	Cardiac Arrest	8	16	12
	Cardio-Respiratory Arrest	7	9	10
	Cardiovascular Insufficiency	2	1	3
	Chest Discomfort	4	2	4
	Choking	0	0	1
	Circulatory Collapse	1	1	1
	Cough	0	1	0
	Dyspnea	12 (0.17%)	16 (0.23%)	9 (0.13%)
	Hypotension	23	17	15
	Edema	0	1	0
	Rash	0	1	0
	Respiratory Arrest	0	1	0
	Respiratory Distress	3	3	2
	Respiratory Failure	8 (0.11%)	15 (0.21%)	8 (0.11%)
	Swelling Face	1	0	0
	Urticaria	0	0	2
Angioedema (SMQ)	Angioedema	0	2	0
	Choking	0	0	1
	Drug Hypersensitivity	1	3	2
	Generalized Edema	1	0	0
	Hypersensitivity	2	1	1
	Obstructive Airways Disorder	1	0	0
	Edema	0	1	0
	Edema Peripheral	2	3	5
	Scrotal Edema	1	0	0
	Swelling Face	1	0	0
	Urticaria	0	0	2
Severe cutaneous adverse reactions (SMQ)	Conjunctivitis	1	0	0
	Drug Eruption	2	1	3
	Drug Rash With Eosinophilia And Systemic	0	1	0
	Erythema Multiforme	0	1	0
	Skin Necrosis	0	1	1
	Stevens-Johnson Syndrome	2	1	0

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Table 89 MedDRA Prefer Terms for Acute central respiratory depress (SMQ) and Interstitial lung disease (SMQ) SAEs

MedDRAM 14.1 SMQ	Prefer Term	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Acute central respiratory depression (SMQ)	Acute Respiratory Distress Syndrome	1	1	1
	Acute Respiratory Failure	9	11	10
	Asphyxia	0	0	1
	Cardiac Arrest	8	16	12
	Cardiopulmonary Failure	5	2	1
	Cardio-Respiratory Arrest	7	9	10
	Dyspnea	12	16	9
	Hypercapnia	0	0	1
	Hypoxia	1	1	0
	Respiratory Arrest	0	1	0
	Respiratory Disorder	0	1	0
	Respiratory Distress	3	3	2
	Respiratory Failure	8	15	8
	Sleep Apnea Syndrome	6	5	2
Interstitial lung disease (SMQ)	Acute Respiratory Distress Syndrome	1	1	1
	Allergic Granulomatous Angiitis	0	0	1
	Alveolitis Allergic	1	0	0
	Bronchiolitis	0	1	1
	Interstitial Lung Disease	7	6	3
	Organizing Pneumonia	2	1	0
	Pneumonitis	2	2	1
	Pulmonary Fibrosis	3	4	1
	Pulmonary Granuloma	0	0	1
	Pulmonary Toxicity	0	2	0
	Radiation Pneumonitis	0	1	0

Reviewer's table, the Applicant's dataset: AEEV1 and

Table 90 Reported ILD status at Baseline*

	Edoxaban 30 mg N = 7002	Edoxaban 60 mg N = 7012	Warfarin N=7012
ILD-related Conditions	76 (1.1%)	66 (0.9%)	66 (0.9%)
Idiopathic Pulmonary Fibrosis	0	0	1 (0.0%)
Interstitial Lung Disease	13 (0.2%)	8 (0.1%)	10 (0.1%)
Pulmonary Fibrosis	65 (0.9%)	59 (0.8%)	56 (0.8%)

Reviewer's Table. Applicant's dataset: MH & DM.

*Pulmonary status was not systematically examined at baseline (i.e. no chest x-ray at baseline). The analyses were based on the reported medical history at baseline.

7.3.3 Dropouts and/or Discontinuations

In ENGAGE AF, subjects were allowed to have multiple interruptions and resumptions of study drug. A study drug interruption was defined as > 3 consecutive days during which the subject did not take study drug. Discontinuation of study drug was evaluated at the end of study based on those subjects who never resumed study drug after the last interruption. Subjects were identified as discontinuation of study drug if they were not on study drug within 30 days of the CSED visit (subjects with a CSED visit) or within 30 days of CSED announcements (subjects without a CSED visit). Data on study drug interruptions/discontinuation and the reasons for interruptions/discontinuation by treatment regimen are shown in Table 91 and Table 92.

Overall, a higher percentage of subjects discontinued study drug temporarily or permanently in dose-adjusted subset compared to no dose-adjusted subset in each of the three treatment groups. The proportion was similar among the three treatments.

There was no imbalance among treatment groups regarding the number of and reason for study drug interruptions. However, the duration of study drug interruptions was longer in both edoxaban groups compared with the warfarin group (Table 91).

The most common reason for discontinuation of study drug was AE or suspected endpoint event in all treatment groups. A slightly higher percent of subjects discontinued study drug due to cardiac ischemic events in the edoxaban 30 mg group (both dose-adjusted and no dose adjusted subsets) and edoxaban 60 mg dose adjusted subset compared with the warfarin group. Also, a higher percent of subjects discontinued study drug due to investigator's decision in the dose adjusted subset of the edoxaban groups compared to the dose adjusted subset of the warfarin group (Table 92). Time to study drug discontinuation was similar among the treatment groups (Figure 25).

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Table 91 Study Drug Interruption by Dose Regimen

	Edoxaban 30mg N = 7002		Edoxaban 60mg N = 7012		Warfarin N = 7012	
	Dose Adj (N = 1774)	No Dose Adj (N = 5228)	Dose Adj (N = 1776)	No Dose Adj (N = 5236)	Dose Adj (N = 1780)	No Dose Adj (N = 5232)
Subjects with at least one study drug interruption, n(%)	1228 (69.2)	3098 (59.3)	1257 (70.8)	3129 (59.8)	1325 (74.4)	3265 (62.4)
Number of Occurrences, n(%)						
≥ 2	482 (27.2)	1219 (23.3)	453 (25.5)	1248 (23.8)	544 (30.6)	1352 (25.8)
≥ 4	95 (5.4)	238 (4.6)	75 (4.2)	238 (4.5)	103 (5.8)	244 (4.7)
≥ 6	13 (<1)	59 (1.1)	14 (<1)	43 (<1)	29 (1.6)	47 (<1)
Median maximum days of interruptions (Days)	99	48	131	50	82	38
Median total days of interruptions (Days)	118	61.5	159	62	103	49
Reason for interruption, n(%)						
AE or Suspected Endpoint Event	689 (38.8)	1567 (30.0)	699 (39.4)	1628 (31.1)	823 (46.2)	1692 (32.3)
Death	75 (4.2)	127 (2.4)	62 (3.5)	142 (2.7)	67 (3.8)	156 (3.0)
Investigator Decision	472 (26.6)	1404 (26.9)	474 (26.7)	1351 (25.8)	485 (27.2)	1456 (27.8)
Subject Decision*	241 (13.6)	677 (12.9)	227 (12.8)	644 (12.3)	248 (13.9)	704 (13.5)
Subject Refused Routine Follow-up	50 (2.8)	106 (2.0)	62 (3.5)	137 (2.6)	58 (3.3)	138 (2.6)
Unknown	2 (<1)	3 (<1)	1 (<1)	3 (<1)	2 (<1)	2 (<1)

This table includes all the interruptions whether or not study drug was reassumed after the interruption.

Reviewer's Table. Applicant's datasets: DM and EX.

Table 12.3 in CSR did not include some patients who discontinued the study drug due to death, withdrawal of consent or unknown reason (The Applicant's response [seq0037] to IR dated on April 11, 2014)

*withdrawal of consent is included in subject decision

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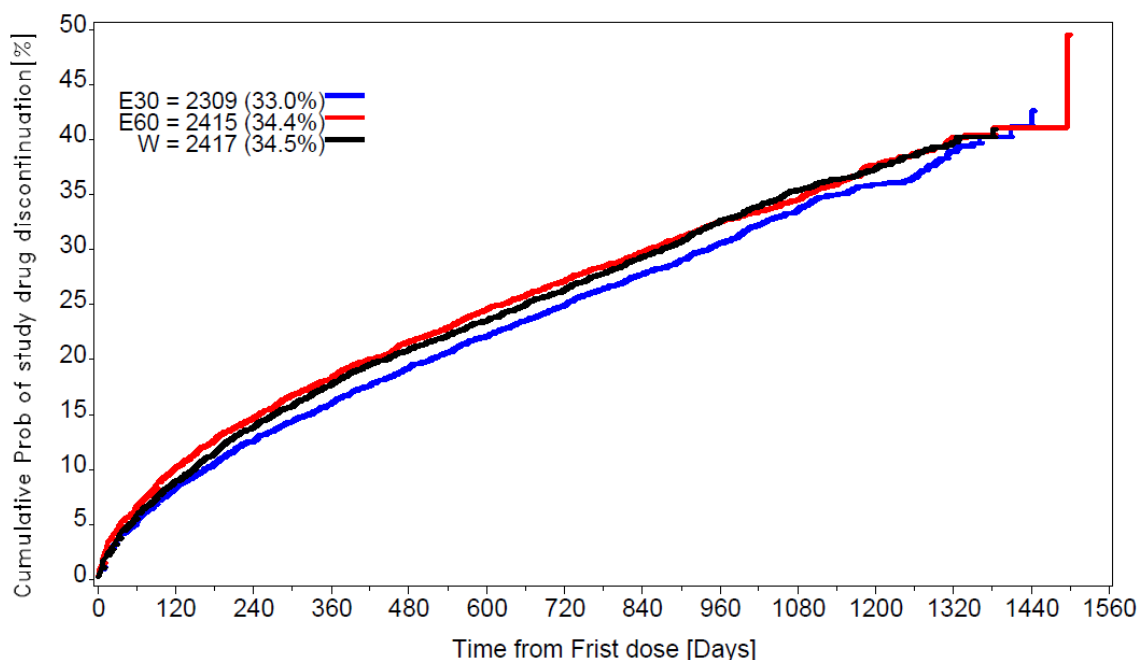
Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Table 92 Study Drug Discontinuation by Dose Regimen

	Edoxaban 30mg N = 7002		Edoxaban 60mg N = 7012		Warfarin N = 7012	
	Dose Adj (N = 1774)	No Dose Adj (N = 5228)	Dose Adj (N = 1776)	No Dose Adj (N = 5236)	Dose Adj (N = 1780)	No Dose Adj (N = 5232)
Subjects who discontinued study drug	774 (43.6)	1535 (29.4)	817 (46.0)	1598 (30.5)	837 (47.0)	1580 (30.2)
Reason for discontinuation, n(%)						
AE or Suspected Endpoint Event	396 (22.3)	697 (13.3)	426 (24.0)	778 (14.9)	476 (26.7)	692 (13.2)
1. Cerebrovascular Event	57 (3.2)	107 (2.0)	52 (2.9)	75 (1.4)	51 (2.9)	98 (1.9)
2. Systemic Embolic Event	3 (0.2)	10 (0.2)	1 (0.1)	5 (0.1)	3 (0.2)	2 (0.0)
3. Bleeding/Surgery	35 (2.0)	111 (2.1)	56 (3.2)	181 (3.5)	77 (4.3)	126 (2.4)
4. Cardiac Ischemic Event	9 (0.5)	44 (0.8)	11 (0.6)	29 (0.6)	6 (0.3)	33 (0.6)
5. Hepatic Event	11 (0.6)	23 (0.4)	12 (0.7)	26 (0.5)	12 (0.7)	25 (0.5)
6. Bone Fracture	15 (0.8)	17 (0.3)	9 (0.5)	12 (0.2)	20 (1.1)	18 (0.3)
7. Malignancy Event	20 (1.1)	54 (1.0)	15 (0.8)	62 (1.2)	21 (1.2)	55 (1.1)
8. Other AE or SAE	246 (13.9)	331 (6.3)	270 (15.2)	388 (7.4)	285 (16.0)	334 (6.4)
Death	72 (4.1)	122 (2.3)	60 (3.4)	137 (2.6)	65 (3.7)	149 (2.8)
Investigator Decision	120 (6.8)	229 (4.4)	127 (7.2)	190 (3.6)	96 (5.4)	222 (4.2)
Subject Decision	139 (7.8)	401 (7.7)	148 (8.3)	375 (7.2)	144 (8.1)	408 (7.8)
Subject Refused Routine Follow-up	45 (2.5)	83 (1.6)	55 (3.1)	114 (2.2)	54 (3.0)	107 (2.0)
Unknown	2 (<1)	3 (<1)	1 (<1)	3 (<1)	2 (<1)	2 (<1)

Reviewer's Table. Applicant's datasets: DM, EX.

Figure 25 Kaplan-Meier Estimate of time to study drug discontinuation



No. at risk														
E30	7002	6403	6110	5872	5644	5446	5251	4528	3400	2099	940	256	32	0
E60	7012	6293	5974	5721	5491	5285	5101	4427	3294	2018	909	236	39	0
W	7012	6380	6030	5758	5540	5358	5160	4443	3250	2017	921	256	42	0

Reviewer's analysis, Source: Applicant dataset: DM

Reviewer's Comment(s): In general, the three treatments groups (both dose and non-dose adjustment subsets) had very similar patterns in terms of dropouts and discontinuation. The observed differences are small and should not significantly impact the study findings.

7.3.4 Significant Adverse Events

The Applicant discussed hepatic abnormalities, malignancy, bone fracture and anemia as adverse events of interest in the CSR. Hepatic abnormalities and malignancies are reviewed in [Section 7.3.5.1](#) and [Section 7.3.5.2](#). Anemia is reviewed in [Section 7.4.1](#). There is no imbalance observed for the frequency and type of bone fracture among the treatment groups. The percentage of new bone fractures was similar in the edoxaban 30 mg, edoxaban 60 mg and warfarin groups (6.3%, 5.7% and 6.4%, respectively)

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Hepatic abnormalities

7.3.5.1.1 Hepatic Laboratory Data

Pre-defined liver laboratory abnormalities and hepatic cases of special interest (SAEs, or AEs leading to study drug interruption/discontinuation) were independently reviewed by two CEC hepatic specialists for adjudication. Table 93 summarizes liver enzyme and bilirubin abnormalities during the study period (on treatment + 30 days). The percentage of subjects in the edoxaban 30 mg, edoxaban 60 mg and warfarin groups with ALT or AST $\geq 3 \times$ ULN was similar (2.5%, 2.6% and 2.5 %, respectively). However, it is noted that the edoxaban 60 mg had more cases with extremely high liver enzyme values compared to the warfarin group. The number of subjects with ALT or AST $\geq 3 \times$ ULN and beyond was consistently higher in the edoxaban 60 mg group compared with the warfarin group. The number of subjects with combination abnormality seems similar among the treatment groups.

Figure 26 shows the potential Hy's law cases using the combination abnormality for liver enzyme and total bilirubin (TBL). All these 51 potential Hy's law cases were adjudicated by the hepatic specialists in the study. The reviewers reviewed the patient profile for each case, including reported AE/SAE, laboratory data, and concomitant medicines. The majority of cases had clear alternative reasons for elevated transaminases or bilirubin. There were a few cases in the edoxaban groups who presented with complex clinical manifestations and the reviewers were not certain about the adjudication results. In combination with the findings from the adjudication results (3 adjudicated Hy's law cases in the edoxaban groups, see [Section 7.3.5.1.2](#)), the reviewers were not totally comfortable about the observed liver data and decided to request an OSE liver consultation. Please see a brief summary of the consultation result in [Section 7.3.5.1.3](#)

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Table 93 Liver Enzyme and Bilirubin Abnormalities – On Treatment Period + 30 days[†]

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Subject with ALT	M = 6917	M = 6915	M = 6938
≥ 2 x ULN	343 (5.0%)	342 (4.9%)	324 (4.7%)
≥ 3 x ULN	145 (2.1%)	137 (2.0%)	132 9 (1.9%)
≥ 5 x ULN	49 (0.7%)	62 (0.9%)	47 (0.7%)
≥ 8 x ULN	21 (0.3%)	30 (0.4%)	18 (0.3%)
≥ 10 x ULN	14 (0.2%)	23 (0.3%)	13 (0.2%)
≥ 20 x ULN	5 (0.1%)	9 (0.1%)	2 (<0.1%)
Subject with ALT or AST	M = 6917	M = 6915	M = 6938
≥ 2 x ULN	419 (6.1%)	436 (6.3%)	411 (5.9%)
≥ 3 x ULN	176 (2.5%)	181 (2.6%)	171 (2.5%)
≥ 5 x ULN	64 (0.9%)	76 (1.1%)	67 (1.0%)
≥ 8 x ULN	29 (0.4%)	38 (0.5%)	28 (0.4%)
≥ 10 x ULN	20 (0.3%)	28 (0.4%)	17 (0.2%)
≥ 20 x ULN	9 (0.1%)	9 (0.1%)	3 (<0.1%)
Subjects with Total Bilirubin	M = 6927	M = 6914	M = 6940
≥ 1.5 x ULN	472 (6.8%)	487 (7.0%)	462 (6.7%)
≥ 2 x ULN	167 (2.4%)	179 (2.6%)	174 (2.5%)
Combination abnormality	M = 6925	M = 6914	M = 6938
ALT or AST > 3 x ULN and concurrent TB > 2 x ULN and ALP < 2 x ULN*	17 (0.2%)	17 (0.2%)	17 (0.2%)

[†]Percentage was calculated based on number of subject (M) who had at least one liver measurement

*Concurrent defined as TBL and ALP within 30 days after the ALT or AST. All lab measurements during on-treatment + 30 days were included. Reviewer's Table. The Applicant's dataset: LB & DM

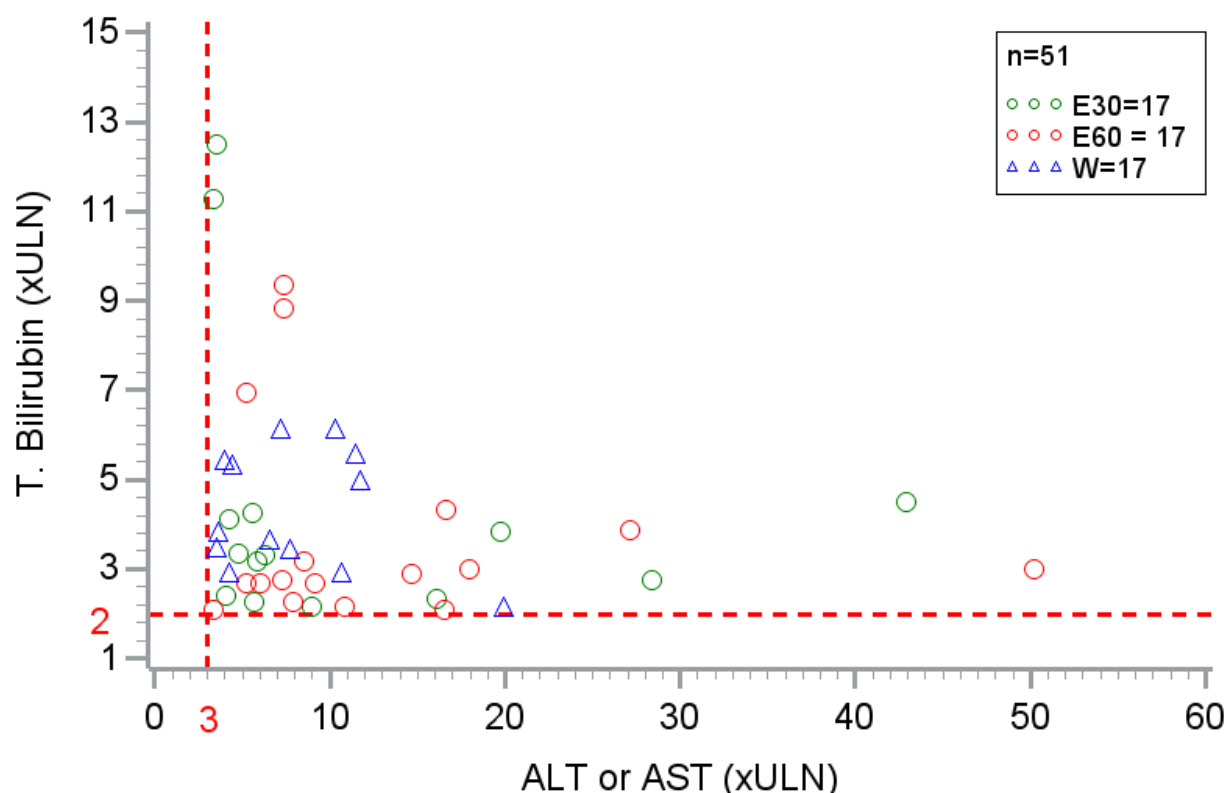
Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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Figure 26 Potential Hy's law subjects based on liver chemistries (Max ALT or AST > 3 x ULN concurrent TBL > 2xULN & AP <2xULN)



Reviewer's analysis. Source: Applicant's dataset: Ibliv. "Concurrent" defined as TB and ALP within 30 days after the ALT or AST. When ALT or AST were greater than 3 x ULN with "concurrent" total bilirubin > 2xULN and ALP < 2x ULN, the ALT or AST with associated TB were plotted. All lab values within 30 days after the last study drug were used for the safety analysis set.

Reviewer's Comment(s): There were different criteria for combination liver abnormality. The reviewer used more "specific" criteria (Max ALT or AST > 3 x ULN concurrent TBL > 2xULN & AP <2xULN) and found no imbalance regarding number of potential Hy's law cases based on liver chemistries.

The reviewer also evaluated the time course of liver abnormalities in each treatment group. The rate of cases with abnormal transaminases was low and very similar among the treatment groups (Figure 27). As for TBL, edoxaban groups had a markedly higher percent of subjects with TBL ≥ 1.5 x ULN compared with the warfarin group at month one after study drug exposure, though the difference diminished over time and was less apparent using the criteria of TBL ≥ 2 x ULN (Figure 28). Overall, there were no clinically meaningful differences among the treatment groups with regard to incidence of liver abnormalities.

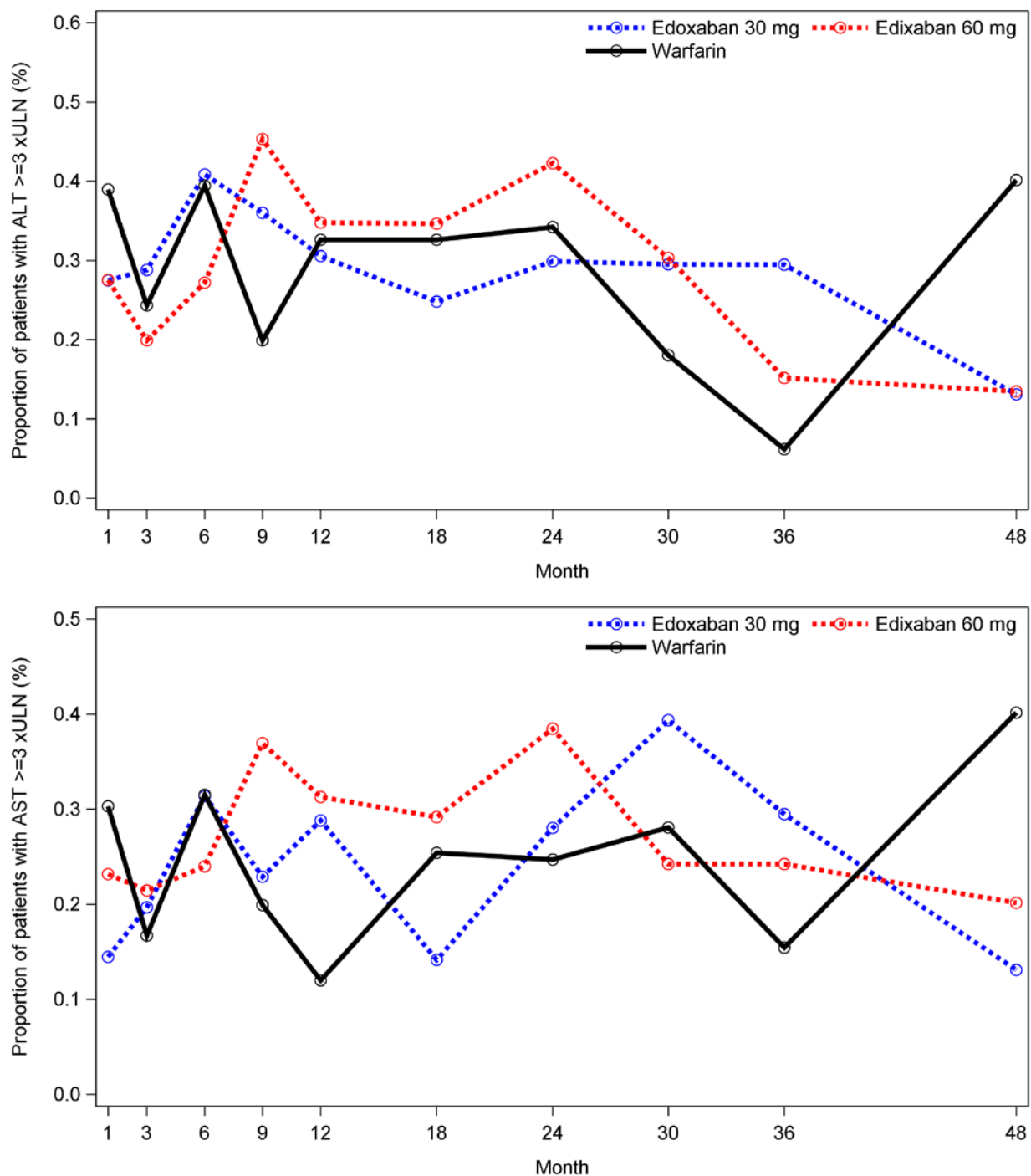
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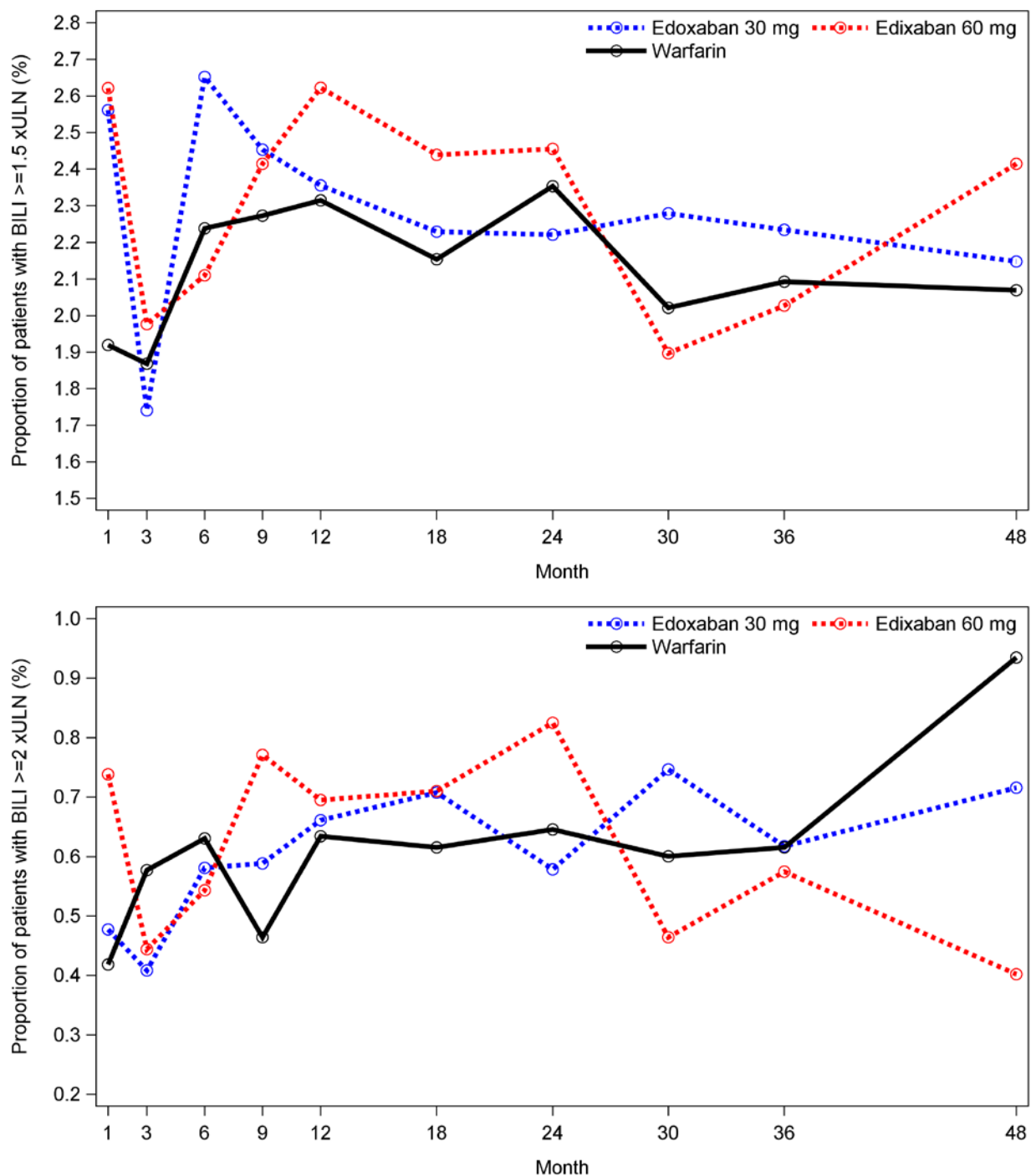
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Figure 27 Percentage of patients with liver enzyme abnormalities across the study period



Reviewer's Figure, the Applicant's dataset: LB & DM. All the liver measurements during on treatment + 30 days were included in the analyses.

Figure 28 Percentage of patients with Total Bilirubin abnormalities



Reviewer's Figure, the Applicant's dataset: LB & DM. All the liver measurements during on treatment + 30 days were included in the analyses.

Clinical Review

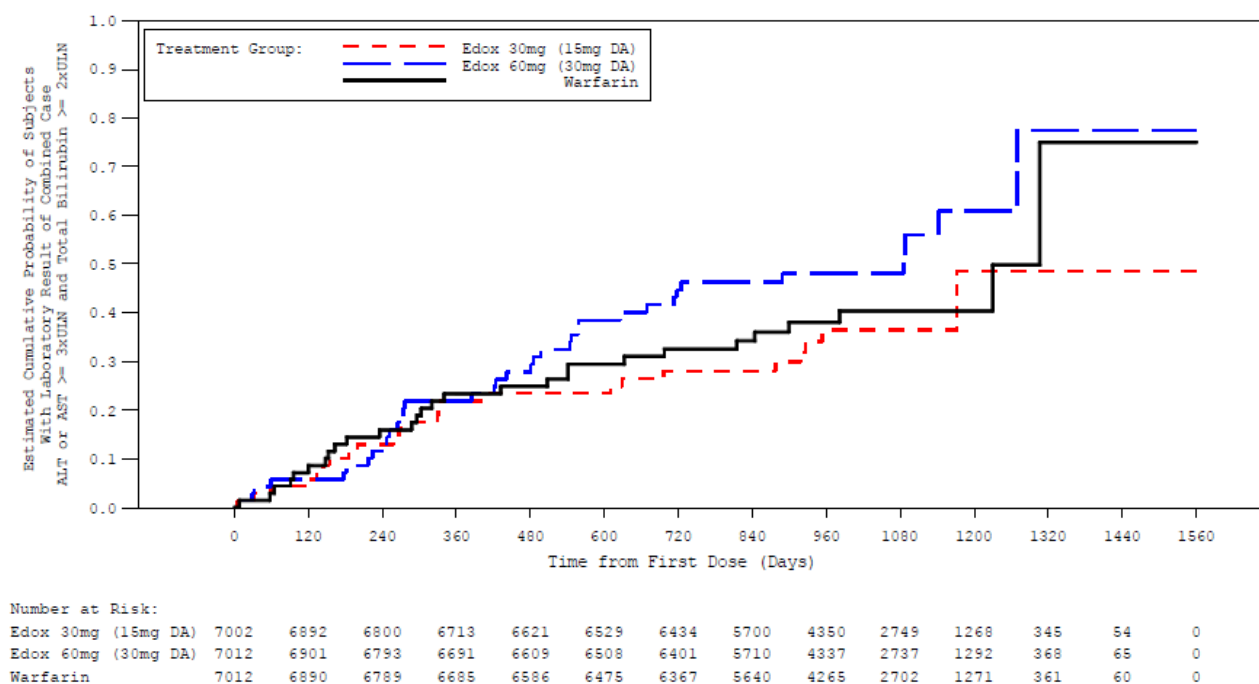
Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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Figure 29 shows the KM curves of time to the first laboratory result of combined ALT or AST $\geq 3 \times \text{ULN}$ and concurrent TBL $\geq 2 \times \text{ULN}$ during the overall study period. The KM curves were very similar for the first 14 months and started separating after that with slightly more subjects in the edoxaban 60mg group having combination liver abnormality.

Figure 29 The KM plot for time to first combination abnormality (ALT or AST $\geq 3 \times \text{ULN}$ and TB $\geq 2 \times \text{ULN}$) during the overall study period



Source: the Applicant's CSR Figure 14.3.1.154

Reviewer's Comment(s): Slightly higher numbers of subjects in the edoxaban 60 mg group compared with warfarin ($n = 22$ vs. 15) had liver combination abnormality defined using more "sensitive" criteria such as Max ALT or AST $\geq 3 \times \text{ULN}$ concurrent with TBL $\geq 2 \times \text{ULN}$.

It is possible that subjects discontinued the study when their transaminases or TBL started going up but not yet reached the Hy's Law criteria for abnormalities. Therefore, the reviewer evaluated liver enzyme and TBL among subjects who permanently discontinued the study to check if there is any imbalance among the treatment groups (Table 94). In general, the percentage of subjects who discontinued and who had liver abnormalities was similar among the treatment groups. There was a slightly higher percentage of subjects in the edoxaban groups, particularly in the edoxaban 30 mg group, compared with the warfarin group with ALT $\geq 1.5 \times \text{ULN}$ before study drug discontinuation.

Table 94 Liver Enzyme and Bilirubin Abnormalities among subjects with permanent discontinuation – On Treatment Period + 30 days[†]

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Subject with ALT	M=2234	M=2318	M=2343
≥ 1.5xULN	224 (10.0%)	222 (9.6%)	213 (9.1%)
≥ 2 x ULN	111 (5.0%)	122 (5.3%)	113 (4.8%)
≥ 3 x ULN	59 (2.6%)	63 (2.7%)	56 (2.4%)
Subject with ALT or AST	M=2235	M=2318	M=2343
≥ 1.5 x ULN	278 (12.4%)	277 (12.0%)	281 (12.0%)
≥ 2 x ULN	142 (6.4%)	159 (6.9%)	151 (6.4%)
≥ 3 x ULN	70 (3.1%)	82 (3.5%)	74 (3.2%)
Subjects with Total Bilirubin	M=2234	M=2317	M=2345
≥ 1.5 x ULN	157 (7%)	169(7.3%)	171(7.3%)
≥ 2 x ULN	56 (2.5%)	65 (2.8%)	73 (3.1%)

[†]Percentage was calculated based on number of subject (M) who had at least one liver measurement of interest . Reviewer's Table, the Applicant's dataset: LB & DM

7.3.5.1.2 Cases Evaluated and Adjudicated by Hepatic Specialists

Table 95 summarizes the results of adjudication performed by the hepatic specialists in ENGAGE AF. The incidence across the types of liver injury was similar among the treatment groups. For the hepatocellular injury events, a slightly higher percent of cases in the edoxaban 60 mg group compared with the warfarin group were adjudicated as possibly related to the study drug and as a severe event. There were 3 adjudicated Hy's law cases, 2 in the edoxaban 60 mg group and 1 in the edoxaban 30 mg group. The adjudication criteria for Hy's law case was liver abnormality of ALT ≥ 3 x ULN and simultaneous TLB ≥ 2 x ULN. Alternative causes (e.g., biliary obstruction) must be excluded to satisfy Hy's law rule.

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Table 95 Hepatic events adjudicated by hepatic specialists – on treatment period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Subjects with Events set for adjudication	146 (2.1%)	145(2.1%)	144 (2.1%)
Number of adjudicated events	170 (2.4%)	163 (2.3%)	164 (2.3%)
Nature of Liver Injury for all events			
Hepatocellular Injury	73 (1.0%)	84 (1.2%)	83 (1.2%)
Mixed Hepatocellular/Cholestasis	19 (0.3%)	16 (0.2%)	21 (0.3%)
Cholestasis	10 (0.1%)	4 (<0.1%)	6 (<0.1%)
Other	47 (0.7%)	41 (0.6%)	37 (0.5%)
Unable to assess due to insufficient data	0	0	0
No liver injury	8 (0.1%)	5 (0.1%)	7(0.1%)
Causal Relationship to Study Drugs of All Hepatocellular Injury Events			
Probably/Possible	11 (0.2%)	23 (0.3%)	12(0.2%)
Unlikely/Unrelated	65 (0.9%)	65 (0.9%)	75 (1.1%)
Severity of All Hepatocellular Injury Events			
Severe Liver Injury	9 (0.1%)	16 (0.2%)	10 (0.1%)
Hy's Rule Satisfied	1 (<0.1)	2 (<0.1)	0 (0.0)
Moderate Liver Injury	11 (0.2%)	9 (0.1%)	12 (0.2%)
Mild Liver Injury	50 (0.7%)	59 (0.8%)	58 (0.8%)
Minimal Liver Injury	4 (0.1%)	1 (<0.1%)	3 (<0.1%)
Unable To Assess Due To Insufficient Data	0 (0.0%)	0 (0.0%)	1 (<0.1%)

Reviewer's analysis, the Applicant's dataset: Hadjinv, DM

Reviewer's Comment(s): The liver laboratory data and the adjudication results of hepatic cases in the trial revealed a slightly worse profile for the edoxaban 60 mg group compared with the warfarin group. Although the imbalance was small, the reviewer requested an OSE liver consultation for a comprehensive review on the liver data in both ENGAGE AF and Hokusai VTE (see [Section 7.3.5.1.3](#))

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

7.3.5.1.3 OSE Liver Consultation

The DCRP requested a liver consultation through OSE dated May 2014 after preliminary review of the liver data in ENGAGE AF. Dr. Senior reviewed data related to liver toxicity in both ENGAGE AF and HOKUSAI VTE trials. He used the eDISH program to review all the cases with both ALT/AST and TBL elevations above 3 x ULN and 2 x ULN (17 cases in HOKUSAI- VTE and 84 cases in ENGAGE AF). The time course of all liver tests (ALT, TBL, AST and ALP) plus a narrative describing all pertinent clinical factors observed and recorded were inspected (see OSE consult review for detail dated September 26, 2014).

Figure 30 showed the eDISH graphs for ENGAGE AF, illustrating the peak observed ALT on the x-axis and TBL concentration on the y-axis for all the randomized subjects and cases in the upper-right quadrant. After thorough review of individual cases in the upper-right quadrant, Dr. Senior did not identify a clear-cut case of edoxaban-induced serious³⁰ and probably³¹ drug-caused hepatocellular jaundice in ENGAGE AF (see [Appendix 12](#) for review of each individual case), as well as HOKUSAI- VTE. As mentioned in [Section 7.3.5.1.2](#), the hepatic adjudication revealed 3 Hy's law cases. However, Dr. Senior did not think those cases met the criteria for serious/probable Hy's law case. Overall, the liver safety profile for edoxaban is consistent with findings for the previously approved drugs in the class.

Dr. Senior pointed out that there was a fairly high incidence of liver test abnormalities, higher and more than seen with most drugs (e.g. ALT or AST > 20x ULN) in ENGAGE AF as well as in other NOACs trials. He believed that this high proportion of liver dysfunction or elevations of ALT and AST seen in ENGAGE AF was secondary to cardiac disease and the diagnosis of "cardiac hepatopathy"³² was overlooked in this AF population. Figure 31 shows an example of the effect of acute heart failure and shock on liver tests illustrated by an extremely sharp rise in serum aminotransferases, AST earlier, faster, and higher than ALT, and very rapid decline of AST and ALT more slowly, with little change in TBL and none in ALP. Dr. Senior stated that there were probably many patients who drifted in and out of mild to moderate heart failure in this study of elderly patients with chronic AF. He stressed the importance of distinguishing cases with "cardiac hepatopathy" from liver disease in order to provide correct management of the care because liver dysfunction could rapidly improve with the proper treatment of heart failure in those cases.

³⁰ Dr. Senior defined serious as liver functional disorder sufficient to disable the patient so he/she can't work, or require hospital care, liver failure with secondary renal or brain dysfunction, death due to liver failure or need for liver transplantation

³¹ Dr. Senior defined probable as more likely than all other possible causes combined, roughly in the range of >50 to 75% likely

³² Dr. Senior used the term "cardiac hepatopathy" to represent hepatic effects and complications caused by vascular shock including terms such as "nutmeg liver", "ischemic hepatitis", "hypoxic hepatitis" and "hypoxic hepatopathy"

Clinical Review

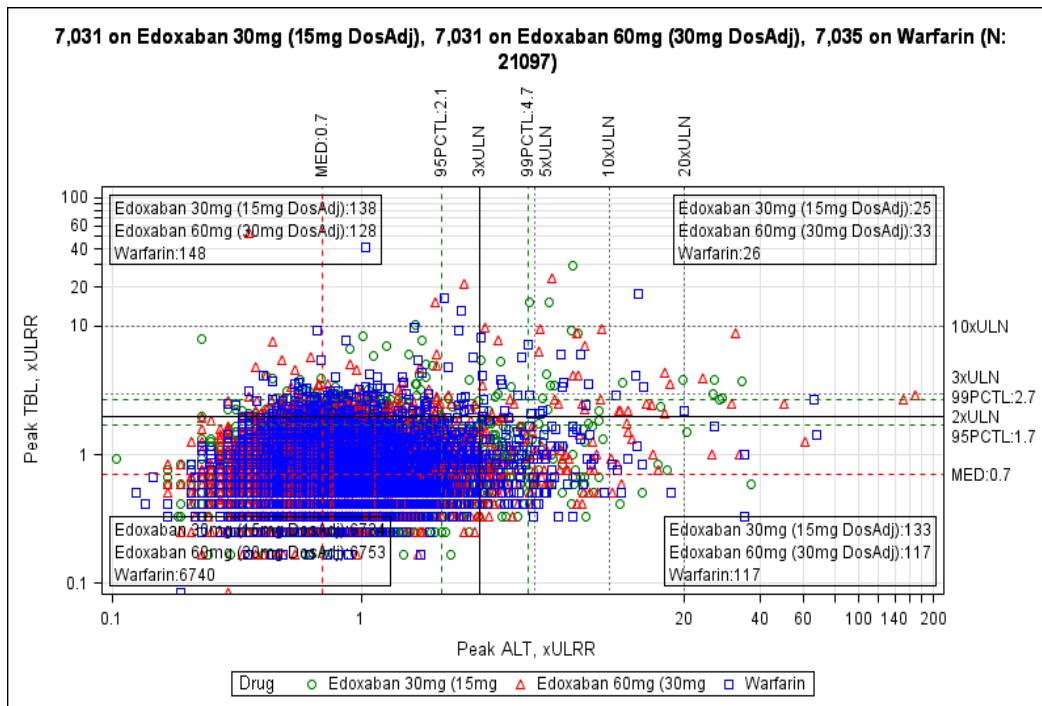
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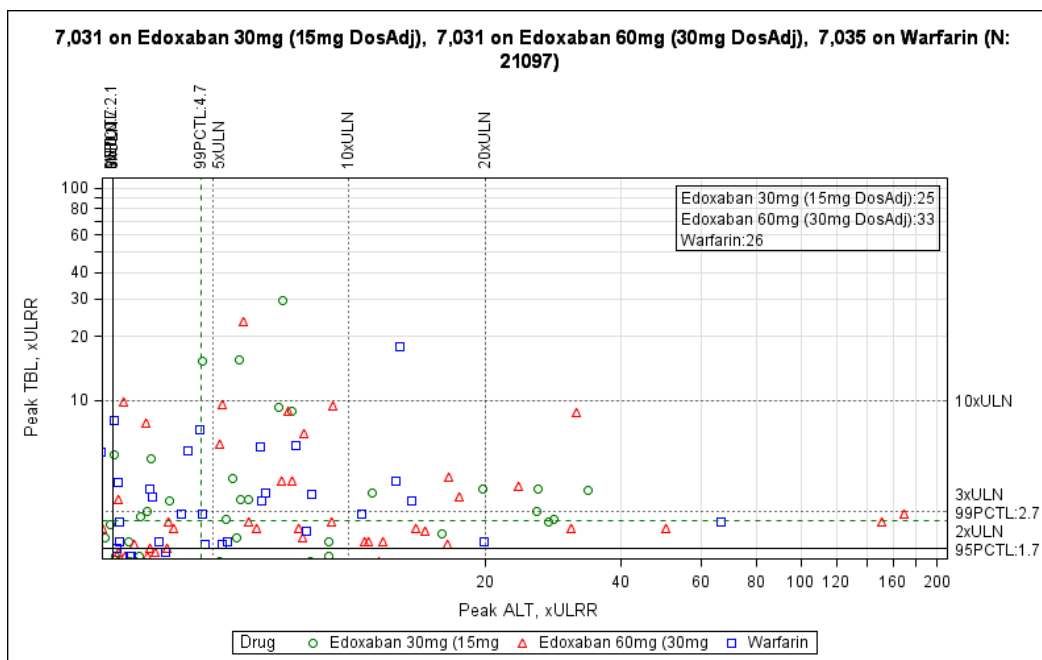
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Figure 30 Liver serum chemistries plot: (a) Peak ALT vs. Peak TBL for all randomized subjects (b) Cases in the upper- right quadrant (Max ALT > 3xULN vs. Max TBL > 2xULN)

(a)



(b)



Source: OSE Hepatology Consultation

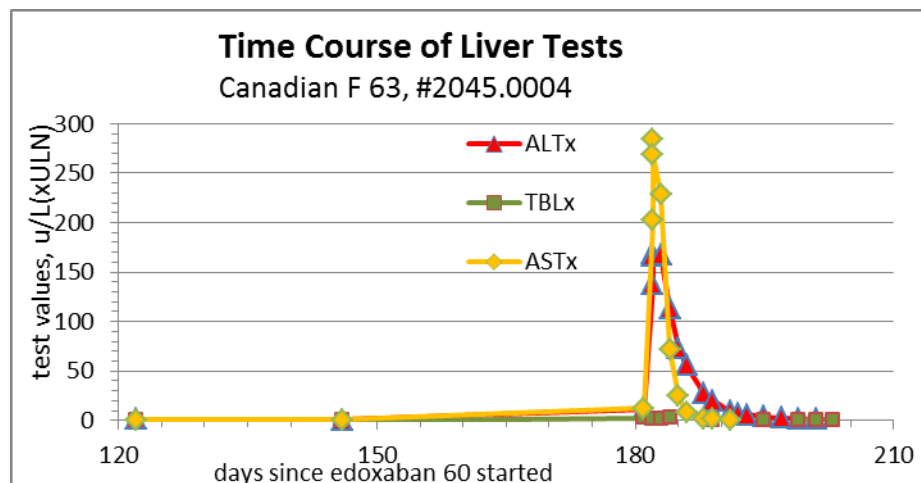
Clinical Review

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Figure 31 A classic picture of cardiac hepatopathy in ENGAGE AF-TIMI48



Source: OSE Hepatology Consultation

Reviewer's Comment(s): The current available data show that edoxaban is unlikely to cause drug-induced liver injury and suggest that edoxaban is not different from warfarin and other approved NOACs with regard to liver toxicity. The fairly frequent elevation of liver transaminases is likely to be associated with an underlying cardiac condition in AF population.

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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7.3.5.2 Malignancy

The incidence of investigator reported clinically evident post randomization malignancies was similar among the edoxaban 30 mg, edoxaban 60mg and warfarin groups (2.5%, 2.7% and 2.6%) (Table 96).

Table 96 Investigator Reported Clinically Evident Post Randomization Malignancies by Location, overall study period

Malignancies Category/Location	Edoxaban 30mg (15mg DosAdj) (N=7002)		Edoxaban 60mg (30mg DosAdj) (N=7012)		Warfarin (N=7012)	
	n	Event Rate (%/yr)	n	Event Rate (%/yr)	n	Event Rate (%/yr)
Any Location	463	2.50	494	2.68	485	2.64
Skin[a]	150	0.80	178	0.95	163	0.87
Small or Large Bowel	51	0.27	52	0.27	60	0.32
Lung	44	0.23	50	0.26	40	0.21
Prostate	48	0.41	48	0.41	53	0.45
Bladder	29	0.15	32	0.17	29	0.15
Breast	21	0.11	25	0.13	27	0.14
Stomach	15	0.08	19	0.10	20	0.11
Other	23	0.12	17	0.09	17	0.09
Pancreatic	16	0.08	16	0.08	10	0.05
Esophageal	13	0.07	14	0.07	4	0.02
Multiple	3	0.02	13	0.07	11	0.06
Liver, Gall Bladder, or Bile Ducts	18	0.09	10	0.05	17	0.09
Lymphoma	6	0.03	10	0.05	8	0.04
Lip, Oral, Pharynx	15	0.08	9	0.05	9	0.05
Uterine	7	0.09	8	0.11	6	0.08
Leukemia	12	0.06	6	0.03	13	0.07
Renal	8	0.04	6	0.03	12	0.06
Thyroid	1	0.01	6	0.03	2	0.01
Brain	6	0.03	5	0.03	8	0.04
Genital	3	0.02	3	0.02	8	0.04
Other Respiratory (Excluding Lung)	1	0.01	2	0.01	1	0.01
Unspecified	8	0.04	2	0.01	4	0.02

Source: CSR Table 12.25

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Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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This reviewer evaluated MedDRA SMQs related to malignancy and did not find any meaningful imbalance among the treatment groups except premalignant disorder SMQ. Most premalignant disorders occurred in the GI tract and the edoxaban 60 mg group had a higher percent of subjects compared with the warfarin group with AEs or SAEs in the GI premalignant disorders SMQ (Table 97).

Pre-clinical carcinogenic studies showed no evidence of increased neoplasia in the animals treated with edoxaban. The observed imbalance in premalignant disorder SMQ might have resulted from the higher rate of GI bleeding events in the edoxaban 60 mg group and a consequent higher rate of diagnostic workup of the GI tract in that treatment arm. The investigator reported GI bleeds were higher in the edoxaban 60 mg group compared with the warfarin group (0.64 vs. 0.47 % per patient-years, respectively).

Table 97 Summary of Premalignant disorder (SMQ) by Treatment group and AE/SAE

SMQ Category	Edoxaban 30mg N = 7002		Edoxaban 60mg N = 7012		Warfarin N = 7012	
	AE	SAE	AE	SAE	AE	SAE
Premalignant disorders (SMQ)	254 (3.6%)	29 (0.4%)	277 (4.0%)	46 (0.7%)	229 (3.3%)	16 (0.2%)
Blood premalignant disorders (SMQ)	7 (0.1%)	3 (<0.1%)	11 (0.2%)	7 (0.1%)	4 (0.1%)	1 (<0.1%)
Gastrointestinal premalignant disorders (SMQ)	169 (2.4%)	26 (0.4%)	212 (3.0%)	37 (0.5%)	170 (2.4%)	13 (0.2%)
Premalignant disorders, general conditions and other site specific disorders (SMQ)	1 (<0.1%)	0	1 (<0.1%)	0	2 (<0.1%)	0
Reproductive premalignant disorders (SMQ)	5 (0.1%)	0	6 (0.1%)	1 (<0.1%)	4 (0.1%)	2 (<0.1%)
Skin premalignant disorders (SMQ)	78 (1.1%)	1 (<0.1%)	54 (0.8%)	1 (<0.1%)	57 (0.8%)	0

Reviewer's Table. The Applicant's datasets: AEEV1 & DM

Clinical Review
Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
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7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The percentage of subjects among the treatment groups that reported non-bleeding AEs was similar during the on-treatment period (Table 98).

Table 98 Overview of AEs in ENGAGE AF

	Edoxaban 30mg (15mg DosAdj) (N=7002) n (%)	Edoxaban 60mg (30mg DosAdj) (N=7012) n (%)	Warfarin (N=7012) n (%)
On-Treatment Period			
Subjects With Non-Bleeding TEAEs[a]			
All	5868 (83.8)	5866 (83.7)	5867 (83.7)
Drug-Related	703 (10.0)	773 (11.0)	856 (12.2)
Severe	1270 (18.1)	1201 (17.1)	1280 (18.3)
With Fatal Outcome	274 (3.9)	284 (4.1)	316 (4.5)
Subjects With Non-Bleeding TESAEs			
All	2418 (34.5)	2315 (33.0)	2516 (35.9)
Drug-Related	66 (0.9)	74 (1.1)	116 (1.7)
Subjects With Non-Bleeding TEAEs that Caused Temporary Study Drug Interruption[b]			
All	2271 (32.4)	2235 (31.9)	2480 (35.4)
Drug-Related	246 (3.5)	281 (4.0)	374 (5.3)
TESAEs	1279 (18.3)	1268 (18.1)	1413 (20.2)
Subjects With Non-Bleeding TEAEs that Caused Study Drug Discontinuation[c]			
All	709 (10.1)	784 (11.2)	768 (11.0)
Drug-Related	132 (1.9)	166 (2.4)	141 (2.0)
TESAEs	377 (5.4)	417 (5.9)	420 (6.0)
Overall Study Period			
Subjects With Non-Bleeding TEAEs[a]			
All	6045 (86.3)	6092 (86.9)	6065 (86.5)
Drug-Related	714 (10.2)	782 (11.2)	869 (12.4)
Severe	1676 (23.9)	1662 (23.7)	1749 (24.9)
With Fatal Outcome	568 (8.1)	632 (9.0)	662 (9.4)
Subjects With Non-Bleeding TESAEs			
All	3031 (43.3)	2979 (42.5)	3118 (44.5)
Drug-Related	72 (1.0)	80 (1.1)	125 (1.8)

Source: The Applicant's CSR Table 12.15

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

The most frequently reported (at least 5% of subjects from each treatment group) non-bleeding AEs is summarized in Table 99. For the most part, the frequency of AEs was similar among the treatment groups except anemia, which was reported more frequently in the edoxaban 60 mg group than in the warfarin group.

Table 99 The most frequent reported AEs[†] by SOC and PT-on treatment

SOC/Preferred Term	Edoxaban 30mg (15mg DosAdj) (N=7002) n (%)	Edoxaban 60mg (30mg DosAdj) (N=7012) n (%)	Warfarin (N=7012) n (%)
Infections And Infestations	3129 (44.7)	3126 (44.6)	3142 (44.8)
Urinary Tract Infection	698 (10.0)	688 (9.8)	703 (10.0)
Nasopharyngitis	645 (9.2)	620 (8.8)	620 (8.8)
Bronchitis	584 (8.3)	567 (8.1)	572 (8.2)
Upper Respiratory Tract Infection	443 (6.3)	411 (5.9)	445 (6.3)
Blood And Lymphatic System Disorders	486 (6.9)	632 (9.0)	475 (6.8)
Anaemia	261 (3.7)	368 (5.2)	242 (3.5)
Nervous System Disorders	1484 (21.2)	1454 (20.7)	1481 (21.1)
Dizziness	537 (7.7)	514 (7.3)	592 (8.4)
Headache	356 (5.1)	334 (4.8)	336 (4.8)
Cardiac Disorders	1759 (25.1)	1711 (24.4)	1784 (25.4)
Atrial Fibrillation	528 (7.5)	474 (6.8)	491 (7.0)
Cardiac Failure	373 (5.3)	425 (6.1)	448 (6.4)
Vascular Disorders	990 (14.1)	985 (14.0)	992 (14.1)
Hypertension	475 (6.8)	481 (6.9)	438 (6.2)
Respiratory, Thoracic And Mediastinal Disorders	1370 (19.6)	1382 (19.7)	1395 (19.9)
Dyspnoea	434 (6.2)	456 (6.5)	470 (6.7)
Cough	416 (5.9)	383 (5.5)	365 (5.2)
Gastrointestinal Disorders	1934 (27.6)	2005 (28.6)	1947 (27.8)
Diarrhoea	486 (6.9)	482 (6.9)	499 (7.1)
Musculoskeletal And Connective Tissue Disorders	1826 (26.1)	1790 (25.5)	1843 (26.3)
Back Pain	496 (7.1)	476 (6.8)	478 (6.8)
Arthralgia	417 (6.0)	385 (5.5)	386 (5.5)
General Disorders And Administration Site Conditions	1490 (21.3)	1476 (21.0)	1589 (22.7)
Oedema Peripheral	578 (8.3)	577 (8.2)	675 (9.6)
Injury, Poisoning And Procedural Complications	1259 (18.0)	1216 (17.3)	1410 (20.1)
Fall	452 (6.5)	453 (6.5)	565 (8.1)

Source: The Applicant's CSR Table 12.16

[†] AEs other than primary efficacy endpoints and bleeding events.

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Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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Table 100 summarizes the incidence and severity of anemia during the overall study period. It is evident that edoxaban 60 mg had more anemia AEs and SAEs compared with the warfarin group. The imbalance increased when the reviewer grouped more relevant PT terms (Table 101).

However, the majority of anemia AEs were mild to moderate and very few lead to discontinuation of study drug (Table 100). Evaluation of laboratory data also indicated more subjects in the edoxaban 60 mg group had > 2 g/dL drop in hemoglobin from baseline (see [Section 7.4.2.2](#)). Moreover, a higher percentage of subjects in the edoxaban 60 mg group compared with the warfarin group had ≥ 2 units of transfusion (5.4% vs. 4.9%, respectively). There was also a higher incidence of anemia-related conditions in the edoxaban group compared with the warfarin group among subjects who did not report any bleed in the study (4.9% vs. 3.1%). These imbalanced findings in anemia-related AEs are likely partly due to a higher incidence of GI bleeds or non-apparent bleeds in the edoxaban 60 mg group compared with the warfarin group.

Table 100 Summary of Anemia AE/SAE during the overall study period

	Edoxaban 30mg (15mg DosAdj) (N=7002) n (%)	Edoxaban 60mg (30mg DosAdj) (N=7012) n (%)	Warfarin (N=7012) n (%)
Anemia TEAEs	339 (4.8)	447 (6.4)	313 (4.5)
by Maximum Severity			
Mild	199 (2.8)	267 (3.8)	165 (2.4)
Moderate	110 (1.6)	141 (2.0)	120 (1.7)
Severe	30 (0.4)	39 (0.6)	28 (0.4)
Anemia TEAEs leading to discontinuation of study drug	14 (0.2)	29 (0.4)	13 (0.2)
Anemia TESAEs	53 (0.8)	70 (1.0)	45 (0.6)
Anemia TEAEs with fatal outcome	0 (0.0)	2 (<0.1)	0 (0.0)

Source: the Applicant's CSR Table 12.26

Table 101 Anemia-related AEs during the on-treatment period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Any Anemia related PTs ^a	403 (5.8%)	578 (8.2%)	396 (5.6%)

a. Anemia-related PTs include hematocrit abnormal, hematocrit decreased, hemoglobin decreased, red blood cell count decreased, and any PT term containing anemia

Reviewer's Table, the Applicant's dataset: DM and AEEV1

7.4.1.1 Other AEs of interest by SMQ or clinical event groups

Additional safety data searching for SMQs (broad terms) or clinical event groups of interest are summarized in Table 102. Both edoxaban 30 mg and 60 mg groups had slightly higher incidence of AEs indicating for acute renal failure SMQ, liver function test elevation and drug related hepatic disorders-severe events only SMQ. However, all these SMQs as SAEs were very similar among the treatment groups (see [Section 7.3.2.2](#)). Further evaluation of the reported PTs for acute renal failure SMQ found that the imbalanced results were largely driven by PTs such as creatinine renal clearance decreased and renal impairment. These AE findings are consistent with our laboratory findings with regard to changes in creatinine clearance and serum creatinine (see Figure 32, Figure 33, Table 103 and Table 104). The edoxaban 60 mg group also had a higher percent of subjects with the hematopoietic erythropenia SMQ compared with the warfarin group (6.0% vs. 4.1%), which is consistent with the findings related to anemia AEs. Unlike the findings in death and SAEs, there was no imbalance among the treatment groups with regard to the AEs related to acute central respiratory depression SMQ and ILD SMQ.

Table 102 AEs by SMQs and clinical event groups- on-treatment period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Hematopoietic erythropenia (SMQ)	291 (4.2%)	419 (6.0%)	289 (4.1%)
Acute central respiratory depression (SMQ)	535 (7.6%)	564 (8.0%)	553 (7.9%)
Interstitial lung disease (SMQ)	34 (0.5%)	40 (0.6%)	41 (0.6%)
Hypersensitivity reactions ^a	1731 (24.7%)	1751 (25.0%)	1862 (26.6%)
Torsade de pointes/QT prolongations (SMQ)	312 (4.5%)	285 (4.1%)	318 (4.5%)
Hepatic Disorder			
Liver function test elevation PTs ^b	426 (6.1%)	407 (5.8%)	398 (5.7%)
Drug related hepatic disorders-comprehensive search (SMQ)	669 (9.6%)	654 (9.3%)	813 (11.6%)
Drug related hepatic disorders-comprehensive search (SMQ)-excluding INR increase PT term	655(9.4%)	639 (9.1%)	642 (9.2%)
Drug related hepatic disorders-severe events only— (SMQ)	114 (1.6%)	121 (1.7%)	103 (1.5%)
Renal Disorder			
Acute Renal Failure (SMQ) ^c	735 (10.5%)	741 (10.6%)	668 (9.5%)
Acute Renal Failure (SMQ) ^c - narrow	346 (4.9%)	355 (5.1%)	305 (4.3%)

a. Hypersensitivity reactions include three SMQs: anaphylactic reaction, angioedema and severe cutaneous adverse reaction

b. PTs include alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, blood bilirubin unconjugated increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, liver function test abnormal and transaminases increased.

c.see [APPENDIX 13](#) for reported PTs

Reviewer's Table. Applicant's dataset: AEEV1 & DM

7.4.2 Laboratory Findings

7.4.2.1 Renal parameters

The time course of change of creatinine clearance (CrCL) from baseline shows that the edoxaban groups on average had slightly greater CrCL decreases during the study period compared with the warfarin group (Figure 32). These differences seem constant between the edoxaban arm and warfarin arm throughout the study. The categorical shift table (Table 103) shows that a slightly higher proportion of subjects shifted from > 50 ml/min or 30-50 ml/min to lower CrCL categories at any point of time during the study

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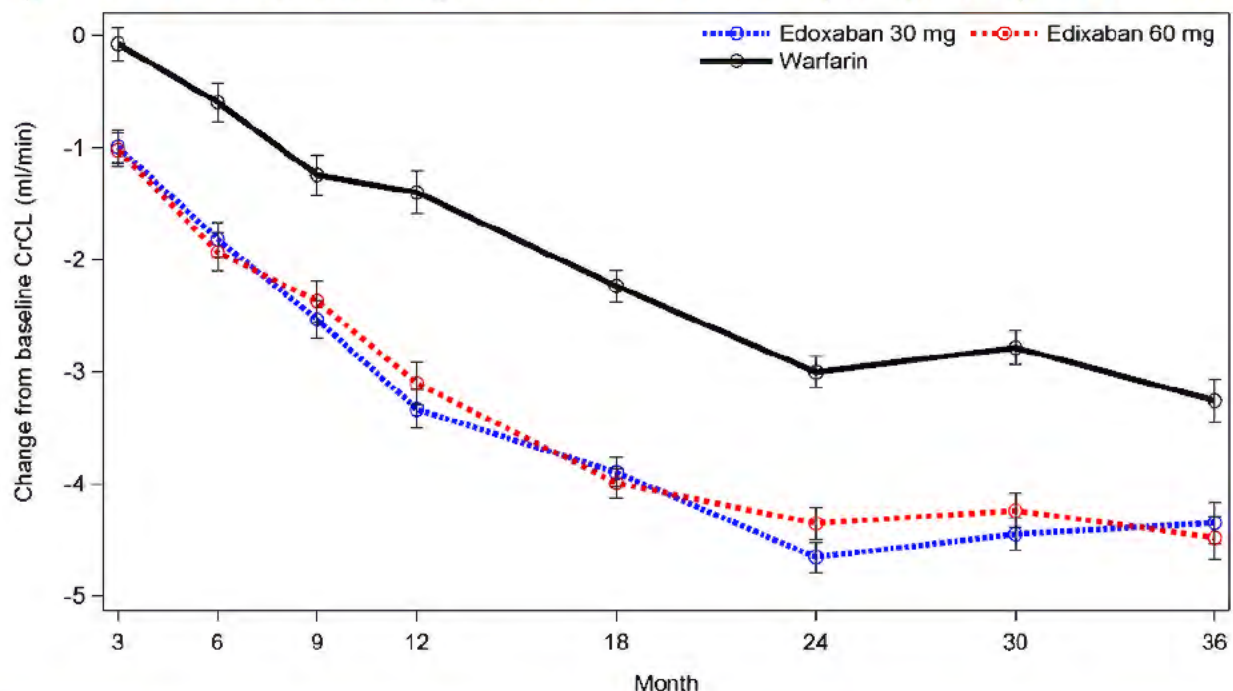
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(on treatment +30 days) in the edoxaban groups compared with the warfarin group. Similarly, a higher proportion of subjects in the edoxaban groups had a greater than 25% decrease in CrCL from baseline compared with warfarin.

Figure 32 Time course of change of Creatinine Clearance (CrCL, ml/min) from baseline



Reviewer's Figure. The Applicant's dataset: LB & DM. The mean creatinine clearance at baseline was similar among the three groups (~ 76 ml/min). All the lab measurements collected during on treatment + 30 days were used for the analysis. Standard error was plotted for each mean CrCL change from baseline by study group and time point.

Table 103 Changes in Creatinine Clearance in ENGAGE AF

	Edoxaban 30 mg N* = 6676	Edoxaban 60 mg N=6609	Warfarin N=6664
Creatinine Clearance decrease			
>50 ml/min shift to 30-50 or <30 ml/min OR 30-50 ml/min shift to < 30 ml/min	1532 (22.9%)	1470 (22.2%)	1375 (20.6%)
≥25% decrease from baseline	1801 (27.0%)	1791 (27.1%)	1656 (24.8%)
≥50% decrease from baseline	159 (2.4%)	178 (2.7%)	151 (2.3%)

Reviewer's Table, Applicant's dataset: LB & DM. *N is number of patients who had at least one creatinine clearance measurement during on treatment + 30 days. Percentage was calculated using N.

Clinical Review

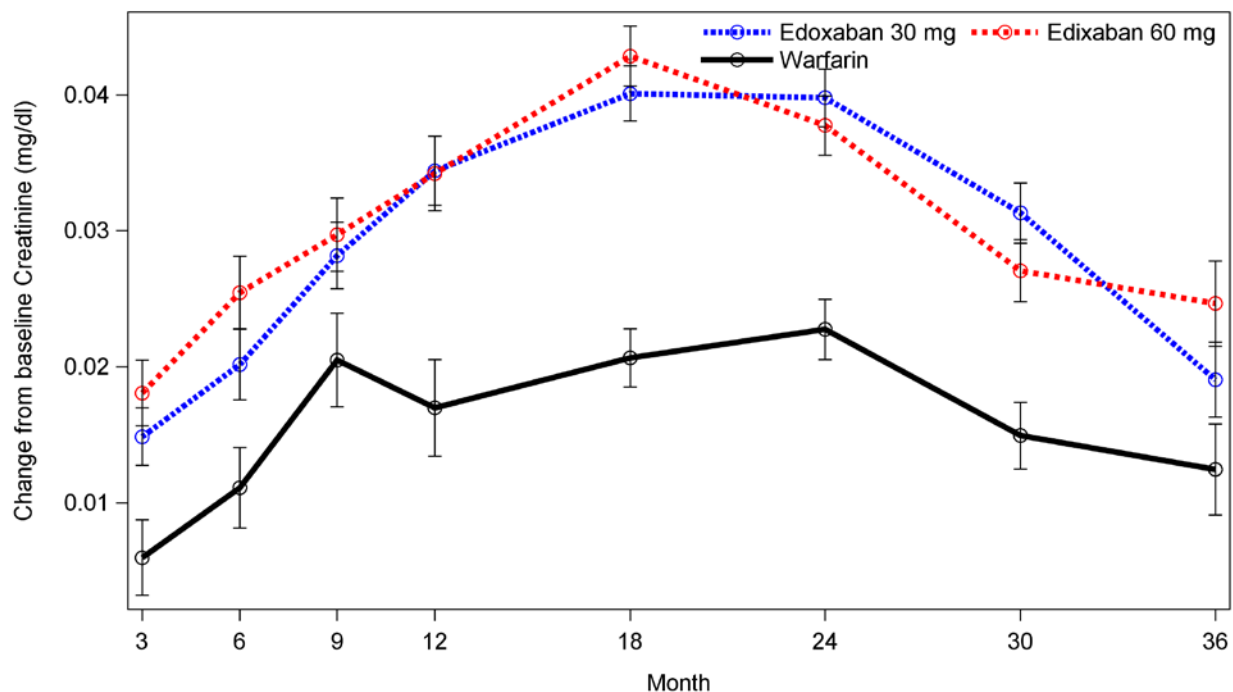
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Subjects in the edoxaban groups also had on average greater serum creatinine increases during the study period compared with the warfarin group (Figure 33). Although the difference was small, a higher percent of subjects in the edoxaban groups compared with the warfarin group had increased serum creatinine greater than the specified criteria (Table 104).

Figure 33 Time Course of Change in Serum Creatinine from Baseline



Reviewer's Figure. The Applicant's dataset: LB & DM. All serum creatinine collected during on treatment + 30 days were used for the analysis. Standard error was plotted for each mean creatinine change from baseline by study group and time point.

Table 104 Changes in Serum Creatinine in ENGAGE AF

	Edoxaban 30 mg N* = 6683	Edoxaban 60 mg N=6627	Warfarin N=6674
Serum Creatinine increase			
≥ 0.3 mg/dL	1637 (24.5%)	1628 (24.6%)	1493 (22.4%)
≥ 0.5 mg/dL	624 (9.3%)	648 (9.8%)	642 (9.6%)
≥25% increase from baseline	2145 (32.1%)	2093 (31.6%)	1945 (29.1%)
≥50% increase from baseline	634 (9.5%)	643 (9.7%)	600 (9.0%)

Reviewer's Table. The Applicant's dataset: LB & DM. *N is number of patients who had at least one serum creatinine measurement during on treatment + 30 days. Percentage was calculated using N.

Reviewer's comment(s): Both edoxaban groups had a slightly worse profile with regard to the renal parameters during the study (on-treatment +30 days). The Applicant did not systematically collect renal parameters after study drug discontinuation. Thus, we do not have sufficient data to evaluate if this phenomenon is reversible once off edoxaban treatment. Pre-clinical studies did not suggest that edoxaban poses a risk to the renal system. These laboratory findings are aligned with the AE results showing that slightly higher percentages of subjects in the edoxaban arms compared to warfarin reported AEs such as decreased creatinine renal clearance and renal impairment (see [APPENDIX 13](#)). Because there were no imbalanced findings with regard to SAEs for acute renal failure and the changes in renal parameters are small, the reviewer does not think these renal findings represent a significant safety concern and could be due to a PD effect of the drug. The reviewer recommends including the information about changes in creatinine clearance and serum creatinine in the label.

7.4.2.2 Hematology

The time course plot shows minor decreases in hemoglobin across all 3 treatment groups (Figure 34). The edoxaban 60 mg group had greater decreases in hemoglobin compared with the warfarin group during the study period. More subjects had hemoglobin drops ≥ 2 g/dL or ≥ 4 g/dL in the edoxaban 60 mg group compared with warfarin. There were no differences between the edoxaban 30 mg and the warfarin group in hemoglobin change from baseline. These results are consistent with the findings of anemia AE. There were no noteworthy changes in other parameters such as platelets and hematocrit.

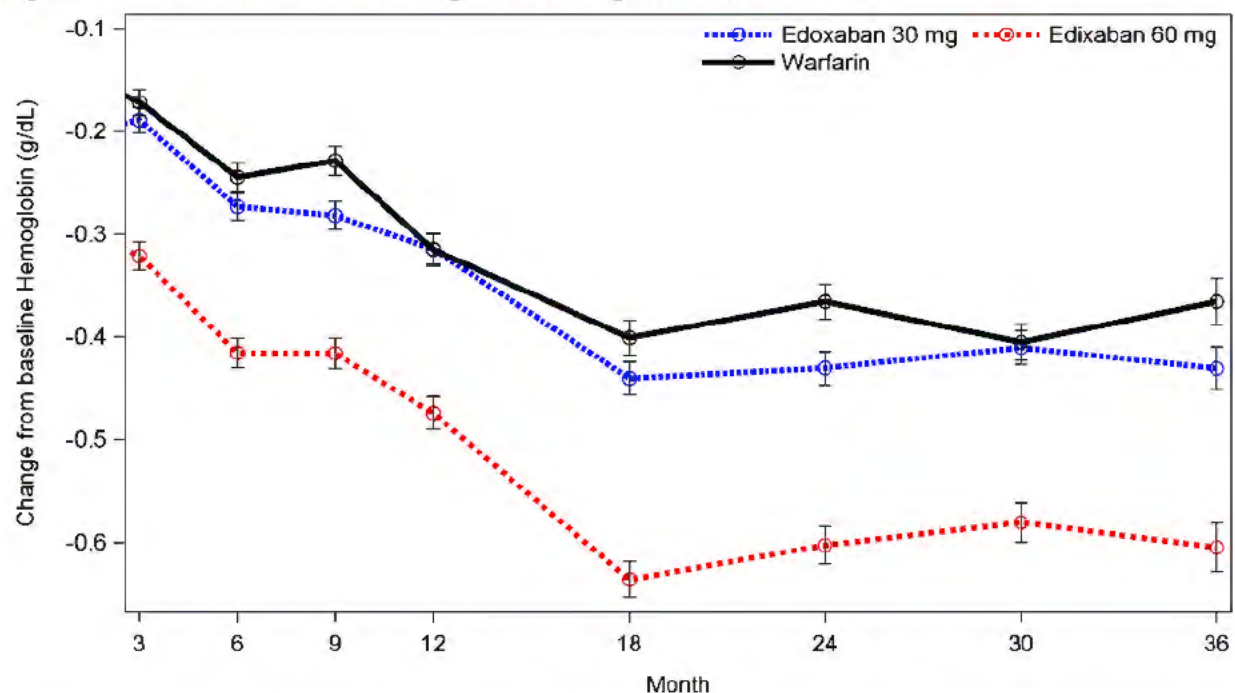
Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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Figure 34 Time Course of Change in Hemoglobin from Baseline



Reviewer's Figure. The Applicant's dataset: LB & DM All hemoglobin collected during on treatment + 30 days were used for the analysis. Standard error was plotted for each mean hemoglobin change from baseline by study group and time point.

Table 105 Changes in Hemoglobin in ENGAGE AF

	Edoxaban 30 mg N* = 6824	Edoxaban 60 mg N=6798	Warfarin N=6833
Hemoglobin Drop			
>2 g/dL	1348 (19.8%)	1628 (23.9%)	1330 (19.5%)
>4 g/dL	264(3.9%)	398 (5.9%)	260 (3.8%)
≥25% decrease from baseline	344 (5.0%)	537 (7.9%)	346 (5.1%)

Reviewer's Table. The Applicant's dataset: LB & DM. *N is number of patients who had at least one hemoglobin measurement during on treatment + 30 days. Percentage was calculated using N.

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

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7.4.2.3 Other laboratory parameters

There were no meaningful difference observe among the treatment groups for other chemistry parameters.

7.4.3 Vital Signs

Vital signs were similar between the edoxaban and warfarin groups. There was no safety signal detected from the vital sign data.

7.4.4 Electrocardiograms (ECGs)

We did not observe clinically relevant difference between treatment groups in AEs/SAEs using Torsade de pointes/QT prolongations (SMQ). Negative results were found in the Thorough QT study (See [Section 7.4.5](#)).

7.4.5 Special Safety Studies/Clinical Trials

The FDA QT Inter-Disciplinary Review Team reviewed the Thorough QT study (DU176b-PRT021), and found no significant QT prolongation effects with edoxaban (90 mg and 180 mg). Please refer to the QT-IRT review (DARRTS date 11/10/2008).

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Anemia was more frequently reported in the edoxaban 60 mg group compared to the edoxaban 30 mg group. AEs related to elevation of liver function tests in edoxaban groups did not seem to be dose-dependent; however SAEs related to elevation of liver function tests were reported more frequently in the edoxaban 60 mg group.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was explored for the primary safety concerns (major bleeding and hepatic abnormality) and review findings are explained in the respective sections.

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

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7.5.3 Drug-Demographic Interactions

See [Section 7.3.2.1.3](#) for subgroup analysis

7.5.4 Drug-Disease Interactions

Renal elimination accounts for ~50% of edoxaban excretion. Subjects with moderate renal impairment (CrCL: 30-50 mL/min) had about 1.75 times increased exposure compared to those with CrCL \geq 80 mL/min in the phase 2 study and received dose adjustment in ENGAGE AF. The subgroup analysis by CrCL levels (Figure 22 and Figure 23) show that major bleeding results were consistent across CrCL subgroups and numerically better in both edoxaban groups compared with warfarin.

According to the efficacy findings and exposure-response analyses, there was convincing evidence suggesting that the proposed dose (60 mg) was not optimal (under-dosed) for subjects with normal renal function. While the efficacy may be attainable by increasing the dose in this subgroup, safety concerns with respect to bleeding risk, particularly GI bleeds, has been raised. The reviewer evaluated the location of major bleeds by CrCL levels to assess further the potential safety impact (Table 106). It is noted that the rate of major bleeding event was markedly decreased among subjects with CrCL \geq 80 mL/min in both treatment groups. These results are expected given that the normal renal function subgroup represents younger and healthier subjects. Among subjects with CrCL \geq 80 mL/min, event rates in all categories of major bleeds, including GI major bleeds, were lower in the edoxaban 60 mg group compared with warfarin. These results are somewhat reassuring. They suggest that there is some wiggle room for bleeding risk, including GI bleeds, if one would increase the dose of edoxaban among subjects with normal renal function. However, an appropriate dose still needs to be identified to balance efficacy and safety in the subgroup.

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

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Table 106 Major Bleeding Results by CrCL and Sub-Categories – on treatment

CRCL min/ml	Event	Edoxaban 60 mg		Warfarin		E60 mg vs. W	
		n/N	ER (%pt-yr)	n/N	ER (%pt-yr)	HR	95 CI
30<=CRCL<=50	Major Bleeding	96 / 1306	3.81	128 / 1352	5.09	0.75	(0.58, 0.98)
	ICH	16	0.62	35	1.36	0.45	(0.25, 0.81)
	Fatal Bleeding	9	0.35	18	0.70	0.52	(0.23, 1.15)
	-ICH	7	0.27	13	0.51	0.55	(0.22, 1.39)
	-Non-ICH	2	0.08	5	0.19	0.42	(0.08, 2.14)
	GI Bleeding	49	1.92	42	1.65	1.15	(0.76, 1.74)
	-Upper GI	35	1.36	21	0.82	1.64	(0.95, 2.82)
	-Lower GI	15	0.58	21	0.82	0.70	(0.36, 1.37)
	GUSTO severe	20	0.77	43	1.68	0.46	(0.27, 0.78)
	-GI	3	0.12	4	0.16	0.75	(0.17, 3.34)
	TIMI Major	34	1.32	59	2.31	0.57	(0.37, 0.87)
	-GI	13	0.50	13	0.51	0.98	(0.45, 2.11)
50<CRCL<80	Major Bleeding	206 / 3062	3.10	235 / 3034	3.45	0.90	(0.74, 1.08)
	ICH	27	0.40	70	1.01	0.39	(0.25, 0.61)
	Fatal Bleeding	13	0.19	27	0.39	0.49	(0.25, 0.95)
	-ICH	9	0.13	19	0.27	0.48	(0.22, 1.07)
	-Non-ICH	4	0.06	8	0.11	0.51	(0.15, 1.69)
	GI Bleeding	124	1.85	79	1.14	1.61	(1.22, 2.14)
	-Upper GI	68	1.01	47	0.68	1.48	(1.02, 2.14)
	-Lower GI	58	0.86	33	0.48	1.81	(1.18, 2.77)
	GUSTO severe	42	0.62	87	1.25	0.49	(0.34, 0.71)
	-GI	9	0.13	10	0.14	0.93	(0.38, 2.28)
	TIMI Major	86	1.27	127	1.84	0.69	(0.53, 0.91)
	-GI	44	0.65	35	0.50	1.29	(0.83, 2.01)
CRCL ≥80	Major Bleeding	108 / 2644	1.73	154 / 2626	2.48	0.70	(0.55, 0.89)
	ICH	16	0.25	25	0.39	0.64	(0.34, 1.21)
	Fatal Bleeding	10	0.16	13	0.20	0.78	(0.34, 1.78)
	-ICH	8	0.13	9	0.14	0.90	(0.35, 2.33)
	-Non-ICH	2	0.03	4	0.06	0.51	(0.09, 2.78)
	GI Bleeding	56	0.89	66	1.05	0.85	(0.59, 1.21)
	-Upper GI	35	0.55	42	0.67	0.84	(0.53, 1.31)
	-Lower GI	22	0.35	25	0.40	0.88	(0.49, 1.55)
	GUSTO severe	28	0.44	41	0.65	0.68	(0.42, 1.10)
	-GI	9	0.14	9	0.14	1.00	(0.40, 2.52)
	TIMI Major	42	0.66	69	1.09	0.61	(0.41, 0.89)
	-GI	22	0.35	34	0.54	0.64	(0.38, 1.10)

Reviewer's Analysis. The Applicant's dataset: BLDDAT, BASEGRP, DM

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

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Pharmacometrics reviewers conducted exposure-response relationships for both efficacy and safety (See [Section 4.4.3.4](#) and clinical pharmacology review for details). In general, these relationships project a decrease in efficacy event rates with increasing edoxaban doses and a subsequent increase in safety event rates with increasing edoxaban doses. One could approach the decreased efficacy in subjects with normal renal function by increasing the dose based on exposure matching. A 90 mg dose is a reasonable choice for patients with normal renal function because it should result in exposures similar to that achieved in the subjects with mild renal dysfunction who received edoxaban 60 mg (the best performing renal function subgroup). The exposure-response models predict an increased dose in the subjects with CrCL ≥ 80 mL/min from 60 mg to 90 mg (to match the exposure to the best performing subgroup: CrCL >50 - <80 mL/min) could reduce ~ 1.4 ischemic strokes per 1,000 patient-years but increase ~ 10.7 major bleeds (~ 8.6 major GI bleeds) and 0.6 hemorrhagic stroke per 1,000 patient-years. Relative to warfarin, edoxaban 90 mg is predicted to have slightly more ischemic strokes (0.8 more events per 1,000 patient-years), more major bleeds (~ 4.8 more events per 1,000 patient-years, particularly more major GI bleeds (~ 8.1 more events per 1,000 patient-years) but ~ 1.4 less life-threatening/fatal bleeds per 1,000 patient-years. Overall, these findings do not suggest an obvious gain in net benefit with edoxaban 90 mg in normal renal function subgroup. It is unclear if the models can accurately predict the net clinical benefit of a higher dose than what was tested in the trial when there is a potential for serious safety consequences. Our concern is that increasing edoxaban dose in subjects with low risk of ischemic stroke would have minimal improvement in efficacy but result in considerably more major bleeding events (See [Section 1.2](#)). The choice of an appropriate edoxaban dose based on the exposure-response analyses 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.

Another uncertainty is that some have speculated that the increased risk of GI bleeds seen with the NOACs may be in part due to high concentrations of active drug in the GI tract. All the models performed by the clinical pharmacology reviewers were assessed based on systemic edoxaban exposure. If local exposure indeed plays a significant role in the probability of developing GI bleeds, the impact of edoxaban 90 mg on the risk of major GI bleeds cannot be assessed adequately and could be underestimated.

Table 107 shows the major bleeding results among subjects without any dose adjustment in both edoxaban groups. Edoxaban 60 mg increased the risk of major bleeds by about 60% compared with edoxaban 30 mg with an absolute risk difference of ~ 1 additional major bleed per 100 patients per year. The increased risk of major bleeds in the edoxaban 60 mg was primarily driven by a higher incidence of major GI bleeds, particularly lower GI bleed. On the contrary, the event rates of ICH and fatal bleeds increased to a relatively small degree in the edoxaban 60 mg group compared with the edoxaban 30 mg group. Similar results were found using more severe major bleeding definitions: GUSTO severe and TIMI major bleeding, though event rates of GI bleeds were much lower using such definitions. Although these findings do not directly support the role of local exposure in the risk of major GI bleeds, it does raise concerns about the possibility.

Table 107 Major Bleeding events by location among subjects without dose adjustment

	<i>Edoxaban 30 mg</i>		<i>Edoxaban 60 mg</i>		<i>Rate difference</i>	<i>Rate Ratio[†]</i>
	<i>No dose adj</i>		<i>No dose adj</i>		<i>E60 vs. E30</i>	<i>E60 vs. E30</i>
	<i>N = 5228</i>		<i>N = 5236</i>			
<i>event</i>	<i>n (%)</i>	<i>ER</i> <i>(%/pt-yr)</i>	<i>n(%)</i>	<i>ER</i> <i>(%/pt-yr)</i>		
Major Bleeding	200 (3.8%)	1.61	314 (6.0%)	2.60	0.99	1.61
GI Bleeding	99 (1.9%)	0.79	182 (3.5%)	1.49	0.70	1.89
-Upper GI	67 (1.3%)	0.54	102 (1.9%)	0.83	0.29	1.54
-Lower GI	34 (0.7%)	0.27	82 (1.6%)	0.67	0.40	2.48
ICH	36 (0.7%)	0.29	41 (0.8%)	0.33	0.04	1.14
Non-ICH	164 (3.1%)	1.32	274 (5.2%)	2.27	0.95	1.72
Fatal	16 (0.3%)	0.13	20 (0.4%)	0.16	0.03	1.23
GUSTO Severe	46 (0.9%)	0.37	67 (1.3%)	0.54	0.17	1.46
-GI	7 (0.1%)	0.06	18 (0.3%)	0.15	0.09	2.50
TIMI Major	87 (1.7%)	0.69	127 (2.4%)	1.04	0.35	1.51
-GI	36 (0.7%)	0.29	68 (1.3%)	0.55	0.26	1.90

Reviewer's Analysis, the Applicant datasets: BLDDAT, BASEGRP, DM

[†]Rate ratio was ratio of the event rate between groups

7.5.5 Drug-Drug Interactions

The results of drug-drug interaction studies were discussed in Section 4 and major bleeding results by concomitant medication of interest can be found in [Section 7.3.2.1.4](#).

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Malignancy was a special event of interest in ENGAGE AF. In general, there was no imbalance found in terms of type and incidence of malignancies among treatments.

Please see [Section 7.3.5.2](#).

7.6.2 Human Reproduction and Pregnancy Data

Edoxaban has not been studied in pregnant or lactating women. There were no pregnancies in ENGAGE AF-TIMI 48. Non-clinical studies in animals suggest that edoxaban did not affect mating and fertility. Edoxaban-associated embryo-fetal toxicity in animals such as fewer live fetuses and lower fetal weight were considered to be secondary effects of maternal toxicity, rather than a direct edoxaban effect (see [Section 4.3](#)).

7.6.3 Pediatrics and Assessment of Effects on Growth

NA

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were only 7 subjects with at least 1 edoxaban overdose/dose error in ENGAGE AF and 11 from postmarketing data including data from 120 day safety updates. There was no major bleeding event associated with edoxaban overdose among the 7 subjects in ENGAGE AF. One subject had taken 96 edoxaban tablets instead of 69 between 07 Sep 2011 to 29 Sep 2011 and had died during sleep on (b) (6). The cause of death was uncertain and no autopsy was performed. There were no signs and symptoms reported prior to the subject's death.

There was only one AE associated with edoxaban overdose among 11 cases from postmarketing data. The AE was a non-serious subcutaneous hemorrhage, vomiting and rash. Overall, the edoxaban overdose cases represent isolated events with different dose and duration, and were not suggestive of safety concern, abuse or unclear packaging/labeling.

There was no evidence suggesting drug abuse/dependence on edoxaban.

7.7 Additional Submissions / Safety Issues

The Applicant submitted the required 120-Day Safety Update, dated 17 April, 2014, which include safety information (cut-off date 31 Dec 2013) from five phase 2 studies, two ongoing Phase 2 studies, post-marketing data for Edoxaban and AEs reported after 06 Aug 2013-31 in ENGAGE AF (database lock date)

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Ongoing Phase 1/2 studies

The safety data in the ongoing phase 1 and 2 studies are generally consistent with the safety profile reported in the edoxaban phase 3 trials.

In an ongoing phase 2 study (56 in the edoxaban group and 28 in the LMWH/warfarin group), there were 2 hepatic abnormality events adjudicated by independent hepatologists, both in the edoxaban group. One was adjudicated as moderate hepatocellular injury, and was considered probably/possibly related to the study drug; the other was adjudicated as severe cholestasis, and was considered unlikely/unrelated to the study drug.

Post marketing data

The Applicant estimates that approximately 20,000 patients were treated with Edoxaban during the reporting period from 01 Oct 2013 through 31 Dec 2013.

A total of 134 AEs were reported in 113 cases (17 SAEs in 12 cases) during this period. Consistent with the safety profile of edoxaban, bleeding was the most frequently reported AEs (haemorrhage subcutaneous was the most frequent reported PT term) and most were non serious.

There were 11 Hepatic related AEs and 3 were serious (1 hepatic enzyme increased, 1 hepatic function abnormal and 1 jaundice). The 3 serious hepatic events were reported in 2 cases. The two cases were both immediate post-operative patients and were not carefully investigated as to the cause of the liver abnormality.

8 Postmarket Experience

Edoxaban was approved in Japan in 2011 for prevention of VTE after orthopedic surgery. It was launched as LIXIANA® on July 19, 2011. The Applicant reported all AEs from the relevant post-marketing safety data sources including spontaneous reports (regulatory authority and literature) as well as Drug Use Survey, which were received between the launch and September 30, 2013.

There were a total of 931 adverse events reported in 724 patients (88 SAEs in 70 cases) among approximately 134,875 patients exposed to Edoxaban. Table shows top 10 most frequent AEs by PT.

Preferred Term (PT)	Drug Use Survey		Spontaneous		Total
	Serious	Non-Serious	Serious	Non-Serious	
Haemorrhage subcutaneous	1	24	5	79	109
Deep vein thrombosis	2	85	1	2	90
Hepatic function abnormal	0	33	1	38	72
Haemorrhage	1	10	7	43	61
Haemoglobin decreased	1	13	1	37	52
Anaemia	5	28	0	8	41
Wound haemorrhage	1	19	5	16	41
Platelet count increased	0	14	0	10	24
Local swelling	0	3	0	20	23
Alanine aminotransferase increased	0	12	0	7	19

Source: The Applicant's Table 2 in Module 5.3.6. post-marketing experience

During the review, we requested the narratives for 2 serious cases (one for hepatic function abnormal, one for liver disorder) and 2 non-serious cases (one for jaundice and one for hyperbilirubinemia). Two hepatic SAEs were spontaneously received cases reported by a healthcare professional. One case had limited information to assess liver abnormality. The other case was a 90 year old female who had elevated liver function tests after several days on edoxaban treatment. Edoxaban was discontinued and the patient was referred to a liver specialist. The doctor considered that edoxaban was suspected to be the cause of the hepatic function disorder. The patient recovered from the hepatic function disorder.

Overall, the post-marketing data are consistent with the known safety profile of edoxaban and no new safety concern has been identified. There were no noticed regulatory actions taken or labeling changes with respect to safety of edoxaban since launch.

9 Appendices

APPENDIX 1: Benefit-Risk Assessment Tables

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

		Benefit Efficacy (Ischemic Stroke/SEE)				Risk Safety (Life Threatening Bleed)				ΔΔ (% pt yr)
	N	Edoxaban 60 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	Edoxaban 60 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	
All	14024	0.9	1.0	-0.1	0.92	0.6	1.1	-0.5	0.53	-0.6
Age										
<64 yr	3328	0.7	0.7	0.0	1.05	0.3	0.4	-0.1	0.73	-0.1
64 to <72	3452	0.9	0.8	0.1	1.12	0.6	1.1	-0.5	0.53	-0.4
72 to <78	3700	1.1	1.2	-0.2	0.86	0.7	1.3	-0.6	0.51	-0.8
≥78	3544	1.1	1.4	-0.3	0.77	0.8	1.6	-0.8	0.48	-1.2
Sex										
Female	5288	1.1	1.1	0.1	1.05	0.2	1.2	-0.9	0.21	-0.8
Male	8736	0.8	1.0	-0.2	0.83	0.8	1.1	-0.3	0.73	-0.5
Elderly										
<75 yrs	2804	0.9	0.7	0.2	1.24	0.2	0.9	-0.7	0.24	-0.5
Female	2484	1.4	1.5	-0.1	0.94	0.3	1.5	-1.2	0.19	-1.3
Elderly										
<75 yrs	5577	0.9	0.8	0.1	1.05	0.6	0.8	-0.2	0.72	-0.2
Male	3159	0.7	1.4	-0.6	0.53	1.1	1.5	-0.4	0.73	-1.1
Weight										
<70 kg	3378	1.3	1.2	0.1	1.07	0.9	1.5	-0.6	0.61	-0.5
70 to <81.8	3584	0.8	1.4	-0.5	0.59	0.5	1.2	-0.7	0.43	-1.2
81.8 to <95	3415	0.8	0.9	-0.2	0.84	0.5	1.0	-0.4	0.55	-0.6
≥95	3647	0.8	0.6	0.3	1.48	0.4	0.8	-0.4	0.54	-0.1
Weight										
<64 kg	1317	1.4	1.3	0.2	1.15	0.3	1.9	-1.6	0.16	-1.4
Female	1268	1.2	1.3	-0.1	0.89	0.4	1.2	-0.8	0.36	-0.9
74 to <86	1396	1.1	1.5	-0.4	0.72	0.2	1.0	-0.8	0.19	-1.2
≥86.2	1307	0.8	0.3	0.6	3.59	0.1	0.7	-0.6	0.10	0.0
Weight										
<75 kg	2172	1.0	1.4	-0.4	0.73	1.4	1.5	-0.1	0.91	-0.5
Male	2102	0.6	1.0	-0.4	0.65	0.6	1.1	-0.5	0.59	-0.8
86 to <99	2278	0.8	0.9	-0.1	0.83	0.6	0.8	-0.2	0.71	-0.4
≥99.2	2184	0.8	0.7	0.2	1.26	0.6	0.8	-0.3	0.67	-0.1
CrCL										
(ml/min)										
30 to ≤50.6	2704	1.3	1.3	-0.1	0.95	0.7	1.6	-0.9	0.45	-1.0
50.6 to <63.6	2737	0.9	1.6	-0.7	0.57	0.5	1.4	-0.9	0.37	-1.5
63.6 to <77.9	2823	0.7	1.0	-0.3	0.68	0.7	1.1	-0.4	0.63	-0.7
77.9 to <98.1	2751	0.9	0.8	0.1	1.14	0.6	0.9	-0.3	0.67	-0.2
≥98.1	2791	0.9	0.5	0.5	2.00	0.3	0.5	-0.2	0.68	0.3
VKA naive										
No	8257	0.9	0.9	0.1	1.07	0.6	1.1	-0.5	0.54	-0.4
Yes	5767	0.9	1.2	-0.3	0.75	0.6	1.1	-0.6	0.51	-0.9
CHADS2										
2-3	10999	0.8	0.8	0.0	1.01	0.5	0.9	-0.4	0.55	-0.4
>3	3025	1.6	2.0	-0.5	0.77	0.8	1.7	-0.9	0.49	-1.3
Stroke/TIA										
No	10073	0.7	0.7	0.0	1.02	0.5	1.0	-0.5	0.51	-0.5
Yes	3951	1.6	1.9	-0.3	0.82	0.8	1.4	-0.6	0.56	-0.9
Diabetes										
No	8958	1.0	1.1	-0.2	0.85	0.6	1.0	-0.4	0.59	-0.6
Yes	5066	0.9	0.8	0.1	1.09	0.5	1.2	-0.7	0.43	-0.6
Aspirin *										
No	8762	0.7	0.7	0	0.96	0.5	0.8	-0.3	0.66	-0.3
Yes	5262	1.3	1.5	-0.2	0.88	0.7	1.7	-1.0	0.43	-1.1
PPI/h2										
blocker*										
No	11320	0.9	0.8	0	1.05	0.5	1.0	-0.5	0.52	-0.4
Yes	2704	1.2	1.8	-0.6	0.67	0.9	1.6	-0.7	0.57	-1.3
Dose Adj										
No	10468	0.8	0.9	-0.1	0.91	0.5	1.0	-0.4	0.57	-0.5
Yes	3556	1.4	1.5	-0.1	0.93	0.7	1.5	-0.8	0.45	-1.0
Location										
Outside US	11439	1.0	1.1	-0.1	0.93	0.6	1.0	-0.4	0.58	-0.5
US	2585	0.5	0.6	-0.1	0.82	0.5	1.4	-0.9	0.35	-1.0

Reviewer's Table. Source: the Applicant's dataset: DM, BASEGRP, POSTGRP, ADJEFFCA and BLDDATA

† A negative value indicates an absolute risk reduction (%/patient-year) of endpoint in the edoxaban group compared with warfarin.

ΔΔ (the net clinical benefit) was assessed based on equal weight of the efficacy and safety endpoint.

††Definition of life threatening bleeds (=GUSTO Severe bleeds): ICH or bleeds causing hemodynamic compromise requiring treatment, including fatal bleeds *Medication was taken at any time on or after the first dose through the last dose

Clinical Review
 Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
 NDA 206316
 Established Drug Name: Edoxaban; Proposed trade name: Savaysa

		Benefit Efficacy (Ischemic Stroke/SEE)					Risk Safety (Major Bleed)				
		N	Edoxaban 60 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	Edoxaban 60 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	ΔΔ (% pt yr)
All		14024	0.9	1.0	-0.1	0.92	2.7	3.3	-0.6	0.80	-0.7
Age	<64 yr	3328	0.7	0.7	0.0	1.05	1.3	1.7	-0.4	0.76	-0.4
	64 to <72	3452	0.9	0.8	0.1	1.12	2.6	3.2	-0.6	0.81	-0.5
	72 to <78	3700	1.1	1.2	-0.2	0.86	3.0	3.5	-0.5	0.85	-0.7
	≥ 78	3544	1.1	1.4	-0.3	0.77	4.0	5.2	-1.2	0.77	-1.6
Sex	Female	5288	1.1	1.1	0.1	1.05	2.4	3.3	-0.9	0.74	-0.8
	Male	8736	0.8	1.0	-0.2	0.83	2.8	3.4	-0.6	0.84	-0.7
Elderly	<75 yrs	2804	0.9	0.7	0.2	1.24	1.9	2.3	-0.4	0.82	-0.2
	≥ 75	2484	1.4	1.5	-0.1	0.94	3.1	4.5	-1.4	0.68	-1.5
Elderly	<75 yrs	5577	0.9	0.8	0.1	1.08	2.0	2.7	-0.7	0.75	-0.6
	≥ 75	3159	0.7	1.4	-0.6	0.53	4.5	4.8	-0.3	0.94	-1.0
Weight	<70 kg	3378	1.3	1.2	0.1	1.07	3.5	3.6	-0.1	0.98	0.0
	70 to <81.8	3584	0.8	1.4	-0.5	0.59	2.5	3.5	-1.0	0.71	-1.6
	81.8 to <95	3415	0.8	0.9	-0.2	0.84	2.5	3.3	-0.8	0.77	-0.9
	≥ 95	3647	0.8	0.6	0.3	1.48	2.3	2.9	-0.7	0.77	-0.4
Weight	<64 kg	1317	1.4	1.3	0.2	1.15	2.9	4.5	-1.5	0.66	-1.4
	64 to <74	1268	1.2	1.3	-0.1	0.89	2.3	3.1	-0.8	0.72	-1.0
	74 to <86	1396	1.1	1.5	-0.4	0.72	2.4	3.2	-0.8	0.75	-1.2
	≥ 86.2	1307	0.8	0.3	0.6	3.59	2.1	2.4	-0.4	0.83	0.2
Weight	<75 kg	2172	1.0	1.4	-0.4	0.73	4.2	3.8	0.4	1.10	0.0
	75 to <86	2102	0.6	1.0	-0.4	0.65	2.4	3.5	-1.1	0.71	-1.4
	86 to <99	2278	0.8	0.9	-0.1	0.83	2.6	3.0	-0.4	0.86	-0.5
	≥ 99.2	2184	0.8	0.7	0.2	1.26	2.2	3.3	-1.1	0.68	-0.9
CrCL (ml/min)	30 to ≤50.6	2704	1.3	1.3	-0.1	0.95	3.7	5.1	-1.3	0.74	-1.4
	50.6 < 63.6	2737	0.9	1.6	-0.7	0.57	3.5	3.8	-0.4	0.90	-1.0
	63.6 < 77.9	2823	0.7	1.0	-0.3	0.68	2.8	2.9	-0.0	0.98	-0.4
	77.9 < 98.1	2751	0.9	0.8	0.1	1.14	2.3	2.9	-0.6	0.80	-0.5
	≥ 98.1	2791	0.9	0.5	0.5	2.00	1.3	2.3	-1.0	0.56	-0.6
VKA naive	No	8257	0.9	0.9	0.1	1.07	2.6	3.3	-0.7	0.79	-0.6
	Yes	5767	0.9	1.2	-0.3	0.75	2.8	3.4	-0.6	0.82	-0.9
CHADS2	2-3	10999	0.8	0.8	0.0	1.01	2.5	3.0	-0.6	0.82	-0.5
	>3	3025	1.6	2.0	-0.5	0.77	3.6	4.7	-1.1	0.77	-1.5
Stroke/TIA	No	10073	0.7	0.7	0.0	1.02	2.5	3.3	-0.7	0.78	-0.7
	Yes	3951	1.6	1.9	-0.3	0.82	3.0	3.6	-0.5	0.86	-0.9
Diabetes	No	8958	1.0	1.1	-0.2	0.85	2.5	3.1	-0.5	0.82	-0.7
	Yes	5066	0.9	0.8	0.1	1.09	3.0	3.8	-0.9	0.78	-0.8
Aspirin*	No	8762	0.7	0.7	0	0.96	2.1	2.6	-0.5	0.82	-0.5
	Yes	5262	1.3	1.5	-0.2	0.88	3.7	4.8	-1.0	0.79	-1.2
PPI/h2 blocker*	No	11320	0.9	0.8	0	1.05	1.8	2.6	-0.8	0.70	-0.7
	Yes	2704	1.2	1.8	-0.6	0.67	6.8	6.8	0	1.01	-0.6
Dose Adj	No	10468	0.8	0.9	-0.1	0.91	2.6	3.0	-0.4	0.88	-0.4
	Yes	3556	1.4	1.5	-0.1	0.93	3.0	4.7	-1.7	0.64	-1.8
Location	Outside US	11439	1.0	1.1	-0.1	0.93	2.4	3.1	-0.6	0.79	-0.7
	US	2585	0.5	0.6	-0.1	0.82	3.9	4.5	-0.7	0.85	-0.8

Reviewer's Table. Source: the Applicant's dataset: DM, BASEGRP, POSTGRP, ADJEFFCA and BLDDATA

† A negative value indicates an absolute risk reduction (%/patient-year) of endpoint in the edoxaban group compared with warfarin.
 ΔΔ (the net clinical benefit) was assessed based on equal weight of the efficacy and safety endpoint.

*Medication was taken at any time on or after the first dose through the last dose

Clinical Review
Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
NDA 206316
Established Drug Name: Edoxaban; Proposed trade name: Savaysa

		N	Benefit				Risk				ΔΔ (% pt yr)
			Efficacy (Ischemic Stroke/SEE)				Safety (Life Threatening Bleed)				
			Edoxaban 30 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	Edoxaban 30 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	
All		14014	1.5	1.0	0.5	1.47	0.3	1.1	-0.8	0.31	-0.3
Age	<64 yrs	3264	1.2	0.7	0.5	1.76	0.1	0.4	-0.3	0.30	0.2
	64 to <72	3554	1.3	0.8	0.5	1.67	0.3	1.1	-0.8	0.29	-0.3
	72 to <78	3685	1.6	1.2	0.4	1.28	0.4	1.3	-0.9	0.30	-0.5
	≥ 78	3511	1.9	1.4	0.5	1.38	0.5	1.6	-1.1	0.33	-0.6
Sex	Female	5347	1.7	1.1	0.7	1.62	0.3	1.2	-0.8	0.28	-0.2
	Male	8667	1.4	1.0	0.4	1.37	0.4	1.1	-0.7	0.34	-0.3
Elderly Female	<75 yrs	2835	1.5	0.7	0.7	2.01	0.2	0.9	-0.7	0.25	0.1
	≥ 75	2512	2.0	1.5	0.5	1.39	0.4	1.5	-1.1	0.29	-0.5
Elderly Male	<75 yrs	5585	1.3	0.8	0.5	1.59	0.3	0.8	-0.6	0.32	-0.1
	≥ 75	3082	1.5	1.4	0.1	1.10	0.5	1.5	-1.0	0.36	-0.9
Weight	<70 kg	3365	2.3	1.2	1.0	1.85	0.4	1.5	-1.0	0.28	0.0
	70 to <81.8	3634	1.4	1.4	0.1	1.05	0.4	1.2	-0.8	0.33	-0.7
	81.8 to <95	3389	1.3	0.9	0.3	1.39	0.4	1.0	-0.6	0.37	-0.3
	≥ 95	3626	1.1	0.6	0.5	1.95	0.2	0.8	-0.6	0.28	-0.1
Weight Female	<64 kg	1318	2.5	1.3	1.2	2.01	0.3	1.9	-1.5	0.19	-0.3
	64 to <74	1264	1.9	1.3	0.6	1.40	0.4	1.2	-0.8	0.34	-0.2
	74 to <86	1402	1.5	1.5	-0.1	0.95	0.1	1.0	-0.8	0.12	-0.9
	≥ 86.2	1363	1.2	0.3	0.9	5.20	0.4	0.7	-0.3	0.61	0.7
Weight Male	<75 kg	2160	2.2	1.4	0.9	1.62	0.5	1.5	-1.0	0.34	-0.1
	75 to <86	2151	1.1	1.0	0.1	1.08	0.4	1.1	-0.7	0.37	-0.7
	86 to <99	2199	1.3	0.9	0.3	1.34	0.4	0.8	-0.5	0.43	-0.1
	≥ 99.2	2157	0.9	0.7	0.3	1.41	0.2	0.8	-0.7	0.22	-0.4
CrCL (ml/min)	30 to ≤50.6	2700	2.4	1.3	1.0	1.75	0.4	1.6	-1.2	0.24	-0.2
	50.6< to 63.6	2794	1.7	1.6	0.1	1.05	0.4	1.4	-1.0	0.27	-0.9
	63.6 < to 77.9	2794	1.3	1.0	0.3	1.28	0.4	1.1	-0.7	0.34	-0.4
	77.9 < to 98.1	2822	1.2	0.8	0.5	1.59	0.4	0.9	-0.5	0.40	-0.1
	≥ 98.1	2731	1.0	0.5	0.5	2.10	0.2	0.5	-0.3	0.46	0.2
VKA naive	No	8268	1.5	0.9	0.6	1.73	0.3	1.1	-0.8	0.29	-0.1
	Yes	5745	1.5	1.2	0.3	1.19	0.4	1.1	-0.7	0.35	-0.5
CHADS2	2-3	10988	1.2	0.8	0.4	1.55	0.3	0.9	-0.7	0.30	-0.2
	>3	3026	2.8	2.0	0.7	1.36	0.6	1.7	-1.1	0.34	-0.4
Stroke/TIA	No	10032	1.1	0.7	0.4	1.64	0.3	1.0	-0.7	0.29	-0.3
	Yes	3982	2.5	1.9	0.6	1.31	0.5	1.4	-0.9	0.35	-0.3
Diabetes	No	8965	1.5	1.1	0.4	1.38	0.3	1.0	-0.7	0.31	-0.3
	Yes	5049	1.4	0.8	0.6	1.71	0.4	1.2	-0.8	0.33	-0.2
Aspirin*	No	8760	1.1	0.7	0.4	1.56	0.3	0.8	-0.4	0.40	0.0
	Yes	5254	2.1	1.5	0.6	1.37	0.4	1.7	-1.3	0.24	-0.7
PPI/h2 blocker*	No	11301	1.2	0.8	0.4	1.49	0.3	1.0	-0.7	0.28	-0.3
	Yes	2713	2.7	1.8	0.8	1.48	0.7	1.6	-1.0	0.41	-0.1
Dose Adj	No	10460	1.2	0.9	0.4	1.40	0.4	1.0	-0.6	0.38	-0.2
	Yes	3554	2.4	1.5	0.9	1.63	0.3	1.5	-1.3	0.17	-0.4
Location	Outside US	11409	1.6	1.1	0.5	1.45	0.3	1.0	-0.7	0.32	-0.2
	US	2605	1.0	0.6	0.4	1.62	0.4	1.4	-1.0	0.30	-0.6

Reviewer's Table. Source: the Applicant's dataset: DM, BASEGRP, POSTGRP, ADJEFFCA and BLDDATA

† A negative value indicates an absolute risk reduction (%/patient-year) of endpoint in the edoxaban group compared with warfarin. $\Delta\Delta$ (the net clinical benefit) was assessed based on equal weight of the efficacy and safety endpoint.

††Definition of life threatening bleeds (=GUSTO Severe bleeds): ICH or bleeds causing hemodynamic compromise requiring treatment, including fatal bleeds

*Medication was taken at any time on or after the first dose through the last dose

Clinical Review
 Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
 NDA 206316
 Established Drug Name: Edoxaban; Proposed trade name: Savaysa

		Benefit					Risk				
		Efficacy (Ischemic Stroke/SEE)					Safety (Major Bleed)				
		N	Edoxaban 30 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	Edoxaban 30 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	ΔΔ (% pt yr)
All		14014	1.5	1.0	0.5	1.47	1.6	3.3	-1.7	0.47	-1.2
Age	<64 yrs	3264	1.2	0.7	0.5	1.76	0.6	1.7	-1.1	0.36	-0.6
	64 to <72	3554	1.3	0.8	0.5	1.67	1.5	3.2	-1.7	0.47	-1.2
	72 to <78	3685	1.6	1.2	0.4	1.28	2.0	3.5	-1.5	0.57	-1.1
	≥78	3511	1.9	1.4	0.5	1.38	2.2	5.2	-3.1	0.42	-2.6
Sex	Female	5347	1.7	1.1	0.7	1.62	1.5	3.3	-1.8	0.46	-1.1
	Male	8667	1.4	1.0	0.4	1.37	1.6	3.4	-1.8	0.48	-1.4
Elderly	<75 yrs	2835	1.5	0.7	0.7	2.01	1.1	2.3	-1.2	0.46	-0.5
Female	≥75	2512	2.0	1.5	0.5	1.39	2.1	4.5	-2.5	0.46	-1.9
Elderly	<75 yrs	5585	1.3	0.8	0.5	1.59	1.3	2.7	-1.4	0.48	-0.9
Male	≥75	3082	1.5	1.4	0.1	1.10	2.3	4.8	-2.5	0.48	-2.4
Weight	<70 kg	3365	2.3	1.2	1.0	1.85	1.6	3.6	-2.1	0.43	-1.0
	70 to <81.8	3634	1.4	1.4	0.1	1.05	1.6	3.5	-2.0	0.44	-1.9
	81.8 to <95	3389	1.3	0.9	0.3	1.39	1.6	3.3	-1.7	0.50	-1.3
	≥95	3626	1.1	0.6	0.5	1.95	1.5	2.9	-1.4	0.51	-0.9
Weight	<64 kg	1318	2.5	1.3	1.2	2.01	1.2	4.5	-3.3	0.27	-2.1
Female	64 to <74	1264	1.9	1.3	0.6	1.40	1.7	3.1	-1.4	0.56	-0.8
	74 to <86	1402	1.5	1.5	-0.1	0.95	1.5	3.2	-1.7	0.45	-1.8
	≥86.2	1363	1.2	0.3	0.9	5.20	1.5	2.4	-0.9	0.63	0.0
Weight	<75 kg	2160	2.2	1.4	0.9	1.62	1.7	3.8	-2.2	0.43	-1.3
Male	75 to <86	2151	1.1	1.0	0.1	1.08	1.8	3.5	-1.7	0.51	-1.7
	86 to <99	2199	1.3	0.9	0.3	1.34	1.5	3.0	-1.5	0.52	-1.1
	≥99.2	2157	0.9	0.7	0.3	1.41	1.5	3.3	-1.7	0.47	-1.5
CrCL (ml/min)	30 to ≤50.6	2700	2.4	1.3	1.0	1.75	2.0	5.1	-3.1	0.39	-2.1
	50.6 < to 63.6	2794	1.7	1.6	0.1	1.05	2.1	3.8	-1.8	0.54	-1.6
	63.6 < to 77.9	2794	1.3	1.0	0.3	1.28	1.8	3.0	-1.1	0.63	-0.8
	77.9 < to 98.1	2822	1.2	0.8	0.5	1.59	1.0	3.1	-1.9	0.36	-1.4
	≥98.1	2731	1.0	0.5	0.5	2.10	1.2	2.2	-1.2	0.50	-0.7
VKA naive	No	8268	1.5	0.9	0.6	1.73	0.0	3.3	-3.3	0.46	-2.7
	Yes	5745	1.5	1.2	0.3	1.19	1.5	3.4	-1.9	0.49	-1.6
CHADS2	2-3	10988	1.2	0.8	0.4	1.55	1.4	3.0	-1.6	0.46	-1.2
	>3	3026	2.8	2.0	0.7	1.36	2.3	4.7	-2.4	0.49	-1.7
Stroke/TIA	No	10032	1.1	0.7	0.4	1.64	1.5	3.3	-1.8	0.46	-1.3
	Yes	3982	2.5	1.9	0.6	1.31	1.7	3.6	-1.8	0.49	-1.2
Diabetes	No	8965	1.5	1.1	0.4	1.38	1.5	3.1	-1.6	0.49	-1.1
	Yes	5049	1.4	0.8	0.6	1.71	1.7	3.8	-2.2	0.44	-1.6
Aspirin*	No	8760	1.1	0.7	0.4	1.56	1.2	2.6	-1.3	0.48	-0.9
	Yes	5254	2.1	1.5	0.6	1.37	2.2	4.8	-2.6	0.46	-2.0
PPI/h2 blocker*	No	11301	1.2	0.8	0.4	1.49	1.1	2.6	-1.5	0.42	-1.1
	Yes	2713	2.7	1.8	0.8	1.48	3.8	6.8	-3.0	0.57	-2.1
Dose Adj	No	10460	1.2	0.9	0.4	1.40	1.6	3.0	-1.3	0.55	-1.0
	Yes	3554	2.4	1.5	0.9	1.63	1.5	4.7	-3.2	0.31	-2.3
Location	Outside US	11409	1.6	1.1	0.5	1.45	1.3	3.1	-1.8	0.43	-1.3
	US	2605	1.0	0.6	0.4	1.62	2.8	4.5	-1.8	0.61	-1.4

Reviewer's Table. Source: the Applicant's dataset: DM, BASEGRP, POSTGRP, ADJEFFCA and BLDDATA

† A negative value indicates an absolute risk reduction (%/patient-year) of endpoint in the edoxaban group compared with warfarin.

ΔΔ (the net clinical benefit) was assessed based on equal weight of the efficacy and safety endpoint.

*Medication was taken at any time on or after the first dose through the last dose

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

APPENDIX 2 Components of the CHADS₂ Score (Source: ENGAGE AF Protocol)

CHADS ₂ Item	Points
Congestive heart failure	1
Hypertension*	1
Age ≥ 75 years	1
Diabetes	1
History of Stroke or TIA	2

*Modified based on: Gage BF, Waterman AD, Shannon W, Boehler M, Rich MW, Radford MJ.

Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70.

Congestive heart failure is defined as the current presence or prior history of clinical congestive heart failure Class C (structural heart disease with prior or current symptoms of heart failure, such as shortness of breath, fatigue, decreased exercise tolerance) or Class D (refractory heart failure requiring specialized interventions).

Hypertension defined as hypertension requiring pharmacologic therapy to maintain a BP < 140/85 mmHg or untreated hypertension documented by BP > 140 mmHg systolic or > 90 mmHg diastolic on two separate occasions.

Diabetes Mellitus includes diabetes requiring treatment with diet only or with pharmacologic therapy (insulin, oral hypoglycemic agents).

Stroke is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit that is generally in the distribution of a single brain artery (including the retinal artery) and that is not due to an identifiable non-vascular cause (i.e., brain tumor or trauma). The deficit must either be associated with symptoms lasting more than 24 hours or result in death within 24 hours of symptom onset.

TIA is defined as an abrupt onset, over minutes to hours, of a focal non-fatal, neurological deficit in the distribution of a single brain artery (including the retinal artery) that lasts less than 24 hours and that does not satisfy the definition of stroke above.

Clinical Review
Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
NDA 206316
Established Drug Name: Edoxaban; Proposed trade name: Savaysa

APPENDIX 3 Visit Schedule

Clinical Review
Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
NDA 206316
Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Table 108: Visit Schedule Year 1

	SQ	Rand	Treatment Year One ^a															
	Day	Day	Day						Month									
	- 60	1	8	15	29	42	60	70	3	4	5	6	7	8	9	10	11	12
Visit Window (days) ^b	n/a	n/a	±3	±3	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7
Study Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Demographic Information	X																	
Medical/Surgical History	X																	
Alcohol and Tobacco Use	X																	
Physical Examination	X ^c																	
Vital Signs		X							X			X			X			X
12-lead ECG		X ^c			X													X
Hepatitis Serology		X ^d																
IXRS Randomization Visit Worksheet		X																
Liver function assessment includes ALT, AST, TBL, and ALP	X ^d	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Serum creatinine and body weight assessment	X ^d	X							X			X			X			X
Serum chemistry panel excluding creatinine		X			X				X			X			X			X
Hematology	X ^d	X			X				X			X			X			X
Urinalysis		X			X				X			X			X			X
AE Reporting ^e																	
SAEs, endpoints and other events of interest reporting ^e (e.g., liver function abnormalities, new bone fractures, and neoplasms)																	

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	SQ	Rand	Treatment Year One ^a															
	Day	Day	Day						Month									
	- 60	1	8	15	29	42	60	70	3	4	5	6	7	8	9	10	11	12
Visit Window (days) ^b	n/a	n/a	±3	±3	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7
QoL (questions 1 and 2) ^f		X							X			X			X			X
Prior and Concomitant Medication	X	X							X			X			X			X
In-clinic study drug administration					X													
Study drug dispensing ^g		X			X		X		X			X			X			X
Review and confirm study medication dosing with the subject using Subject Medication Dosing calendar		X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Review and confirm by telephone subject's understanding of the dosing instructions						X		X										
Study drug compliance					X		X		X			X			X			X
Contact IXRS for study drug assignment		X			X		X		X			X			X			X
Contact IXRS to enter subject status changes or for unscheduled drug assignments	----- as needed -----																	
INR ^h measurement with IXRS contact	X ⁱ	X ⁱ	X	X	X		X		X	X	X	X	X	X	X	X	X	X
D-dimer sampling		X							X									
PK Sampling					X ^j				X ^k									X ^k
Record date and time of subject's last dose (before PK sampling)					X				X									X
Pharmacogenomics informed consent (optional)	X																	

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	SQ	Rand	Treatment Year One ^a															
	Day	Day	Day						Month									
	- 60	1	8	15	29	42	60	70	3	4	5	6	7	8	9	10	11	12
Visit Window (days) ^b	n/a	n/a	±3	±3	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7
Pharmacogenomic sampling (optional)		X ¹																

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CSED = common study end date; ECG = electrocardiogram; eCRF = electronic case report form; INR = international normalized ratio; IXRS = interactive voice and web response system; MI = myocardial infarction; PD = pharmacodynamics; PK = pharmacokinetics; QoL = quality of life; Rand = randomization; SAE = serious adverse event; SQ = study qualification; SEE = systemic embolic event; TBL = total bilirubin; TIA = transient ischemic attack; VKA = vitamin K antagonist.

a: Subjects no longer taking study drug will be followed for SAEs, endpoints, and other events of interest (e.g., liver function abnormalities, new bone fractures, and neoplasms) by visit or telephone contact every 3 months until the CSED Visit. The subjects with temporary study drug interruptions are expected to have eCRFs completed for study drug temporary interruptions. The targeted concomitant medications eCRF should also be completed every three months during study drug temporary interruptions or permanent discontinuations. The subjects with permanent study drug discontinuation prior to CSED Visit are expected to have both a Study Drug Discontinuation Visit and a CSED Visit.

b: Scheduling of visits within visit windows should be done with caution to the drug supply available in a dispensing unit.

c: Targeted physical exam performed by an Investigator or other healthcare professional designated by the Investigator. Physical examination at study qualification includes vital signs. If an ECG was done ≤ 4 days before randomization, it can serve as the baseline ECG and there is no need to repeat the ECG at the randomization visit.

d: Samples taken as part of routine care outside study auspices may be analyzed by local laboratories and the results used to qualify the subject provided the tests were performed ≤ 60 days before randomization. Alternatively, the central laboratory may be utilized for these laboratory tests. Although ALP is part of the liver panel at visits during the treatment period, it is not required as part of study qualification.

e: SAEs, endpoint events, and other events of interest should be reported as soon as site personnel learn of the event. Endpoint event reporting should occur throughout the study and not be restricted to specific visits. Also, AE reporting should occur throughout the study and not be restricted to specific visits.

f: QoL questions 1 and 2 are for outpatient evaluation and diagnostic tests.

g: Study drug assigned by the IXRS every 3 months may be dispensed as a 3 month supply or in smaller amounts sufficient to last until the next visit (e.g., one month supply).

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h: INR assessment for adjustment of warfarin dosages will be done every month. Additional interim evaluations may be done at the discretion of the Investigator.

i: For subjects not taking any open-label VKA during the 60 days prior to randomization, INR must be ≤ 2.5 within 60 days prior to randomization, provided that the subject did not receive any VKA between that INR measurement and randomization. For subjects receiving open-label VKA at the time of randomization, INR value must be ≤ 2.5 within 48 hours prior to randomization, provided that the VKA dose had not been increased within those 48 hours.

j: Two PK samples will be collected during the Day 29 visit: a pre-dose sample (prior to administration of study drug) and a post-dose sample (1 to 3 hours post-dose). It is critical to record the date/time of the last dose the day before the PK sample, the date/time of the dose on Day 29, and the date/time of the PK sample collections.

k: One PK sample will be collected during the specified visits. It is critical to record the date/time of the last dose before the PK sample and the date/time of the PK sample collection.

l: Pharmacogenomics sample may be collected at any treatment visit if it was not obtained at Day 1 and a Pharmacogenomics Informed Consent has been obtained.

Source: ENGAGE AF, CSR

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Table 109: Visit Schedule Year 2

Study Period	Treatment Year Two ^{a, b}												Study Drug Discontinuation Visit ^c	Common Study End Date Visit ^d
Month	13	14	15	16	17	18	19	20	21	22	23	24	n/a	n/a
Visit Window (days) ^e	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	n/a	n/a
Physical Examination ^f													X	X
Vital Signs			X			X			X			X	X	X
12-lead ECG												X	X	X
Liver function assessment includes ALT, AST, TBL, and ALP			X			X			X			X	X	X
Serum creatinine and body weight assessment			X			X			X			X	X	X
Serum chemistry panel excluding creatinine						X						X	X	X
Hematology						X						X	X	X
Urinalysis						X						X	X	X
AE Reporting ^g													
SAEs, endpoints, and other events of interest reporting ^g (e.g., liver function abnormalities, new bone fractures, and neoplasms)													
QoL (questions 1 and 2) ^h			X			X			X			X		
Prior and Concomitant Medication			X			X			X			X	X	X
Study drug dispensing ⁱ			X			X			X			X		
Review and confirm study medication dosing with the subject using the Subject Medication Dosing calendar	X	X	X	X	X	X	X	X	X	X	X	X		
Study drug compliance			X			X			X			X	X ^j	X ^j

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Study Period	Treatment Year Two ^{a, b}												Study Drug Discontinuation Visit ^c	Common Study End Date Visit ^d
Month	13	14	15	16	17	18	19	20	21	22	23	24	n/a	n/a
Visit Window (days) ^e	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	n/a	n/a
Contact IXRS for study drug assignment			X			X			X			X	X	X
Contact IXRS to enter subject status changes or for unscheduled drug assignments	----- as needed -----													
INR ^k measurement with IXRS contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sampling													X ^l	
Record date and time of subject's last dose (before PK sampling)													X ^l	X ^l

a: Subjects no longer taking study drug will be followed for SAEs, endpoints, and other events of interest (e.g., liver function abnormalities, new bone fractures, and neoplasms) by visit or telephone contact every 3 months until the CSED Visit. The subjects with temporary study drug interruptions are expected to have eCRFs completed for temporary study drug interruptions. The targeted concomitant medications eCRF should also be completed every three months during study drug temporary interruptions or permanent discontinuations. The subjects with permanent study drug discontinuation prior to CSED Visit are expected to have both a Study Drug Discontinuation Visit and a CSED Visit.

b: Subsequent treatment years will follow the same visit schedule as year two.

c: This visit is for subjects who permanently discontinue study drug before the CSED. Subjects who do not permanently discontinue study drug but have temporary study drug interruptions will not have this visit; however, the eCRF for temporary study drug interruption will be completed.

d: For all subjects, the CSED Visit will be performed. This includes subjects who temporarily interrupted or permanently discontinued study drug. All randomized subjects with final dose within 30 days of the CSED Visit or on the day of the CSED Visit will have a post-final-dose follow-up visit or telephone contact 30 to 37 days after the CSED Visit to collect data on SAEs, endpoints and other events of interest (e.g., liver function abnormalities, new bone fractures, and neoplasms). Subjects transitioning to open-label VKA should have INR testing on Day 4. In addition, INR testing is recommended as needed on Day 8 (window 7-9 days), Day 12 (window 11-14 days), Day 28, and at least monthly thereafter.

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e: Scheduling of visits within visit windows should be done with caution to the drug supply available in a dispensing unit.

f: Full physical exam performed by an Investigator or other healthcare professional designated by the Investigator.

g: SAEs, endpoint events, and other events of interest should be reported as soon as site personnel learn of the event. Endpoint event reporting should occur throughout the study and not be restricted to specific visits. Also, AE reporting should occur throughout the study and not be restricted to specific visits.

h: QoL questions 1 and 2 are for outpatient evaluation and diagnostic tests.

i: Study drug assigned by the IXRS every 3 months may be dispensed as a 3 month supply or in smaller amounts sufficient to last until the next visit (e.g., one month supply).

j: Record date/time of last/final dose of study drug.

k: INR assessment for adjustment of warfarin dosages will be done every month. Additional interim evaluations may be done at the discretion of the Investigator.

l: One PK sample will be collected during the specified visits only if they occur before the Month 12 visit. It is critical to record the date/time of the last dose before the PK sample and the date/time of the PK sample collection. For the Study Drug Discontinuation Visit, PK sample will only be taken if the subject is still on study drug at the time of the visit and the visit occurs before the Month 12 visit.

Source: ENGAGE AF CSR

APPENDIX 4 Guidelines for INR-Based Dose Adjustments for Warfarin

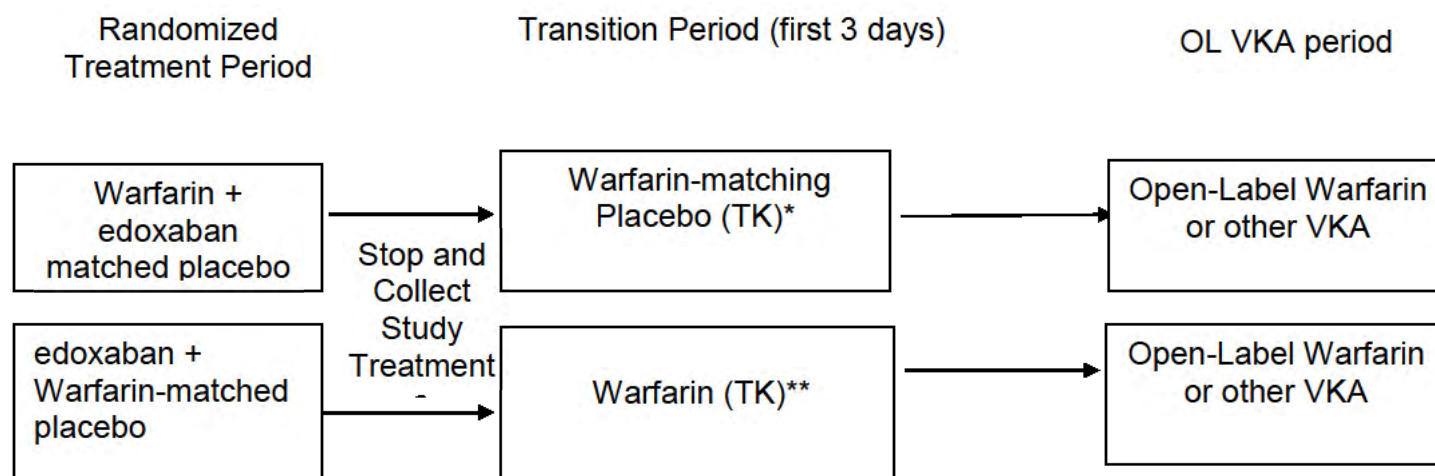
The following guidelines for adjusting the warfarin dose to maintain this INR were not meant to supersede the clinical judgment of the investigators or investigator designees.

INR	Suggested Warfarin/Placebo Dose Adjustment
< 1.5	Increase weekly dose of warfarin/placebo by 10% to 20%. Consider giving one extra dose of warfarin/placebo. Retest INR in 4 to 8 days or sooner per Investigator discretion.
1.5 to < 2	Increase weekly dose of warfarin/placebo by 5% to 10%. Retest INR in 7 to 14 days or sooner per Investigator discretion.
2.0 to 3.0	No Change
> 3.0 to 3.5	Decrease weekly dose of warfarin/placebo by 0% to 20%. Retest INR in 2 to 4 weeks or sooner per Investigator discretion.
> 3.5 to 4.0	Withhold 0 to 1 dose and/or decrease weekly dose of warfarin/placebo by 0% to 20%. Retest INR in 1 to 2 weeks or sooner per Investigator Discretion.
> 4.0 but < 5.0	Withhold both double-blind study drugs for 1-2 days, and retest INR. When INR < 3.0 restart both study drugs with a 0-20% decrease in the warfarin/placebo study drug. Retest INR in 3 to 7 days or sooner per Investigator discretion.
5.0 to < 9.0 without significant bleeding	Withhold both double-blind study drugs for 1 to 2 days. Retest INR in 1 to 2 days or sooner per Investigator discretion. Resume dosing once INR < 3.0, but with weekly dose decreased by 5% to 20%. If the subject needs urgent surgery, then the subject should receive Fresh Frozen Plasma (FFP). If necessary, contact (b) (4) HOTLINE (US/Canada: (b) (4); Other countries: (b) (4); Email (b) (4) for consultation.
≥ 9.0 without significant bleeding	Withhold study drug. Give Vitamin K (single 2.5 to 5 mg oral dose) Repeat INR test daily until INR < 5.0. If INR remains too high, more Vitamin K doses can be considered. Resume dosing once INR < 3.0, but with weekly dose decreased by 10% to 20%. If the subject needs urgent surgery, then the subject should receive FFP. If necessary, contact (b) (4) HOTLINE (US/Canada: (b) (4); Other countries: (b) (4); Email: (b) (4) for consultation.

Source: ENGAGE AF CSR

APPENDIX 5 Transition Plans and Study Stop Transition Plans

Figure 35: Temporary Transition to VKA

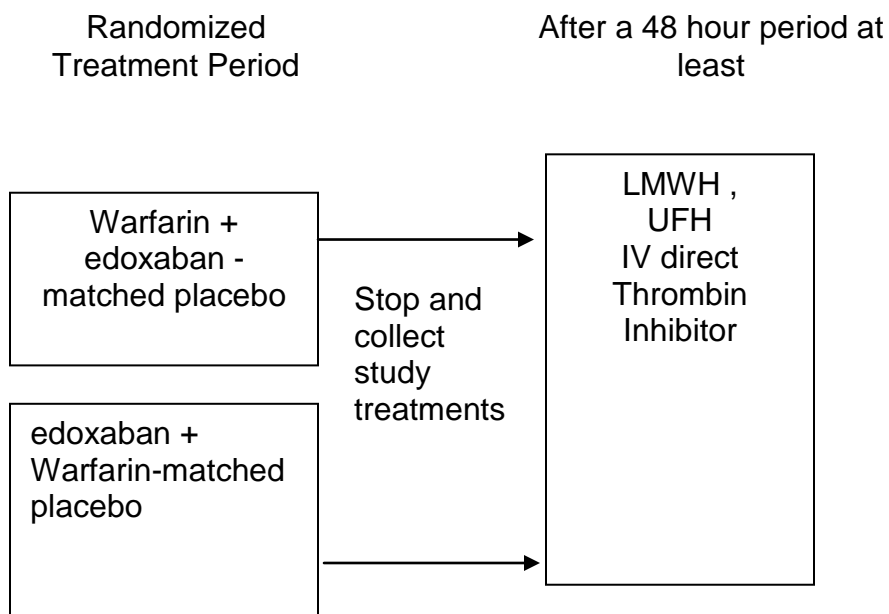


*Prescribed by Investigator; dose and duration of treatment at Investigator's discretion

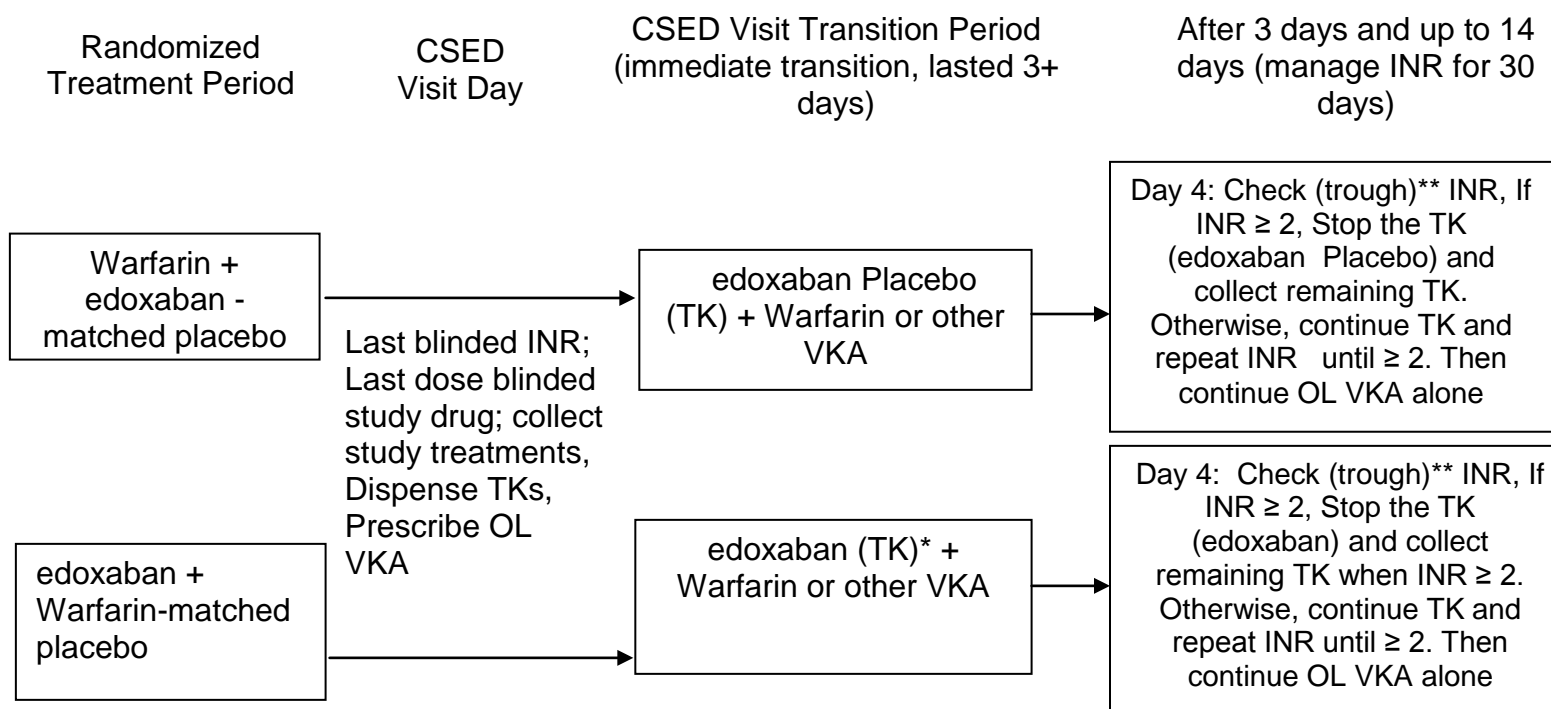
**Use of TK was optional, at the Investigator's discretion

Source: Applicant Communication during review period

Figure 36: Temporary Transition to LMWH, UFH or IV direct Thrombin Inhibitor



Source: Applicant Communication during review period



* The schema used to determine the dose of edoxaban used in the EOS Transition Plan is shown in

Table 110. According to the applicant, this information was not included in the study protocol but was provided to the sites during the training for study closeout procedures.

** The trough INR had to be taken at least 8 hours after the most recent dose of edoxaban/ edoxaban placebo + warfarin. Source: Applicant Communication during review period

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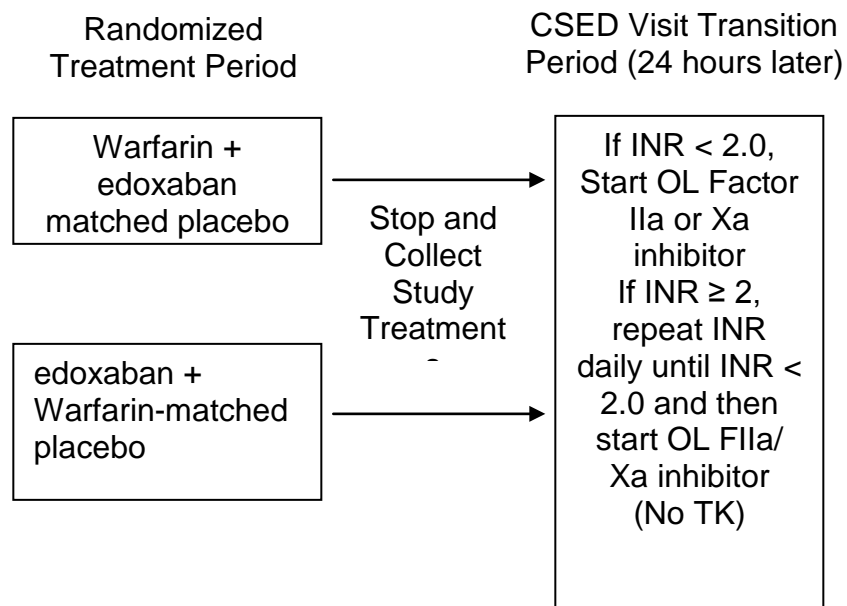
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Table 110: Dose used in end of study (EOS) transition plan

Treatment Group	Study Drug Dose at the Time of CSED Visit	Edoxaban Dose in the EOS Transition Plan
Edoxaban High Exposure	60 mg	30 mg
	30 mg (dose reduced)	15 mg
Edoxaban Low Exposure	30 mg	30 mg
	15 mg (dose reduced)	15 mg
Warfarin	Warfarin (INR based)	Edoxaban-matching Placebo

Source: Applicant Communication during review period

Figure 38: Study Stop – Transition to Factor IIa/Xa inhibitor



Source: Applicant Communication during review period

APPENDIX 6 Synopsis of CEC Definitions (source: CEC Charter):

1. Cerebrovascular Events

a. Stroke

A stroke is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit that is generally in the distribution of a single brain artery (including the retinal artery) and that is not due to an identifiable non-vascular cause (i.e., brain tumor or trauma). The deficit must either be associated with symptoms lasting more than 24 hours or result in death within 24 hours of symptom onset. Since strokes may have variable clinical presentations (e.g., a large hemorrhagic stroke presenting with sudden syncope, embolic stroke with multiple deficits in >1 vascular territory), the use of supplementary information such as brain imaging, may be used by the CEC to determine if a stroke has occurred. CT and/or MRI scan reports, operative notes, autopsy results and other clinical data will be considered by the CEC to support the clinical impression, and to permit subclassification of the type of stroke.

All strokes will be sub-classified as “primary ischemic” or “primary hemorrhagic” based on imaging data, if available, or “uncertain cause” if imaging data is not available according to the definitions below. Primary ischemic strokes will be further subclassified by type in to the following categories:

- Ischemic Stroke with no hemorrhage
- Stroke without focal collections of intracerebral blood on a brain imaging. (This category will be sub-classified into atherosclerotic vs. lacunar, and embolic vs. other)
- Cerebral infarction with small foci (<10 mm) of hypointense signals on gradient-echo MRI sequences
- Ischemic Stroke with Hemorrhagic Conversion
- Cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage. Hemorrhagic conversion usually occurs on the cortical surface. Hemorrhagic conversion in the deeper brain requires evidence of nonhemorrhagic infarction in the same vascular territory
- Ischemic Stroke with Microhemorrhage (not considered to be consistent with a hemorrhagic conversion endpoint)

Primary hemorrhagic strokes will be classified by the location of bleeding (multiple locations may be checked if appropriate).

- Primary Hemorrhagic
 - Intracerebral Hemorrhage
 - Stroke with focal collections of intracerebral blood seen on a brain image (CT or MRI) or a postmortem examination, not likely to represent hemorrhagic conversion. Primary hemorrhages cause hematomas which are usually easily discriminated by their cortical location and rounded or elliptical shape. Microhemorrhages incidentally discovered on brain

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imaging are not considered a primary hemorrhagic stroke endpoint event, and will be otherwise classified.

- Subarachnoid hemorrhage – High density fluid collection in subarachnoid space on brain images or blood in the subarachnoid space on autopsy
- Uncertain – Any stroke without brain image (CT or MRI), autopsy documentation, or other diagnostic information that permits sub-classification of the stroke, or if the tests are inconclusive

The severity of Stroke will be measured with the modified Rankin score at the next scheduled visit, i.e., 1-4 months after the event.

Stroke should be confirmed by either autopsy or brain imaging (CT or MRI); where these are unavailable the initial clinical presentation must be typical of stroke.

2. Subdural hematoma

A subdural hematoma is defined as a high density fluid collection in subdural space on brain images or blood in the subdural space on autopsy. *NOTE: A subdural hematoma is considered an intracranial hemorrhage but will not be classified as a hemorrhagic stroke.*

3. Epidural hematoma

An epidural (or extradural) hematoma is defined as a collection of high density fluid collection on brain images or blood occurring between the dura mater and the skull. *NOTE: An epidural hematoma is considered an intracranial hemorrhages but will not be classified as a hemorrhagic stroke.*

4. Microhemorrhages

Microhemorrhages are defined as rounded foci of <10 mm that appear hypointense and that are distinct from other causes of signal loss on gradient-echo MRI sequences (e.g., vascular flow voids, leptomeningeal hemosiderosis, or non-hemorrhagic subcortical mineralization). Since epidemiological studies have shown as high as ~40% rate of microhemorrhage in stable asymptomatic elderly patients undergoing gradient echo MRI (but not other imaging modalities), and the clinical significance of these findings is not clear, findings of a microhemorrhage by itself will not be considered to satisfy the criteria for an ICH, stroke, or bleeding event. Instead microhemorrhages will be classified as either:

- a. Microhemorrhage in association with an ischemic stroke
- b. Isolated microhemorrhage (not an ICH, stroke, or bleed)

5. Transient ischemic attack (TIA)

A TIA as an abrupt onset over minutes to hours of a focal non-fatal, neurological deficit in the distribution of a single brain artery (including the retinal artery) that lasts less than 24 hours and that does not satisfy the definition of stroke above.

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For each case that the CEC confirms satisfies the protocol definition of TIA, the CEC Adjudicators will indicate whether brain imaging demonstrated evidence of a new ischemic brain injury or not.

6. Systemic Embolic Event (SEE) A Systemic Embolic Event is defined as an abrupt episode of arterial insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). Arterial embolic events involving the CNS (including the eye), coronary, and pulmonary arterial circulation are not considered SEEs, but will be classified respectively as stroke/TIA, myocardial infarction, and pulmonary embolism. In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.
7. Death Classification
 - a. Death will be classified as *Cardiovascular, Malignancy, or Non-cardiovascular/Nonmalignancy*. The cause of death is determined by the principal condition that caused the death, not the immediate mode of death. All deaths will be assumed to be cardiovascular in nature unless a malignant or a non-cardiovascular cause can be clearly shown.
 - i. Cardiovascular death is defined as death due to documented cardiovascular cause, including deaths due to bleeding. Causes of cardiovascular deaths include, but are not limited to, deaths resulting from atherosclerotic coronary heart disease (acute myocardial infarction, sudden cardiac death, non-sudden death with gradually worsening cardiac symptoms, unwitnessed death without clear alternate cause, procedural death related to cardiac surgery or coronary angiography), atherosclerotic vascular disease (cerebrovascular disease including stroke and hemorrhage, aortic, mesenteric, renovascular, peripheral arterial disease, or complication of a non-coronary vascular procedure), other cardiovascular (pulmonary embolism, endocarditis, congestive heart failure, valvular heart disease, arrhythmia), and deaths due to bleeding.
 - ii. Malignancy-related deaths will include deaths that are directly a consequence of a malignancy, such as a brain tumor that causes herniation, coma, and respiratory arrest. Deaths due to malignancy will be further subclassified by organ system and timing of diagnosis (before vs. after randomization).
 - iii. Non-cardiovascular/non-malignancy deaths include those caused primarily by infection, pulmonary, gastrointestinal, accidental, renal, trauma, or non-cardiovascular organ system failure.

- b. For all deaths, the relationship of the death to bleeding and malignancy will be adjudicated as follows:
 - i. Relationship to Bleeding (categories are mutually exclusive)
 - o Fatal bleeding – death in which a bleeding event directly led to death within 7 days. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death must be either intracranial or nonintracranial bleeding.
 - o Bleeding contributed to death – a death in which a bleeding event was part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but bleeding was not directly and/or immediately related to subject's death.
 - o Deaths unrelated to a bleeding event – The case of death was unrelated to bleeding, either because there was no clinical significant bleeding in the month prior to death or the bleeding event did not contribute to the subject's death. In these cases, the cause of death cannot be intracranial / non-intracranial bleeding.
- 8. Relationship to Malignancy
 - a. Death directly related to malignancy – Death in which the mode of death can be attributed to the direct effects of a malignancy. In such cases, the cause of death adjudicated by the CEC must be malignancy.
 - b. Death due to a consequence related to malignancy. This would include deaths due to other processes (e.g., infection in a patient who becomes septic and neutropenic due to acute leukemia) that are a known complication of the malignancy. The underlying malignancy should be on the causal pathway leading to death, but not the immediate cause of death. In such cases, the cause of death adjudicated by the CEC cannot be malignancy, but instead should be the other process (e.g., infection).
 - c. Death not related to a malignancy. Either no malignancy has been diagnoses or the malignancy that is present was not related to the cause of death. The cause of death must be something other than malignancy.
- 9. Sudden Cardiovascular Death

Sudden CV death is defined as a sudden, unexpected death that was either:

 - a. witnessed, occurring within 60 min from the onset of new symptoms, in the absence of a clear cause other than cardiovascular; or
 - b. unwitnessed, within 24 hours of being observed alive, in the absence of pre-existing progressive circulatory failure or other non-cardiovascular causes of death;

10. Non-sudden Cardiovascular Death

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This category refers to a patient who had symptoms of a cardiovascular nature and had gradual deterioration prior to death. It includes all patients with CV death who do not meet criteria for sudden death or unwitnessed CV death.

11. Unwitnessed CV Death -- Death that occurred unexpectedly, *without* patient being seen within 24 hours, and for which no known other major causes of death are identified.

APPENDIX 7 Overview of Bleeding Category Definition

Major bleeding event:

A clinically overt bleeding event (i.e., bleeding that is visualized by examination or radiologic imaging) that meets at least one of the following:

- a) Fatal bleeding
- b) Symptomatic bleeding in a critical area or organ such as:
 - Retroperitoneal
 - Intracranial
 - Intraocular
 - Intraspinal
 - Intra-articular
 - Pericardial
 - Intramuscular with compartment syndrome
- c) A clinically overt bleeding event that causes a fall in hemoglobin level of 2.0 g/dL (>1.24 mMol/L) or more, adjusted for transfusions. Each 1 unit of packed RBC or whole blood is counted as a 1.0 g/dL decrease in hemoglobin. In the case of surgical procedural related bleeding, the bleeding must be in excess of that normally associated with the surgery/procedure. In the absence of hemoglobin data, a fall of hematocrit of 6.0% or more, adjusted for transfusion, will satisfy the criteria for a major bleeding event.

Major bleeding events were also further subclassified as life-threatening or non-life threatening.

A **life-threatening major bleed** is defined as a bleeding event that is either intracranial or is associated with hemodynamic compromise requiring intervention.

Intracranial hemorrhage :

Intracranial hemorrhage (ICH) included:

- Primary hemorrhagic stroke, including sub-arachnoid hemorrhage
- Primary ischemic stroke with major hemorrhagic conversion
- Subdural hematoma
- Epidural hematoma

Any ICH is major bleed. ICH could be fatal or non-fatal bleed.

Primary Hemorrhagic stroke included:

- Intracerebral Hemorrhage – Stroke with focal collections of intracerebral blood seen on a brain image (CT or MRI) or a postmortem examination, not likely to represent hemorrhagic conversion. Primary hemorrhages cause hematomas which are usually easily discriminated by their cortical

location and rounded or elliptical shape. Microhemorrhages incidentally discovered on brain imaging are not considered a primary hemorrhagic stroke endpoint event, but will be otherwise classified (see below 6.1.4).

- Subarachnoid hemorrhage – High density fluid collection in subarachnoid space on brain images or blood in the subarachnoid space on autopsy

Primary ischemic stroke with Hemorrhagic Conversion – Cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage. Hemorrhagic conversion usually occurs on the cortical surface. Hemorrhagic conversion in the deeper brain requires evidence of nonhemorrhagic infarction in the same vascular territory. Microhemorrhages evident on MRI, whether in the cortex or deep brain structures, are not considered to be consistent with a hemorrhagic conversion endpoint.

Subdural hematoma: A subdural hematoma is defined as a high density fluid collection in subdural space on brain images or blood in the subdural space on autopsy. NOTE: A subdural hematoma is considered an intracranial hemorrhage but will not be classified as a hemorrhagic stroke.

Epidural hematoma: An epidural (or extradural) hematoma is defined as a collection of high density fluid collection on brain images or blood occurring between the dura mater and the skull. NOTE: An epidural hematoma is considered an intracranial hemorrhages but will not be classified as a hemorrhagic stroke.

Fatal bleed:

Fatal bleed includes both fatal ICH and fatal non-ICH. Any fatal bleed is major bleed. or all deaths, the relationship of the death to bleeding was adjudicated as follows
Relationship to Bleeding (categories are mutually exclusive)

Fatal bleeding – death in which a bleeding event directly led to death within 7 days. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death must be either intracranial or non-intracranial bleeding.

Bleeding contributed to death – a death in which a bleeding event was part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but bleeding was not directly and/or immediately related to subject's death. An example of bleeding contributing to death is a large retroperitoneal bleed that leads to surgical evacuation, development of a subsequent abscess in the area of bleeding that leads to sepsis, multiorgan failure and death 10 days after the onset of bleeding. If bleeding has contributed to death (but the bleeding was not categorized as "fatal"), then the cause of death must be recorded as something other than intracranial / non-intracranial bleeding.

Deaths unrelated to a bleeding event – The case of death was unrelated to bleeding,

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either because there was no clinical significant bleeding in the month prior to death or the bleeding event did not contribute to the subject's death. An example of a death unrelated to bleeding is an episode of guaiac positive stools in a patient who dies of postobstructive pneumonia due to lung cancer. In these cases, the cause of death cannot be intracranial / non-intracranial bleeding.

Clinically relevant non-major bleeding events (CRNM):

A clinically overt bleeding event that requires medical attention. Examples of bleeding requiring medical attention include, but are not limited to, bleeding events that result in the following:

- Diagnostic or therapeutic measures:
- Requires or prolongs hospitalization
- Laboratory evaluation
- Imaging studies
- Endoscopy, colonoscopy, cystoscopy, or bronchoscopy
- Nasal packing
- Compression
- Ultrasound guided closure of an aneurysm
- Coil embolization
- Inotropic support
- Surgery
- Interruption or stopping study medication at the advice of a physician
- Changing concomitant therapies (e.g., reducing the dose of or discontinuing aspirin) at the advice of a physician
- Note: an outpatient visit without any of the above or similar diagnostic/therapeutic measures does not satisfy the criteria for "requiring medical attention"

Clinically relevant non-major bleeding will be classified according to site as follows:

- Cutaneous or soft tissue
- Epistaxis
- Ear-nose-throat (ENT)
- Gastrointestinal (subclassified as upper vs lower)
- Hemoptysis
- Hematuria (macroscopic only) / urethral
- Oral / Pharyngeal
- Puncture site
- Surgical site
- Vaginal
- Other (including any other bleeding event considered clinically significant by the CEC)

Clinically overt bleeding requires visualization of bleeding by examination or radiologic imaging.

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Minor (not clinically relevant) bleeding events:

Other overt bleeding events that do not fulfill the criteria of a major bleeding event or a clinically relevant non-major bleeding event (e.g., epistaxis that does not require medical attention) will be classified as a minor bleeding event.

Minor bleeding events that do not result in changes in therapy, medical evaluation, testing, or medical treatment / management by a physician or other health care provider as identified by the actions taken on the bleeding eCRF form will not be sent for review to the CEC. The final status for these events will be “minor bleed.”

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APPENDIX 8 Screening Failures

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Table 111: Tabular Listing of Reasons for Screening Failure

	Overall n(%)
Screen Failure Subjects	4392 (17.2)
Reasons for Screen Failure:	
Protocol Eligibility Not Met	2523 (57.4)
INR>2.5	129 (2.9)
Inclusion/Exclusion Criteria	1693 (38.5)
Other	701 (16.0)
Investigator's decision	619 (14.1)
Subject's decision	1245 (28.3)
Reason not available	5 (< .01)
Subjects with Exclusion Criteria:	
Severe Renal Failure (CrCL <30 mL/min)	333 (7.6)
HGB <10g/dL, Platelets <100k or WBC <3k	207 (4.7)
Conditions Associated with High Bleeding Risk	149 (3.4)
Active Liver Disease or Persistent Liver Enzyme Elevation	147 (3.3)
Non-Compliant to Study Protocol	99 (2.3)
Medical Conditions (e.g., Active Cancer, Chemotherapy), Life Expectancy <12 Mths	96(2.2)
Clinically Relevant Lab Abnormalities	45 (1.0)
Acute Cardiac Events Within Previous 30Days (AMI or ACS or PCI)	37 (0.8)
Pre-planned Invasive Procedures/Surgeries With Anticipated Bleeding	37 (0.8)
Structural Factors (MS, Atrial Myxoma, or Mechanical Valve)	35 (0.8)
History of Positive Hepatitis B Antigen or Hepatitis C Antibody Prior to Randomization	28 (0.6)
Receiving Concomitant Prohibited Therapy	24 (0.5)
Increased Safety Risk Due to Medical Conditions as deemed by the Investigator	20 (0.5)
History of Left Atrial Appendage Exclusion (Surgery or Procedure)	17 (0.4)
Receiving/Planned Dual Antiplatelet Agents During Study	16 (0.4)
Chronic OAC Therapy Not Warranted	14 (0.3)
Previously Randomized in an Edoxaban Study	14 (0.3)
Transient AF Due to Reversible Factors	12 (0.3)
Alcohol/Drug Dependence in Past 12 Months	9 (0.2)
Intracardial Mass or LV Thrombus	9 (0.2)
Contraindicated for OAC Therapy	8 (0.2)
Females with Childbearing Potential	8 (0.2)
Receiving Investigational Agent (Drugs/Device) Within 30 Days Prior to Randomization	6 (0.1)
Receiving Concomitant Cyclosporine Therapy	2 (<0.2)
Known History of Positive HIV	1 (<0.1)

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	Overall n(%)
Subjects Failed Inclusion Criteria:	
History of Documented AF by ECG Within Past 12 months and OAC Planned for Duration of the Study	277 (6.3)
CHADS ₂ Score ≥ 2	100 (2.3)
Male or Female With Age ≥ 21 yrs	6 (0.1)
Able to Provide Written IC	1 (<0.1)
Investigator's decision	619 (14.1)
Subject's decision	1245 (28.3)
Reason not available	5 (< .01)

Reviewer's Table; Data Source: ENGAGE AF Clinical Study Report

APPENDIX 9 PRT-018, Dose-finding phase 2 study

Title: A Phase 2, randomized, parallel group, multi-center, multi-national study for the evaluation of safety of four fixed dose regimens of DU-176b in subjects with non-valvular atrial fibrillation

Important Study Dates:

Date First Subject Enrolled: First subject randomized date: 02 Jul 2007

Date Last Subject Completed: Last subject last follow-up date: 10 Jun 2008

Primary Objective:

The stated primary objective was to evaluate the safety of four fixed dose regimens of edoxaban (30 mg qd, 30 mg bid, 60 mg qd, and 60 mg bid) in subjects with NVAF. Warfarin was included as an active control. Evaluation of bleeding events and liver enzymes/bilirubin were the primary safety endpoints.

Study Design:

This was a randomized, double-blind (DU-176b) and open-label (warfarin), parallel group, multi-center, multi-national study.

Treatments and Doses:

Edoxaban 30 mg qd, edoxaban 30 mg bid, edoxaban 60 mg qd, and edoxaban 60 mg bid, (only subjects randomized before 14 Jan 2008), and warfarin tablets (open-label) qd with dose adjusted to maintain an INR between 2.0 and 3.0.

Data from previous PK and PD studies of edoxaban supported qd and bid dosing regimens.

The doses of edoxaban used in this study, 30 mg and 60 mg, administered either once or twice daily, had been studied previously in healthy volunteers and in subjects undergoing hip replacement surgery. These doses and higher (up to 180 mg daily) had been previously studied but the studies were small and the longest duration of administration in these previous studies was 14 days.

Population:

Male and female subjects, 18 to 85 years of age, inclusive, with NVAF and at least a moderate yearly risk of stroke (based on the CHADS₂ index score of ≥ 2).

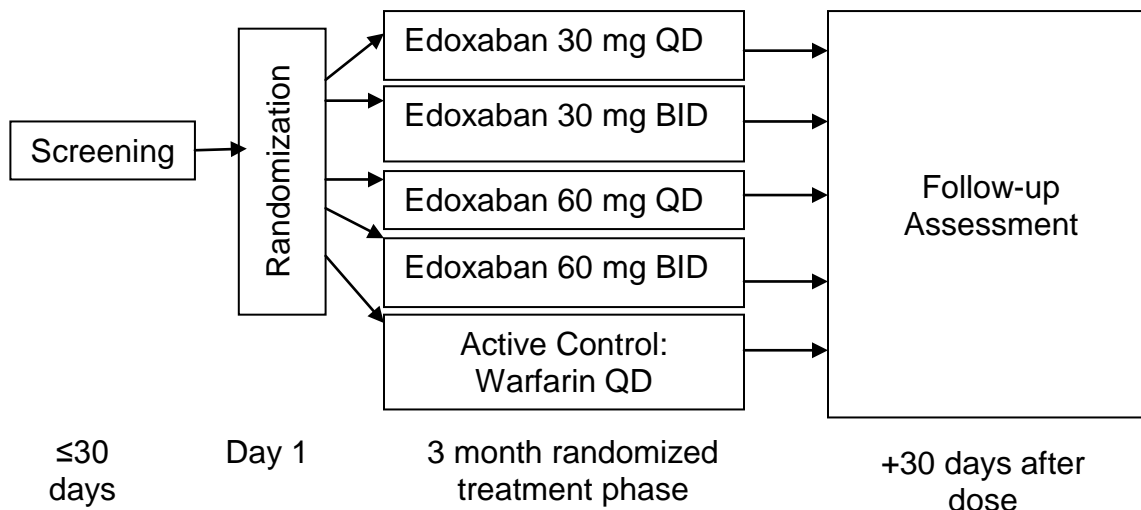
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Schema:



Note: Edoxaban 60 mg bid dose regimen was terminated by IDMC recommendation on 14 Jan 2008. Before the IDMC recommended termination of the 60 mg bid edoxaban dose regimen, subjects were randomized in a 1:1:1:1:1 ratio to treatment with one of four edoxaban dose regimens or warfarin. After the IDMC recommendation, subjects were randomized to one of the remaining three edoxaban dose regimens or warfarin.

PD sampling occurred before dosing on the Day 1 visit and on Day 28 ± 2 days. AEs were collected throughout the trial. PK samples were acquired between 1 and 3 hours after dosing on day 28± 2 days.

Primary safety endpoints: ALT or AST elevations ≥3 times the upper limit of normal (ULN) and/or total bilirubin (TBL) elevations ≥2 times the ULN and major plus other clinically relevant non-major bleeding events.

The definition of major bleeding events in this study was derived from the International Society on Thrombosis and Hemostasis. Analysis of bleeding events was based on the adjudication provided by the blinded and independent CEC.

Main enrollment criteria:

1. Male or female and 18 to 85 years of age, inclusive.
2. Persistent NVAf
3. A CHADS₂ index score of at least 2
4. Not have a condition associated with high risk of bleeding or other acute or serious chronic condition

Blinding:

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Subjects, the Investigator, and the Sponsor were blinded to the edoxaban dose regimen (i.e., 30 mg qd, 30 mg bid, 60 mg qd, or 60 mg bid), but not to randomization to edoxaban or warfarin, which was administered open-label. To maintain the edoxaban dose regimen blind, matching placebo for edoxaban was used for the second dose of the day for those subjects randomized to the qd regimens.

Primary Safety Variables:

1. Major bleeding events, clinically relevant non-major bleeding events, or both.
2. ALT or AST $\geq 3 \times$ ULN, TBL $\geq 2 \times$ ULN, or both (not necessarily simultaneously)

Primary Efficacy Analysis:

Although the study was not designed to evaluate efficacy, MACEs were recorded. The proportion of subjects experiencing MACE during the 3-month treatment period was summarized by treatment group with a 95% Clopper-Pearson confidence interval (CI) for the Safety Analysis Set. MACE was defined as stroke (ischemic or hemorrhagic), SEE, MI, cardiovascular death, and hospitalization for any cardiac condition.

Clinical Events Committee:

The CEC followed its own charter for processing and adjudicating bleeding events. The CEC adjudicated bleeding events independently of the Investigators' assessments and were blinded to the subject's treatment.

Amendments:

There were 5 amendments but only amendment # 3 (23 Jan 2008) is important to include in this summary because it substantively altered the conduct of the study. The amendment stated that in accordance with the recommendation of the IDMC (14 Jan 2008), randomization to the 60 mg bid dose regimen group was discontinued and Investigators were notified that subjects previously randomized to the 60 mg bid dose regimen were to discontinue study medication immediately and be evaluated at an end-of-treatment visit. The reason for the IDMC recommendation was an increased incidence of bleeding in the 60 mg bid regimen relative to the other treatment arms.

Disposition of Subjects:

There was an average of 242 (minimum 235 to maximum 251) subjects randomized to all treatment groups except for the edoxaban 60 mg bid group which had only 180 subjects, less than expected because of the IDMC's recommendation to discontinue this group before the completion of the study for excessive major bleeding rates. Almost all subjects were in the per protocol analysis and in the pharmacodynamic analysis set.

Study completion status of subjects in the safety analysis set is shown in Table 112. Most subjects completed except in the 60 mg bid arm. Approximately 30% of the subjects who were randomized to the 60 mg bid arm had completed before the IDMC decision to discontinue the arm of the study. The rest of the subjects in that arm (~70%) were withdrawn prematurely. There were more withdrawals in the edoxaban groups than in the warfarin group, mostly because of "withdrawal of consent" or adverse

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events. Because warfarin was open-label subjects and investigators knew if they were on or dispensing edoxaban. This along with the knowledge that the IDMC recommended discontinuation of one of the edoxaban treatment arms probably biased the early withdrawals.

Table 112: Disposition of Subjects: Safety Analysis Set

Variable	Edoxaban Daily Dose				Warfarin (N = 250)
	30 mg qd (N = 235)	30 mg bid (N = 244)	60 mg qd (N = 234)	60 mg bid (N = 180)	
n (%) Completed	200 (85.1)	207 (84.8)	204 (87.2)	52 (28.9)	226 (90.4)
n (%) Withdrawn	35 (14.9)	37 (15.2)	30 (12.8)	128 (71.1)	24 (9.6)
During Treatment	34 (14.5)	35 (14.3)	27 (11.5)	118 (65.6)	23 (9.2)
After Treatment	1 (0.4)	2 (0.8)	3 (1.3)	10 (5.6)	1 (0.4)
Reasons for Withdrawal					
Adverse Event ^a	11 (4.7)	11 (4.5)	14 (6.0)	13 (7.2)	5 (2.0)
Protocol Violation	1 (0.4)	3 (1.2)	2 (0.9)	1 (0.6)	2 (0.8)
Death	3 (1.3)	3 (1.2)	1 (0.4)	0 (0.0)	2 (0.8)
Lost to Follow-up	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.6)	1 (0.4)
Withdrawal of Consent	16 (6.8)	16 (6.6)	7 (3.0)	8 (4.4)	12 (4.8)
Administrative	0 (0.0)	2 (0.8)	2 (0.9)	1 (0.6)	2 (0.8)
Not meet entry criteria	2 (0.9)	0 (0.0)	1 (0.4)	1 (0.6)	0 (0.0)
Other	2 (0.9)	2 (0.8)	2 (0.9)	103 (57.2)	0 (0.0)
IDMC Decision	N/A	N/A	N/A	100 (55.6)	N/A

Source: PRT018 clinical study report, p. 55

Most subjects except for those in the 60 mg BID group had ≥ 84 days of treatment. Aside from the 60 mg BID treatment group, the exposure among groups was relatively well matched.

Table 113: Extent of Exposure: Number (%) of subjects in Safety Analysis Set

	DU-176b Daily					
Statistics	Any Dose (N = 893)	30 mg qd (N = 235)	30 mg bid (N = 244)	60 mg qd (N = 234)	60 mg bid (N = 180)	Warfarin (N = 250)
Cumulative days on treatment						
≥1 - <7	37 (4.1)	10 (4.3)	10 (4.1)	6 (2.6)	11 (6.1)	6 (2.4)
≥7 - <15	36 (4.0)	3 (1.3)	7 (2.9)	5 (2.1)	21 (11.7)	5 (2.0)
≥15 - <21	13 (1.5)	4 (1.7)	2 (0.8)	2 (0.9)	5 (2.8)	1 (0.4)
≥21 - <28	19 2.1)	5 (2.1)	4 (1.6)	5 (2.1)	5 (2.8)	2 (0.8)
≥28 - <42	37 (4.1)	6 (2.6)	4 (1.6)	4 (1.7)	23 (12.8)	5 (2.0)
≥42 - <56	41 (4.6)	2 (0.9)	5 (2.0)	4 (1.7)	30 (16.7)	1 (0.4)
≥56 - <70	22 (2.5)	3 (1.3)	2 (0.8)	1 (0.4)	16 (8.9)	4 (1.6)
≥70 - <84	201 (22.5)	54 (23.0)	62 (25.4)	55 (23.5)	30 (16.7)	87 (34.8)
≥84	487 (54.5)	148 (63.0)	148 (60.7)	152 (65.0)	39 (21.7)	137 (54.8)
Mean duration (Days)	71.5	75.8	76.0	77.5	52.3	79.6
Mean daily dose, mg	63.3	29.8	59.2	59.7	117.1	4.5
Mean Compliance (%)	98.4	98.8	98.4	98.8	97.3	98.2

Source: PRT018 clinical study report, p. 65

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Demographic Characteristics:

The demographic and other baseline characteristics were well matched across treatment groups. However, the demographic and baseline characteristics were somewhat different than what was seen in ENGAGE AF with the subjects in PRT-018 being younger, more often Caucasian, and almost entirely from Eastern Europe. Also, subjects in PRT-018 were more likely to be on aspirin at baseline, and have more ischemic heart disease and heart failure. However, they were at lower risk for endpoint events (fewer subjects with CHADS₂ scores ≥ 3).

Table 114: Demographic Characteristics of the Phase 2 and 3 trials (Safety analysis set)

Characteristic	PRT-018 Range by treatment group	ENGAGE AF Range by treatment group
Caucasian	97.2% to 98.0%	80.7% -81%
Eastern European	90.6% to 93.3%	33.8% -33.9%
Male	59.6% to 65.2%	61.2% -62.5%
Age	64.7 to 66.0 years	70.5 -70.6 years
Warfarin naïve	57.4% to 67.7%	40.8% -41.2%
Aspirin at baseline	49.6% to 52.8%	28.7% -29.7%
Mean weight	87.75 kg to 88.95 kg	83.7 kg -84.2 kg
CHADS ₂ score ≥ 3	36% to 37.2%	52.6% -54%
Prior Diabetes	17.9% -25%	35.9% - 36.4%
Prior Stroke or TIA	16.8% - 21.7%	28.1% - 28.5%
Prior Ischemic Heart Disease	62.7% -69.6%	32.9% - 33.7%
Prior Congestive Heart Failure	87.2% -88.8%	56.6% - 58.3%

Source: PRT-018 CSR, p. 57, 58 and source for ENGAGE AF data is CSR, p. 108 and 130.

Efficacy Endpoint: This study was neither designed nor powered to evaluate efficacy. Nevertheless, it is interesting to examine the major adverse cardiovascular events (MACE) that occurred during the treatment period. MACE, a secondary endpoint, was defined as the composite of stroke [ischemic or hemorrhagic], SEE, MI, CV death, and hospitalization for any cardiac condition. No central adjudication was done for these events. The analysis was based on Investigators' interpretations.

Subjects with MACEs during the treatment period are summarized in Table 115. The treatment period was defined as the time from the first dose of study drug through the day after the last dose. The numbers in the rows are events; a subject with multiple MACEs will show up in multiple rows and a subject with one MACE that fits multiple categories will appear in multiple rows. The number of MACEs during the treatment period was low in each treatment group but the lowest frequency of events was seen in

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the 60 mg bid group suggesting the possibility of a dose relationship. Because of the low number of overall events, the applicant felt that conclusions regarding the dose of edoxaban could not be made based on this endpoint. Nevertheless, if they were aiming for noninferiority on efficacy for their Phase 3 trial, the 30 mg and 60 mg qd doses appeared to have similar rates of MACE compared to warfarin.

Table 115: Major Adverse Cardiovascular Events in Study PRT-018

	Edoxaban Daily Dose				Warfarin (N = 250)
	30 mg qd (N = 235)	30 mg bid (N = 244)	60 mg qd (N = 234)	60 mg bid (N = 180)	
MACE, n (%) [CI]	4 (1.7) [0.5, 4.3]	6 (2.5) [0.9, 5.3]	10 (4.3) [2.1, 7.7]	2 (1.1) [0.1, 4.0]	6 (2.4) [0.9, 5.2]
Any Stroke, n (%) [CI]	1 (0.4) [0.0, 2.3]	2 (0.8) [0.1, 2.9]	1 (0.4) [0.0, 2.4]	2 (1.1) [0.1, 4.0]	4 (1.6) [0.4, 4.0]
SEE, n (%) [CI]	1 (0.4) [0.0, 2.3]	1 (0.4) [0.0, 2.3]	0 (0.0) [0.0, 1.6]	0 (0.0) [0.0, 2.0]	0 (0.0) [0.0, 1.5]
Any Stroke and/or SEE, n (%) [CI]	1 (0.4) [0.0, 2.3]	3 (1.2) [0.3, 3.6]	1 (0.4) [0.0, 2.4]	2 (1.1) [0.1, 4.0]	4 (1.6) [0.4, 4.0]
MI, n (%) [CI]	2 (0.9) [0.1, 3.0]	1 (0.4) [0.0, 2.3]	2 (0.9) [0.1, 3.1]	0 (0.0) [0.0, 2.0]	0 (0.0) [0.0, 1.5]
Cardiovascular Death, n (%) [CI]	2 (0.9) [0.1, 3.0]	4 (1.6) [0.4, 4.1]	0 (0.0) [0.0, 1.6]	0 (0.0) [0.0, 2.0]	2 (0.8) [0.1, 2.9]
Hospitalization for any Cardiac Condition, n (%) [CI]	2 (0.9) [0.1, 3.0]	2 (0.8) [0.1, 2.9]	7 (3.0) [1.2, 6.1]	0 (0.0) [0.0, 2.0]	1 (0.4) [0.0, 2.2]
Acute pulmonary edema	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Angina pectoris	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Angina unstable	1 (0.4)	1 (0.4)	3 (1.3)	0 (0.0)	0 (0.0)
Aortic aneurysm	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Cardiac failure	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiomyopathy	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intestinal angina	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: PRT-018 CSR

Safety: It is important to note that the exposure to the 60 mg bid was less than exposure in the other treatment groups and this should be kept in mind when evaluating the results. The mean duration of exposure was about 77 days in all treatment groups except for the 60 mg bid group which was 52.3 days because the IDMC recommended early termination of this group. Compliance was close to 99%.

All reported bleeding events were centrally adjudicated by the CEC and categorized as major, clinically relevant non-major, or minor based on prespecified criteria (Table 116).

The incidence of 3 different categories of bleeding in PRT-018 (overall, major bleeding and major bleeding or clinically relevant non-major bleeding) is shown in Table 117. The edoxaban 60 mg bid group had the highest incidence of bleeding events during the treatment period. The differences between the edoxaban 60 mg bid group and the

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warfarin group in the incidences of overall bleeding events, major and major or clinically relevant non-major bleeding events were statistically significant.

The edoxaban 30 mg bid group also had a statistically higher observed incidence than the warfarin group for major or clinically relevant non-major bleeding events, but not for major bleeding alone or overall bleeding.

The edoxaban 30 and 60 mg qd groups were comparable in bleeding rates to warfarin.

Table 116: Bleeding Event Adjudication

Major bleeding events:	<p>Symptomatic bleeding in critical areas or organs:</p> <ul style="list-style-type: none">• Retroperitoneal• Intracranial• Intraocular• Intraspinous• Intra-articular• Pericardial• Intramuscular with compartment syndrome <p>Any other overt bleeding event associated with one of the following outcomes:</p> <ul style="list-style-type: none">• Fatal• Hemoglobin drop of ≥ 2 g/dL (1.24 mmol L^{-1})• Transfusion ≥ 2 units of packed red blood cells or whole blood• Hemoglobin drop of ≥ 1 g/dL AND transfusion ≥ 1 unit of packed red blood cells or whole blood
Clinically relevant non-major bleeding events:	<ul style="list-style-type: none">• Any bleeding event reported as an SAE that does not fit the definition of a major bleeding event• Any bleeding event resulting in temporary discontinuation of study medication or other anti-platelet agent• Any bleeding event resulting in permanent discontinuation of study medication or other anti-platelet agent• Spontaneous skin hematoma $\geq 25 \text{ cm}^2$• Spontaneous ear-nose-throat (ENT) bleeding ≥ 5 minutes requiring medical attention• Macroscopic hematuria or urethral bleeding requiring medical attention• Spontaneous gastrointestinal (GI) or rectal bleeding requiring medical attention• Gingival bleeding ≥ 5 minutes requiring medical attention• Any other bleeding event reported by the Investigator, considered clinically significant by the CEC
Minor bleeding events:	Minor bleeding events that do not fulfill the criteria of a major bleeding event or a clinically relevant non-major bleeding event

Source: PRT-018 CSR, p. 33

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Table 117: Incidence of Bleeding in PRT-018 during the treatment period

	Edoxaban Daily					Warfarin (N = 250)
	Any Dose	30 mg qd (N = 235)	30 mg bid (N = 244)	60 mg qd (N = 234)	60 mg bid (N = 180)	
All bleeding, n (%)	94 (10.5)	13 (5.5)	31 (12.7)	17 (7.3)	33 (18.3)	20 (8.0)
95% CI ^a	8.6, 12.7	3.0, 9.3	8.8, 17.5	4.3, 11.4	13.0, 24.8	5.0, 12.1
Difference vs warfarin		-2.5%	4.7%	-0.7%	10.3%	
95% CI ^b		-6.9, 2.0	-0.7, 10.1	-5.5, 4.0	3.8, 16.9	
p-value ^c		0.367	0.104	0.864	0.002	
Major or CR non-major bleeding, n (%)	54 (6.0)	7 (3.0)	19 (7.8)	9 (3.8)	19 (10.6)	8 (3.2)
95% CI ^a	4.6, 7.8	1.2, 6.0	4.8, 11.9	1.8, 7.2	6.5, 16.0	1.4, 6.2
Difference vs warfarin		-0.2%	4.6%	0.6%	7.4%	
95% CI ^b		-3.3, 2.9	0.6, 8.6	-2.6, 3.9	2.4, 12.3	
p-value ^c		1.000	0.029	0.807	0.002	
Major bleeding, n(%)	12 (1.3)	0 (0.0)	5 (2.0)	1 (0.4)	6 (3.3)	1 (0.4)
95% CI ^a	0.7, 2.3	0.0, 1.6	0.7, 4.7	0.0, 2.4	1.2, 7.1	0.0, 2.2
Difference vs warfarin		-0.4%	1.6%	0.0%	2.9%	
95% CI ^b		-1.2, 0.4	-0.3, 3.6	-1.1, 1.2	0.2, 5.7	
p-value ^c		1.000	0.119	1.000	0.023	

Percentages are based on the number of patients in each group in the safety analysis set.

Note: CR = clinically relevant; CI = confidence interval.

a: 95% Clopper-Pearson confidence interval within treatment group.

b: 95% confidence interval for the difference in percentages between each DU-176b group and the warfarin group.

c: Fisher's exact test p-value for incidence of DU-176b dose group versus warfarin.

Source: PRT-018 CSR

Warfarin management:

It is important to evaluate how well the warfarin group was managed in order to ensure comparability of treatment arms. The time in target INR, below target and above target is shown in Table 118. It took half the treatment period to achieve time in therapeutic range (TTR) over 50%. TTR ranged from a minimum of 6.6% at baseline to a maximum of 50.4% at Day 42. Most of the subjects outside of therapeutic range were subtherapeutic (ranging from 93% at time 0 to 40.5% at the last week of treatment), with supratherapeutic values occurring much less often (ranging from 0.4% at time 0 to 11% at Day 21). It is hard to evaluate the comparability of the bleeding rates in the edoxaban arms to coumadin when the warfarin arm was not managed well. Nevertheless, the sponsors decided to use this dose ranging trial to select their dose. A more prudent approach may have been to redo this trial and add a higher QD dose.

Clinical Review
Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
NDA 206316
Established Drug Name: Edoxaban; Proposed trade name: Savaysa

Table 118: Time in Target INR, below target INR and above target INR in the warfarin treatment group

INR Range	Number (%) of Subjects in the Warfarin Group								
	Baseline (N = 243)	Day 7 (N= 234)	Day 14 (N = 227)	Day 21 (N = 228)	Day 28 (N = 229)	Day 42 (N = 228)	Day 56 (N = 224)	Day 70 (N = 224)	Day 84 (N = 215)
< 2.0	226 (93.0)	174 (74.4)	129 (56.8)	122 (53.5)	106 (46.3)	93 (40.8)	93 (41.5)	93 (41.5)	87 (40.5)
≥ 2.0 to ≤ 3.0 (target)	16 (6.6)	50 (21.4)	74 (32.6)	81 (35.5)	98 (42.8)	115 (50.4)	114 (50.9)	110 (49.1)	108 (50.2)
> 3.0	1 (0.4)	10 (4.3)	24 (10.6)	25 (11.0)	25 (10.9)	20 (8.8)	17 (7.6)	21 (9.4)	20 (9.3)

Note: Investigators adjusted warfarin doses based on local laboratory INR readings.

Source: Table 10.2 of Clinical Study Report DU176b-PRT018. Percentages are based on number of subjects at each visit.

Clinical Review
 Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
 NDA 206316
 Established Drug Name: Edoxaban; Proposed trade name: Savaysa

APPENDIX 10 Comparison between ENGAGE AF and other trials with novel anticoagulants (NOACs) and warfarin/ placebo trials

Table 119: Constancy Assumption Table comparing ENGAGE-AF to other NOAC Trials

	Apix vs. W ARISTOTLE (53 mos/1.7 yr med tx duration)	Riva vs. W ROCKET (46 mos/ 1.4 yr med. tx duration)	Dabi vs. W RE-LY (40 months/ 1.8 yr med treatment duration)	Edox vs. W ENGAGE AF (53 mos/2.5 yr med tx duration)
N(ITT)	18201	14171	12098	21105
Blinding	Double dummy (DD)	DD	Open-label	DD
% female	35	40	36	38
% with h/o stroke/TIA/SEE	19	55	22	28
Mean CHADS₂ Score	2.1	3.5	2.1	2.5
% w prior VKA therapy	56	62	61	59
Mean TTR (%)	62	56	64	65
Study Drug Int. (%)	39.8 (counted > 3 d)	35.2 (counted >3d)	29 (counted all)	63.3 (counted > 3d)
Study Drug Discontinuation (%)	26.4	35	17.9	34
Primary endpoint	Stroke/SEE	Stroke/SEE	Stroke/SEE	Stroke/SEE in mITT/on Tx
Stroke/SEE Event rate warfarin (%/yr)	1.60	2.4	1.71	1.5
Stroke/SEE Event rate test agent (%/yr)	1.27	2.1	1.11	1.18
HR or Δ (95% CI)	0.79 (95% CI=0.66, 0.95)	0.88(95% CI=(0.74, 1.03)	0.65 (95% CI=0.52, 0.81)	0.79 (97.5% CI=0.63, 0.99)

Reviewer's Table

Table 120: Constancy Assumption Table comparing ENGAGE-AF to Warfarin/Placebo Trials

	5 primary prevention studies (W vs. Pbo)	EAFT (W vs. pbo)³³	ENGAGE-AF
N (ITT)	2461	439	21105
% female	0-47	43	38
% with h/o stroke/TIA/SEE	6	100	28
Target INR	1.4-2.8 to 2.0-4.5	2.5-4.0	2-3
Mean TTR or % in range	42-83	59	65
Endpoint	Ischemic stroke; to Str/TIA/SEE	Stroke	Stroke + SEE
Event rate W (%/yr)	0.62 – 3.08	4	1.5
Event rate Experimental Drug or Pbo (%/yr)	2.99-8.2	12	1.18
HR (95% CI)	0.21 – 0.65	0.34 (0.2, 0.57)	0.79 (97% CI=0.63, 0.99)

Reviewer's Table

³³ Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) study group. Lancet 1993;342:1255-62.

APPENDIX 11 SAEs results during the overall study period

Table 121 Incidence of SAEs by SOC ($\geq 0.5\%$ more frequently in the Edoxaban group) and related PT terms during overall period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Subjects with at least one SAE	3031 (43.3%)	2979 (42.5%)	3118 (44.5%)
Blood And Lymphatic System Disorders	89 (1.3%)	128 (1.8%)	83 (1.2%)
Anemia	53 (0.8%)	70 (1.0%)	45 (0.6%)
Iron Deficiency Anemia	13 (0.2%)	29 (0.4%)	11 (0.2%)
Any Anemia Related PT*	77 (1.1%)	113 (1.6%)	68 (0.9%)
Respiratory, Thoracic And Mediastinal Disorders	306 (4.4%)	297 (4.2%)	270 (3.9%)
Chronic Obstructive Pulmonary Disease	105 (1.5%)	93 (1.3%)	88 (1.3%)
Dyspnea related PT*	28 (0.4%)	27 (0.4%)	12 (0.3%)
Respiratory Failure	26 (0.4%)	29 (0.4%)	20 (0.3%)
Pleural Effusion	23(0.3%)	14 (0.2%)	19 (0.3%)
Pulmonary Edema	12 (0.2%)	11 (0.2%)	8 (0.1%)
Interstitial Lung Disease	8 (0.1%)	9 (0.1%)	4 (0.06%)

Reviewer's analysis using the Applicant's dataset: AEEV1, DM and CDER CSC MAED tool

*Anemia-related PT include hematocrit abnormal, hematocrit decreased, hemoglobin decreased, red blood cell count decreased, and any PT term containing anemia

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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Table 122 Incidence of SAEs by SMQ of interest[†] during the overall study period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Hematopoietic erythropenia (SMQ)	58 (0.8%)	76 (1.1%)	53 (0.8%)
Acute central respiratory depression (SMQ)	111 (1.6%)	144 (2.1%)	117 (1.7%)
Interstitial lung disease (SMQ)	18 (0.3%)	24 (0.3%)	12 (0.2%)
Acute Renal Failure (SMQ)	94 (1.3%)	97 (1.4%)	107 (1.5%)
Hypersensitivity reactions ^a	175 (2.5%)	189 (2.7%)	173 (2.5%)
Torsade de pointes/QT prolongations (SMQ)	205 (2.9%)	199 (2.8%)	239 (3.4%)
Hepatic Disorder			
Liver function test elevation PTs ^b	13 (0.2%)	24 (0.3%)	16 (0.2%)
Drug related hepatic disorders-comprehensive search (SMQ)	84 (1.2%)	72 (1.0%)	134 (1.9%)
Drug related hepatic disorders-comprehensive search (SMQ), excluding INR increased PT	61 (0.9%)	59 (0.8%)	63 (0.9%)
Drug related hepatic disorders-severe events only— (SMQ)	37 (0.5%)	32 (0.5%)	33 (0.5%)
Hepatitis, non-infectious (SMQ)	9 (0.1%)	9 (0.1%)	3 (<0.1%)

Reviewer's analysis using the Applicant's dataset: AEEV1, DM and CDER CSC MAED tool

[†] SMQ broad terms were used for the analysis

- Hypersensitivity reactions include three SMQs: anaphylactic reaction, angioedema and severe cutaneous adverse reaction
- PTs include alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, blood bilirubin unconjugated increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, liver function test abnormal and transaminases increase

Clinical Review
 Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)
 NDA 206316
 Established Drug Name: Edoxaban; Proposed trade name: Savaysa

APPENDIX 12 OSE review of hepatic cases in ENGAGE AF

USUBJID	AGE	SEX	BMI	country	Txt	pALTx	pASTx	pALPx	pTBLx	severity	most likely cause
1004.0015	70	M	44.82	USA	E 30	11.27	7.6	2.8	3.67	moderate	common duct stone most likely
1031.0002	83	M	31.39	USA	E 30	3.65	2.8	3.4	5.33	serious	CA pancreatic head; later fatal
1130.0051	85	F	30.58	Argentina	E 30	5.54	2.94	1.6	4.25	fatal	pancreatic CA
1143.0042	72	M	28.69	Argentina	warf	7.63	8.47	3.7	6.08	serious	unexplained; cholestasi; warfarin unlikely
1167.0011	83	M	26.4	Argentina	E 60	9.17	12.6	2.37	2.67	fatal	myocardial infarction, pulmonary embolus
1726.0001	78	M	24.38	Germany	E 60	11.02	8.56	1.19	2.17	moderate	unexplained; negative rechallenge, Gilbert's
1905.0024	54	M	33.06	Czech R	warf	4.4	2.44	2.34	5.75	moderate	unexplained; negative rechallenge
1905.0052	74	F	32.87	Czech R	E 60	14.07	9.77	1.28	2.5	serious	no cause found; edoxaban 2 yrs. unlikely
1913.0028	70	M	34.72	Czech R	E 30	3.02	1.71	1.15	5.5	mild	common duct sludge, stone
2908.0071	74	M	24.84	Brazil	E 60	9.21	6.49	1.52	9.42	serious	common duct stone after 2 yrs edoxaban
3013.0002	58	M	25.16	Russia	E 60	3.33	2.52	0.59	2.02	mild	heart failure; Gilbert's syndrome
3018.0014	54	M	25.42	Russia	E 60	7.31	7.22	2.07	8.83	serious	gallbladder stones; cholecystectomy
3022.004	54	F	41.58	Russia	warf	3.62	8.56	1.33	3.83	serious	congestive heart failure
3061.0013	66	F	34.97	Russia	warf	10.65	4.39	5.95	2.92	mild	possible amiodarone-hepatitis
3108.0013	66	M	26.51	Columbia	warf	13.73	10.04	0.88	3.33	serious	heart failure; Gilbert's syndrome
3506.0006	65	M	29.83	Italy	E 60	5.23	8.04	8.29	9.58	serious	bile duct CA; died later
4005.0015	54	M	34.09	Ukraine	E 60	7.88	14.53	0.83	2.25	moderate	alcoholic hepatitis; negative rechallenge
4012.0038	34	M	28.62	Ukraine	warf	5.23	4.09	0.53	2.08	moderate	occult alcoholic hepatitis; not warfarin
4039.0006	63	M	22.98	Ukraine	E 60	3.98	4.91	0.58	2.67	moderate	uncertain; autoimmune hepatitis
4042.0013	68	M	26.18	Ukraine	E 60	4.08	3.54	1.72	2.5	fatal	heart failure, after 2 yrs on edoxaban
4335.0015	76	M	26.99	China	warf	8.25	2.51	1.4	3.58	serious	pneumonia, heart failure; no warfarin
4402.0012	46	M	31.35	India	E 60	23.73	25.11	1.57	3.92	serious	acute viral hepatitis E
4411.0004	70	M	20.2	India	warf	19.9	5.51	1.11	2.17	fatal	sepsis, heart failure, shock
4411.005	40	M	20.31	India	E 60	50.21	83.78	2.82	2.5	fatal	pneumonia, heart failure, shock
5003.0007	75	M	27.99	Poland	E 30	28.35	59.91	0.82	2.75	life-threatening	heart failure, shock - recovered
5031.0093	80	F	26.03	Poland	E 30	18.08	22.03	2.28	2.33	serious	probable heart failure
5032.0034	76	F	29.62	Poland	E 60	16.59	16.14	2.01	4.33	moderate	uncertain; negative rechallenge 3 yrs.
5033.0057	80	F	27.82	Poland	E 60	3.18	3.56	2.48	9.75	serious	pancreatic CA; later died

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

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5056.0039	77	M	26.9	Poland	E 60	16.54	11.24	1.17	2.08	serious	common duct stone; not edoxaban
5304.001	64	M	24.45	Bulgaria	E 30	5.63	7.62	1.04	2.25	mild	Gilbert syndrome; mild heart failure
5404.001	64	M	30.46	Hungary	E 30	19.77	22.13	2.49	3.83	serious	worse heart failure; Gilbert's syndrome
5409.001	64	M	38.4	Hungary	E 30	9	7.11	1.39	2.17	moderate	alcoholic hepatitis
5513.0004	79	M	33.5	Israel	warf	6.54	5.96	1.26	3.67	serious	gallbladder stones; later fatal sepsis
5609.0006	80	M	23.7	Romania	E 60	17.46	25.04	1.21	3.5	moderate	increased alcohol + acute viral hepatitis E
5622.0012	63	F	25.64	Romania	E 60	11.86	18.92	1.05	2.17	mild	uncertain; ?CHF; negative E rechallenge
6117.0011	76	M	27.11	Japan	E 60	7.06	7.93	1.72	4.17	serious	common duct stone
6186.0002	77	M	22.14	Japan	warf	4.67	2.84	16.23	7.25	serious	pancreatic CA; lost to follow-up
7003.0011	77	F	29.84	UK	E 60	3.54	2.92	3.73	7.75	serious	pancreatic CA; later fatal
7035.0002	66	M	32.2	UK	E 60	10.81	10.11	1.04	2.17	mild	uncertain; possible E-DILI;
7101.0002	43	M	31.24	USA	E 60	7.73	6.38	1.37	2.56	moderate	possible amiodarone; E rechallenge neg
7155.0004	82	F	19.18	USA	warf	4.24	3.56	2.42	2.92	mild	uti, poss nitrofur tox; E rechallenge neg
7306.0006	84	M	21.48	USA	warf	3.1	0.25	0.43	2.67	mild	uncertain; unlikely W; Gilbert's syndrome
7406.0039	68	F	32.44	India	warf	12.97	29.17	1.32	17.83	moderate	acute viral hepatitis B
1014.0005	78	M	31.63	USA	E 60	5.17	3.76	0.47	6.25	serious	not edoxaban; probable CA pancreas
1016.001	83	F	26.9	USA	E 60	5.84	5.31	6.35	23.58	serious	CA head of pancreas
1022.003	73	M	25.1	USA	Warf	66.56	109.04	0.72	2.67	fatal	acute heart failure, sepsis
1041.0011	78	F	35.94	USA	E 60	7.46	16.47	3.56	4.17	serious	very unlikely E; probable autoimmune hepatitis
1041.0035	73	M	38.35	USA	E 30	5.77	9.13	1.32	3.42	serious	probable heart failure; Klebsiella pneumonia
1095.0007	52	F	26.71	USA	Warf	12.7	8.72	1.37	4.17	serious	not warfarin, probable common duct stones
1127.0008	66	M	27.92	Argentina	E 60	6.23	8.67	0.93	2.5	fatal	heart failure, ischemic hepatopathy
1129.0045	73	M	24.5	Argentina	E 30	7.13	9.27	2.83	29.5	fatal	heart failure, ischemic hepatopathy
1408.0008	70	M	34.6	Peru	E 60	7.96	8.71	2.94	7	serious	not edoxaban; probable common duct stones
1627.0005	82	M	23.09	Canada	E 30	6	7.78	1.24	3.42	serious	common duct stones,
1908.0062	68	M	30.07	Czech R	E 30	3.25	1.62	0.65	2.17	mild	Gilbert syndrome; gallbladder stones
2035.0027	53	F	39.79	Canada	E 30	6.97	3.22	5.31	9.33	mild	very unlikely edoxaan; possible viral hepatitis
2045.0004	63	F	33.63	Canada	E 60	168.78	284.28	0.87	2.93	fatal	acute heart failure, shock
7440.0005	76	M	24.03	India	E 30	33.75	n.d.	2.61	3.75	fatal	cardiac arrest

Reviewer's Table. Source: OSE Hepatology Consultation

APPENDIX 13 Reported MedDRA Prefer Terms (PTs) for (a) Acute Renal Failure, SMQ (broad term), (b) Acute Renal Failure, SMQ (narrow term)

(a)

SMQ or PT Terms	Edoxaban 30mg (15mg DosAdj)	Edoxaban 60mg (30mg DosAdj)	Warfarin
Acute Renal Failure, SMQ	735 (10.50%)	741 (10.57%)	668 (9.53%)
Acute Prerenal Failure	3 (0.04%)	7 (0.10%)	3 (0.04%)
Albuminuria	2 (0.03%)	1 (0.01%)	0 (0.00%)
Anuria	0 (0.00%)	1 (0.01%)	0 (0.00%)
Azotemia	9 (0.13%)	3 (0.04%)	8 (0.11%)
Blood Creatinine Abnormal	0 (0.00%)	1 (0.01%)	0 (0.00%)
Blood Creatinine Increased	120 (1.71%)	129 (1.84%)	119 (1.70%)
Blood Urea Increased	70 (1.00%)	80 (1.14%)	82 (1.17%)
Creatinine Renal Clearance Abnormal	2 (0.03%)	1 (0.01%)	2 (0.03%)
Creatinine Renal Clearance Decreased	225 (3.21%)	242 (3.45%)	208 (2.97%)
Glomerular Filtration Rate Decreased	5 (0.07%)	12 (0.17%)	10 (0.14%)
Hypercreatininemia	3 (0.04%)	1 (0.01%)	2 (0.03%)
Nephritis	1 (0.01%)	0 (0.00%)	0 (0.00%)
Oliguria	1 (0.01%)	1 (0.01%)	2 (0.03%)
Proteinuria	86 (1.23%)	87 (1.24%)	86 (1.23%)
Renal Failure	117 (1.67%)	130 (1.85%)	136 (1.94%)
Renal Failure Acute	81 (1.16%)	65 (0.93%)	70 (1.00%)
Renal Function Test Abnormal	2 (0.03%)	1 (0.01%)	4 (0.06%)
Renal Impairment	144 (2.06%)	159 (2.27%)	99 (1.41%)
Renal Tubular Necrosis	1 (0.01%)	0 (0.00%)	1 (0.01%)
Tubulointerstitial Nephritis	2 (0.03%)	1 (0.01%)	2 (0.03%)
Urine Output Decreased	4 (0.06%)	0 (0.00%)	1 (0.01%)

Reviewer's Table, the Applicant's dataset: DM & AEEV1

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

(b)

SMQ or PT Terms	Edoxaban 30mg (15mg DosAdj)	Edoxaban 60mg (30mg DosAdj)	Warfarin
Acute Renal Failure, SMQ	346 (4.94%)	355 (5.06%)	305 (4.35%)
Acute Prerenal Failure	3 (0.04%)	7 (0.10%)	3 (0.04%)
Anuria	0 (0.00%)	1 (0.01%)	0 (0.00%)
Azotemia	9 (0.13%)	3 (0.04%)	8 (0.11%)
Oliguria	1 (0.01%)	1 (0.01%)	2 (0.03%)
Renal Failure	117 (1.67%)	130 (1.85%)	136 (1.94%)
Renal Failure Acute	81 (1.16%)	65 (0.93%)	70 (1.00%)
Renal Impairment	144 (2.06%)	159 (2.27%)	99 (1.41%)

Reviewer's Table, the Applicant's dataset: DM & AEEV

Clinical Review

Melanie Blank (clinical efficacy) and Tzu-Yun McDowell (clinical safety)

NDA 206316

Established Drug Name: Edoxaban; Proposed trade name: Savaysa

9.1 Literature Review/References

All references are in footnotes.

9.2 Labeling Recommendations

Possible labeling recommendations related to the observed elevated risk of stroke compared to warfarin in subjects with normal renal function are discussed Sec. 1 above, starting on p. 19.

9.3 Advisory Committee Meeting

A meeting of the CRDAC to discuss this NDA is scheduled for October 30, 2012. The expected focus of the meeting will be the observed increased relative risk of stroke compared to warfarin in subjects with normal renal function.

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/s/

MELANIE J BLANK
10/09/2014

MARTIN ROSE
10/09/2014

TZU-YUN C MCDOWELL
10/10/2014

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 ($\text{CrCL} \geq 80 \text{ mL/min}$), 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 $\text{CrCL} \geq 80 \text{ mL/min}$. 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 ($\text{CrCL} \geq 50 - < 80 \text{ mL/min}$), 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 \geq 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 carboxylesterase 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

(b) (4)

Drug product

(b) (4)

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 ($K_i=0.651$ nM) and factor Xa in the prothrombinase complex ($K_i= 0.903$ 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 formation².

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 populations³. 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.

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 bleeding⁴ 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 (K_i=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 CHADS₂ 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).

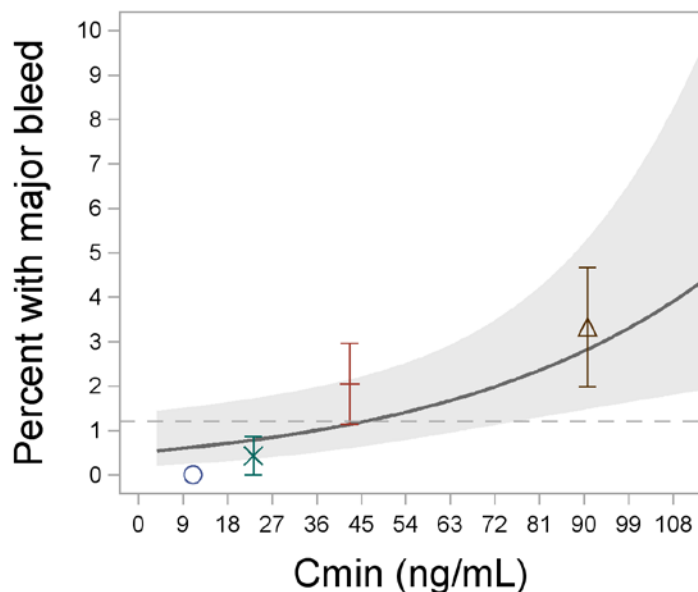


Figure 1: Pre-dose edoxaban concentration (Cmin) is a significant predictor of a major bleed.

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 (△)). 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 \geq 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)
\geq 80	1.41 (0.97 – 2.06)
>50 - <80	0.53 (0.40 – 0.70)
30 - \leq 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)
\geq 80	0.71 (0.55 – 0.90)
>50 - <80	0.90 (0.75 – 1.08)
30 - \leq 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 \geq 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)
\geq 80	60	27.3 (23.8 – 30.8)
>50 - <80	60	36.6 (33.0 – 40.6)
30 - \leq 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.

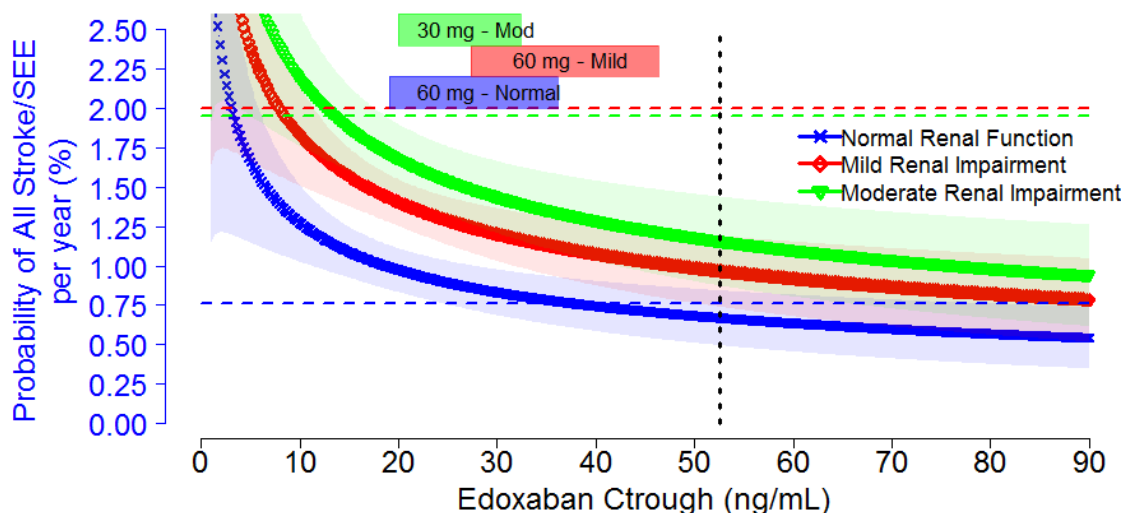


Figure 2: The exposure-response relationship for all stroke/SEE suggests a lower probability of stroke/SEE within 1 year with increasing edoxaban trough concentrations

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 (5th to 95th percentile) for edoxaban in each renal function group. The vertical dashed line indicates the 99th percentile of Edoxaban C_{trough} concentration.

Source: FDA Reviewer's Analysis

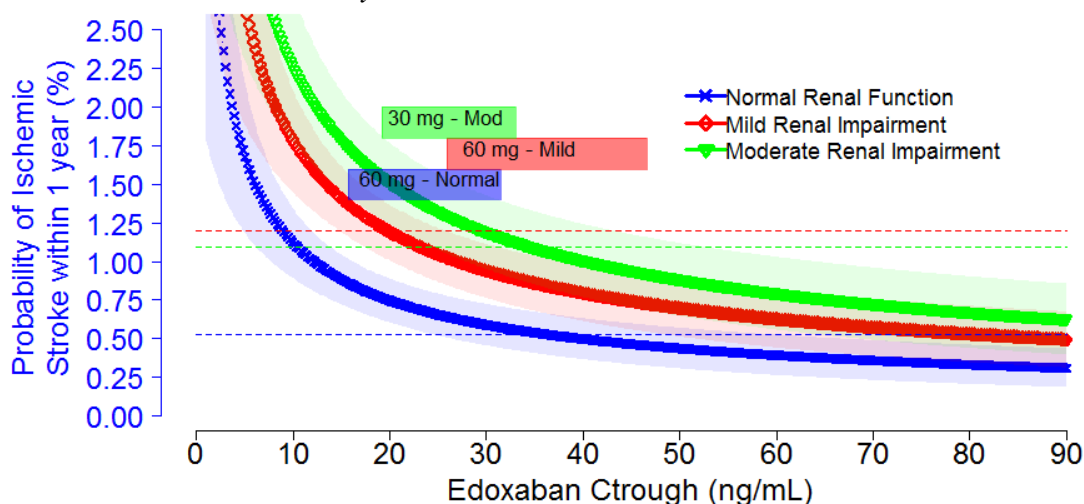


Figure 3: The exposure-response relationship for ischemic stroke suggests a lower probability of an ischemic stroke within 1 year with increasing edoxaban trough concentrations

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/fatal⁵ 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.

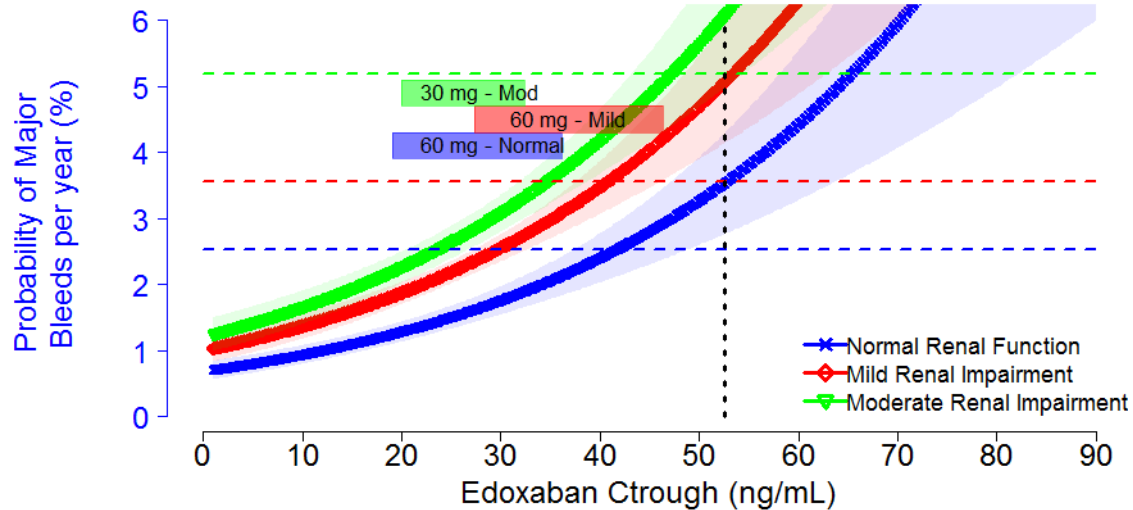


Figure 4: Exposure-Response relationship for major bleeds suggests increasing events with increasing edoxaban concentrations.

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 (5th to 95th percentile) for edoxaban in each renal function group in the edoxaban high dose arm. The vertical dashed line indicates the 99th 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

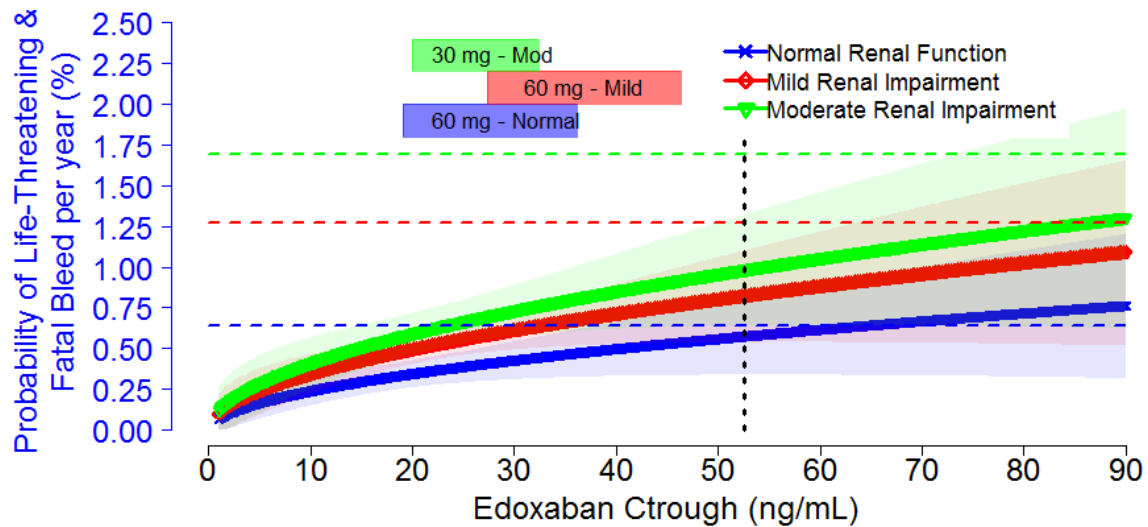


Figure 5: Exposure-Response relationship for life-threatening bleeds and fatal bleeds suggests increasing events with increasing edoxaban concentrations.

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.

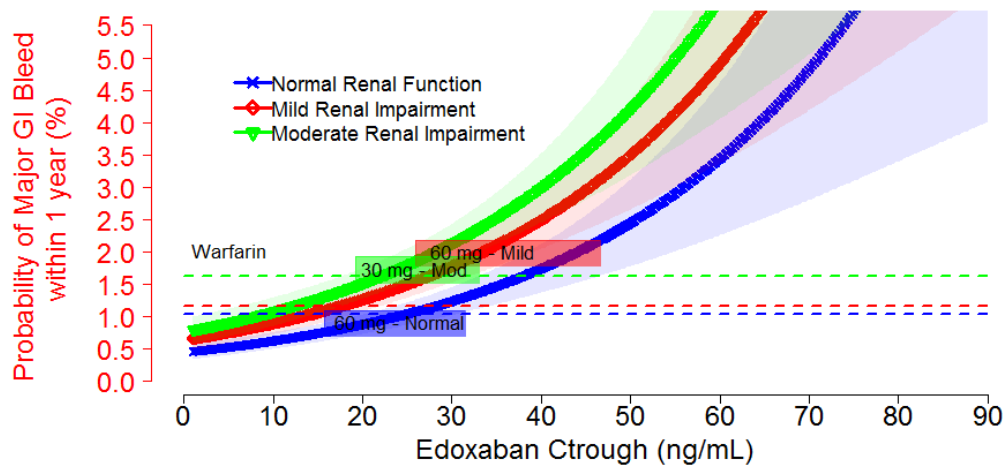


Figure 6: Exposure-Response relationship for major GI bleeds suggests increasing events with increasing edoxaban concentrations.

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).

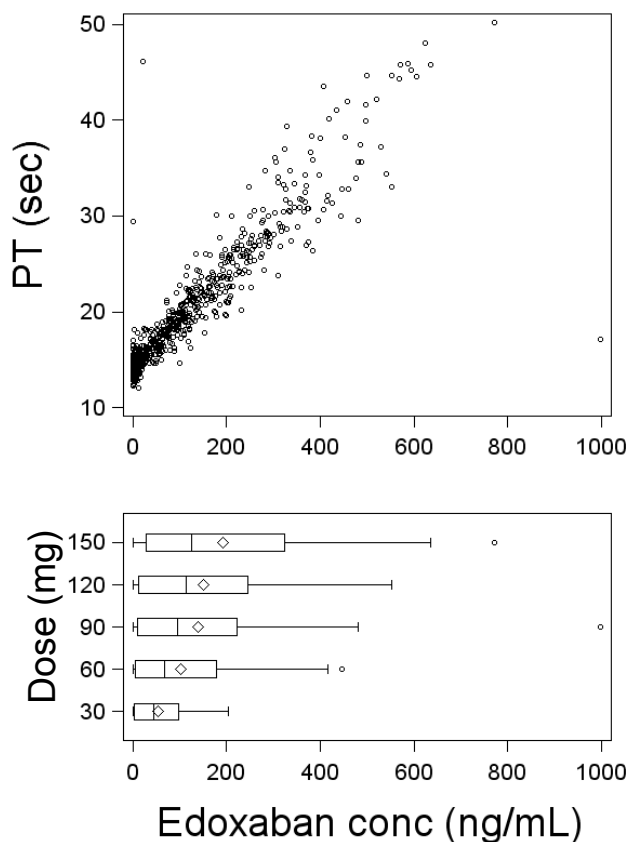


Figure 7: Edoxaban concentration – prothrombin time (PT) relationship in healthy subjects (n=10/group) following administration of a single oral dose of edoxaban tablet (Study PRT001).

Source: FDA Reviewer's Analysis

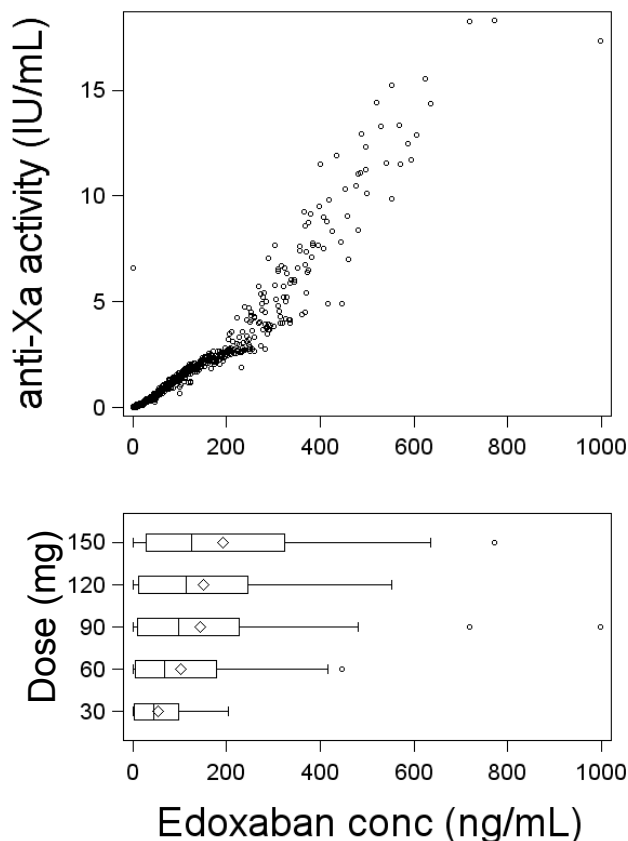


Figure 8: Edoxaban concentration - anti-Xa activity relationship in healthy subjects (n=5-10/group) following administration of a single oral dose of edoxaban tablet (Study PRT001).

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/mL⁶ 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 [¹⁴C]-edoxaban as a solution (Study PRT019), about 35% and 62% of the administered dose⁷ 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).

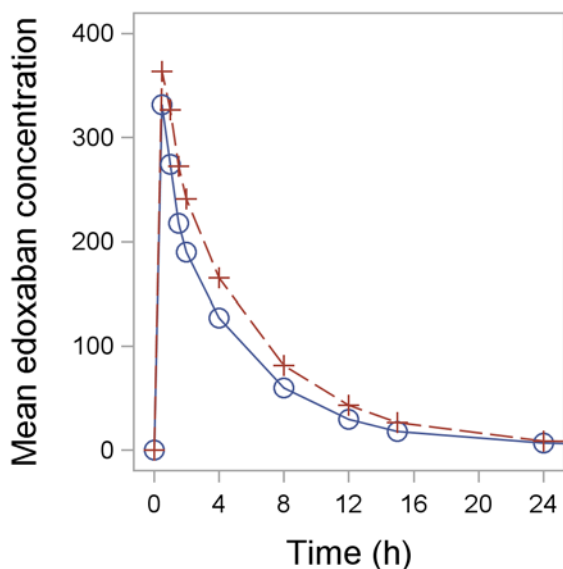


Figure 9: Mean plasma total radioactivity (+, ng eq/mL) and edoxaban (○, ng/mL) concentration versus time profile following administration of 60 mg ¹⁴C-edoxaban solution in six healthy individuals.

Source: FDA Reviewer's Analysis

⁶ Edoxaban C_{max} @ 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 carboxylesterase 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



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).

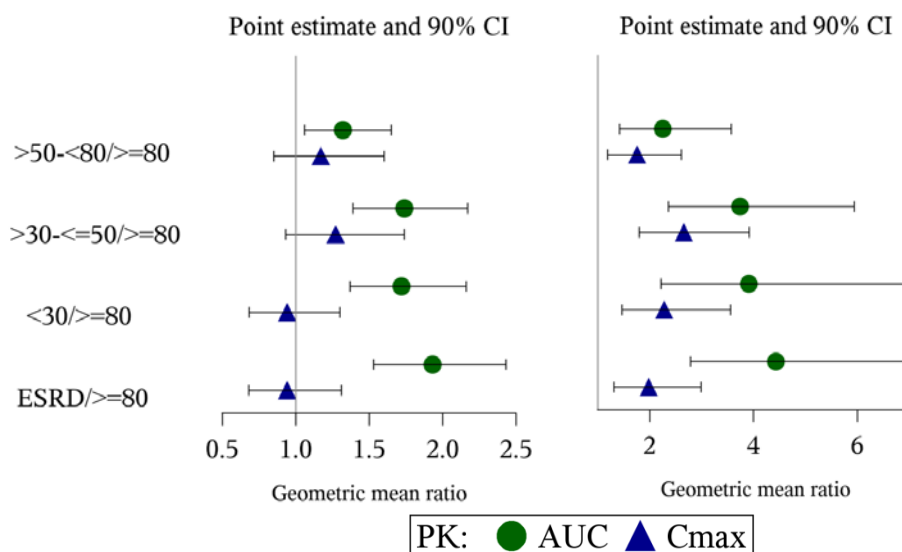


Figure 11: Total systemic exposure to edoxaban and D21-2393* is increased in individuals with impaired renal function. The closed circles represent the geometric mean ratio (test/reference) for AUCinf and Cmax and the horizontal line represents the 90%CI associated with the mean. *considered exploratory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

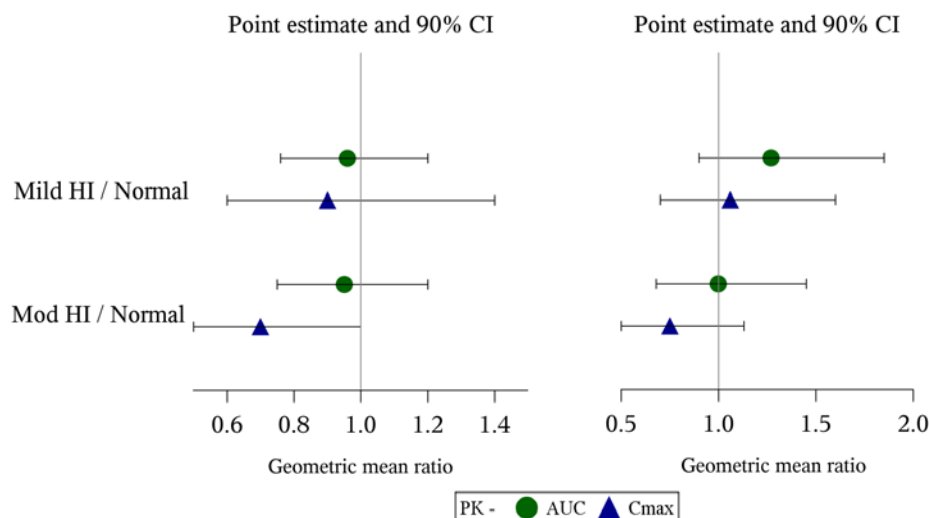


Figure 12: Total systemic exposure to edoxaban and D21-2393 in individuals with impaired hepatic function is similar to that in individuals with normal hepatic function. The closed circles represent the geometric mean ratio (test/reference) for AUCinf and Cmax; horizontal line represents the 90%CI associated 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	<i>ABCB1</i> 345 C/C	<i>ABCB1</i> 345 C/T	<i>ABCB1</i> 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 (CHADS₂ 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 ≤ 60 Kg was ~ 2 X 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 \leq 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 \leq 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 μ M) (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 its exposure $\geq 50\%$ 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.

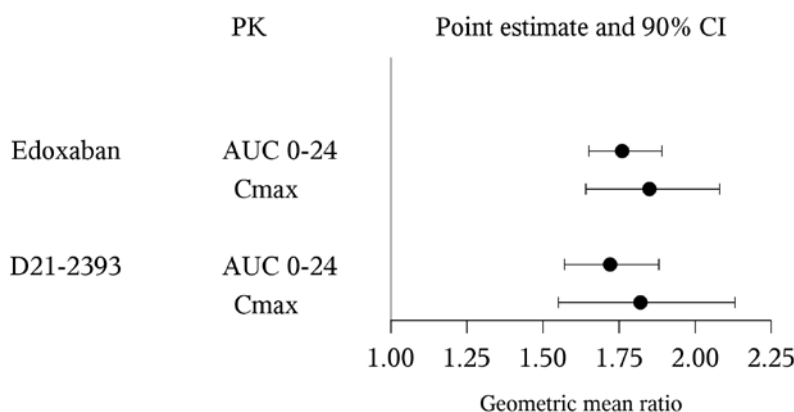


Figure 13: Co-administration of quinidine and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean

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.

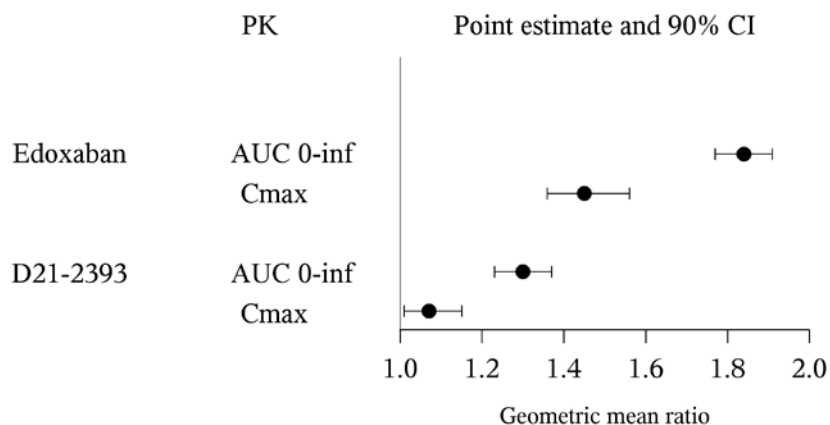


Figure 14: Co-administration of dronedarone and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

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).

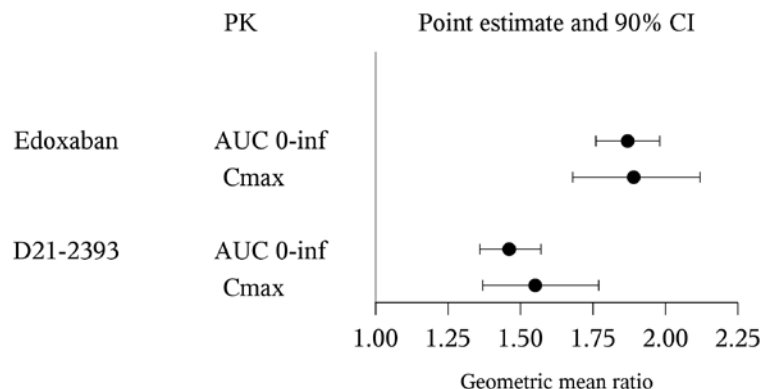


Figure 15: Co-administration of ketoconazole and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

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).

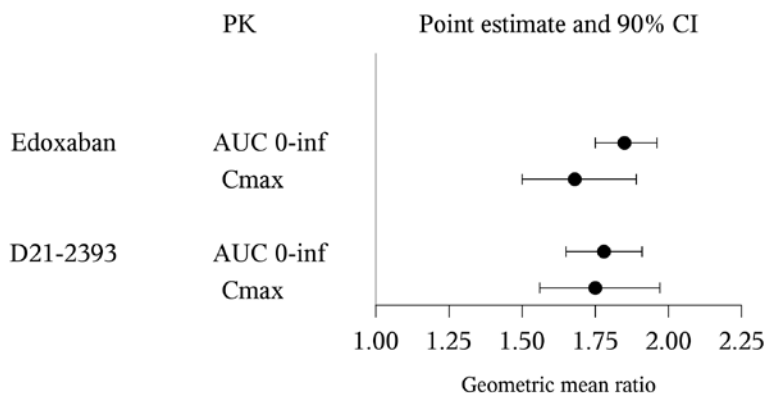


Figure 16: Co-administration of erythromycin and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

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).

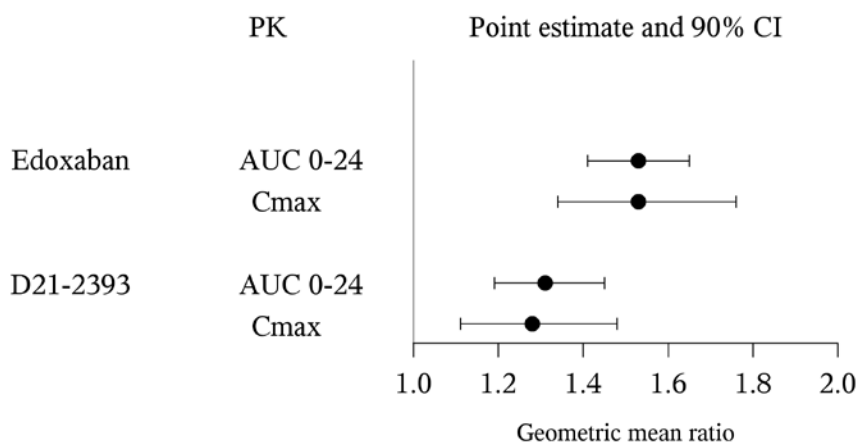


Figure 17: Co-administration of verapamil and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

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).

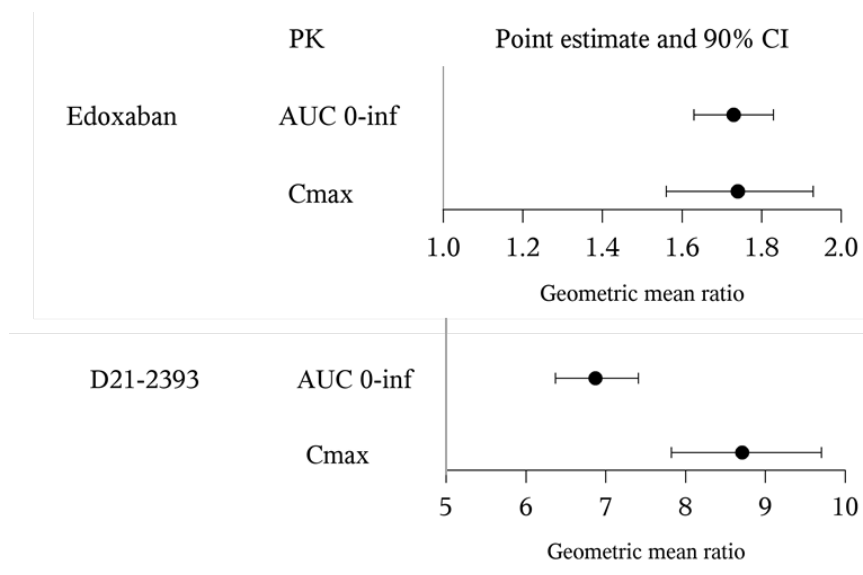


Figure 18: Co-administration of cyclosporine and edoxaban increases systemic exposure to edoxaban. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

Source: FDA Reviewer's Analysis

Metabolite to parent ratios increased from approximately 10 to 39% for AUC and from approximately 10 to 49% for C_{max}. 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 than that for warfarin (HR 0.97 (95%CI 0.74, 1.27) for edoxaban 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 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 $\mu\text{mol/L}$ was 4.53, 4.13, 3.97, 3.77 and 2.28×10^{-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 C_{24} 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 ($CRCL \geq 80$ 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 ($CRCL \geq 50 - <80$ 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.

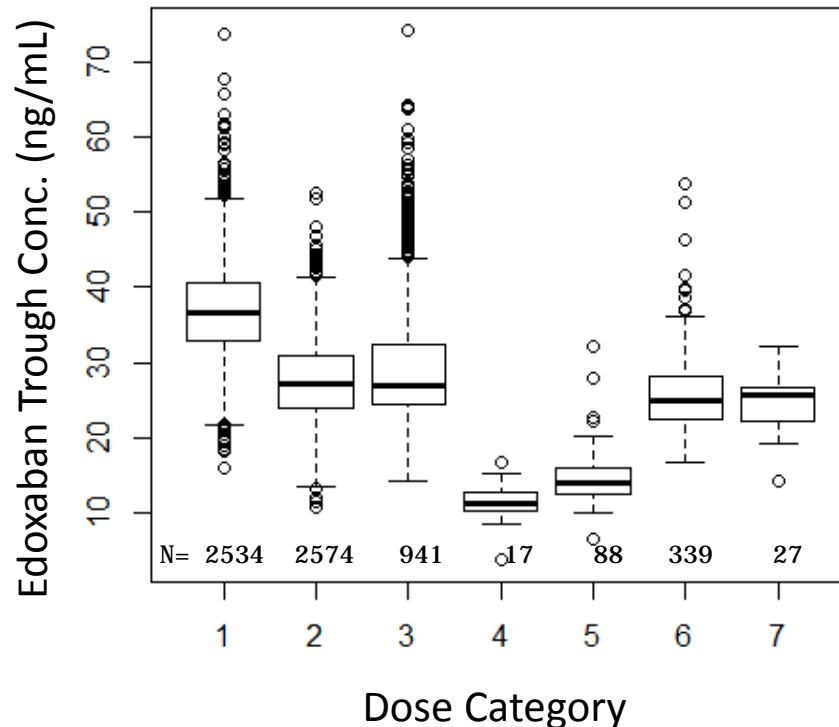
Table 12. Summary of edoxaban PK parameters C_{trough} and AUC by dose and patient demographic.

Patient Description					C _{trough}				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.

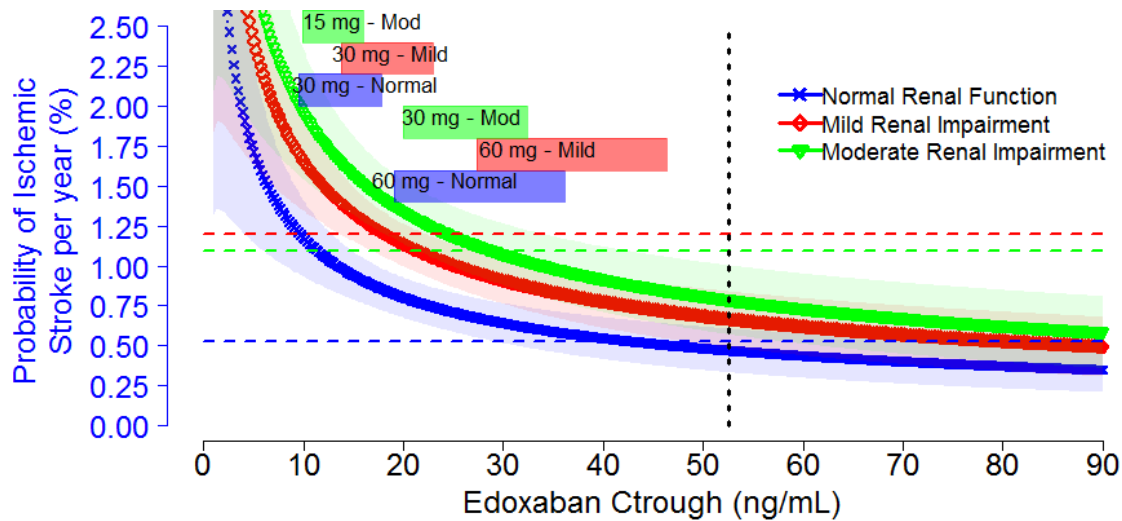
The analysis that has carried the most weight to date has been the comparison of ischemic stroke with life-threatening and fatal bleeds.

- 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.

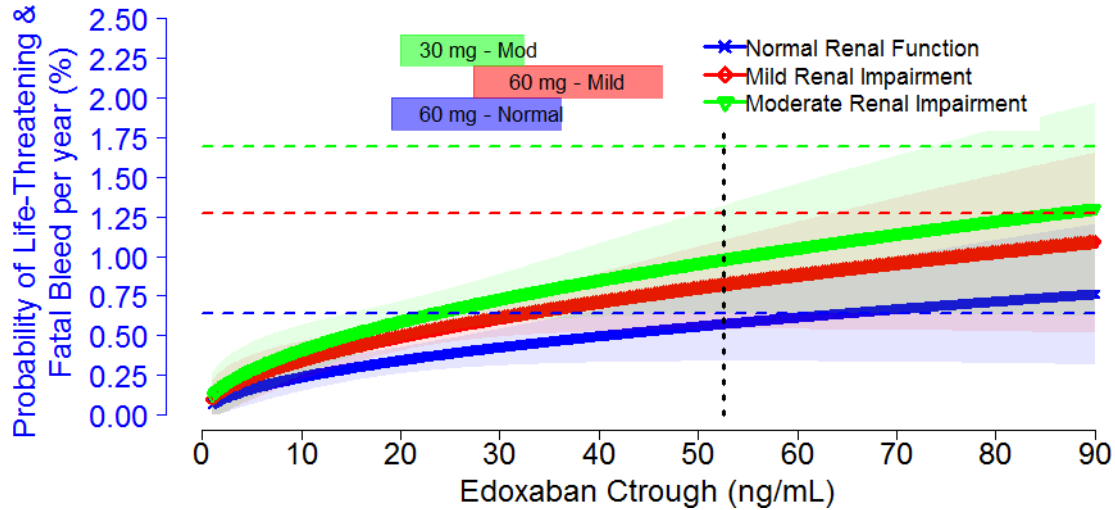


Source: FDA Reviewer's Analysis

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:

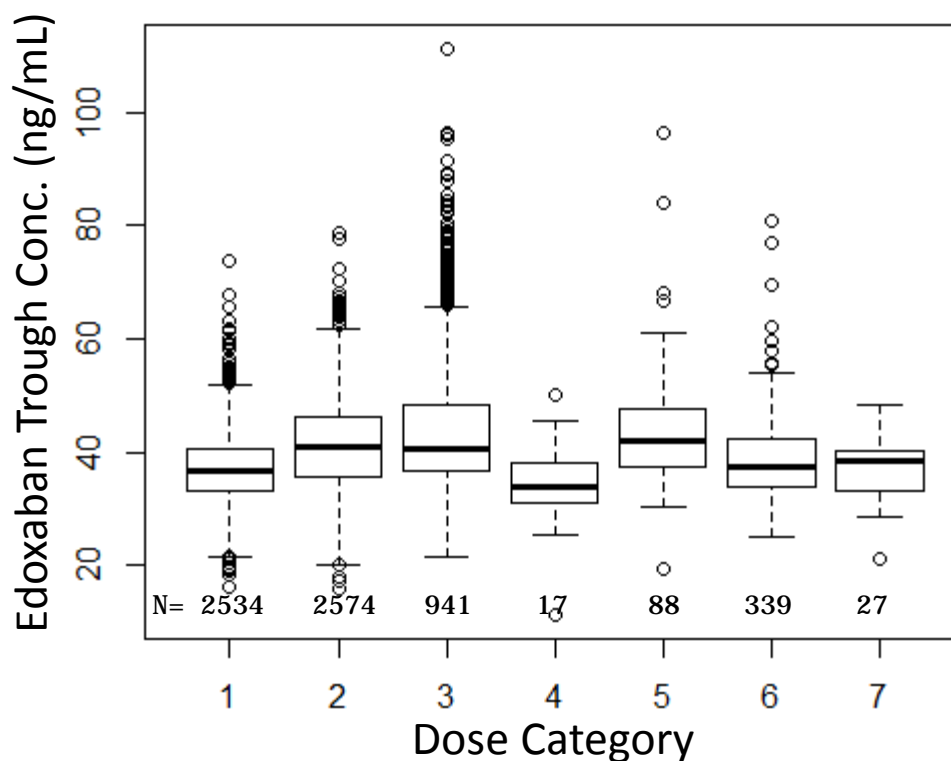
- 90 mg QD for patients with normal renal function
- 60 mg QD for patients with mild renal impairment
- 45 mg QD for patients with moderate renal impairment
- No dose reduction for patients with normal renal function or mild renal impairment based on body weight < 60 kg OR concomitant p-gp use

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-threatening/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
Normal (>80 mL/min)	60 mg Observed vs Warf Observed	31	-20
	60 mg Predicted Vs Warf Observed	22	-23
	75 mg Predicted Vs Warf Observed	14	-17
	90 mg Predicted Vs Warf Observed	8	-14
Moderate (30 - 50 mL/min)	30 mg Observed Vs Warf Observed	10	-92
	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 ($CRCL \geq 80$ 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 ($CRCL \geq 50 - 80$ 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	\\Cdsub1\evsprod\NDA206316\0000\m5\datasets\du176b-c-u301\analysis\legacy\datasets
DU176B-C-301	adjeffca.xpt, adjsafca.xpt	\\Cdsub1\evsprod\NDA206316\0009\m5\datasets\du176b-c-u301\analysis\legacy\datasets
DU176B-D-305	dm.xpt, basegrp.xpt, adjeff.xpt, adjsaf.xpt	\\Cdsub1\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 $\alpha=0.05$. Covariates were eliminated from the model during a backwards elimination evaluation if based on a significance of the parameter at $\alpha=0.05$. 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

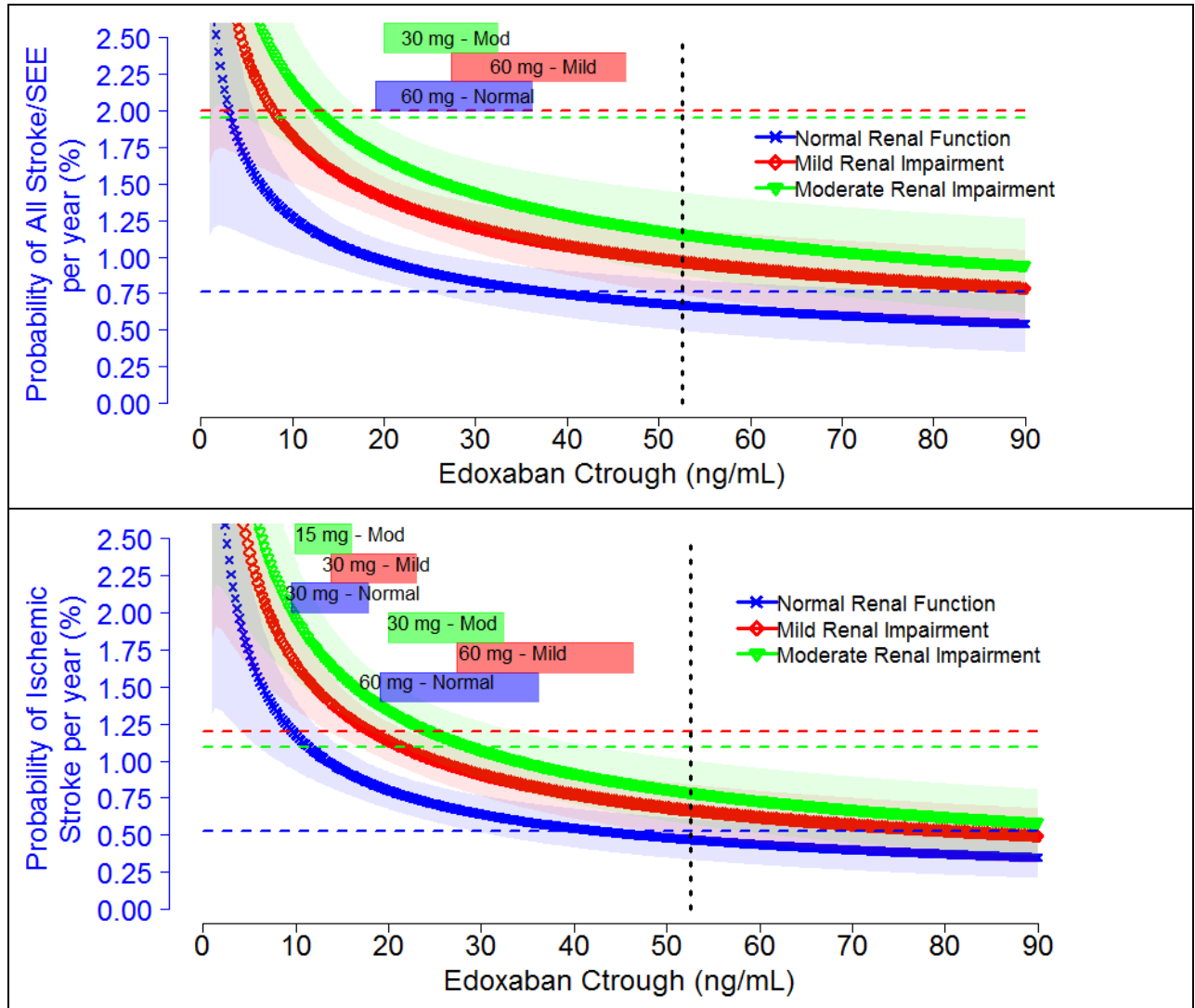
2.4.1.1 Time to Event Exposure-Response Analysis of the Efficacy Endpoints

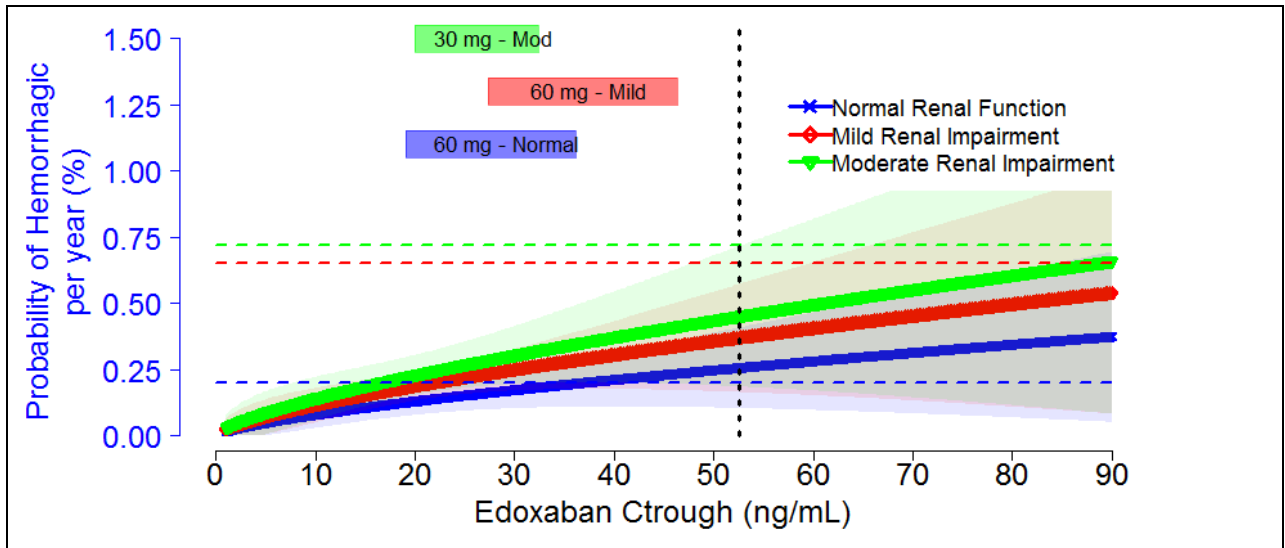
The exposure-response analysis based on the Cox proportional hazards models are represented below in two formats. The first is a prediction of the exposure-response relationship for the typical patient with normal renal function, mild renal impairment, or moderate renal impairment (Figure 23) based on 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 5th and 95th 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

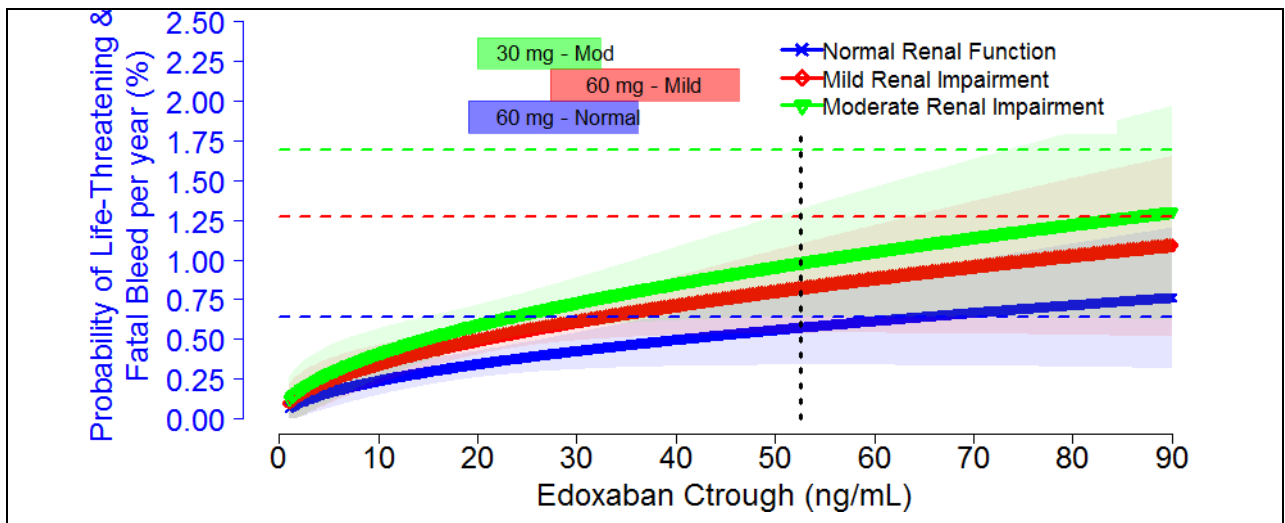
2.4.1.2 Time-to-Event Exposure-Response Analysis of Safety Endpoints:

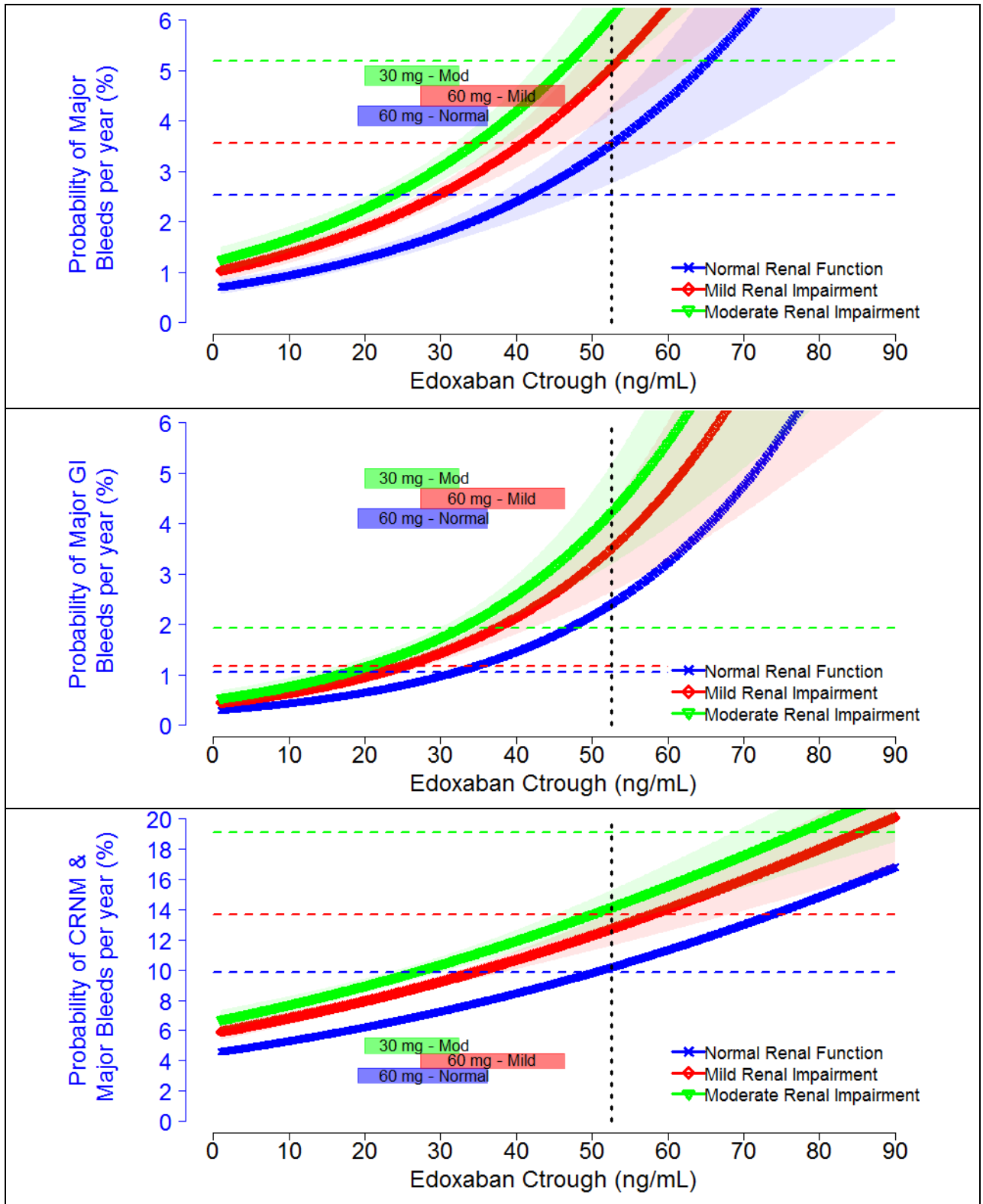
The exposure-response safety analyses based on the Cox proportional hazards models are represented below similarly to that for the stroke endpoints. (Figure 24, Table 27, Table 28, and Table 29).

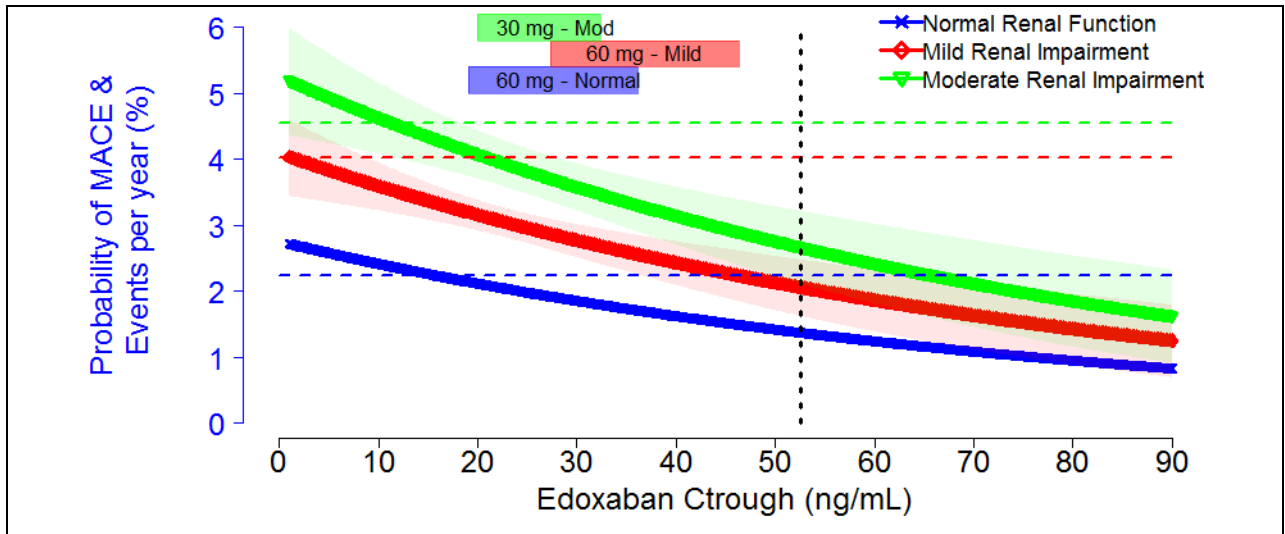
The key points of the safety analysis are:

- 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.







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
Normal (>80 mL/min)	60 mg Observed vs Warf Observed	31	-20
	60 mg Predicted Vs Warf Observed	22	-23
	75 mg Predicted Vs Warf Observed	14	-17
	90 mg Predicted Vs Warf Observed	8	-14
Moderate (30 - 50 mL/min)	30 mg Observed Vs Warf Observed	10	-92
	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
Normal (>80 mL/min)	60 mg Observed vs Warf Observed	-3	-16
	60 mg Predicted Vs Warf Observed	-5	-5
	75 mg Predicted Vs Warf Observed	-3	34
	90 mg Predicted Vs Warf Observed	1	81
Moderate (30 - 50 mL/min)	30 mg Observed Vs Warf Observed	-29	-30
	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
Normal (>80 mL/min)	60 mg Observed vs Warf Observed	-120	29
	60 mg Predicted Vs Warf Observed	-162	0
	75 mg Predicted Vs Warf Observed	-60	-19
	90 mg Predicted Vs Warf Observed	40	-38
Moderate (30 - 50 mL/min)	30 mg Observed Vs Warf Observed	-539	-34
	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

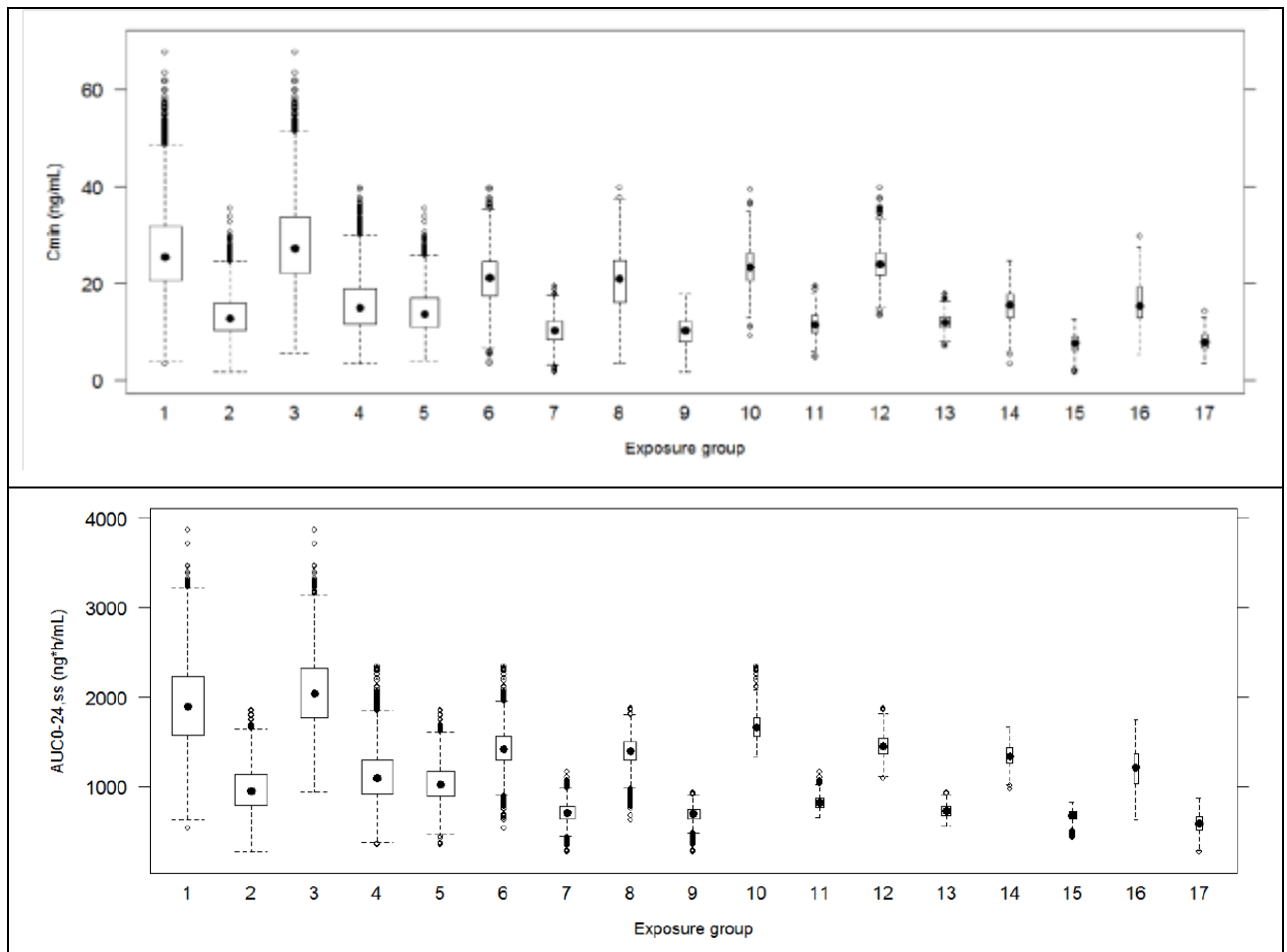
This PopPK analysis was performed using a dataset including relevant data from both Phase 1 (PRT016, AU120, AU127, AU128, AU129, AU130, AU131, AE132, AE133, AU136, AU137, AU138, AU141) (see: Table 9.1) and Phase 3 (ENGAGE-AF) studies. The Phase 1 studies were selected to inform and stabilize the structural 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 C_{min} (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 CL_{cr} adjusted high exposure treatment group
13. Only CL_{cr} 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	25 th Percentile	75 th Percentile	Min	Max	Observation
<i>Based on all observations in Analysis Dataset</i>							
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 CL _{cr} ≤ 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 CL _{cr} ≤ 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 CL _{cr} + 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 CL _{cr} + 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 CL _{cr} + 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 CL _{cr} + 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 CL _{cr} + 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 CL _{cr} + 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 CL _{cr} ≤ 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
<i>Based on baseline observation in Analysis Dataset³</i>							
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 ($CL_{Cr} \geq 30$ 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 ($CL_{Cr} \geq 30$ 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 by (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 C_{av} , $AUC_{0-24,ss}$, 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

Risk Factor	Abbreviation	Endpoints	
		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_{TLA}	0.9185	$[0.7342 - 1.103]$	2.51
$\beta_{E_{max}}$	-2.268	$[-2.915 - -1.621]$	-
$\beta_{EC_{50}}$ [ng/mL]	20.4	$[2.999 - 37.80]$	-

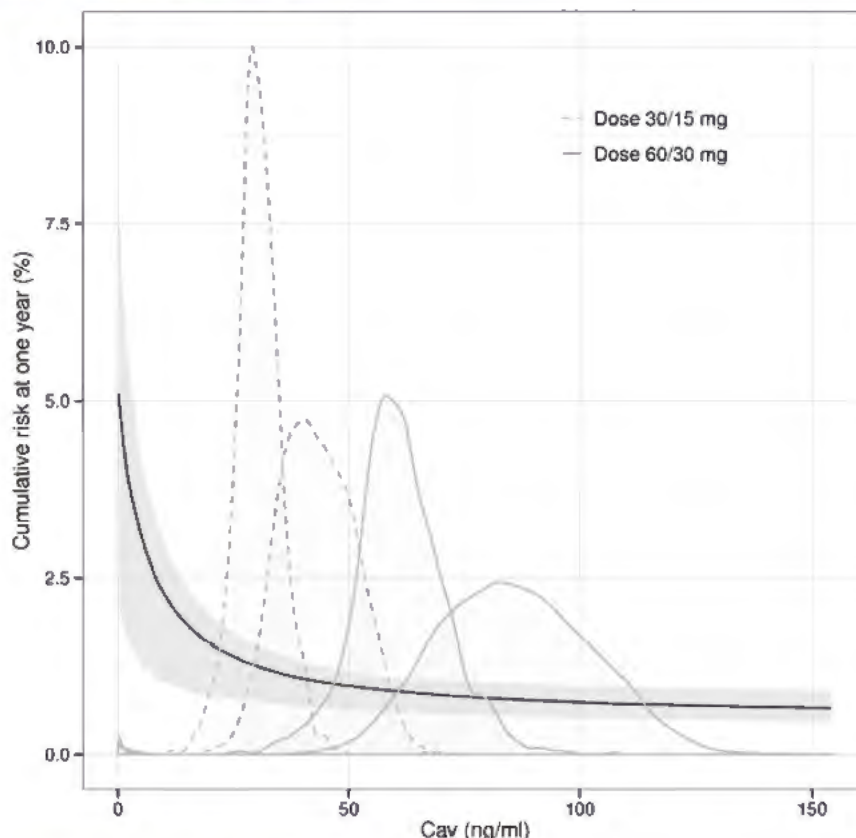
a: The estimates of the risk factors are parameterised as log hazard ratio

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; TLA 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_{TLA}	0.9567	[0.7596 - 1.154]	2.60
$\beta_{E_{\text{max}}}$	-2.752	[-3.457 - -2.043]	-
$\beta_{EC_{50}}$ [ng/mL]	27.72	[6.481 - 48.92]	-

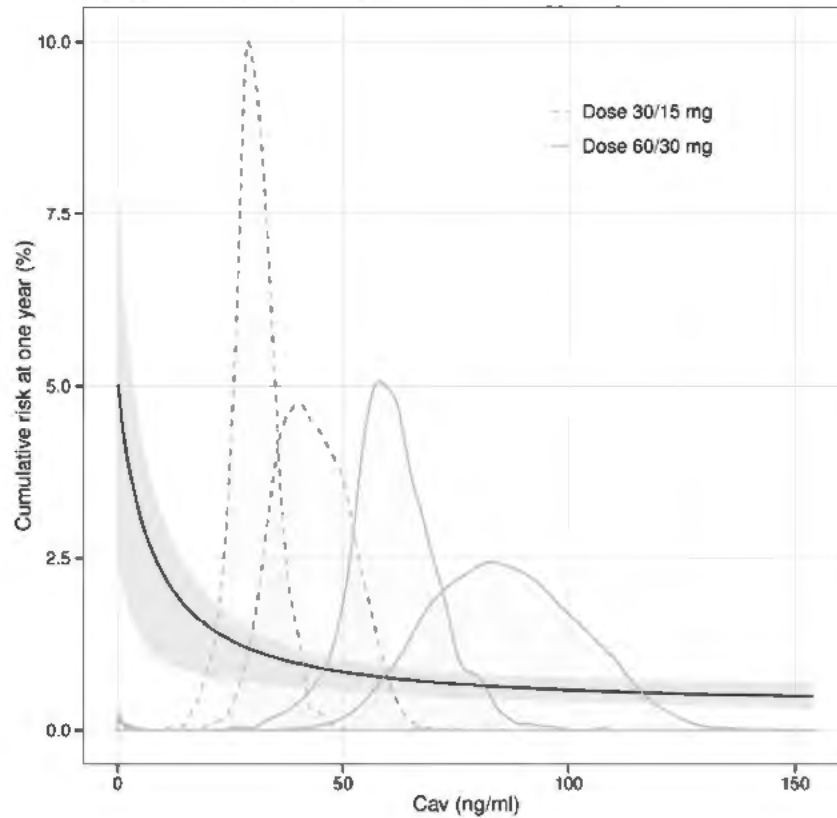
a: The estimates of the risk factors are parameterised as log hazard ratio

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; TLA 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

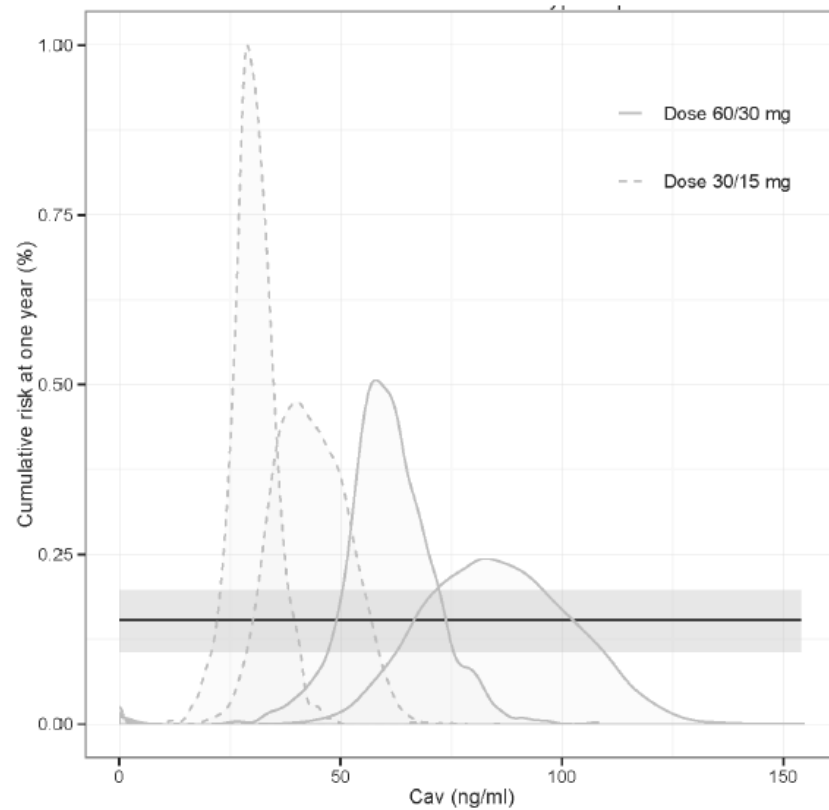
a: The estimates of the risk factors are parameterized as log hazard ratio

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
$\beta_{L, C_{min}}$ [(ng/mL) ⁻¹]	0.02902	[0.02198 – 0.03607]	1.03

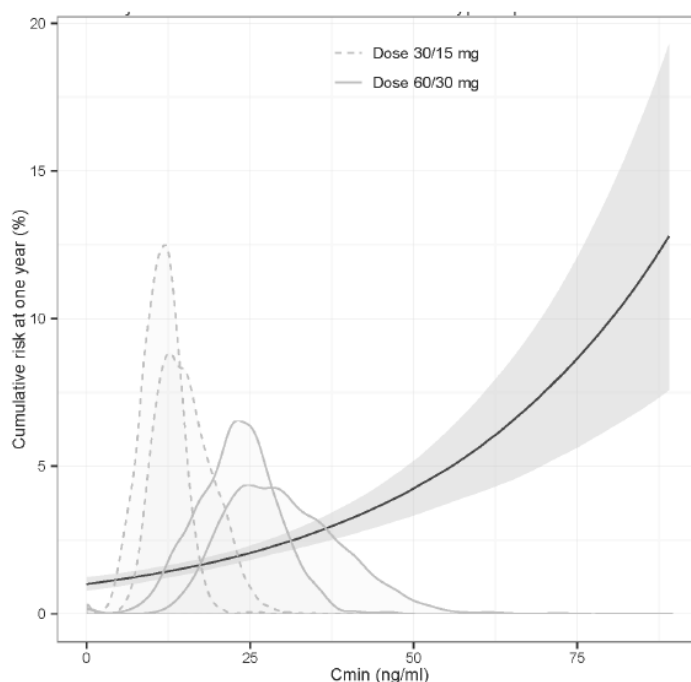
a: The estimates of the risk factor effects are parameterised as log hazard ratio

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)

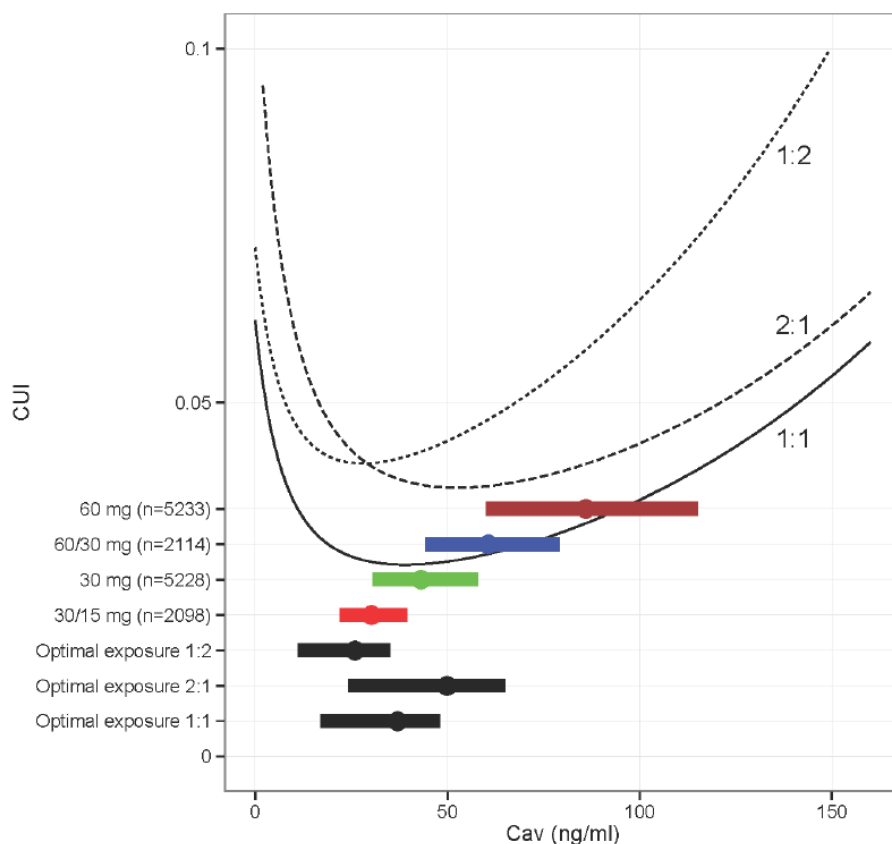
Reviewer's Comments:

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.

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/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 characterisitcs. Defer SPAF dose and exposure-response conclusions to DCP1 and Pharmacometrics teams.

JEFFRY FLORIAN
09/30/2014

RAJANIKANTH MADABUSHI
09/30/2014



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 206-316
Supplement #:
Drug Name: Edoxaban
Indication(s): Delay time to stroke or systemic embolic event in patients with Atrial Fibrillation
Applicant: Daiichi Sankyo
Date(s): 1/8/2014
Review Priority: Standard

Biometrics Division: DBI
Statistical Reviewer: John Lawrence, Ph D
Concurring Reviewers: Jim Hung

Medical Division: Cardiorenal.
Clinical Team: Melanie Blank MD, Tzu-Yun McDowell MD, Martin Rose MD
Project Manager: Alison Blaus

Keywords: active control/non-inferiority, Cox regression

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EXECUTIVE SUMMARY

There was only one phase 3 trial for this indication in the submission. Two dose regimens were studied. Both regimens were safe and effective.

INTRODUCTION

1.1 Overview

Table 1 List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
<i>Study DU176B-C-U301</i>	<i>Phase 3</i>	<i>2.5 years</i>	<i>2.8 years</i>	<i>7002 (low dose edoxaban), 7012 (high dose), 7012 (warfarin)</i>	<i>subjects with documented AF within the preceding 12 months and in whom anticoagulant therapy was indicated.</i>

Source: Study Report.

1.2 Data Sources

Electronic datasets and Study Reports:

<\\cdsesub1\evsprod\NDA206316\206316.enx>

<\\cdsesub1\evsprod\NDA206316\0009\m5\datasets\du176b-c-u301\analysis\legacy\datasets>

STATISTICAL EVALUATION

1.3 Data and Analysis Quality

Some of the datasets were too large to be used. The laboratory dataset was 8.6 Gb and I could not copy it to my hard drive or open it in any software on my computer. Other datasets that I could open were also very large (on the order of 0.5 Gb). Files of this size are difficult to work with. It takes a long time to copy them from one place to another and takes a long time to open and do any analysis. The structure of the datasets was complicated and made it difficult to understand how to do simple analyses such as counting the number of primary endpoint events in

each group or how much time of exposure in each group. I needed to communicate with the sponsor several times to understand how to do things that should have been simple if the datasets had been designed in a better way. In defense of the sponsor, this is a common and recurring problem across many applications. I would judge the data quality as fair.

The analysis was complicated because the sponsor used an on-treatment approach. In my opinion, the intention to treat analysis should be used for the primary analysis, even in an active control, non-inferiority trial. Some people have concerns that low compliance in all treatment arms could bias the results toward showing no difference between the two arms, which could increase the chances that an inferior drug could be demonstrated as non-inferior. That is something to be concerned about, but using the on treatment analysis approach is not the way to fix the problem. Instead, steps should be taken to make sure every subject stays on their randomized treatment. The intention to treat analysis should be the primary analysis. The on treatment analysis should be a sensitivity analysis. Studies with a large amount of non-compliance to either treatment or a large amount of loss to follow-up are not interpretable. When the amount of non-compliance is small, the two approaches should give the same results. To the extent that they differ, the reasons for the difference should be explored. Although I disagree with the approach used, the data analysis, given the decision was made to use that approach, was excellent.

1.4 Evaluation of Efficacy

1.4.1 Study Design and Endpoints

Study DU176B-C-U301, also called the ENGAGE AF-TIMI 48 trial, was a phase 3, randomized, double-blind, double-dummy, parallel-group, multi-center, multi-national study for evaluation of efficacy and safety of du-176b (edoxaban) versus warfarin in subjects with atrial fibrillation (AF). Subjects needed to be at least 21 years old, with a history of AF documented by any electrical tracing within the prior 12 months and for which anticoagulation therapy was indicated and planned for the duration of the study. Subjects with or without previous vitamin K antagonist experience (abbreviated VKA, warfarin is one such VKA) were allowed; it was anticipated that approximately 40% of subjects would be VKA-naïve). Subjects needed a CHADS₂ index score ≥ 2 . The CHADS₂ scoring was performed by assigning 1 point each for a history of congestive heart failure (CHF), hypertension, age ≥ 75 years, or diabetes mellitus; and by assigning 2 points for history of stroke or transient ischemic attack (TIA).

Eligible subjects were stratified by CHADS₂ risk score at randomization (2 or 3 vs. 4, 5, or 6). Within each CHADS₂ stratum, subjects were further stratified based on whether or not a

subject required edoxaban dose reduction for factors such as low estimated creatinine clearance using the Cockcroft-Gault equation (eCrCL less than 50 mL/min), low body weight (less than 60 kg), or a need for concomitant treatment with P-glycoprotein (P-gp) inhibitors such as quinidine and/or verapamil. Randomization was stratified by these two stratification factors.

Warfarin was the active control used in this study. Warfarin was titrated within each subject to achieve a target INR between 2.0 and 3.0. There were two experimental treatment arms. The usual dose in the high dose edoxaban arm was 60 mg qd. The usual dose in the low dose edoxaban arm was 30 mg qd. Within each treatment arm, subjects who required a dose adjustment (for low eCrCL, low body weight, or concomitant treatment with P-gp inhibitors) was cut in half of the usual dose, i.e. 30 mg in the high dose arm and 15 mg in the low dose arm. In order to maintain the study blind, a double dummy strategy was used and sham INR values were reported for subject given warfarin placebo. It is difficult to conduct a double-blind trial with warfarin. The sponsor is commended for making the effort to do this because a double-blind trial is more credible than an open label trial.

The primary endpoint was time to first stroke (of any kind) or systemic embolic event (SEE) while on treatment. Subjects were considered on treatment for 3 days after their last dose. If a study drug interruption occurred and the subject returned to study drug later, they were considered on treatment during the first 3 days with no treatment, not on treatment the remaining days with no treatment, then back on treatment when they continued treatment. Any events that occurred during the off-treatment period did not count in the primary analysis.

This was an event-driven study. The statistical considerations and plan for the study required approximately 672 primary endpoints overall, with 448 on-treatment primary endpoint (composite of stroke and SEE) events for each of the following 2 pairwise comparisons: i) edoxaban 30 mg group versus warfarin ii) edoxaban 60 mg group versus warfarin.

There were three secondary endpoints: i) composite of stroke, SEE, and CV mortality; ii) MACE, which is the composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding; iii) composite of stroke, SEE, and all-cause mortality.

1.4.2 Statistical Methodologies

The analysis of the primary endpoint used the modified intent-to-treat (mITT) population, which was defined as subjects who were randomized and received at least one dose of study drug. The analysis approach used the on-treatment period to count events. Subjects were excluded from the at risk set during periods of treatment interruptions. Subjects were considered on treatment for 3

days after last dose and back on treatment if the treatment recommenced. The primary analysis used the counting process approach to include only subjects at risk in each time interval in the Cox proportional hazards regression model analysis. The Cox proportional hazards model included treatments and the following 2 stratification factors as covariates:

1. The dichotomized CHADS2 score (1 if CHADS2 \geq 4; 0 otherwise)
2. The dichotomized dose adjustment variable (1 if eCrCL \leq 50 mL/min, or body weight \leq 60 kg, or taking verapamil or quinidine; 0 otherwise)

Because there were two treatment arms being compared simultaneously to the active control group, a Bonferroni type approach was used to control the overall error rate. The two-sided 97.5% confidence interval (CI) for the hazard ratios (each edoxaban treatment group versus warfarin) was estimated using the proportional hazards model. If the upper limit of this CI of the hazard ratio was below 1.38, then non-inferiority to warfarin was considered established for the corresponding edoxaban treatment group. The margin of 1.38 was appropriate and has been used in many other studies for this indication. It was derived from the estimated effect of warfarin compared to placebo in historical trials.

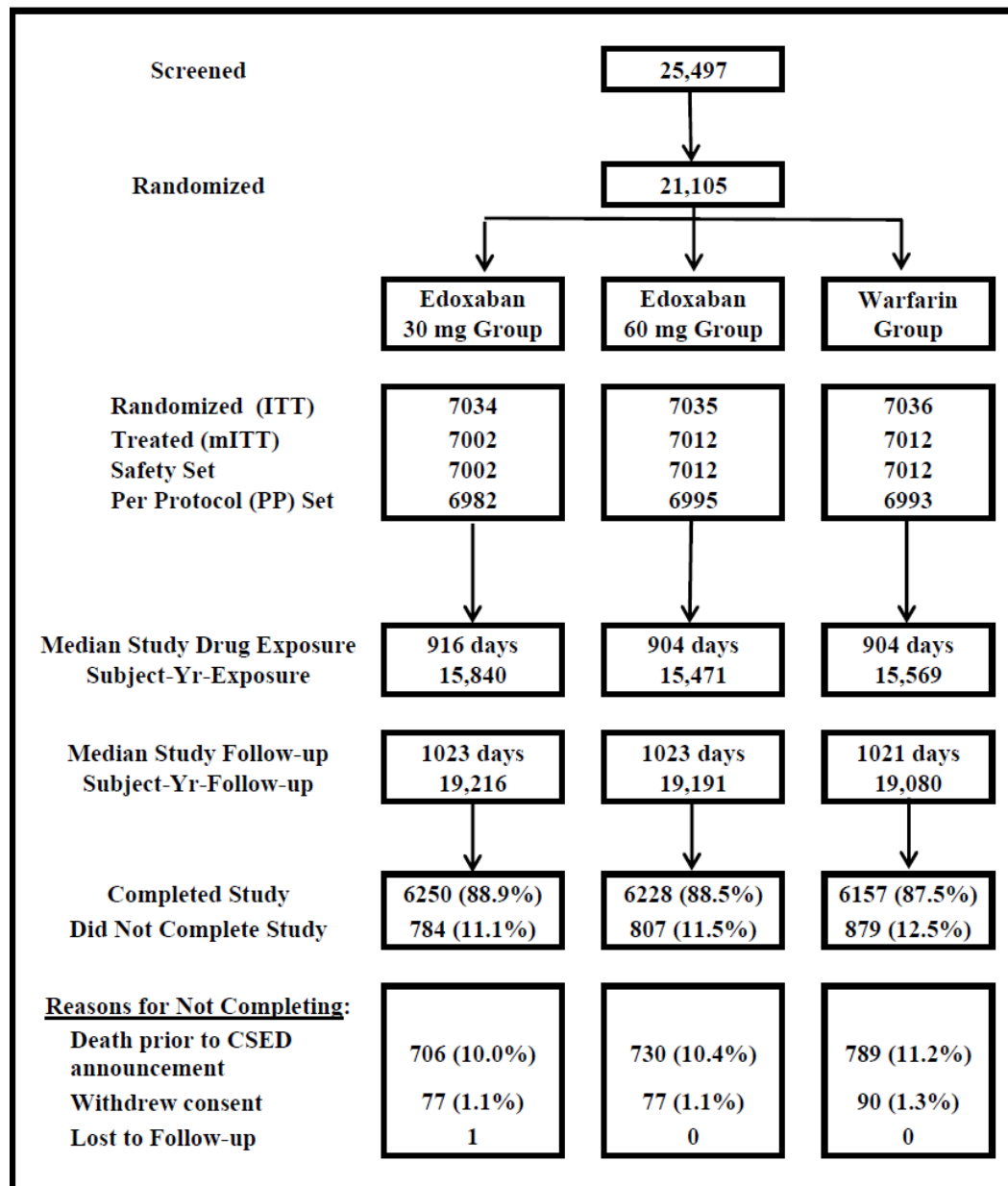
If the high dose arm was noninferior to warfarin, then the high dose would be compared to warfarin for superiority on the primary endpoint using two-sided error rate of $\alpha=0.01$. For the test of superiority, the ITT analysis and overall study period would be used (i.e. all events would be counted, not just the on-treatment events). If superiority was concluded, then the three secondary endpoints would be tested in order using the same approach (ITT analysis with $\alpha=0.01$). No testing for superiority of the primary or any secondary endpoints was planned for the low dose arm.

1.4.3 Patient Disposition, Demographic and Baseline Characteristics

The patient disposition is shown in Figure 1 and the baseline and demographic characteristics are shown in Table 2. The figure shows that very few subjects were lost to follow-up or did not complete the study except for those who died. However, nearly $\frac{1}{4}$ of the follow-up time was not included in the primary analysis because it only included on-treatment periods. A strength of the trial is that there is very little loss to follow-up and subjects were followed after stopping study drug. However, the amount of information that is intentionally censored (during the off-treatment period) could be a problem. The duration off-treatment in the three arms seems to be roughly equal. If that had not been the case, then it would be even more concerning. Still, that does not prove that the censored information can be ignored. In consideration of that, we should look carefully at the consistency between the analysis of the on-treatment period events with the analysis of the overall study period events. In Table 2, it is seen that the average age was about 70

years, 60% were male, $\frac{3}{4}$ of the subjects fell in the usual dose category, 80% were Caucasian. There were no significant differences in the demographics between groups. In addition to what is shown in Table 2, other useful demographic information includes: approximately 18% of the subjects were from the US region and about half of the subjects were VKA naive.

Figure 1 Patient disposition



Source: Figure 10-1 of Study Report.

Table 2 Patient demographic and baseline characteristics

	Edoxaban 30 mg (15mg DosAdj) (N=7002)	Edoxaban 60 mg (30mg DosAdj) (N=7012)	Warfarin (N=7012)
Age (years), n	7002	7012	7012
Mean	70.6	70.6	70.5
SD	9.31	9.51	9.44
Median	72.0	72.0	72.0
Minimum	27	25	27
Maximum	95	96	95
>= 65 years n(%)	5218 (74.5)	5182 (73.9)	5143 (73.3)
>= 75 years n(%)	2789 (39.8)	2838 (40.5)	2805 (40.0)
>= 80 years n(%)	1197 (17.1)	1177 (16.8)	1195 (17.0)
Gender, n (%)	7002	7012	7012
Male	4284 (61.2)	4353 (62.1)	4383 (62.5)
Female	2718 (38.8)	2659 (37.9)	2629 (37.5)
Race, n (%) [a]	7001	7012	7012
Caucasian	5650 (80.7)	5679 (81.0)	5679 (81.0)
Black	94 (1.3)	96 (1.4)	88 (1.3)
Asian	975 (13.9)	956 (13.6)	963 (13.7)
Other	282 (4.0)	281 (4.0)	282 (4.0)
Edoxaban/Placebo Dose Adjusted at Randomization, n (%)	7002	7012	7012
Yes	1774 (25.3)	1776 (25.3)	1780 (25.4)
No	5228 (74.7)	5236 (74.7)	5232 (74.6)
CrCL (mL/min), n (%) [b]	6961	6954	6973
< 30	42 (0.6)	70 (1.0)	51 (0.7)
30 - <= 50	1274 (18.2)	1287 (18.4)	1297 (18.5)
> 50 - < 80	3034 (43.3)	2985 (42.6)	3030 (43.2)
>= 80	2611 (37.3)	2612 (37.3)	2595 (37.0)
Weight (kg), n (%) [c]	6996	7007	7007
<= 50	148 (2.1)	158 (2.3)	172 (2.5)
<= 60	692 (9.9)	681 (9.7)	697 (9.9)
> 60	6304 (90.0)	6326 (90.2)	6310 (90.0)
Mean (SD)	83.9 (20.11)	84.2 (20.40)	83.7 (20.09)

Source: Table 10.4 of Study Report.

1.4.4 Results and Conclusions

Both doses were non-inferior to warfarin on the primary endpoint. The results are shown in Table 3. The primary analysis is in the first row of the table (mITT Analysis Set, On Treatment Period). Both doses were non-inferior to warfarin because the upper limit of both two-sided 97.5% confidence intervals were less than the margin of 1.38. The primary analysis did not include events that happened during treatment interruptions. The second row is the sensitivity analysis which includes all of the events. There were about 50% more subjects with events in each group when these off-treatment events were counted. As stated before (Section 1.3 of this review), I believe that it would have been best to make this the primary analysis. In any case, both methods of analysis showed that both doses were non-inferior to warfarin.

Table 3 Adjudicated Primary Endpoint (Stroke or SEE), mITT Analysis Set - On-Treatment and Overall Study Period (Non-Inferiority)

Primary Endpoint	Edoxaban 30 mg (15mg DosAdj) (N=7002)		Edoxaban 60 mg (30mg DosAdj) (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg (15mg DosAdj) vs Warfarin		Edoxaban 60 mg (30mg DosAdj) vs Warfarin	
	# of events	Event Rate (%/yr) [a]	# of events	Event Rate (%/yr) [a]	# of events	Event Rate (%/yr) [a]	HR (97.5% CI)	p-value[b]	HR (97.5% CI)	p-value[b]
First Stroke or SEE										
mITT Analysis Set On Treatment Period	253	1.61	182	1.18	232	1.50	1.07 (0.874, 1.314)	0.0055	0.79 (0.632, 0.985)	<0.0001
mITT Analysis Set Overall Study Period	382	2.04	292	1.55	336	1.80	1.13 (0.955, 1.336)	0.0074	0.86 (0.719, 1.029)	<0.0001

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, mITT = Modified Intent-to-Treat, SEE = Systemic Embolic Event, yr = year.

[a]: The event rate (%/yr) is calculated as # of events/subject-year exposure.

[b]: The two-sided p-value is based on the non-inferiority margin of 1.38

Source: Table 11.2 of Study Report and confirmed by FDA.

In any active control study, we want to make sure that the active control was used appropriately. Table 4 shows the time in therapeutic range (INR 2-3) and also the percent time in other ranges. The TTR was about 65%, which is very good. 23% of the time, the subjects had INR<2 and 12% of the time, the subjects had INR>3. In the range INR<2, the warfarin dose is too low, leading to subjects having a greater risk of ischemic stroke. In the range INR>3, the warfarin dose is too high, leading to greater risk of bleeding. Overall, this is about as good as can be expected in a clinical trial and I do not think that this causes any concern with respect to the interpretation of the non-inferiority of the two edoxaban doses.

Table 4 Time in various INR ranges for subjects randomized to warfarin, safety analysis set – on treatment period, excluding initial 7 days

	Percent Time in INR Range[a]								
	<1.5	1.5-2.0	<2	2-3 (TTR)	>3	>=4	>5	>=8	1.8-3.2
Overall (N=6897)									
Mean (SD)	6.10(13.8)	22.70(13.3)	22.80(18.9)	64.90(18.7)	12.40(10.3)	1.80(4.5)	0.30(2.3)	0.00(0.8)	78.40(18.1)
Median	1.90	21.00	17.70	68.40	10.80	0.40	0.00	0.00	83.10

Abbreviations: INR = International Normalized Ratio, SD = Standard Deviation, TTR = Time in Therapeutic Range.

[a]: Percent Time in INR range is defined by the percentage of days the subjects have been within the specified range. Percent Time in Therapeutic Range (TTR) is calculated as the mean percentage in the range 2-3.

Note: N = Number of subjects with at least 1 INR recorded beyond Day 7.

Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.

Note: Analyses of INR use a linear interpolation method to impute INR for study days that do not have an actual INR value.

Source: Table 10.10 of Study Report.

The components of the primary endpoint and the results for different types of strokes are shown in Table 5. There were nearly equal numbers of ischemic strokes in the high dose and warfarin groups, but more in the low dose group. The low dose group had the fewest number of hemorrhagic strokes and the warfarin group had the most. All groups had about the same number of fatal strokes, but the low dose group had very few fatal hemorrhagic strokes. The low dose had the most disabling strokes.

Table 5 Components of the primary endpoint and different types of strokes (mITT analysis set, on-treatment period)

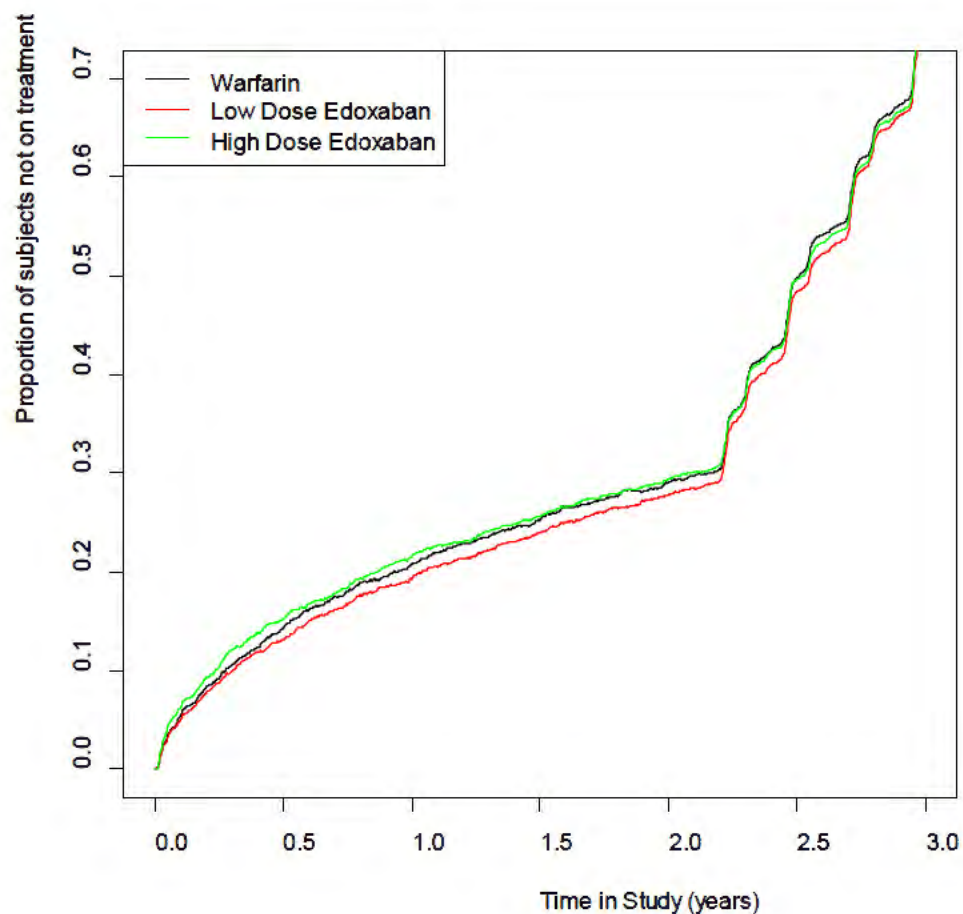
Endpoint	Edoxaban low dose	Edoxaban high dose	Warfarin
Stroke/SEE	253	182	232
First Stroke	244	174	219
First Ischemic Stroke	226	135	144
First Hemorrhagic Stroke	18	40	76
Fatal Stroke	40	45	43
Fatal Ischemic Stroke	35	22	13
Fatal Hemorrhagic Stroke	5	23	30
First Disabling Stroke	57	35	41
First SEE	11	8	13

Source: Tables 14.2.1.10 and 14.2.1.15 of Study Report.

In a normal time to event analysis, subjects can be right censored and I would draw a figure that shows the percent of subject still remaining at risk at each time point in the trial to compare the

dropout rates between groups. In this trial, the rate of loss to followup (not including death) was almost 0 in all groups. But the percent of subjects at risk over time changes because people go in and out of the on-treatment period. For this trial, I made a figure that shows the percent of subject days missing from the analysis at each time point. For example, at 1 year, the percentage of people not on treatment was about 19.3% (low dose), 21.5% (high dose), and 20.7% (warfarin). That is a high percentage of people being censored in the analysis.

Figure 2 Proportion of subjects not included in primary analysis over time in the study.

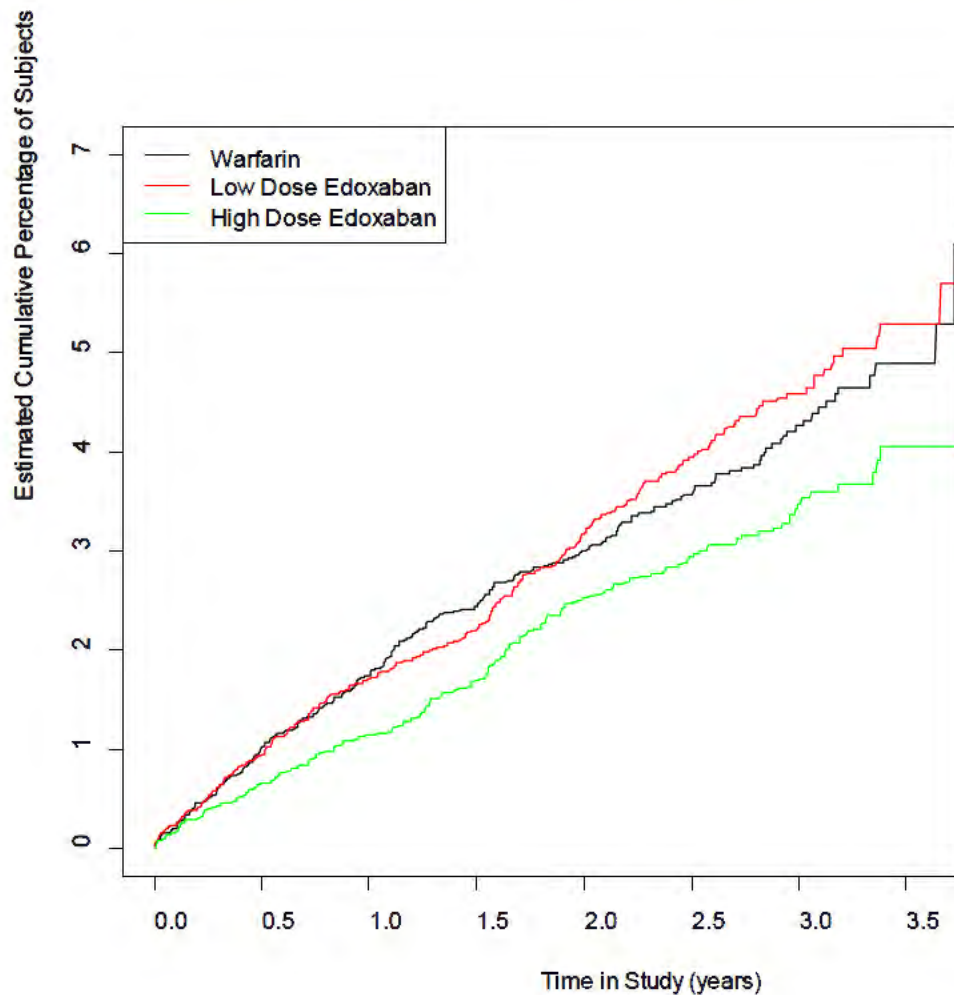


Source: FDA analysis.

Next, in Figure 3, the Kaplan-Meier estimates for the primary endpoint are shown. This shows the estimate of the proportion of people without a first on-treatment stroke/SEE. In this figure, no proportional hazards assumption is made and no adjustment is made for any factors. Figure 4 is similar to Figure 3, but transforms both the x and y-axis. In Figure 4, $\log(-\log(\text{estimated survival}))$ is on the y-axis and $\log(\text{time})$ in the x-axis. The reason for drawing this latter figure is to check

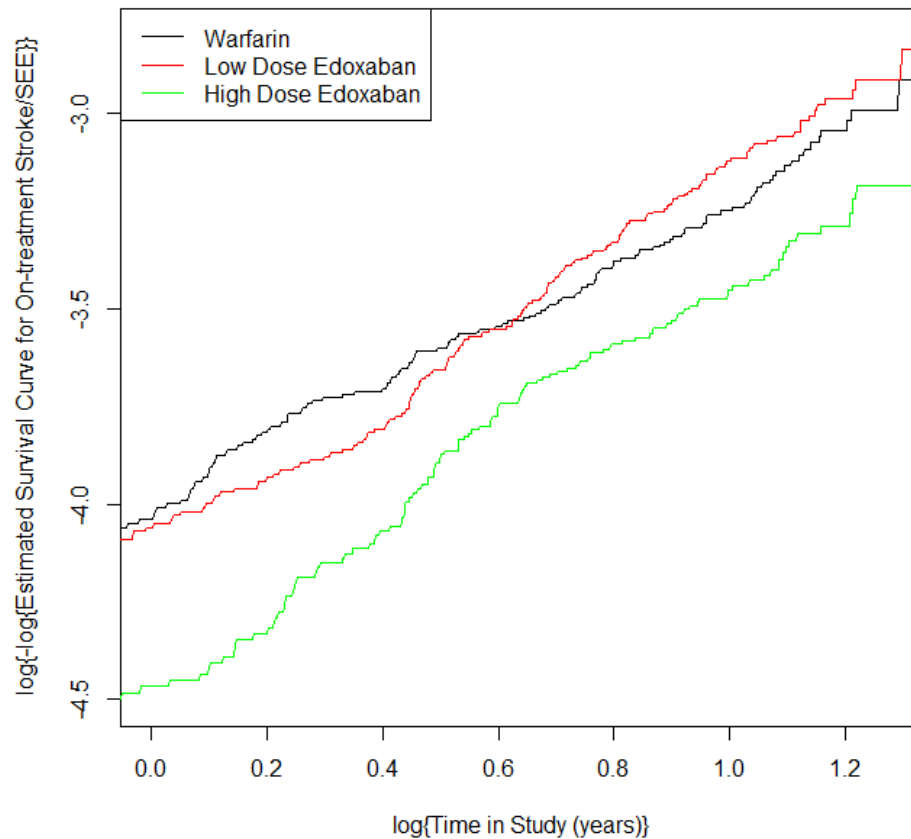
whether the proportional hazards assumption is correct. In addition, we can use this figure to check whether the distributions can be approximated by a Weibull distribution. Since the curves cross each other (red and black), the curves are not quite parallel and the hazards are not proportional. The curves are not exactly straight lines, but Weibull distributions may be a reasonable approximation to the true survival curves depending on the purpose.

Figure 3 Kaplan-Meier estimates of event rates over time (mITT, On treatment period).



Source: FDA analysis

Figure 4 Log{-log(survival)) plot (mITT, On treatment period).

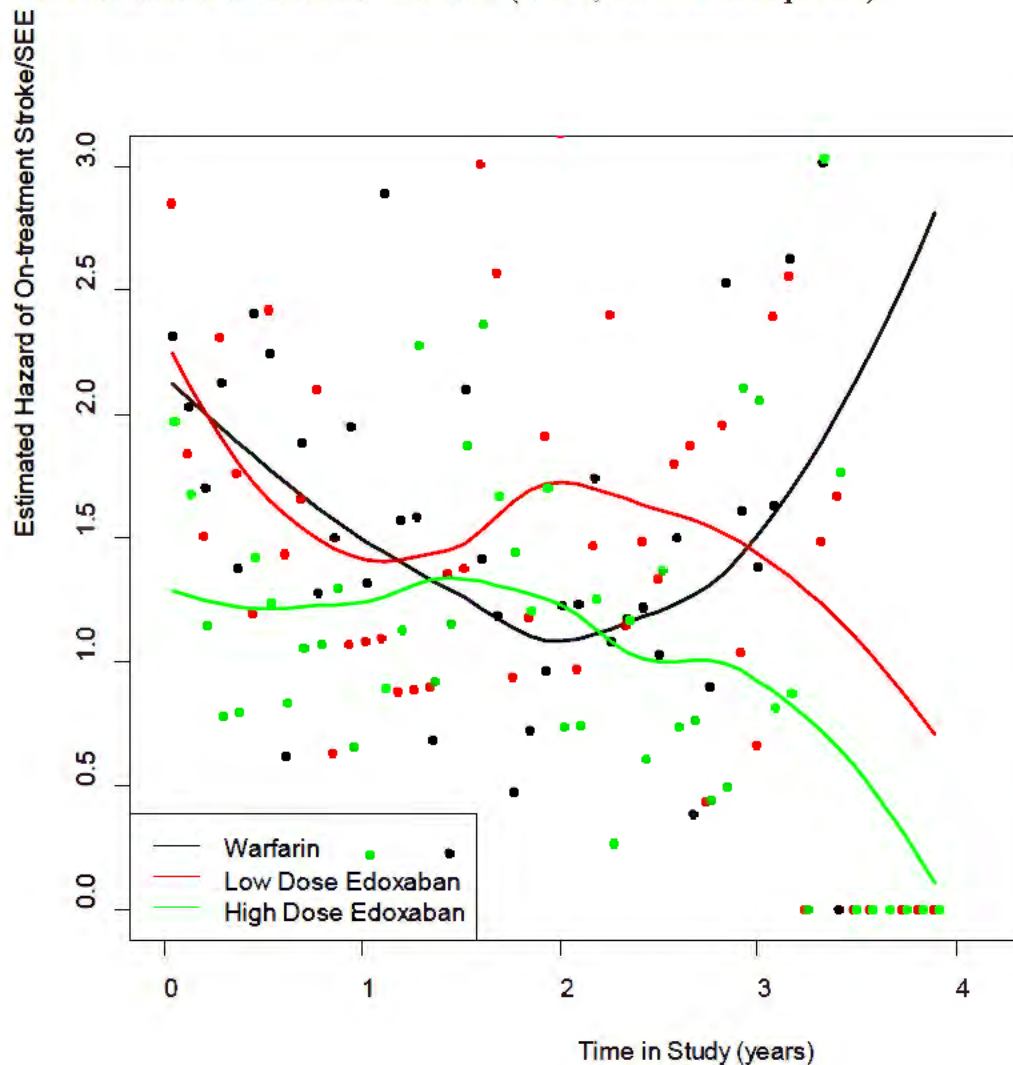


Source: FDA analysis

In the next figure, Figure 5, the estimated hazard functions are shown for each group. As in Figure 3, each hazard function is estimated independently and no adjustments are made for any covariates. I found these estimated hazard functions by first finding the number of events in each 30 day period and dividing by the amount of subject time on treatment during those time intervals. There should be 12 dots of each color within each year interval. If that many cannot be seen, then some are hidden behind dots of other color; 1 or 2 dots have a y-coordinate greater than 3 and are not shown. I then used a locally weighted regression (weighting each point by the duration of exposure in the denominator) to draw smooth curves through these points. Of note, referring back to Figure 2, it can be seen that at any given time after 3 years, only about 30% or less of the subjects are on treatment. Therefore, the curves are not very reliable beyond 3 years. The green curve starts out below the other two and stays fairly constant for the first 3 years. The red and black curves start out higher than the green curve, but decline over time. One possible explanation for the decline in the black curve in particular, is that warfarin is difficult to titrate initially. Therefore, I separated each group into the subjects who were VKA naive 30 days before

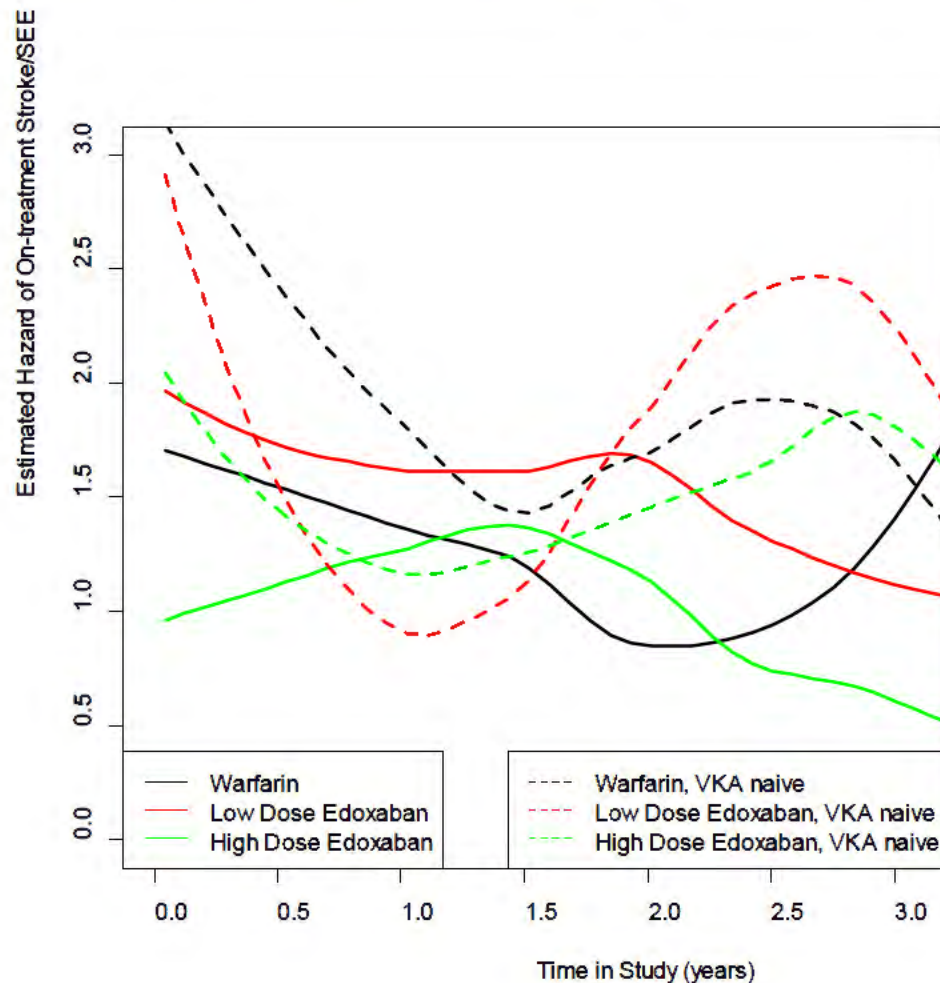
randomization and those who were not. I drew similar hazard function curves for the 6 different groups. Within each treatment group, not only in the warfarin assigned group, the subjects who were VKA naive started out with a higher hazard rate. In the warfarin group, the dashed curve (VKA naive) stayed higher throughout the first 3 years, so it may not just be an issue of initial warfarin titration.

Figure 5 Estimated hazard functions over time (mITT, On treatment period).



Source: FDA analysis

Figure 6 Estimated hazard functions over time (mITT, On treatment period) by VKA naive status (solid curves are not VKA naive at randomization, dashed curves are VKA naive).



Source: FDA analysis

I tried to fit different parametric survival distributions for the primary endpoint. As can be seen from Figure 5, a constant hazard function model (exponential distribution) would not fit the data very well. In addition, the hazard functions do not appear to be proportional, nor do they appear to satisfy the assumptions for an accelerated failure time model. I tried the Weibull family, which includes the Exponential family as a special case. I did not include any covariates or adjust for other factors. Rather, I fit one set of parameters for each treatment arm separately. See the Appendix for more details.

For a discussion of results in special subgroups, including subgroups defined by renal function, see Section 1.8.

The superiority test for the primary endpoint (high dose vs. warfarin) was not significant at the pre-specified two-sided 0.01 level. Thus, according to the analysis plan, none of the secondary endpoints would be tested for superiority. Although none of the mortality results would be statistically significant using the analysis plan, they are shown in Table 6. The low dose had substantially fewer deaths than the high dose group, which in turn had substantially fewer deaths than the warfarin group.

Table 6 Mortality results (ITT, overall study period).

	Statistic	Edoxaban 30mg (15mg DosAdj) (N=7034)	Edoxaban 60mg (30mg DosAdj) (N=7035)	Warfarin (N=7036)
All Cause Mortality	# of Events	737	773	839
	Subj Yr Expo	19414.02	19355.51	19286.20
	Event Rate (%/yr)	3.80	3.99	4.35
	HR (95% CI)	0.87 (0.788, 0.960)	0.92 (0.831, 1.011)	
	p-value	0.0058	0.0816	
Cardiovascular Mortality	# of Events	527	530	611
	Subj Yr Expo	19414.02	19355.51	19286.20
	Event Rate (%/yr)	2.71	2.74	3.17
	HR (95% CI)	0.85 (0.760, 0.960)	0.86 (0.768, 0.970)	
	p-value	0.0080	0.0133	

Source: Table 14.2.2.6 of Study Report.

1.5 Evaluation of Safety

See clinical review.

1.6 Benefit-Risk Assessment (Optional)

See clinical review.

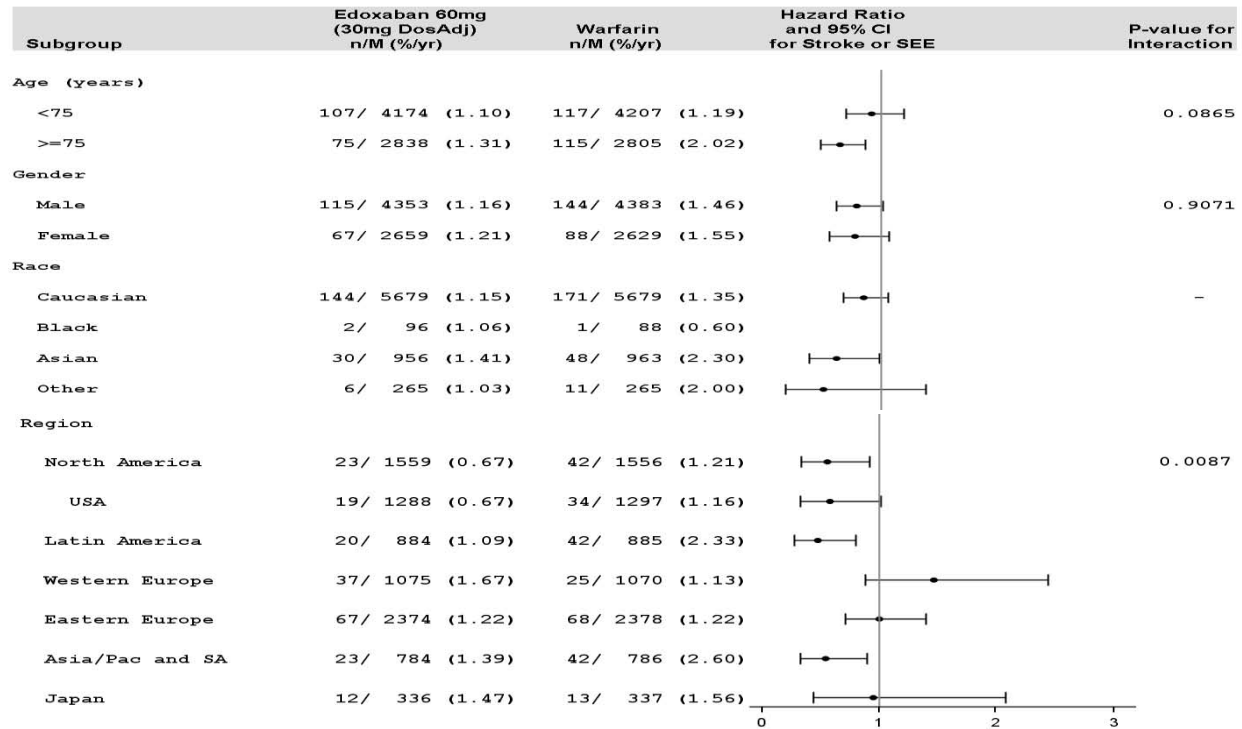
FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

1.7 Gender, Race, Age, and Geographic Region

The results comparing the high dose to warfarin for these subgroups for the primary endpoint are shown in Figure 7. The only significant interaction was by geographic region. In Eastern Europe, Western Europe, and Japan, warfarin tended to be better than edoxaban. In the remaining

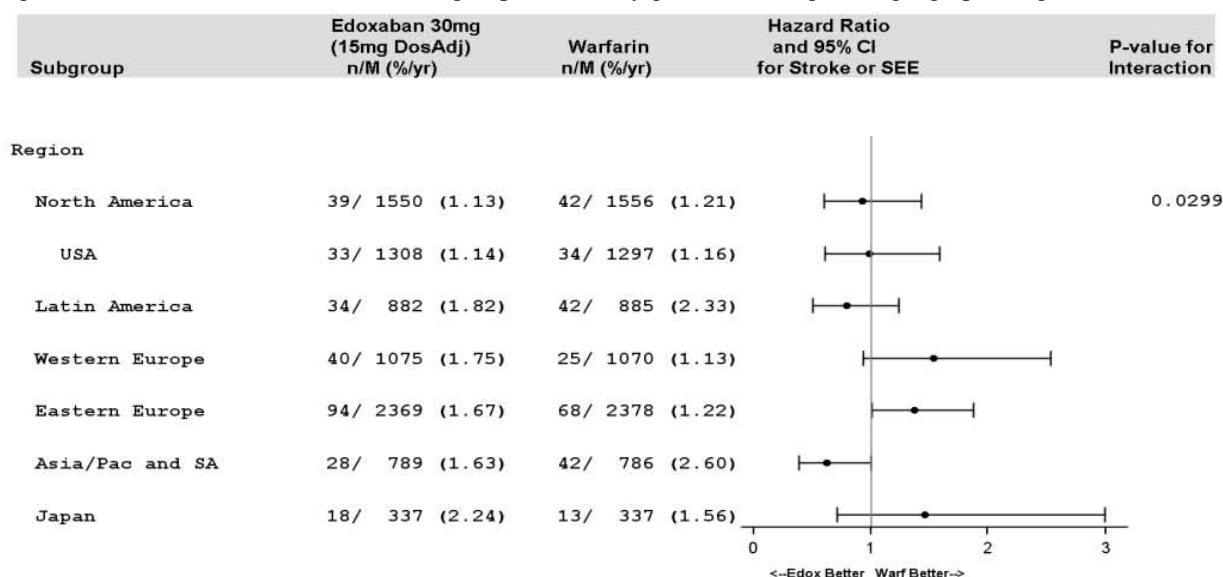
regions, edoxaban tended to be better than warfarin. This same trend was also suggested when comparing the low dose regimen to warfarin (Figure 8). One possible explanation is that this observation has something to do with how warfarin is performing across those regions.

Figure 7 High dose/warfarin results for subgroups defined by gender, race, age, and geographic region.



Source: Figure 11-3 of Study Report.

Figure 8 Low dose/warfarin results for subgroups defined by gender, race, age, and geographic region.

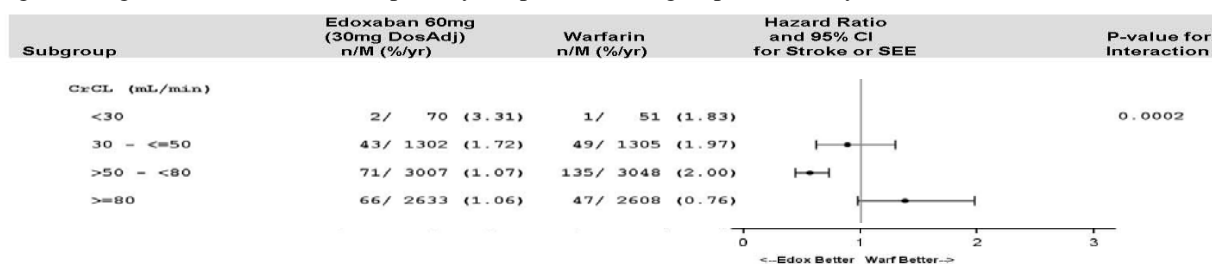


Source: Figure 11-3 of Study Report.

1.8 Other Special/Subgroup Populations

The results for the high dose compared to warfarin in subgroups defined by baseline eCrCL are shown in Figure 9. Similar results were observed when comparing the low dose regimen to warfarin (not shown).

Figure 9 High dose/warfarin results (primary endpoint) for subgroups defined by baseline eCrCL.



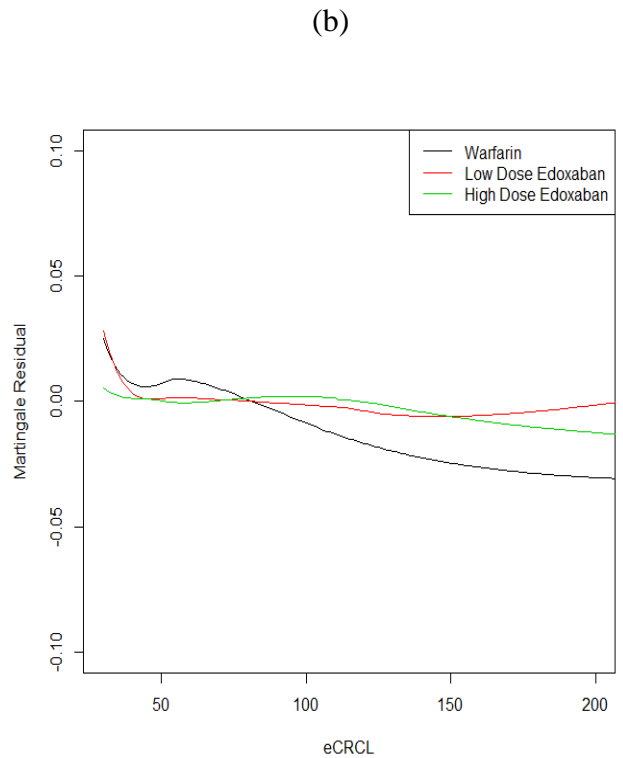
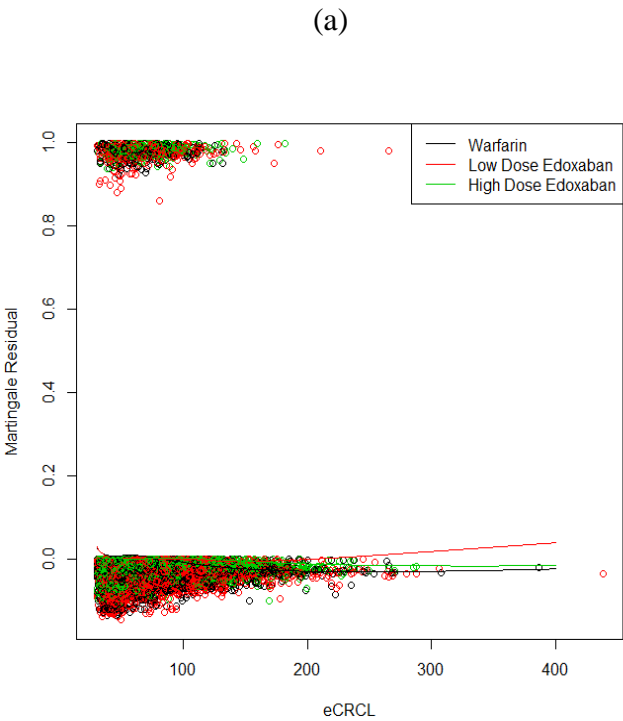
Source: Figure 11-3 of Study Report.

The first question I will look at is whether there is a qualitative interaction. A qualitative interaction, roughly, is when one confidence interval is completely below 1 and the other confidence interval is completely above 1. I will look only at the two subgroups $eCrCL \geq 80$ and $50 \leq eCrCL < 80$ because the patients in the subgroup with $eCrCL < 50$ were supposed to receive a

dose adjustment by half. If we look at the treatment effect in those two subgroups (high dose vs. warfarin only) adjusting only for chads score variable and treatment, the estimated hazard ratios are 0.53 ($50 \leq \text{eCrCL} < 80$ subgroup) and 1.41 ($\text{eCrCL} \geq 80$ subgroup). The corresponding estimated log-hazard ratios and standard errors are -0.641 (s.e. 0.146) and 0.346 (s.e. 0.191). Using the likelihood ratio test for a qualitative interaction relative to a test for superiority (Gail, M., and R. Simon. "Testing for qualitative interactions between treatment effects and patient subsets." *Biometrics* (1985): 361-372.), the p-value is $\Phi\left(\frac{0.346}{0.191}\right) = 0.035$ where $\Phi(x)$ is the standard normal distribution function. However, I would argue this is the wrong test in this situation. The study was not designed primarily to show superiority. A qualitative interaction with respect to the noninferiority margin of 1.38 would happen if one confidence interval was below 1.38 (edoxaban was effective) and the other was completely above 1.38 (edoxaban was not effective). The corresponding p-value for testing for a qualitative interaction with regard to noninferiority is $\Phi\left(\frac{0.346 - \log(1.38)}{0.191}\right) = 0.45$. In the Appendix, there is a discussion about how likely it is to see a qualitative interaction for superiority in a noninferiority trial.

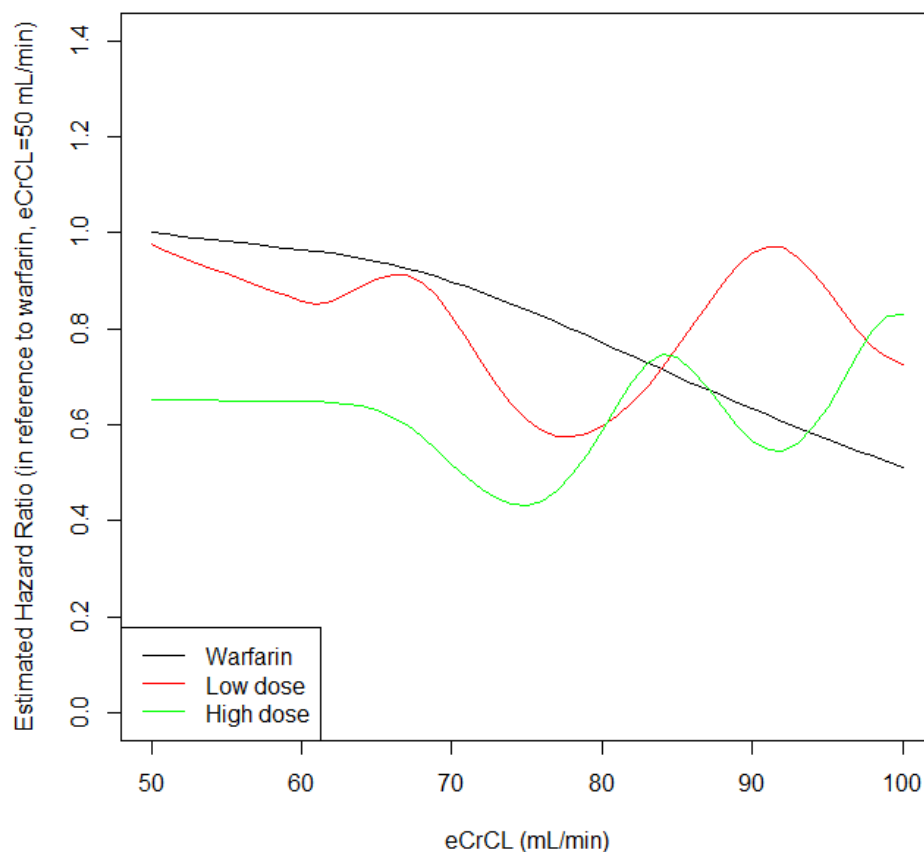
Next, I looked at the martingale residuals to see if there was any additional predictive value of eCrCL and what functional form to use in the model. The martingale residuals are the difference between the expected number of events and the observed number of events for each individual conditional on their exposure times. The residuals and the loess curves fit to them are shown in Figure 10. In panel (b), I zoomed into the part of the graph where the curves are and removed the points. Since the red and green curves are nearly constant, there is no predictive ability in the low and high dose groups, but the black curve shows there may be some added predictive ability for the warfarin group. In Figure 11 the estimated hazard ratios are shown as a function of eCrCL using splines (cubic splines with boundary knots at 60 and 100). For this figure, I started with the model used in the primary analysis and included the cubic spline function of eCrCL together with the two way interactions between dose and eCrCL.

Figure 10 Martingale residuals (primary endpoint) as a function of eCrCL.



Source:FDA analysis.

Figure 11 Hazard ratios (primary endpoint) as a function of eCrCL.

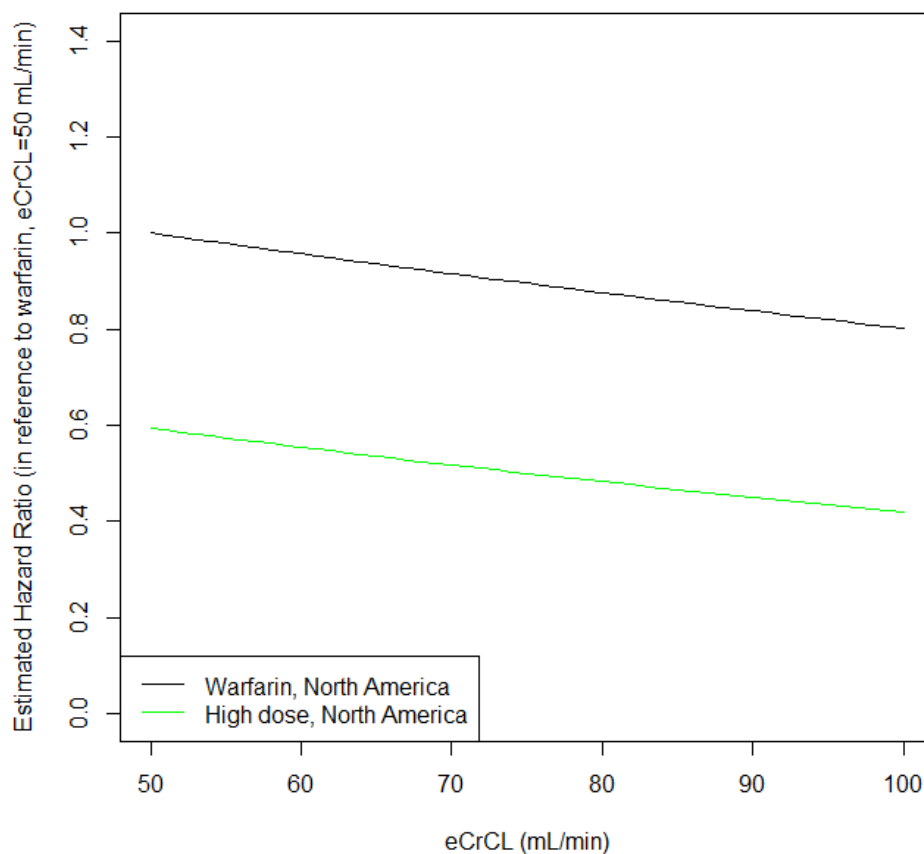


Source:FDA analysis.

Since we noticed that the effect of edoxaban varied across regions (Figure 7 and Figure 8), I wanted to look at the relative efficacy as a function of eCrCL across the regions. In particular, one region of interest to me was the North American region (mostly US subjects). To do this, I started with the proportional hazards model used in the primary analysis and added terms for eCrCL as a continuous variable, the 6 regions, and all the two-way interactions between region, dose and eCrCL. The estimated hazard ratio in the North American region from this model as a function of eCrCL is shown in Figure 12. This figure suggests that in North America, the high dose is consistently better than warfarin across the entire range of eCrCL. Furthermore, I did a similar analysis where I pooled the 3 regions where warfarin appeared to be better than edoxaban (Eastern Europe, Western Europe, and Japan) and did the same analysis. The hazard ratios for those regions as a function of eCrCL are shown in Figure 13. This figure suggests that in the

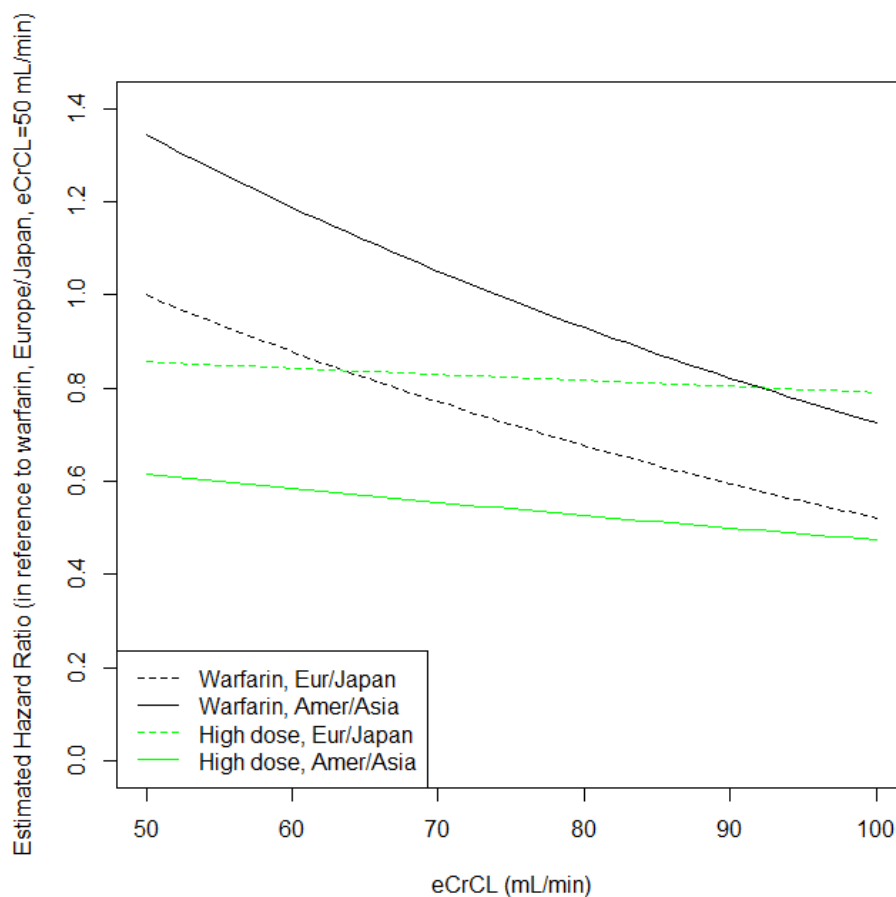
regions where warfarin performed well (dashed curves), warfarin did not do so well in the low eCrCL range, but improved with higher eCrCL (>65 mL/min). However, in the regions where warfarin did not do well (North America, Latin America, Asia/Pac and SA), edoxaban was consistently better across the entire range of eCrCL.

Figure 12 Estimated hazard ratios (primary endpoint) as a function of eCrCL in high dose/warfarin groups in North American region.



Source:FDA analysis.

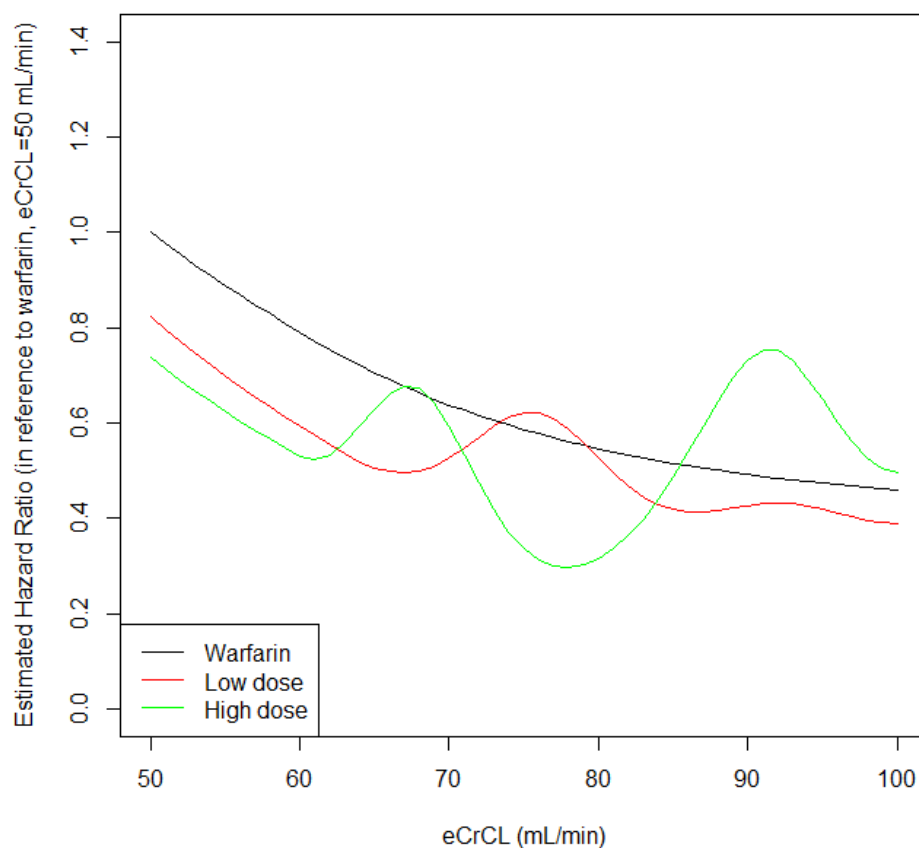
Figure 13 Estimated hazard ratios (primary endpoint) as a function of eCrCL in high dose/warfarin groups in different regions.



Source:FDA analysis.

In Figure 14, the hazard ratios for the endpoint of CV death are shown. I used the same model as I used to make Figure 11. Here, the low dose (red curve) seems to be consistently better than warfarin for the entire range of eCrCL. The high dose seems to be less effective for higher eCrCL. However, the evidence such as it is, suggests that an even higher dose would not decrease the rate of CV death for patients with higher eCrCL; a higher dose may even increase the risk of CV death.

Figure 14 Estimated hazard ratios (overall CV death) as a function of eCrCL.



Source:FDA analysis.

The cause of death in the subgroup with eCrCL>80 mL/min is shown in **Table 7**. This table is for the subgroup with eCrCL>80 mL/min and who had no dose adjustment indicated (i.e. weight >60 kg etc.). The table is divided into two sections. The top section includes people who had a history of stroke or TIA. The bottom section is for those with no history of stroke/TIA. The information in the table seems to suggest that there might be a tradeoff between different causes of death between the low dose and the high dose in this subgroup. However, it does not suggest that an even higher dose than the high dose used in the study (60 mg) could provide any further benefit on CV mortality and may do harm.

Table 7 Cause of death in subgroup with eCrCL>80 mL/min with no dose adjustment indicated.

A. eCrCL >80, no dose adjustment, history of stroke/TIA

	low (N=612)	high (N=594)	warfarin (N=614)
SUDDEN OR UNWITNESSED DEATH	14	17	17
CONGESTIVE HEART FAILURE/CARDIOGENIC SHOCK	2	7	4
OTHER	3	3	2
ISCHEMIC STROKE	7	4	3
INTRACRANIAL HEMORRHAGE	1	3	3
DYSRHYTHMIA	1	0	0
ATHEROSCLEROTIC VASCULAR DISEASE (EXCLUDING CORONARY)	0	0	1
DIRECTLY RELATED TO REVASCULARIZATION (CABG OR PCI)	0	0	0
NON-INTRACRANIAL HEMORRHAGE	1	0	0
PULMONARY EMBOLISM	1	0	1
SYSTEMIC ARTERIAL EMBOLIC EVENT	0	0	0

B. eCrCL>80, no dose adjustment, no history of stroke/TIA

	low (N=1879)	high (N=1894)	warfarin (N=1868)
SUDDEN OR UNWITNESSED DEATH	46	60	51
CONGESTIVE HEART FAILURE/CARDIOGENIC SHOCK	13	18	19
OTHER	7	9	5
ISCHEMIC STROKE	5	4	8
INTRACRANIAL HEMORRHAGE	0	9	6
DYSRHYTHMIA	7	2	3
ATHEROSCLEROTIC VASCULAR DISEASE (EXCLUDING CORONARY)	1	0	1
DIRECTLY RELATED TO REVASCULARIZATION (CABG OR PCI)	0	2	0
NON-INTRACRANIAL HEMORRHAGE	2	3	4
PULMONARY EMBOLISM	2	0	0
SYSTEMIC ARTERIAL EMBOLIC EVENT	0	0	0

Putting all of the analyses in this section together, the relative efficacy for the primary endpoint of a fixed dose of edoxaban (with dose adjustment as done in the study) to warfarin changes as a function of eCrCL. One possible explanation is that the effect of warfarin improves with higher eCrCL. Another possible theory is that the concentration of edoxaban is lower for people with higher eCrCL and therefore, they need a higher dose of edoxaban to achieve the same efficacy as their counterparts with lower eCrCL. It has not been proven that there exists any higher dose that

would be safe and effective. Secondly, even if there were, we do not know what dose would be high enough to achieve greater efficacy nor when to stop to maintain safety. Third, if we were to accept that some dose would be more safe and effective, there could be dosing errors caused by people using the wrong estimating equation (e.g. MDRD or CKD-EPI instead of Cockcroft-Gault). Of note, in the ENGAGE trial, there were people who should have gotten a dose adjustment according to the protocol because their eCrCL was less than 50 mL/min but did not (and vice versa).

SUMMARY AND CONCLUSIONS

1.9 Statistical Issues

The major statistical issues are the margin used to test for noninferiority and the use of the on-treatment period for the analysis. For Atrial Fibrillation trials using warfarin as the active control and the endpoint of Stroke/SEE, the issue of the margin has been more or less settled. The margin of 1.38 has been used in other trials and the FDA has accepted this margin. The on-treatment analysis can be problematic because a subject can have a period of study drug interruption for several weeks and have an event during that period, which would not count in the analysis. I prefer the intent-to-treat approach even in a non-inferiority trial. If the results are significantly different (which could only happen if there was a substantial amount of time when people were interrupting study drug), I think it would be difficult to interpret. In this study, the results for the overall treatment period were nearly identical to the on-treatment analysis even though there was a substantial number of events that happened off treatment. So, there was no problem interpreting this trial as positive.

1.10 Collective Evidence

There was only one phase 3 trial for this indication in the submission. Two dose regimens were studied. Both regimens were safe and effective.

1.11 Conclusions and Recommendations

The 3 doses used in the study (15 mg, 30 mg, 60 mg) were safe and effective. This range of doses should be sufficient to provide doses for individual treatment needs and I think all should be approved. Most people should take the 60 mg dose with dose adjustment based on renal

function and other factors such as body weight and concomitant medications. The strategy for adjusting dose for individuals that was used in the trial may not be the best one.

1.12 Labeling Recommendations (as applicable)

NA.

APPENDICES

Tests for qualitative interaction with respect to superiority in a noninferiority study

Suppose a study is designed to show a test drug is noninferior to warfarin using a margin of 1.38 and there are two subgroups of interest. This discussion is about a hypothetical scenario and not necessarily anything specific to the ENGAGE-AF trial. The true log hazard ratios in the two subgroups are λ_1 and λ_2 ; the estimated log hazard ratios in the two subgroups are denoted by $\hat{\lambda}_1$ and $\hat{\lambda}_2$ and the standard errors are s_1 and s_2 . The overall estimated treatment effect is

$\hat{\lambda} = \frac{\frac{\hat{\lambda}_1}{s_1^2} + \frac{\hat{\lambda}_2}{s_2^2}}{\frac{1}{s_1^2} + \frac{1}{s_2^2}}$ and its standard error is $s = \left(\frac{1}{s_1^2} + \frac{1}{s_2^2} \right)^{-1/2}$. If the study has 90% power to show

noninferiority, then the test statistic $\frac{\hat{\lambda} - \log(1.38)}{s}$ has expected value

$\Phi^{-1}(0.1) + \Phi^{-1}(0.025) = -3.24$. Assuming that $E\hat{\lambda} = 0$, this implies $\lambda_2 = \frac{-\lambda_1 s_2^2}{s_1^2}$ and

$s_2 = \frac{(1 - \log(1.38))s_1}{\sqrt{(3.24s_1)^2 - (1 - \log(1.38))^2}}$. Now, a statistically significant qualitative interaction for superiority

will happen when the test statistics in both subgroups are statistically significant at one-sided

level 0.05 and have opposite signs. This means either $\left\{ \frac{\hat{\lambda}_1}{s_1} < -z_{0.05} \text{ and } \frac{\hat{\lambda}_2}{s_2} > z_{0.05} \right\}$ or

$\left\{ \frac{\hat{\lambda}_1}{s_1} > z_{0.05} \text{ and } \frac{\hat{\lambda}_2}{s_2} < -z_{0.05} \right\}$ where $z_{0.05} \approx 1.645$ is the upper 0.05 quantile of the standard normal distribution. The unconditional probability of the events can be found because the statistics are independent and the events are disjoint,

$$\Phi\left(-z_{0.05} - \frac{\lambda_1}{s_1}\right) \left(1 - \Phi\left(z_{0.05} - \frac{\lambda_2}{s_2}\right)\right) + \left(1 - \Phi\left(z_{0.05} - \frac{\lambda_1}{s_1}\right)\right) \Phi\left(-z_{0.05} - \frac{\lambda_2}{s_2}\right).$$

Moreover, conditional on an overall positive result for noninferiority, the conditional probability of a statistically significant qualitative interaction will be

$$\frac{P\left[\left\{\left\{\frac{\hat{\lambda}_1}{s_1} < -z_{0.05} \& \frac{\hat{\lambda}_2}{s_2} > z_{0.05}\right\} \text{ or } \left\{\frac{\hat{\lambda}_1}{s_1} < -z_{0.05} \& \frac{\hat{\lambda}_2}{s_2} > z_{0.05}\right\}\right\} \& \frac{\hat{\lambda} - \log(1.38)}{s} < -z_{0.025}\right]}{P\left[\frac{\hat{\lambda} - \log(1.38)}{s} < -z_{0.025}\right]}$$

Since we are assuming the study has 90% power, the denominator is 0.9. The numerator can be expressed as the sum of two terms. The calculations below show how to find the first term; the other term in the numerator is similar to the first term with the indices 1 and 2 interchanged.

Let $x_1 = \frac{\hat{\lambda}_1}{s_1}$ and $x_2 = \frac{\hat{\lambda}_2}{s_2}$. The first term is

$$P\left[\frac{\hat{\lambda}_1}{s_1} < -z_{0.05} \& \frac{\hat{\lambda}_2}{s_2} > z_{0.05} \& \frac{\hat{\lambda} - \log(1.38)}{s} < -z_{0.025}\right]$$

$$\begin{aligned}
&= P \left[x_1 < -z_{0.05} \text{ \& } x_2 > z_{0.05} \text{ \& } \frac{\frac{\frac{x_1}{s_1} + \frac{x_2}{s_2}}{\frac{1}{s_1^2} + \frac{1}{s_2^2}} - \log(1.38)}{s} < -z_{0.025} \right] \\
&= \int_{z_{0.05}}^{\infty} \Phi \left(\min \left\{ -z_{0.05}, \frac{s_1(\log(1.38) s_2 - s(sx_2 + s_2 z_{0.025}))}{s^2 s_2} \right\} - \frac{\lambda_1}{s_1} \right) \phi \left(x_2 - \frac{\lambda_2}{s_2} \right) dx_2
\end{aligned}$$

Now, we have to consider two cases:

Case 1) $s_2 \left(\frac{\log(1.38)}{s^2} - \frac{z_{0.025}}{s} + \frac{z_{0.05}}{s_1} \right) < z_{0.05}$. In this case, over the range of integration

$\min \left\{ -z_{0.05}, \frac{s_1(\log(1.38) s_2 - s(sx_2 + s_2 z_{0.025}))}{s^2 s_2} \right\} = \frac{s_1(\log(1.38) s_2 - s(sx_2 + s_2 z_{0.025}))}{s^2 s_2}$ and the integral is

$$\int_{z_{0.05}}^{\infty} \Phi \left(\frac{s_1(\log(1.38) s_2 - s(sx_2 + s_2 z_{0.025}))}{s^2 s_2} - \frac{\lambda_1}{s_1} \right) \phi \left(x_2 - \frac{\lambda_2}{s_2} \right) dx_2$$

Case 2) $s_2 \left(\frac{\log(1.38)}{s^2} - \frac{z_{0.025}}{s} + \frac{z_{0.05}}{s_1} \right) > z_{0.05}$. In this case, the integral is

$$\begin{aligned}
&\int_{s_2 \left(\frac{\log(1.38)}{s^2} - \frac{z_{0.025}}{s} + \frac{z_{0.05}}{s_1} \right)}^{\infty} \Phi \left(\frac{s_1(\log(1.38) s_2 - s(sx_2 + s_2 z_{0.025}))}{s^2 s_2} - \frac{\lambda_1}{s_1} \right) \phi \left(x_2 - \frac{\lambda_2}{s_2} \right) dx_2 \\
&+ \Phi \left(-z_{0.05} - \frac{\lambda_1}{s_1} \right) \left(\Phi \left(s_2 \left(\frac{\log(1.38)}{s^2} - \frac{z_{0.025}}{s} + \frac{z_{0.05}}{s_1} \right) - \frac{\lambda_2}{s_2} \right) - \Phi \left(z_{0.05} - \frac{\lambda_2}{s_2} \right) \right)
\end{aligned}$$

In the example shown in the R program below, the hazard ratios in the two subgroups are 0.77 and 1.3. This means the drug is truly noninferior in both subgroups (with respect to the margin 1.38). But, there is about a 37% chance of finding a qualitative interaction with respect to superiority conditional on an overall positive result for the study. The program calculates this two different ways; by simulation and also using the exact formulas derived above.

#R program to estimate conditional probability of qualitative interaction.

```
nsim=10000000
z025=qnorm(0.975)
z05=qnorm(0.95)
l1=-0.26
s1=0.14
s2=log(1.38)*s1/sqrt((3.24*s1)^2-(log(1.38))^2)
l2=-l1*s2^2/s1^2
s2
exp(l1)
exp(l2)
s=1/sqrt(1/s1^2+1/s2^2)
lam1=rnorm(nsim,l1,s1)
lam2=rnorm(nsim,l2,s2)
x1=lam1/s1
x2=lam2/s2
lamhat=((x1/s1+x2/s2)/(1/s1^2+1/s2^2))
mean(lamhat) #check the mean is 0
mean((lamhat-log(1.38))/s<(-z025)) #90% power for noninferiority

#unconditional prob of qual inter. using simulation and using exact formula
mean((x1>z05 & x2<(-z05)) | (x2>z05 & x1<(-z05)))
pnorm(-z05-l1/s1)*(1-pnorm(z05-l2/s2))+(1-pnorm(z05-l1/s1))*pnorm(-z05-l2/s2)

#this section calculates the two integrals in the numerator
f1=function(x, l1,l2,s1,s2,s,delta,z025) {
pnorm((s1*(log(1.38)*s2 - s*(s*x + s2*z025)))/(s^2*s2)-l1/s1)*dnorm(x-l2/s2)}

if (s2*(log(1.38)/s^2-z025/s+z05/s1)<z05) i1= integrate(f1,lower= z05,upper=Inf,
l1=l1,l2=l2,s1=s1,s2=s2,s=s,delta=log(1.38),z025=z025)$val else i1=pnorm(-z05-l1/s1)*
(pnorm(s2*(log(1.38)/s^2 - z025/s + z05/s1)-l2/s2)-pnorm(z05-l2/s2))+
integrate(f1,lower= s2*(log(1.38)/s^2 - z025/s + z05/s1),upper=Inf,
l1=l1,l2=l2,s1=s1,s2=s2,s=s,delta=log(1.38),z025=z025)$val

f2=function(x, l1,l2,s1,s2,s,delta,z025) {
pnorm((s2*(log(1.38)*s1 - s*(s*x + s1*z025)))/(s^2*s1)-l2/s2)*dnorm(x-l1/s1)}

if (s1*(log(1.38)/s^2-z025/s+z05/s2)<z05) i2= integrate(f2,lower= z05,upper=Inf,
```

```

l2=l2,l1=l1,s2=s2,s1=s1,s=s,delta=log(1.38),z025=z025)$val else i2=pnorm(-z05-l2/s2)*
(pnorm(s1*(log(1.38)/s^2 - z025/s + z05/s2)-l1/s1)-pnorm(z05-l1/s1))+
integrate(f2,lower= s1*(log(1.38)/s^2 - z025/s + z05/s2),upper=Inf,
l2=l2,l1=l1,s2=s2,s1=s1,s=s,delta=log(1.38),z025=z025)$val

#conditional prob. of qual. int. using simulation and exact formula
mean(((x1>z05 & x2<(-z05)) | (x2>z05 & x1<(-z05))) & (lamhat-log(1.38))/s<(-z025))/0.9
(i1+i2)/0.9

```

Fitting parametric distributions

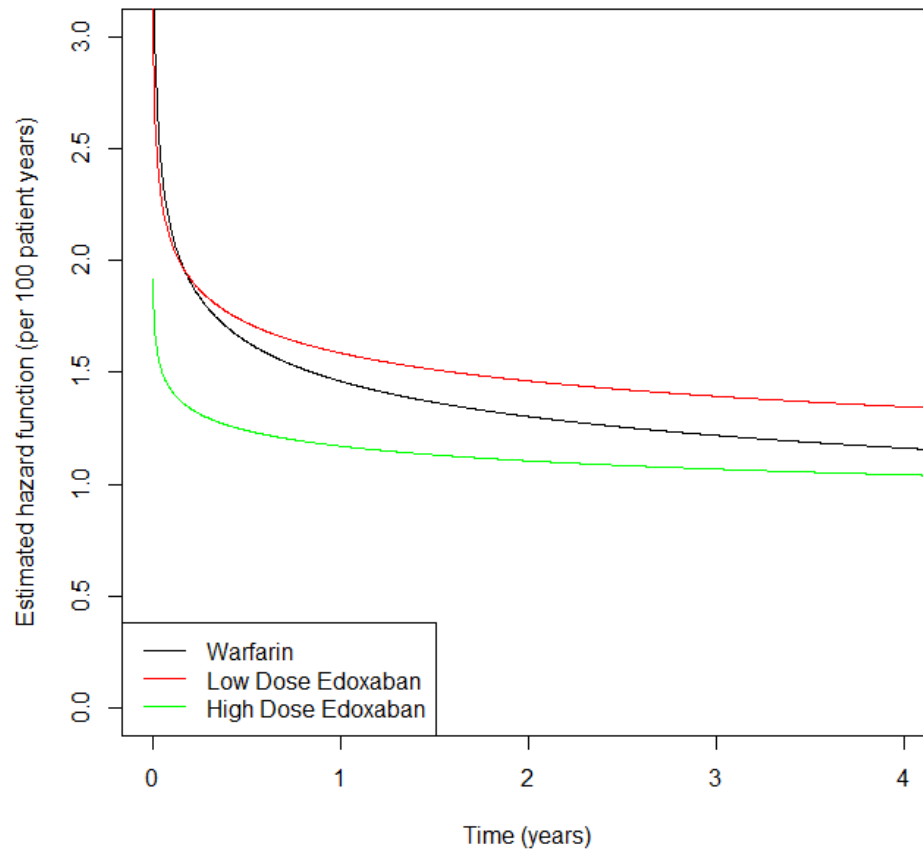
The cumulative distribution function is denoted by $F(x)$, the density is $f(x)$, the hazard function is $h(x) = \frac{f(x)}{1-F(x)}$, and cumulative hazard function, $H(x) = -\log\{1 - F(x)\}$. Suppose subject i has exposure at time intervals $(s_{i,1}, t_{i,1}), (s_{i,2}, t_{i,2}), \dots, (s_{i,m_i}, t_{i,m_i})$ where $0 = s_{i,1} \leq t_{i,1} < s_{i,2} \leq t_{i,2} < \dots < s_{i,m_i} \leq t_{i,m_i}$, the number of subjects is n and they have been ordered so that the first D subjects have events and the remainder do not. Then the log-likelihood is

$$\sum_{i=1}^n \sum_{j=1}^{m_i} \{H(s_{i,j}) - H(t_{i,j})\} + \sum_{i=1}^D \log\{h(t_{i,m_i})\}$$

For the Weibull family, the density is $f(x) = \frac{a}{b} \left[\frac{x}{b}\right]^{a-1} e^{-(x/b)^a}$. The best fitting parameters for each group are shown below and the estimated hazard functions are in Figure A1 that follows.

Group	a	b
warfarin:	0.835	127
low:	0.882	95.3
high:	0.916	116

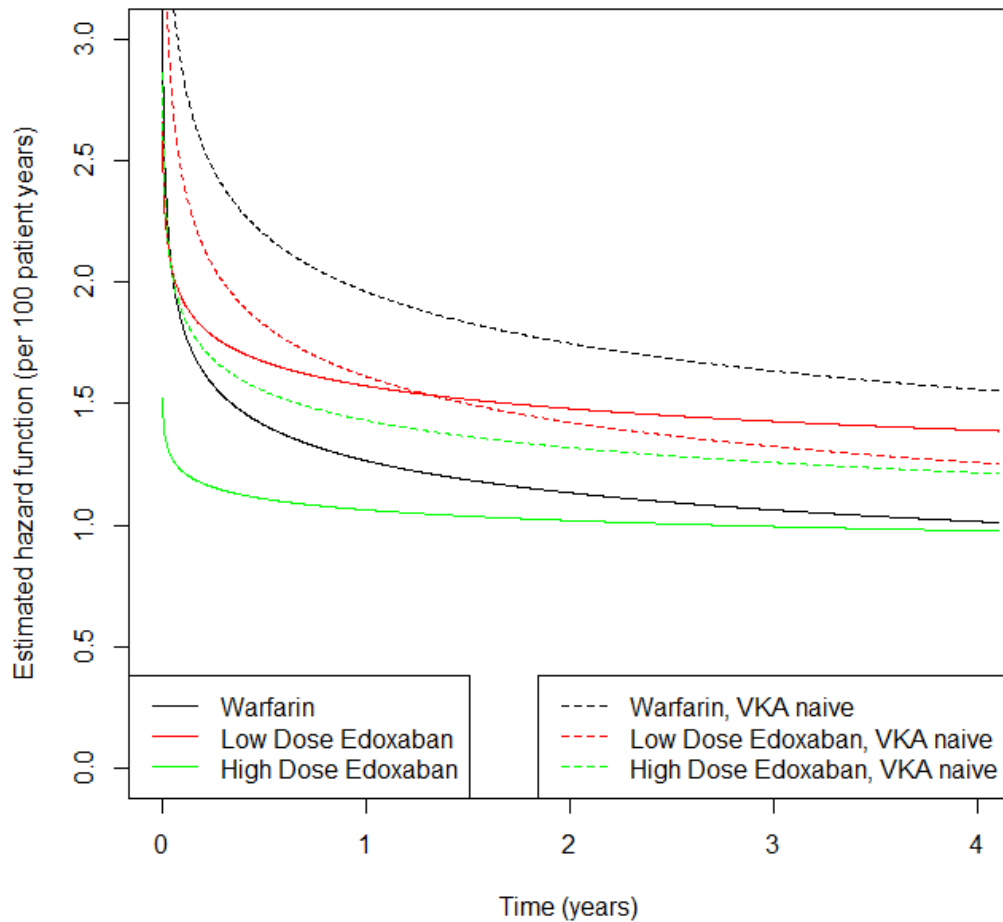
Figure A1. Estimated hazard functions using the Weibull distribution (primary endpoint, mITT, on treatment).



Source: FDA analysis

The next figure (A2) shows the estimated hazard functions in each group separated by VKA use 30 within 30 days before randomization. As in Figure 6, this figure suggests that the subjects who were VKA naive had a higher hazard rate, particularly in the warfarin group.

Figure A2. Estimated hazard functions using the Weibull distribution by VKA status (primary endpoint, mITT, on treatment). Solid curves are for the subgroups of patients who were not VKA naive, dashed curves are for VKA naive subgroups.



Source: FDA analysis

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09/22/2014