CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206316Orig1Orig2s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 22,2014
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	206316
Applicant	Daiichi Sankyo, Inc.
Date of Submission	January 8, 2014
PDUFA Goal Date	January 8, 2015
Proprietary Name / Established (USAN) names	Savaysa (edoxaban) Tablets
Dosage forms / Strength	Oral
Proposed Indication(s)	"for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), (b) (4)
Recommended:	Approval for the indication: for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (b) (4)

1. Introduction

Edoxaban (DU-176b) is an orally active, selective Factor Xa inhibitor being developed for anticoagulant indications. This is the first marketing application for this product. The sponsor is seeking approval of edoxaban for indications as follows:

- In atrial fibrillation: for reduction of the risk of stroke and systemic embolic events in subjects with non-valvular atrial fibrillation

- In VTE: for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), (b) (4)

The atrial fibrillation indication is being reviewed by the Division of Cardiovascular and Renal Products (DCRP) and is not addressed in this review. The VTE indications are being reviewed in the Division of Hematology Products (DHP).

For the VTE indications the proposed dose is 60 mg once daily for treatment (b) (4) of VTE (b) (4) For patients with moderate to severe renal impairment (CrCL 15-50 mL/min), low body weight ≤60 kg, or concomitant use of P-glycoprotein (P-gp) inhibitors (b) (4) a dose of 30 mg once daily is proposed.

Edoxaban is marketed in Japan (approved 4/22/2011) for thromboprophylaxis following total knee replacement, total hip replacement, and hip fracture surgery.

2. CMC/Device

In this NDA the sponsor is seeking approval of edoxaban immediate release (IR) tablets 15 mg, 30 mg and 60 mg. The detailed chemistry, manufacturing and controls (CMC) review is presented in the CMC review by A Khairuzzaman, D Ghosh, and Y Tang, signed in DARRTS on 9/8/2014. The CMC review team for this application consisted of the following:

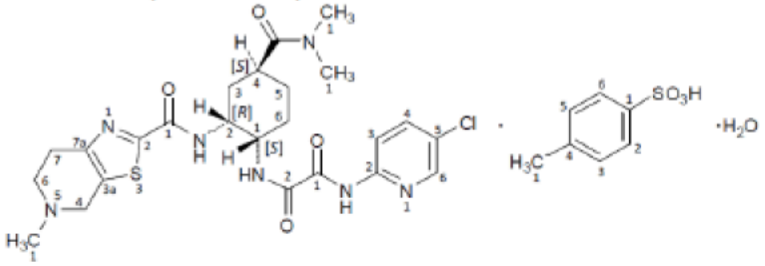
Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh	Branch II/ Division I
Drug Product	Akm Khairuzzaman	Branch I/ Division I
NIR Procedures	Yubing Tang	Branch VI/ Division II
Microbiology	Steve Donald	
Facility	Vibhakar Shah, Vipul Dholakia	
Biopharmaceutics	Sandra Suarez	
CMC Lead	Kasturi Srinivasachar (DCRP), Janice Brown (DHP)	
Project Manager	Yvonne Knight	
Technical Lead	Sharmista Chatterjee	
Laboratory (OTR)	John Kauffman, Jason Rodriguez	OTR/DPA
ORA Lead		
Environmental Assessment (EA)		

from CMC review by A Khairuzzaman, D Ghosh, and Y Tang, completed in DARRTS on 9/8/2014

The 9/8/2014 CMC Review shows the name and chemical structure of Edoxaban (DU-176b) as follows:

Chemical Name or IUPAC Name/Structure
Endoxaban tosylate monohydrate



The drug substance quality summary in the CMC Review identified a potential problem stating that, "Based on NDA, edoxaban tosylate in the [redacted] (b) (4)

The CMC review indicates the drug product (SAVAYSA Tablets) will be packaged in all aluminum blisters as well as in HDPE bottles and states, "The proposed shelf life is 36 months at long term storage conditions of 25ºC/60%RH, which is supported by 24 months of registration stability batch data and 48 months of clinical (phase 3) batch stability data. Batches used in the registration stability program were manufactured by the final commercial process at pilot-scale." No issues were identified for the final drug product.

Site inspections were conducted by the Division of Bioequivalence and GLP Compliance (DBGLPC), Office of Scientific Investigations for the bioequivalence study of the round shape tablet and the current tablet formulation of edoxaban (Study DU176b-A-U142). Clinical site Celerion (Neptune, NJ) and analytical site [redacted] (b) (4) were inspected. No issues were identified. The EIR Memorandum (H Chen, 11/17/2014) states:

> **Conclusion:**
> Following the above inspections, this DBGLPC scientist concludes that both clinical and bioanalytical data from study DU176b-A-U142 are acceptable for further Agency review.

Subsequently, Dr. Khairuzzaman in a CMC Memo to the File on 12/15/2014 states:

> Pursuant the overall "acceptable" recommendation given on 14-Nov-2014 for the manufacturing facilities by the Office of Compliance, the CMC recommendation is no changed to "**Recommended for Approval**" from CMC perspective.

Methods Validation review was conducted by Division of Pharmaceutical Assessment (C Guo, DPA Chemist) (M Trehy and JF Kauffmann, final signature 6/25/2014). Review of the near infrared (NIR) methods for the application was conducted by the Division of Pharmaceutical Analysis (JD Rodriguez, Chemist)(review in DARRTS 9/5/2014, M Trehy) and found the information, as amended in response to an Information Request from DPA to the sponsor, adequate.

A CMC Memorandum providing IQA Risk Assessment for edoxaban was completed (J Brown, 8/22/2014). The NDA risk assessment table is shown below:

NDA RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations / Comments
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L			
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M			
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L			
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L			
Dissolution	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipment • Site	M			

CMC Memo, J Brown, 8/22/2014

Tertiary CMC review (RK Sood, 10/7/2014) summarized the findings of the CMC review and noted the biopharmaceutics recommendation for a Post-Marketing Commitment "to develop an improved discriminating and canonical method and set the final dissolution acceptance criteria for the product using the new method". Dr. Sood found the application adequate from CMC perspective and recommended for **"Approval"** from CMC perspective pending a final overall "Acceptable" recommendation from the Office of Compliance about the manufacturing facilities.

3. Nonclinical Pharmacology/Toxicology

The non-clinical Pharmacology/Toxicology primary review of this application was conducted by S-L Lee (final signature 8/19/2014) and B. Yang (final signature 8/12/2014). Dr. Lee's review addresses the primary and secondary pharmacology studies conducted with edoxaban (DU-176b). Dr. Yang's review addresses results of safety pharmacology, ADME, and toxicology studies and includes recommendation on approval and labeling.

As described in Dr. Lee's review, edoxaban (DU-176b) is an anti-coagulant exerting its pharmacodynamics effects mainly via inhibition of activated coagulation factor X (Factor Xa;

FXa). Edoxaban also had inhibitory activity against thrombin to a lesser degree (Ki for FXa was ~0.6 nM and for thrombin was 6 mcM). FXa inhibition was comparable in human, rabbit, and cynomolgus and less in rat plasma. The three metabolites of edoxaban (D21-1402-0201, D21-2135-0101, D21-2393) also had anti-FXa activity and caused clotting time prolongation. The human specific metabolite D21-2393 (10% of the total exposure in healthy human subjects) showed comparable anti-coagulant effects as edoxaban. The review states, "In various animal models, oral administration of edoxaban resulted in dose-dependent anti-thrombotic activity, as manifested by reduced weight of thrombi, as well as prolongation of clotting time. Under the conditions tested, the antithrombotic effects, in terms of PT prolongation and inhibition of thrombosis, of edoxaban were comparable to enoxaparin (a low molecular weight heparin, which inhibits both FXa and thrombin) and warfarin (vitamin K antagonist)." Edoxaban also was found to inhibit platelet aggregation induced by thrombin, possibly via inhibition of thrombin, since edoxaban did not affect ADP. The review also comments that, "in the *in vitro* studies, recombinant FVIIa, FEIBA (a plasma-derived activated prothrombin complex concentrate) or PPSB-HT (a prothrombin complex concentrate) were used to determine the reversibility of edoxaban-induced anticoagulant activities. Under the conditions tested, reversibility of edoxaban-induced anticoagulation was demonstrated when these plasma factors were added to the mixture. Despite this reversibility, a conclusion cannot be made on the antidote effect of plasma factors in animals or in humans due to limitations of an in vitro study."

The summary toxicology findings of Dr. Yang's review included: (I) increased polyploidy in chromosomal aberration tests; (II) hemorrhage in mice, rats, rabbits, and monkeys; (III) more post-implantation loss, less live fetuses, lower fetal weight, increased gall bladder and skeletal variations, and delayed avoidance response in a learning test in F1 females, which were associated with maternal hemorrhagic toxicity; and (IV) higher mortality in male rats at the high dose in a 2-year carcinogenicity study that was associated with higher incidence and greater severity of centrilobular hepatocellular degeneration/ necrosis.

The review described that in animal toxicity studies (monkeys, mice, rats, rabbits) hemorrhagic findings and anemia leading to deteriorated animal condition or animal deaths occurred. These findings are thought to be the exaggerated anticoagulant effect of DU-176b (its principal pharmacological action), which constitutes the dose-limiting toxicity for this compound. The pharmacological activity of DU-176b in the cynomolgus monkey was found to be comparable to that in humans. The review states that since the pharmacological activity of DU-176b in the cynomolgus monkey was comparable to that in humans, safety margins for hemorrhagic risk were estimated by comparison of exposures between cynomolgus monkeys and humans. The mean AUC0-24h values at NOAEL (5 mg/kg/day) in the 52-week repeated dose oral toxicity study in cynomolgus monkeys were approximately 1.5 times the exposures in human subjects given DU-176b at the maximum recommended human dose (MRHD) of 60 mg/day.

As described in Dr. Yang's review, DU-176b was embryo-fetal toxic and developmental toxic in both rats and rabbits showing higher post-implantation loss in the rat, more post-implantation loss, less live fetuses, lower fetal weight, and increased variation in the gall bladder in rabbits, and increased 13th full ribs and 27 presacral vertebrae in rabbits. There was

delayed avoidance response during a learning test in F1 rats at ~2.9 times the human exposure at adult MRHD of 60 mg/day based on AUC0-24h, and moderately lower body weight in juvenile rats at ~2.2 times the human exposure at adult MRHD of 60 mg/day based on AUC0-24h). Maternal toxicity including dam deaths and abortion, decreased food consumption and body weight, hemorrhage in uterus, or vaginal hemorrhage also occurred. The DU-176b associated embryo-fetal toxicity in rats and rabbits and developmental toxicity in rats were considered to be secondary effects of maternal toxicity, rather than direct DU-176b effect.

Dr. Yang's review discusses that DU-176 systemic exposure and liver findings suggested that (1) male rats had higher liver DU-176 metabolite rate (first-pass) which led to low systemic exposure; (2) DU-176 metabolic processes in liver were toxic, and (3) long term, persistent, and excessive DU-176 metabolic processes in liver led to centrilobular hepatocellular degeneration/necrosis that contributed to higher mortality, indicating that liver toxicity may be a potential safety issue for long-term high dose. DU-176b along with increased liver metabolism, although such findings were not seen in mice and monkeys orally administrated with DU-176b.

Dr. Yang's review commented that numerical chromosome aberrations (polyploidy) observed in DU-176b or D21-2393-treated Chinese Hamster Lung (CHL) cells and human peripheral lymphocytes were the only positive finding among a battery tests for genotoxicity and concluded that, "Based upon a weight of evidence approach, DU-176b is not considered to pose a genotoxic risk."

Dr. Yang's review concluded "Yes" on recommendation for approvability and provided a number of labeling comments. In particular, Pregnancy category C was recommended. Also, wording was provided for 8.2 Labor and Delivery, 8.3 Nursing Mothers, description of a results of a juvenile rat study under 8.4 Pediatric Use and additional recommendations for non-clinical toxicity. See Dr. Yang's 8/12/2014 review for full Pharmacology/Toxicology recommendations for labeling.

Statistical Review of 2 carcinogenicity studies (one in rat one in mice) was conducted by MA Rahman (final signature 7/8/2014). In the rat study the findings showed statistically significant dose response relationship in mortality across control and treated groups in male rats. The pairwise comparisons showed statistically significant increased mortality in the male rat high dose group compared to their control. The tests did not show statistically significant dose response relationship in any observed tumor type in either sex. The pairwise comparison also did not show statistically significant increased incidence in any observed tumor type in any treated group in either sex compared to their respective control. In the mouse study results showed a statistically significant dose response relationship in mortality across the treatment groups in male mice. The pairwise comparison showed statistically significant increased mortality in male mice high dose group compared to their control. The tests did not show a statistically significant dose response relationship in any observed tumor type in either sex. The pairwise comparisons showed statistically significant increased incidence of adrenal cortex B-adenoma in subcapsular cell in low dose male mice and whole body cavities M-hemangiosarcoma in medium dose female mice compared to their respective control. Dr. Rahman commented that in the review "dose response relationship" refers to "the linear

component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as the dose increases".

Tertiary Pharmacology Review by PC Brown (11/7/2014) concurred that the nonclinical information is adequate to support approval of edoxaban tosylate for the indications being sought.

4. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review of the application with regard to the VTE indications (based on the Hokusai VTE Study) was completed by D Menon-Andersen, YJ Moon, and J Earp (10/31/2014). The review concludes, "The exposure-response analysis suggests that patients with varying degrees of renal function have similar or improved efficacy and safety compared to warfarin. Based subgroup analysis of efficacy and safety, a dose reduction to 30 mg in patients with low body weight or who are taking concomitant P-gp inhibitors is not necessary. The dose reduction to 30 mg in patients with moderate renal impairment as studied in Hokusai VTE is acceptable and will be included in product labeling."

The key findings of the review were summarized as follows:

Pharmacokinetics and Pharmacodynamics

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

Effect of intrinsic factors

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

Effect of extrinsic factors

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

Exposure-response relationships

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

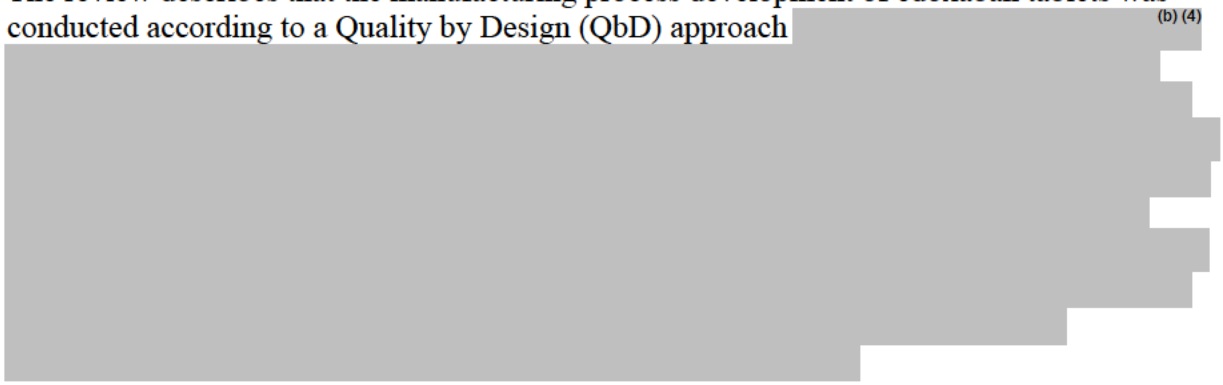
It should be noted that the Clinical Pharmacology Review conducted for the indication to prevent stroke and systemic embolism in patients with non-valvular atrial fibrillation (a-fib indication) (Divya Menon-Andersen, Young-Jin Moon, Justin Earp, Robert Schuck, 9/30/2014) found a significant treatment-by-renal function interaction in the clinical trial for this indication (ENGAGE-AF). That review states, "Subgroup analyses of ENGAGE-AF identified unfavorable findings in patients with normal renal function (CrCL ≥ 80 mL/min), who comprised a large fraction of the target population (~37% in ENGAGE-AF). The HR for stroke/SEE in this subgroup for edoxaban 60 mg was 1.41 (0.97 – 2.05). The treatment by

renal function interaction was nominally significant ($p < 0.001$) for both edoxaban dose groups. Less favorable results were also observed for the components of the primary efficacy endpoint across edoxaban dose groups in patients with CrCL≥80 mL/min." The review concluded that 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. Optimization of dose for the a-fib indication in patients with normal renal function based on exposure-response analyses was discussed at a meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting on Oct 30, 2014. See the Minutes of the CRDAC meeting and the 9/30/2014 Clinical Pharmacology Review for more detailed presentation and discussion of this issue for the a-fib indication.

For the VTE indications the 10/31/2014 Clinical Pharmacology Review states, "The predicted event rate corresponding to exposures at the studied dose (60 mg QD) suggests the dosing produces numerically lower results than warfarin. Unlike the SAPF indication (see Clinical Pharmacology review dated September 30, 2014), a significant interaction between renal function and the overall efficacy results was not identified."

In an Addendum to the Clinical Pharmacology review (Jeffry Florian, Rajnikanth Madabushi, signed 12/19/2014) following the October 30, 2014 CRDAC meeting Office of Clinical Pharmacology provided additional analyses, discussion and updated recommendations for the application. For the a-fib indication the review recommended: "In consideration of the findings presented in the primary clinical pharmacology review, discussion at the CRDAC, and additional analyses conducted following the Advisory Committee, the Office of Clinical Pharmacology recommends that a dose higher than 60 mg (e.g., 75-90 mg q.d.) should be approved for use in patients with CrCL > 80 mL/min for the indication of reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation." Recommendations for the VTE indications were unchanged. The 12/19/2014 review states: "Consistent with the recommendations provided in the original Clinical Pharmacology Reviews for the atrial fibrillation (9/30/2014 by Dr. Divya Menon-Andersen) and deep vein thrombosis/pulmonary embolism (10/31/2014 by Dr. Young-Jin Moon) indications, the Office of Clinical Pharmacology recommends that dose reductions to edoxaban 30 mg are not necessary for patients with low body weight or in patients concomitantly treated with P-gp inhibitors."

The Biopharmaceutics Review was completed by S Suarez Sharp and A Dorantes (9/9/2014). The review describes that the manufacturing process development of edoxaban tablets was conducted according to a Quality by Design (QbD) approach (b) (4)



The review found the sponsor did not submit adequate information to support the dissolution method. The deficiencies are described as follows:

> The Applicant did not submit adequate/sufficient information to support the discriminating ability of the dissolution method. The following summarizes the concerns about the dissolution method:
>
> (b) (4)
>
> (b) (4)

The review identified problems with the (b) (4) dissolution model proposed by the sponsor and found the (b) (4) developed for the 15mg, 30 mg, and 60 mg tablets are not acceptable. The problems were discussed with the sponsor and the sponsor subsequently agreed to withdraw the dissolution model from the NDA submission. See the Biopharmaceutics Review (S Suarez Sharp and A Dorantes, 9/9/2014) for detailed discussion. The review states that following discussion between the sponsor and the Biopharmaceutics team, the sponsor agreed to a Post-Marketing Commitment for: i) development of a new dissolution method, which shows greater discriminating ability (b) (4) and ii) setting of the final dissolution acceptance criterion of their drug product using the new method and the overall dissolution profile data from a minimum of 12 commercial batches.

The Biopharmaceutics review did not identify any issues with regard to appropriate bridging throughout the phases of drug development. There were no manufacturing changes implemented to the clinical trial formulation. The product will be manufactured by Daiichi Sankyo Propharma Co., Ltd., Hiratsuka, Japan. The review noted that the 60 mg tablets were not tested in phase 3 clinical trials and approval of the 60 mg tablet is based on the results of bioequivalence (BE) study A-U142. In that study the pharmacokinetic parameters Cmax, AUCt, and AUCinf met the criteria for BE for both edoxaban and its major metabolite when the round 60 mg proposed commercial tablet formulation to the Phase 3 tablet formulation (30 mg round tablets), when both tablets are dosed at 60 mg under fasting conditions.

The Biopharmaceutics review made the following recommendation:

II) RECOMMENDATION

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

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

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

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

5. Clinical Microbiology

Product Quality Microbiology Review by SP Donald (signed 4/3/2014) states, "No product quality microbiology deficiencies were identified based upon the information provided" and recommended the application for approval.

6. Clinical/Statistical- Efficacy

The sponsor conducted a single randomized, double-blind, double dummy, active controlled study for the treatment of DVT, treatment of PE and prevention of recurrence of VTE. The detailed Clinical Review of this application for the VTE indications was conducted by S Ayache (signed 9/8/2014) and Statistical Review was conducted by Y Wang (final signature 9/9/2014). See those reviews for detailed discussion of efficacy findings.

The major features of the clinical trial design are described as follows in Dr. Wang's Statistical Review:

> The pivotal trial Hokusai VTE was a Phase III, randomized, multi-center, double-blind, double-dummy, study with two parallel treatment groups: Edoxaban and Warfarin. Approximately 7500 patients were planned to be randomized 1:1 to the 2 treatment arms via an interactive voice/web response system (IXRS). Eligible subjects were stratified by presenting diagnosis: PE with or without DVT vs. DVT only. Within each diagnostic stratum, eligible subjects were further stratified by baseline risk factors (a. temporary risk factors only [such as trauma, surgery, immobilization, estrogen therapy, etc.] vs. b. all others), and need for adjustment (body weight ≤ 60 Kg; creatinine clearance [CrCL] between 30 and 50 mL/min inclusive, and concomitant use of the P-gp inhibitors verapamil or quinidine).
>
> The primary objective of the Study Hokusai VTE was to evaluate whether Edoxaban was non-inferior to Warfarin in the treatment of subjects with acute symptomatic VTE.

> The study was designed to accumulate approximately 220 symptomatic recurrent VTE events in the mITT analysis set. This design would have a power of 85% and type I error of 0.05 to demonstrate that Edoxaban is non-inferior to Warfarin, with a non-inferiority margin for the hazard ratio of 1.5. Assuming an incidence rate of 3.0% for symptomatic recurrent VTE during the study period of 12 months, 7500 subjects were expected to be randomized.
>
> Non-inferiority margin was derived based on indirect confidence interval comparison method. This method focused on identifying the maximally acceptable loss of active treatment benefit. Active treatment benefit was defined as the difference in treatment effect between available "more effective" treatment and "less effective" treatment, such as placebo or no treatment. Based on 14 historical studies, the odds ratio for available "more effective" treatment in comparison to "less effective" treatment was 0.18 (95% CI: 0.14 to 0.25). Considering the upper 95% confidence limit of 0.25 as the active treatment benefit, non-inferiority margin would be (1/0.25)^(1-0.7) = 1.5 to retain at least 70% of available treatment benefit and (1/0.25)^(1-0.9) = 1.15 to retain at least 90% of available treatment benefit.
>
> The primary efficacy endpoint was time to first symptomatic recurrent VTE and VTE-related death (i.e., the composite of DVT, non-fatal PE, and fatal PE), which was defined as time from the day of randomization to the first symptomatic recurrent VTE and VTE-related death experienced by a subject during the 12-month study period. Subjects who did not have a primary efficacy outcome during the 12-month study period would be censored at Day 365 or the last day the subject had a complete assessment for the study outcome, whichever came first. All events were adjudicated by CEC.
>
> The secondary efficacy endpoint was time to composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality. Similar definition and censoring rules for the primary efficacy endpoint were applied to the secondary efficacy endpoint.

The Hokusai VTE study enrolled adult patients with confirmed acute DVT and/or PE. Major exclusion criteria are listed in the Clinical Review which states:

> The main exclusion criteria included thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE; indication for warfarin other than DVT and/or PE; more than 48 hours pretreatment with therapeutic dosages of anticoagulant treatment (LMW heparin, unfractionated heparin, and fondaparinux per local labeling) or more than a single dose of a VKA prior to randomization to treat the current episode, calculated CrCL < 30 mL/min, and significant liver disease.

This study was conducted from January 28, 2010 to June 12, 2013. A total of 8292 subjects were randomized to the edoxaban (N=4143) or warfarin (N=4149) treatment arms. Enrolled patients were from 439 sites in 37 countries in Europe, Asia, North America, South America, and Africa (South Africa only). About 54% of patients were from Europe and 9.9% were from the U.S. and Canada. There were 7 sites noted as having "data of suspect authenticity"; however these accounted for only 24 randomized subjects. Twenty-five patients in the edoxaban arm and 27 patients in the warfarin arm did not receive any study drug and are excluded from the mITT and safety analysis populations. (Among these the vast majority were simply indicated as "IP not administered"; 2 patients died; 1 was diagnosed with pancreatic cancer). Overall, about 96% of patients completed the study with completion defined as having completed 12-month followup (or <12 month followup due to truncation of the study), regardless of actual duration of study drug treatment. Overall, 74.4% of treated patients completed full 12-month study followup and 21.4% had less than 12 months followup due to study truncation. An additional 4.2% of treated patients did not complete 12 months followup due to: death (3.2%), withdrew consent (0.8%), lost to followup (0.1%) or

investigator or subject decision (0.1%). Rates of study completion and followup and reasons for premature withdrawal were comparable in the two treatment arms. Disposition of patients in the study is shown in the sponsor's table below.

Table 10.1: Disposition of All Subjects Randomized

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

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

Sponsor's table from Study report for DU176b-D-U305 (Hokusai VTE)

The demographic and baseline characteristics were similar in the two treatment groups. Overall, mean age was 55.8 years. About one-third of patients were age 65 years or older. There were slightly more males than females (57.2% vs 42.8%). About 70% were Caucasian and 21% were Asian. About 40.7% had pulmonary embolism with or without DVT as the presenting diagnosis and 59.3% had DVT only as presenting diagnosis. Treatment duration was intended to be 12 months in 72.3% of patients at study enrollment. The vast majority of patients (93.4%) had creatinine clearance greater than 50 mL/min at randomization.

Underlying diseases were similarly distributed between the two treatment groups. About 39% of patients had history of hypertension, 10.5% had history of diabetes, 9% had history of cancer, and <1% had history of bleeding (0.6% edoxaban, 0.9% warfarin) or active/high risk of bleeding (0.2% edoxaban, 0.4% warfarin). About 40% of patients had history of smoking/tobacco use and 34% had current alcohol use.

Only 17.6% of patients were assigned to treatment with the 30 mg edoxaban (or edoxaban placebo) dose at randomization (733 in edoxaban arm; 719 in warfarin arm). These included patients with low body weight (≤ 60kg), moderate renal impairment (CrCL 30 to 50 ml/min), or taking pre-specified concomitant medications (e.g. verapamil, quinidine). Overall, mean age of the patients assigned to the 30 mg dose group was 60.1 years as compared to 54.9 years for the 60 mg dose group, 66.55 of patients in the 30 mg dose group were females as compared

to 37.7% of patients in the 30 mg dose group, and 46.0% of patients in the 30 mg dose group were Asian as compared to 15.6% of patients in the 30 mg dose group. Distribution of characteristics was similar between treatment groups.

Demographic and baseline characteristics for the Per Protocol and Safety Analysis Sets were comparable to those for the mITT Analysis Sets.

The Statistical Review summarized the efficacy findings of the Hokusai VTE study as follows:

> The support of Edoxaban for the treatment of DVT and PE was based on one pivotal trial, Study Hokusai VTE (DU176b-D-U305), which was a Phase III, randomized, multi-center, double-blind, double-dummy, and parallel-group study with two parallel treatment groups: (low molecular weight [LMW]) Heparin/Edoxaban and [LMW] Heparin/Warfarin. The primary efficacy objective of the Study Hokusai VTE was to evaluate whether initial [LMW] Heparin followed by Edoxaban([LMW] Heparin/Edoxaban) was non-inferior to initial [LMW] Heparin overlapping with Warfarin, followed by Warfarin ([LMW] Heparin/Warfarin) in the treatment of subjects with acute symptomatic VTE.
>
> Study Hokusai VTE randomized 8292 patients, 4143 to Heparin/Edoxaban arm and 4149 to Heparin/Warfarin arm respectively. Primary efficacy analysis was based on modified intent-to-treat (mITT) population, which consisted of 8240 patients who received at least one dose of study treatment. Non-inferiority was demonstrated in the primary efficacy endpoint, time to symptomatic recurrent VTE or VTE-related death, for patients treated with Heparin/Edoxaban versus Heparin/Warfarin. The estimated hazard ratio (HR) for time to symptomatic recurrent VTE or VTE-related death was 0.89 (95% confidence interval: 0.70 – 1.13) for the Heparin/Edoxaban arm versus Heparin/Warfarin arm based on 276 recurrent VTE or VTE-related death. The upper 95% confidence limit of 1.13 demonstrated that treatment with Heparin/Edoxaban retained at least 91% treatment effect of Heparin/Warfarin. The median time to symptomatic recurrent VTE or VTE-related death was not reached in either treatment arm.

The primary efficacy analysis and component endpoints from the Statistics Review (9/8/2014) are shown below:

TABLE 7: PRIMARY EFFICACY ANALYSIS RESULTS, MITT POPULATION

Primary efficacy endpoint	Edoxaban (N=4118)	Warfarin (N=4122)
Subjects with recurrent VTE or VTE-related death, n (%)	130 (3.2)	146 (3.5)
PE with/without DVT, n (%)	73 (1.8)	83 (2.0)
Fatal PE, n (%)	24 (0.6)	24 (0.6)
DVT only, n (%)	57 (1.4)	63 (1.5)
Un-stratified Hazard Ratio (95% CI)	0.89 (0.70, 1.13)	
Nominal P value for non-inferiority	< 0.0001	

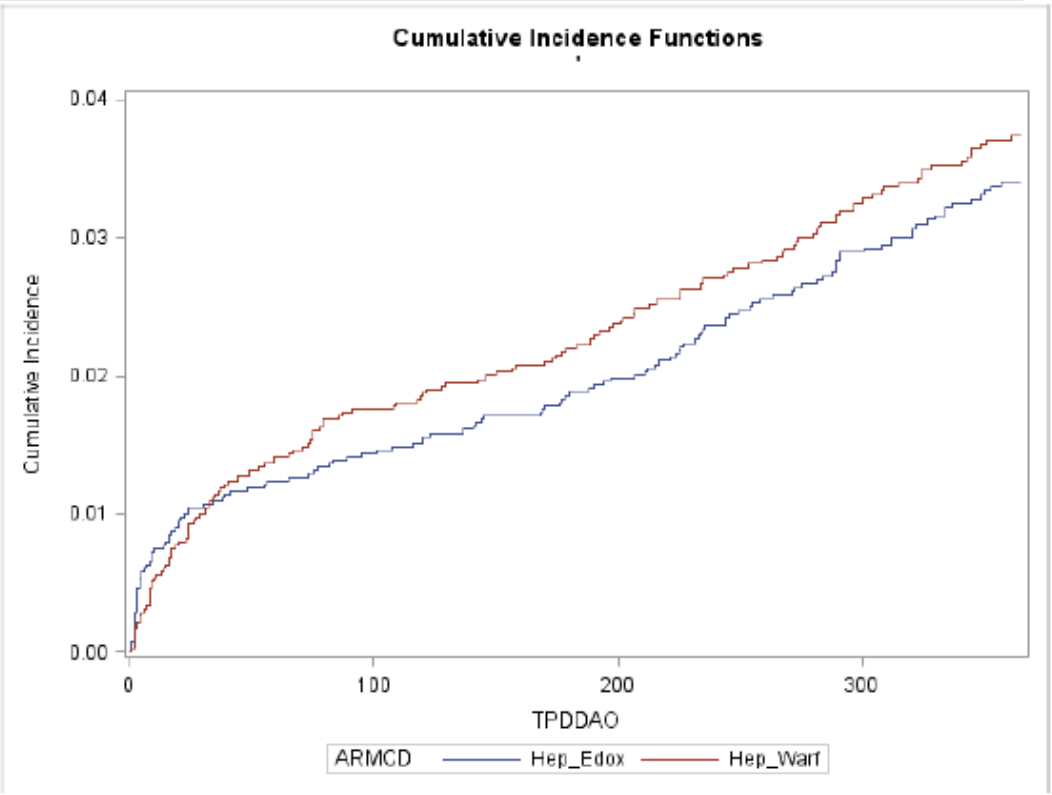
- CI: confidence interval;
- P value from asymptotic normal test.
- Hazard ratio is from un-stratified proportional hazard model. Hazard ratio < 1 favors Edoxaban arm.

[Source: Study Hokusai CSR Page 99 Table 11.2 and statistical reviewer's analysis]

Regarding the non-inferiority margin, the Statistics Review commented that the nominal P value of <0.0001 for non-inferiority testing was based on a non-inferiority margin of 1.5 for upper 95% confidence limit for HR, which the Agency and the Applicant had not reached agreement upon and which only retained about 70% of the warfarin treatment effect. The Agency recommended greater percentage (85-90%) retention of Warfarin effect. The review stated the nominal P-value for testing superiority in primary efficacy endpoint was 0.34, and therefore, the edoxaban arm was not superior to the Warfarin arm for efficacy.

The Kaplan-Meier plot of cumulative incidence of recurrent VTE during the study from the Statistical Review is shown below:

FIGURE 1: CUMULATIVE INCIDENCE RATE FOR VTE OR VTE-RELATED DEATH, MITT POPULATION



TPDDAO: days since randomization.
[Source: Statistical reviewer's analysis.]

Because treatment dose was reduced (to 30 mg daily instead of 60 mg daily), based on decreased renal function (CrCL 15 to 50 mL/min), low body weight (≤60 kg), and concomitant use of Pgp inhibitors, an analysis of response by treatment dose was performed. The results are shown in the following table from the Statistics Review:

TABLE 8: PRIMARY EFFICACY ANALYSIS BY EDOXABAN DOSE ADJUSTMENT AT BASELINE, MITT POPULATION

	Dose of 30mg		Dose of 60 mg	
Primary efficacy endpoint	**Edoxaban (N=733) n (%)**	**Placebo* (N=719) n (%)**	**Edoxaban (N=3385) n (%)**	**Placebo* (N=3403) n (%)**
Subjects with recurrent VTE or VTE-related death, n (%)	22 (3.0)	30 (4.2)	108 (3.2)	116 (3.4)
PE with/without DVT, n (%)	14 (1.9)	19 (2.6)	59 (1.7)	64 (1.9)
Fatal PE, n (%)	7 (1.0)	10 (1.4)	17 (0.5)	14 (0.4)
DVT only, n (%)	8 (1.1)	11 (1.5)	49 (1.4)	52 (1.5)
Un-stratified Hazard Ratio (95% CI)	0.73 (0.42, 1.26)		0.93 (0.72, 1.21)	

* In active Warfarin arm, Edoxaban placebo dose was adjusted based on the specified risk factors.
- CI: confidence interval;
- Hazard ratio is from un-stratified proportional hazard model. Hazard ratio < 1 favors Edoxaban arm.
[Source: Statistical reviewer's analysis]

The Statistical Review sensitivity analyses performed for the primary efficacy endpoint were consistent with the primary efficacy analysis. The analysis results of the secondary efficacy endpoint time to recurrent VTE or all-cause mortality did not show a greater treatment benefit on recurrent VTE or all-cause mortality for edoxaban (228/4118,(5.5%))as compared to warfarin (228/4122, (5.5%)). Finally, the review noted that all-cause mortality was numerically higher in the Edoxaban arm (122/4118, (3.0%)) compared to the warfarin arm (106/4122, (2.5%)).

Regarding efficacy the Statistical Review concludes:

> The pivotal Study Hokusai VTE demonstrated non-inferiority in primary efficacy endpoint, time to recurrent VTE or VTE-related death, for Edoxaban compared to Warfarin in subjects with acute symptomatic VTE. Sensitivity analyses support the non-inferiority in primary efficacy endpoint. However, superiority was not established for neither primary nor secondary efficacy endpoints. Numerically higher incidence of all-cause mortality was observed in Edoxaban arm compared to Warfarin arm.
>
> Based on exploratory analyses, the differences in treatment effect on primary efficacy endpoint between Edoxaban arm and Warfarin arm were mainly observed in subjects received dose of 30mg.

(b) (4)

(b) (4)

Inspections of clinical sites were conducted by GCP Assessment Branch/Division of Good Clinical Practice Compliance/Office of Scientific Investigations (OSI) (Summary Report, A. Orencia, 10/1/2014). Five clinical sites were inspected (3 U.S., 2 foreign) and the sponsor was also inspected. The recommendations from the inspections were stated as follows:

> The regulatory classification for Dr. Sebastian Schellong is No Action Indicated (NAI). The final regulatory classification for Drs. Barry Jacobson and Edwin Kingsley is Voluntary Action Indicated (VAI). The preliminary regulatory classification for Dr. Roger Lyons is No Action Indicated (NAI). The preliminary regulatory classification for the Daiichi Sankyo Pharma Development audit is Voluntary Action Indicated (VAI). The study data collected from this clinical site appears reliable in support of the requested indication.
> Note: *The inspectional observations noted above for Dr. Lyons and Daiichi Sankyo Pharma Development are based on preliminary communications with the field investigator and/or preliminary review of the EIR. A clinical inspection summary addendum will be generated, if conclusions on the current inspection report changes significantly, upon receipt the Establishment Inspection Report (EIR). CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.*

7. Safety

The detailed Clinical Review of this application for the VTE indications was conducted by S Ayache (signed 9/8/2014) and Statistical Review was conducted by Y Wang (final signature 9/9/2014). See those reviews for detailed presentation of the clinical safety findings.

The Clinical Review summarizes the safety findings for the application as follows:

The major risk of edoxaban treatment is bleeding. In the Hokusai VTE trial, edoxaban was shown to be superior to warfarin for the bleeding endpoint. The rate of the primary safety endpoint of adjudicated major/clinically relevant non-major (CRNM) bleeding was 8.5% in the edoxaban group compared to 10.3% in the warfarin group. The HR of edoxaban group versus warfarin was 0.81 with 95% CI of (0.71, 0.94) and P=0.004 for superiority. The rate of major bleeding events was 1.4% in the edoxaban group compared to 1.6% in the warfarin group. However, there was a numerical increase in major gastrointestinal (GI) bleed observed among edoxaban treated subjects 27 (0.7%) compared to warfarin treated subjects 18 (0.4%). In addition, there was a higher rate of any vaginal bleeding events among women in the edoxaban group 9% than that in the warfarin group 7.1%. There were 81 (4.6%) major/CRNM vaginal bleeding events in the edoxaban group compared with 56 (3.2%) in the warfarin group. The percentage of the MACE (non-fatal MI, non-fatal stroke, non-fatal SEE, and cardiovascular death) events observed in the edoxaban group was slightly higher in the edoxaban group than that in the warfarin group (1.2% vs 1.0%). More patients in the edoxaban group reported MI events 20 (0.5%) than in the warfarin group 13 (0.3%). Although there were numerical elevations in hepatic transaminases seen in treated edoxaban subjects, no hepatic Hy's rule cases were observed in the edoxaban subjects.

The primary safety endpoint was time to major or clinically relevant non-major (CRNM) bleeding. The Statistical Review states that Study Hokusai VTE was adequately powered to test superiority in primary safety endpoint for Edoxaban compared to Warfarin. The primary safety analysis is shown in the following table:

TABLE 11: PRIMARY SAFETY ENDPOINT ANALYSIS RESULTS, SAFETY POPULATION

	Edoxaban (N=4118)	Warfarin (N=4122)
Subjects with major or CRNM bleeding, n (%)	349 (8.5)	423 (10.3)
Major bleeding	56 (1.4)	66 (1.6)
CRNM bleeding	298 (7.2)	368 (8.9)
Hazard Ratio (95% CI)	0.81 (0.71, 0.94)	
P value	0.004	

CRNM: clinically relevant non-major; CI: confidence interval;

- P value from un-stratified log-rank test.

- Hazard ratio is from un-stratified proportional hazard model. Hazard ratio < 1 favors Edoxaban arm.

[Source: Study Hokusai CSR Page 130 Table 12.6]

From Statistical Review, Y Wang, 9/9/2014

The review states that edoxaban was superior to Warfarin in reducing major or CRNM bleeding (p value=0.004).

In the Clinical Review Dr. Ayache lists the major safety findings as shown below:

Bleeding:

The primary outcome was the composite of major and clinically relevant non-major bleeding events. The results suggested the following:

- Edoxaban was superior to warfarin in the primary safety endpoint of clinically relevant bleeding (Major and CRNM bleeding). The rate of primary endpoint of major/CRNM bleeding was 8.5% in the edoxaban group and 10.3% in the warfarin group (HR: 0.81; 95% CI: 0.705, 0.936; p = 0.004 for superiority).
- The rate of major bleeding events was comparable between the edoxaban and warfarin groups (1.4% vs 1.6%, respectively).
- There were numerically lower fatal events in edoxaban than warfarin (3 subjects vs 10 subjects, respectively). Fatal intracranial bleeding occurred in 0 subjects in the edoxaban group vs. 6 subjects in warfarin group.
- The number of non-fatal major bleeding events in critical sites was lower in the edoxaban than warfarin group (13 vs 32). However, the number of non-fatal major bleeding events in non- critical sites was higher in edoxaban than warfarin (43 vs 34).
- There was a numerical increase in major gastrointestinal (GI) bleed observed among edoxaban treated subjects 27 (0.7%) compared to warfarin treated subjects 18 (0.4%).
- There was a higher rate of any vaginal bleeding events among women in the edoxaban group 9.0% than that in the warfarin group 7.1%. There were 81 (4.6%) Major/CRNM vaginal bleeding events in the edoxaban group compared with 56 (3.2%) in the warfarin group. Major vaginal bleed occurred in 9 subjects (0.5%) in the edoxaban group vs 3 subjects (0.2%) in the warfarin group. Only 8 cases of vaginal bleed (5 in edoxaban and 3 in warfarin) led to permanent discontinuation of study drug.
- Major or CRNM bleeding rates were comparable between subjects received 30 mg and 60 mg dosing.

The Clinical Review also stated the following additional safety findings:

- The primary safety endpoint results were consistent across a large number of subgroups.
- The percentage of the MACE (non-fatal MI, non-fatal stroke, non-fatal SEE, and cardiovascular death) events observed in the edoxaban group was slightly higher in the edoxaban group than that in the warfarin group (1.2% vs 1.0%). A numerically larger number of patients in the edoxaban group reported MI events 20 (0.5%) than that in the warfarin group 13 (0.3%).
- Although there were numerical elevations in hepatic transaminases seen in treated edoxaban subjects, no hepatic Hy's rule cases were observed in the edoxaban subjects. The incidence of liver enzyme elevations in edoxaban group was comparable to warfarin group.
- The percentage of TEAEs and TESAEs On-Treatment was generally comparable between treatment arms. A higher number of subjects treated with edoxaban than with warfarin had TESAEs leading to permanent study drug discontinuation (2.9% vs. 2.5%) and TESAE with fatal outcome (1.7% vs. 1.5%).

Detailed review of the application database to evaluate for possible hepatic toxicity was conducted by Dr. J. Senior, Office of Pharmacovigilance and Epidemiology (OPE) and a Hepatology Consultation Memorandum was provided (9/25/2014). Regarding risk of liver injury the review concluded: "Despite the fairly careful search for evidence of serious liver injury and dysfunction attributable to edoxaban in this gigantic study of more than 21,000 subjects, there were no cases of clear-cut DILI found, either by the sponsor or by our review, This is consistent with findings for the two previously approved drugs in the class, rivaroxaban and apixaban, and for dabigatran (but not for ximelagatran)." The memorandum stated the following recommendation:

Iconcur with the DCRP opinion that edoxaan is approvable, and recommend that the labeling include warning about the fairly frequent elevation of liver tests and suggest that some form of serum transaminase monitoring be instituted in patients with AFib being started on this drug, which may be of clinical value not only in detecting liver injury but also early evidence of heart failure that may be asymptomatic but treatable. Test abnormalities should be followed closely and repeatedly until it is clear what is going on in the patient and why, which is simply good medical practice.

Regarding use of edoxaban during pregnancy, Dr. Ayache's Clinical Review states the following:

Women who were pregnant or planning to become pregnant during the trial were excluded from the Hokusai VTE trial. There were 21 pregnancy cases reported in the trial, 11 cases in the edoxaban arm and 10 cases in the warfarin arm. There were 18 cases with fetal exposure to study drug (no fetal study drug exposure was considered if the positive pregnancy test occurred off study drug). There were a total of 4 live births (3 in edoxaban; 1 in warfarin) with no congenital anomalies reported and 4 ongoing pregnancies (3 in edoxaban; 1 in warfarin). Three cases (1 in the edoxaban and 2 in the warfarin) were discontinued the study drug, one in each arm due to induced abortion and one in the warfarin arm discontinue due to open wound.

Of the 18 cases meeting criteria for fetal drug exposure, 10 occurred in subjects randomized to the edoxaban group and 8 occurred in subjects randomized to the warfarin group.

There were 10 fatal pregnancy cases reported in the edoxaban group as follow:

- Six live births cases: (4 full term deliveries and 2 preterm deliveries)
- One spontaneous abortion case: The case occurred in the first trimester miscarriage.
- Three cases of elective terminations of pregnancies.

There were 8 pregnancy cases reported in the warfarin group that resulted in fetal exposure as follows:

- Two Live Births (2 full term deliveries).
- One case of non-developing fetus resulted in induced abortion
- One case of spontaneous abortion
- One case of ectopic pregnancy resulted in induced abortion.
- Three cases of elective terminations of pregnancies.

Note: Under the description of 18 pregnancy cases meeting criteria for fetal drug exposure, the sentence: (b) (4)

(b) (4) *should read:* (b) (4)

The Clinical Review concludes there is a favorable benefit-risk profile for edoxaban for the treatment of VTE and recommends that edoxaban should be approved for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5 -10 days.

8. Advisory Committee Meeting

No advisory committee meeting was held for the VTE indications for this application.

The atrial fibrillation indication was presented and discussed at a meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting on Oct 30, 2014 as mentioned under section 4 Clinical Pharmacology/Biopharmaceutics above. See the review documents from Division of Cardiovascular and Renal Drugs (DCRP) review of the atrial fibrillation indication for results and details of the CRDAC.

9. Pediatrics

No pediatric patients were studied for the current NDA. On June 4, 2013 the sponsor submitted the initial pediatric study plan (iPSP) for edoxaban to IND 63266. Advice for the PSP was sent to the sponsor (letter date 8/16/2013). The sponsor submitted the final Agreed-Upon PSP to IND 63266 on October 15, 2014. In the 9/8/2014 Clinical Review Dr. Ayache describes the PSP as follows:

The Agreed Upon initial PSP proposes 3 clinical studies to assess the safety and efficacy of edoxaban in pediatric population (b) (4) (b) (4)

The proposed pediatric studies include the following:

- Study 1: Relative Bioavailability/Food Effects Study of an Edoxaban Pediatric Formulation (open-label, randomized, 3-way crossover). The study was started on June 2013. The study will enroll 24 adult subjects. The purpose of this study is to characterize PK of edoxaban oral suspension, assess relative bioavailability vs oral tablet; assess food effects and palatability of pediatric formulation.
- Study 2: Title: "A Phase 1, Open-Label, Single-Dose, Non-Randomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Pediatric Patients." The protocol is under review. The study proposes to start in June 2014. The study will enrolled (b) (4) pediatric patients at risk for VTE requiring anticoagulant or recently completing standard of care anticoagulation. Patients from 4 age cohorts, <18-12, <12-6, <6- 2, and <2-0 years (12 patients per age cohort) will receive a single dose of edoxaban. Patients will be evaluated for PK to identify the dose for the phase 3 trial.

- Study 3: A Phase 3, multicenter, open-label, randomized, active control study in pediatric patients with VTE. The Applicant proposes [redacted] The trial will enroll [redacted] pediatric patients with documented VTE. The objective of the trial is [redacted]

As stated in the Clinical Review (S Ayache, 9/8/2014), "The sponsor requested a deferral of pediatric studies from birth to <18 years of age under PMRs to meet the requirements of Pediatric Research Equity Act (PREA). The proposed studies include: 1) a relative bioavailability study of an oral suspension versus oral tablet in adults 2) a single dose PK/PD study in pediatric patients age birth to <18 years and 3) a phase 3 study [redacted] The review also noted that the sponsor is pursuing the development of an antidote to the anticoagulant effect of edoxaban.

10. Other Relevant Regulatory Issues

Division of Medication Error Prevention and Analysis (DMEPA) review (DV Baugh, 3/14/2014) of the proposed proprietary name SAVAYSA found the name acceptable from a promotional and safety perspective.

Risk Evaluation and Mitigation Strategy (REMS) Review was conducted by CL Yancy, Division of Risk Management (DRM) (final signature 9/17/2014). The sponsor did not submit a risk mitigation strategy for edoxaban beyond professional labeling and a Medication Guide (MG). Dr. Yancy's review summarized risk management and relevant safety information for related novel oral anticoagulant (NOAC) products stating, "Each of the three NOAC drug products and Brilinta (ticagrelor) have a Medication Guide in the approved drug product labeling. There are no new serious risks reported with edoxaban in the 120-Day SUR to NDA 206-316. At this time, each of the approved NOAC drug products is monitored via a routine pharmacovigilance plan. The target audience for the proposed edoxaban indication (treatment of DVT and PE) appears to be the same audience that the Agency targeted for the FDA Drug Safety Communication on Pradaxa (dabigatran), "Lower Risk for Stroke and Death, but Higher Risk for GI Bleeding Compared to Warfarin," specifically, cardiology, patients, pulmonary, Internal Medicine, Orthopedics and Neurology. Based on three NOAC drug product REMS assessment report provider survey results of knowledge assessment, the physicians most likely to prescribe edoxaban, if approved, are familiar with the known serious risks associated with use of a NOAC drug product as well as warfarin." The review concluded, "The DRISK and the DHP concur that a REMS is not required for edoxaban to ensure that the benefits out weigh the risks for the proposed treatment of patients with DVT and PE who have been treated with a parenteral anticoagulant for 5 to 10 days (in the DHP). Based on the totality of the clinical efficacy and safety data, this reviewer does not recommend a REMS, at this time, to ensure that the benefits of edoxaban (proposed for the treatment of DVT and of PE) outweigh the risks. The DHP should consult the DRISK if additional safety

information is identified that warrants re-evaluation of the risk management measures for edoxaban oral tablets."

Risk Evaluation and Mitigation Strategy (REMS) Review was conducted by CA Miller, Division of Risk Management (DRM) (final signature 10/9/2014) for the a-fib indication and concluded, "DRISK defers further comment at this time on the appropriate risk management strategy for edoxaban (NDA 206316) indicated for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular AF. A complete evaluation of the need for a REMS for edoxaban will be undertaken by DRISK after key decisions are made with regard to the safety, efficacy and the indicated patient population for edoxaban for the AF indication."

11. Labeling

The sponsor included proposed labeling in the submission.

Final wording for the labeling for the VTE indications has been developed by the DHP review team with discussion and consideration of the recommendations from each of the review disciplines and consulting review divisions and with negotiation with the sponsor.

The recommended wording for the VTE indications is as follows:

1.2 Treatment of Deep Vein Thrombosis and Pulmonary Embolism (b) (4)

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (b) (4)

For treatment of DVT and PE the recommended dose of SAVAYSA is 60 mg taken orally once daily following initial use 5 to 10 days of heparin. In accordance with the edoxaban dosing in the Hokusai VTE Study, it is recommended to reduce dose to 30 mg once daily in patients with CrCL 15 to 50 mL/min or body weight less than or equal to 60 kg or concomitant use of Pgp inhibitors.

Labeling recommendations from the Clinical Review (S. Ayache, 9/8/2014) include the following:

The following were recommended in the edoxaban label.

- A box warning to convey the risk of spinal/epidural hematomas which may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. As a class labeling consistent with other anticoagulants.
- Edoxaban should be indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (b) (4) (b) (4)

(b) (4)

Labeling recommendations were provided by the Division of Medication Error Prevention and Analysis (DMEPA)/Office of Medication Error Prevention and Risk Management (OMEPRM) (DV Baugh, 10/15/2014). The review recommended improvements to the proposed container label, carton labeling, and package insert (PI) to better differentiate between the strengths and to increase the prominence of important drug identifying information on the label and labeling in order to promote the safe use of the product and to clarify important dosing and administration information. See Dr. Baugh's review for detailed recommendations.

12. Recommendations/Risk Benefit Assessment

Regarding benefit/risk for the VTE indications being sought the Clinical Review states the following.

The overall benefit of edoxaban treatment is considered to outweigh the risk for the proposed indication of treatment of DVT and PE. (b) (4)

(b) (4)

Recommendations for Postmarketing requirements include studies to fulfill PREA requirements:

- Perform, complete and submit the full study report for a single-dose study of pharmacokinetic and pharmacodynamics (PK/PD) of edoxaban in pediatric patients at risk for VTE, requiring anticoagulation or recently completing standard of care anticoagulation in accordance with your October 31, 2013 Agreed Upon iPSP.
- Perform, complete and submit the full study report for a phase 3 multicenter, randomized, active control trial of edoxaban in pediatric patients with documented venous thromboembolism in accordance with your October 31, 2013 Agreed Upon iPSP.

Also, there is a post-marketing requirement from CMC "to develop an improved discriminating and canonical method and set the final dissolution and acceptance criteria for the product using the new method".

It is also noted that the sponsor is developing an antidote for edoxaban. This development program is to be encouraged.

In conclusion, the application is acceptable for approval for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (b) (4) pending final agreement on the wording of the labeling and post-marketing commitments.

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/s/

KATHY M ROBIE SUH
12/24/2014

Cross-Discipline Team Leader Review Memorandum

Date	8 December 2014
From	Martin Rose, MD, JD
Subject	Cross-Discipline Team Leader Review
NDA #	206316 (Original – 1))
Applicant	Daiichi Sankyo, Inc. (Edison, NJ)
Date of Submission	8 January 2014 (date received)
PDUFA Goal Date	8 January 2015
Proprietary Name / Established (USAN) Name	Savaysa® / Edoxaban tosylate
Dosage forms / Strength	Immediate release oral tablets / 15, 30 and 60 mg
Proposed Indication(s)	To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
Recommended:	Approval with revised dosing instructions (b) (4) [redacted]

1. Introduction

Edoxaban tosylate is a salt of edoxaban, an orally available Factor Xa inhibitor. This NDA was administratively split into (b) (4) parts based on proposed indication. The indication to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (Original-1, termed the A Fib indication) is the sole focus of this review. Submissions Original-2 (regarding treatment of venous thromboembolism (VTE) and pulmonary embolism (PE)) (b) (4) [redacted] under review in the Division of Hematology Products (DHP). The DHP review team and Director support approval of the DVT/PE treatment indication.

Issues raised by the various components of the A Fib review team are:

1. CMC/Biopharmaceutics: There is a recently-arising issue that might affect approval that relates to the Applicant's (b) (4) [redacted]

The proposed dissolution method and acceptance criteria are acceptable only on a temporary basis. The applicant has agreed to a PMC to develop an acceptable method and acceptance criteria within 15 months of approval.

An advice letter describing deficiencies in carton, container and blister card labeling was sent on 22 October 2014. The applicant has responded with revisions and the response is under review.

2. Pharmacology/Toxicology: No issues affect approval.

3. Clinical Pharmacology/Biopharmaceutics: The OCP review team, who have collaborated extensively with the Clinical review team, have serious concerns regarding the Applicant's proposed dosing regimen (60 mg daily for those with normal or mildly impaired renal function, which yields substantially reduced exposure to edoxaban in patients with normal renal function, defined as estimated creatinine clearance ≥80 mL/min. This subgroup of patients made up about a third of patients in ENGAGE and had an increased rate of ischemic stroke and total stroke with edoxaban compared to warfarin. (HR = 1.41, 95% CI, 0.97 – 2.05). Thus, the point estimate for the hazard of primary endpoint in this subgroup was above the pre-specified NI margin of 1.38, although the overall results for the primary endpoint have a hazard well below 1 and meet the NI standard. There is a substantial amount of information that was quite consistent in suggesting that the normal renal function subgroup results should be considered a real effect and not the play of chance. This information includes, but is not limited to, a strong inverse relationship between estimated creatinine clearance and edoxaban exposure (as one would expect with a drug that has a high degree of renal excretion), a strong inverse relationship between exposure and the risk of ischemic stroke, a strong direct relationship between exposure and the risk of bleeding, and a directionally similar pattern of efficacy results in renal function subgroups for dabigatran, which also has a high degree of renal excretion, .

   The OCP and Clinical primary reviewers were unanimous in believing that edoxaban should not be approved with a recommended dose of 60 mg for those with normal renal function because of the substantially increased risk of ischemic stroke in that population, with consequential risk of death or irreversible morbidity. However, there was not universal agreement on the implications of that view for action on this application. Three views were expressed:

   i) The majority of review team members, as well as the Office signatory and Division Director, believe that it is both feasible and appropriate to use PK modeling and exposure matching to determine a dose that would produce exposure in patients with normal renal function that is similar to exposure in patients with mild renal impairment who received 60 mg daily. (b) (4)

   ii) Initially, some reviewers believed that there are too many unknowns and too much sensitivity in the medical community regarding bleeding risk to approve a dose that is higher than any dose used in Phase 3. They believed that edoxaban should be approved with a highest recommended dose of 60 mg daily and labeling that discourages or prohibits use in patients with normal renal function. (b) (4)

(b) (4)

iii) The primary statistical reviewer is the only reviewer who agreed that the Applicant's proposed dosing regimen should be approved without modifications.

Notably, no one's first choice is a complete response, but that option would be a logical choice if none of the previously described options are deemed acceptable or are not feasible.

4. Clinical: The Clinical team has no issues affecting approval other than the issue relating to the appropriate dose for patients with normal renal function described immediately above. (b) (4)

I did not identify any other major issues in my review of the NDA. Accordingly, this review will focus primarily on the topics described above.

2. Background

Atrial fibrillation is a common condition in the elderly. A recent publication estimates a US prevalence of ~ 5 million persons in 2014, and its annual incidence has been increasing as the population ages due to improved longevity as well as the aging of the large baby boom generation, which is much larger than the generation before it. By 2030, the estimated US prevalence of atrial fibrillation will be about 15 million persons if the incidence rate continues to rise as it did from 2001 to 2007 and about 11 persons if the incidence rate remains the same as in 2007.(1)

Embolic events, primarily ischemic strokes, are an important complication of atrial fibrillation. Currently, warfarin, a vitamin K antagonist first marketed 60 years ago and 3 non-VKA antagonist oral anticoagulants (NOACs), all approved since 2010, are marketed in the US to reduce the risk of stroke and systemic embolism in patients with atrial fibrillation. In order of approval (first to most recent) the NOACs are dabigatran (a Factor IIa (thrombin) inhibitor), rivaroxaban and apixaban. The last two are FXa inhibitors, like edoxaban.

Because stroke is both a life-threatening and disabling condition, it is important to understand the benefits and risks of currently approved therapies to prevent stroke in patients with atrial fibrillation. Warfarin's effect on preventing ischemic strokes in patients with atrial fibrillation is one of the largest known pharmacologic effects on a major cardiovascular outcome. In an FDA meta-analysis that is described in the Agency's guidance on non-inferiority trials, results from 6 placebo-controlled trials of this use of warfarin were used to generate an estimated risk reduction for stroke of 64% for warfarin compared to placebo. Because in 2 of the 6 studies (including the largest study) hemorrhagic strokes were included in this analysis, and warfarin increases the rate of hemorrhagic stroke compared to no treatment, the effect on ischemic stroke is larger than the estimate from the meta-analysis. Each of the 3 NOACs was approved on the basis of a single large trial comparing the new drug to warfarin. The pre-specified

endpoint in each trial, as in the confirmatory trial of edoxaban, was non-inferiority to warfarin for the endpoint of time to the composite of stroke (all types) and systemic embolism (SE). In each case, a non-inferiority (NI) margin of 1.38 was specified, based on the results of the meta-analysis described above and the determination that at least half of the effect of warfarin should be maintained by a new agent. Results for the ITT analysis of efficacy events (used to assess superiority) shown in labeling and results for major bleeding on treatment are displayed below.

Table 1 – Primary Efficacy Endpoint, Stroke Subtype and Major Bleeding Results in Confirmatory Trials of Marketed NOACs vs. Warfarin
(Hazard ratio and 95% CI)

NOAC	Primary Endpoint: Stroke/SE	Ischem. Stroke	Hem. Stroke	Major Bleeding
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)	0.99 (0.82, 1.20)	0.58 (0.38, 0.89)	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)

Abbreviations: SE: Systemic embolism; Ischem: Ischemic; Hem: Hemorrhagic
Source: Labeling for each marketed NOAC; Rivaroxaban NDA 202439, ROCKET AF (protocol 39039039AFL3001) study report: Table 53 & Attachment 6.44

Note that two of the NOACS (dabigatran and apixaban) were superior to warfarin in reducing the rate of primary endpoint of stroke and systemic embolism, while rivaroxaban was non-inferior. Only dabigatran was superior to warfarin for ischemic stroke, which is the type of stroke caused by atrial fibrillation. However, all 3 NOACs reduced the rate of hemorrhagic stroke compared to warfarin. Notably, hemorrhagic strokes in the setting of anticoagulant treatment of A Fib are thought to usually represent a complication of treatment rather than a direct result of A Fib. In addition, apixaban had less major bleeding than warfarin, while the other two drugs had similar bleeding rates as warfarin. For each NOAC, the only important risk is bleeding. Each NOAC had a numerically lower rate of all-cause death than warfarin, but the difference was statistically significant only for apixaban, but just barely. Dabigatran barely missed superiority for death and the HR and confidence interval were quite similar to those for apixaban (data not shown).

Edoxaban has not been approved anywhere for use in A Fib. However, it was approved in Japan in 2011 for prevention of VTE in patients undergoing knee and hip replacement and hip fracture surgery.

3. CMC

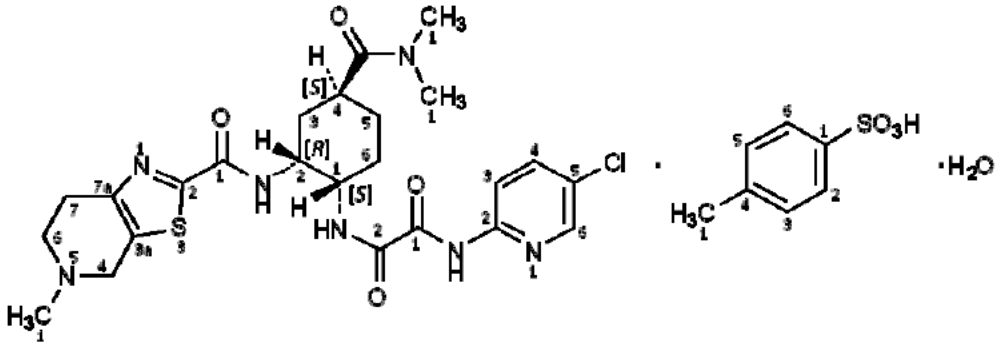
There is an issue (b) (4) and may affect approval (see **Drug Product**). There is another CMC issue that will not need to be resolved by the time of approval regarding dissolution testing, which may be resolved with satisfaction of a post-marketing commitment.

Drug substance:

Although the drug is referred to as edoxaban tosylate, the drug substance is edoxaban tosylate monohydrate, a synthetic small molecule. Its molecular weight is 738.27 Daltons, its molecular

formula is $C_{24}H_{30}ClN_7O_4S.C_7H_8O_3S.H_2O$ and the IUPAC name is *N*-(5-Chloropyridin-2-yl)-*N'*-[(1*S*,2*R*,4*S*)-4-(*N*,*N*-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-*c*]pyridine-2-carboxamido)cyclohexyl]oxamide mono(4-methylbenzenesulfonate) monohydrate. The molecular weight of the anhydrous base is 548.06. The molecular structure is shown below.

Figure 1 – Structure of Edoxaban Tosylate Monohydrate



Edoxaban tosylate [redacted] white to pale yellowish crystalline powder. Edoxaban tosylate is BCS class 4 (low permeability, low solubility).

There are no outstanding issues with the drug substance. However, it should be noted that the drug substance [redacted] (see Sec. 5 Clinical Pharmacology and photos of gel below).

Figure 2 Drug Substance [redacted]

Source: Clinical Pharmacology Review

Issues explored and resolved during the review cycle included:

(b) (4)

Drug product:

Edoxaban tosylate is proposed for marketing as film coated (b) (4) immediate release tablets with strengths of 15 mg (with an orange coating), 30 mg (pink coating) or 60 mg (yellow coating). Strength here refers to equivalent mass of free edoxaban. The actual mass of edoxaban tosylate monohydrate in each strength of tablet is 20.20 mg, 40.41 mg, and 80.82 mg for the 3 tablet strengths, respectively. Tablet excipients are all commonly used and are of USP grade: mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, magnesium stearate, talc, and carnauba wax. The color coatings (b) (4) contain hypromellose, titanium dioxide, talc, polyethylene glycol 8000, iron oxide yellow (60 mg tablets and 15 mg tablets), and iron oxide red (30 mg tablets and 15 mg tablets). Conventional manufacturing methods are used. The to-be-marketed tablets are shown below.

Figure 3 Proposed Savaysa Commercial Tablets

Item	15 mg tablets	30 mg tablets	60 mg tablets
Description (appearance)	Orange round-shaped film-coated tablets debossed with "DSC L15"	Pink round-shaped film-coated tablets debossed with "DSC L30"	Yellow round-shaped film-coated tablets debossed with "DSC L60"
Dosage form	Immediate release film-coated tablets	Immediate release film-coated tablets	Immediate release film-coated tablets
ID code (debossing)			

Source: NDA, Mod. 2.3 – Drug Product

(b) (4)

Comment: (b) (4)

With the exception of colorants, the to-be-marketed 15 and 30 mg tablets are identical to the corresponding tablets used in Phase 3, but there was no 60 mg tablet used in Phase 3. However, a BE study between the 30 mg tablets and the proposed 60 mg tablet supports marketing of the latter tablet.

There is an unresolved issue regarding the drug product with the exception of dissolution testing. Dr. Suarez found the Applicant's proposed dissolution method and acceptance criterion to be acceptable only on an interim basis. The proposed method is: Use of USP apparatus II, spindle rotation of 50 rpm, volume of 900 mL, temperature of 37°C, citrate/phosphate buffer pH 6.0, and Q ≥ (b) (4)% in 30 minutes. Her rationale was that there was no adequate information to support the discriminating ability of this method. The following findings regarding dissolution results were of concern:

(b) (4)

The Biopharmaceutics team believes these findings may be related to the (b) (4)

After discussions with the Agency, the Applicant agreed to a Post-Marketing Commitment to develop within 15 months from the Action Date the following: i) "a new dissolution method, which shows greater discriminating ability (b) (4) " and ii) "final dissolution acceptance criterion of their drug product using the new method and the overall dissolution profile data from a minimum of 12 commercial batches."

> Comment: The team should consider requiring the Applicant to provide interim updates at suitable intervals, perhaps at least every six months, on the progress of the Applicant towards meeting the terms of the PMC if edoxaban is approved.

Issues (b) (4)

Just after our Post-AC meeting with the Sponsor held on November 17, the Applicant notified us (b) (4) The CMC team indicates that the tablet strengths that could be approved are 15, 30, and 60 mg in bottles and blister strips. All are strengths are (b) (4) immediate-release tablets made with a (b) (4) (b) (4)

(b) (4)

Packaging:

An advice letter describing deficiencies in carton, container and blister card labeling was sent on 23 October 2014. The cited issues relate to layout, color and font size and ought to be remediable. The applicant has responded with two sets of revisions and the response is under review.

Facility Inspections:

The manufacturing facilities for the drug substance (b) (4) for making the drug product are operated by Daiichi Sankyo in Japan. They have not yet been inspected. Packaging will occur at a Daiichi Sankyo facility in Bethlehem, Pennsylvania. This facility will not be inspected because it is "Acceptable" based on previous history.

4. Nonclinical Pharmacology/Toxicology

Dr. Yang's primary review indicates that there are no unresolved pharmacology/toxicology issues. Note that Dr. Shwu-Luan Lee of the Division of Hematology Oncology Toxicology (DHOT) reviewed primary and secondary pharmacology studies for this NDA, and recommends a minor labeling revision in Sec. 12.1 related to edoxaban's thrombin inhibitory activity (see below).

While Dr. Yang recommends approval of edoxaban, she also proposes labeling revisions related to findings in the reproductive, developmental and carcinogenicity studies. These are discussed below.

General nonclinical pharmacology/toxicology considerations: Edoxaban reversibly binds to and inhibits the activity of the activated form of human coagulation Factor X (FXa) with a Ki of 0.561 nM. FXa is a protease that converts prothrombin to thrombin. In turn, thrombin converts fibrinogen to fibrin resulting in formation of a blood clot. While edoxaban lacks notable inhibitory activity when tested against plasmin, t-PA, and several other serine proteases, it inhibits thrombin with a Ki of 6 µM, not far above observed C_{max} values in some patients in the population PK subset of ENGAGE AF treated with 60 mg daily (i.e., about 1 µM). In addition, edoxaban inhibited thrombin-induced platelet aggregation with an IC_{50} of 2.90 µM (95 CI, 1.99 - 3.81) and doubled thrombin time from baseline in human plasma at a concentration of 5 µM. These findings suggest that the effect of edoxaban on thrombin activity might be medically important in the case of an edoxaban overdose or possibly during treatment with the Applicant's recommended doses under circumstances promoting low drug clearance, such as unrecognized renal impairment and/or concomitant use of P-gp inhibitors. While the results of ENGAGE are generally reassuring about the bleeding risk of edoxaban compared to warfarin, if a hypothetical antidote to edoxaban for use in the case of uncontrolled bleeding targeted only edoxaban's effects on FXa, pathological bleeding might persist after treatment with the antidote due to edoxaban's effects on thrombin. This could be a labeling issue.

The major toxicity of edoxaban in preclinical studies was its on-target effects: prolongation of coagulation parameters and increased rates of bleeding.

Carcinogenicity: In his tertiary pharmacology/toxicology review, Dr. Brown states that the Executive Carcinogenicity Assessment Committee found that that the carcinogenicity studies in rats and mice were acceptable and that there were no drug-related neoplasms in either study.

Reproductive toxicology: In pregnant rats, edoxaban crossed the placenta and was taken up by fetal tissues after a single oral dose of 3mg/kg. In nursing rats, edoxaban concentrations were higher in milk than in plasma (based on radioactivity) at all time points between 1 and 48 hours after a single 3 mg/kg oral dose of radioactive (^{14}C) edoxaban.

Fertility, early embryo, embryo-fetal development and pre-/postnatal development studies were felt to be adequate. There were findings of embryo-fetal and developmental toxicity in studies in rats and rabbits, as follows:

- higher post-implantation loss in rat at ≥ 300 mg/kg/day (~48 times the human exposure at MRHD (maximum recommended human dose) of 60 mg/day based on surface area);
- more post-implantation loss, fewer live fetuses, lower fetal weight, and increased variation in gall bladder anatomy in rabbits at ≥ 200 mg/kg/day (~63 times the human exposure at the MRHD);
- increased findings of 13th full ribs and 27 presacral vertebrae in rabbits at 600 mg/kg/day (~190 times the human exposure at the MRHD);
- delayed avoidance response during a learning test in F1 rats at 30 mg/kg/day (~2.9 times the human exposure at the MRHD); and

Maternal toxicity including dam deaths and abortion, decreased food consumption and body weight, hemorrhage in uterus, or vaginal hemorrhage occurred at the same or lower edoxaban doses that led to embryo-fetal/developmental toxicity. Consequently, embryo-fetal toxicity in rats and rabbits and developmental toxicity in rats might be secondary effects of maternal toxicity, rather than direct effects of edoxaban. There was no impairment of fertility.

Juvenile rat studies: Dr. Yang note that there was moderately lower body weight in juvenile rats at 20 mg/kg/day (~2.2 times the human exposure at the MRHD). .

Recommendations: Dr. Yang indicated that edoxaban was approvable from the pharmacology/toxicology standpoint. She had recommendations for labeling revisions based on refinements of the descriptions of several of the adverse findings above in Secs. 8.2 and 8.4. She also recommended addition of information (b) (4) [redacted]. However, this last addition was removed by Dr. Papoian (b) (4) [redacted]

Comment: I agree with Dr. Papoian (b) (4) [redacted]

In addition, Dr. Lee (who reviewed the general pharmacology of edoxaban) recommended the addition of language to Sec. 12.1 indicating that edoxaban "inhibits thrombin-induced platelet aggregation." This seems appropriate. After discussions with OCP on this issue, we might propose additional information related to the effects of edoxaban on thrombin activity to be added to Sec. 12 and possibly Sec. 10 (Overdosage).

5. Clinical Pharmacology

The primary reviewers in OCP were Drs. Menon-Anderson, Moon, Earp and Schuck. Based on their excellent review, the following CP attributes of edoxaban and their implications for labeling for the atrial fibrillation indication are described:

5.1. General clinical pharmacology/biopharmaceutics

PD effects:

Concentration-dependent changes in anti-Factor Xa activity, prothrombin time (PT) and accelerated partial thromboplastin time (APTT) were observed. The relationship between anti-Factor Xa activity and edoxaban plasma concentration was close to linear and fairly tight in the range of 0 to slightly more than 200 ng/mL, far above mean and median trough values for patients in ENGAGE AF with mild renal impairment who received 60 mg daily (37 ng/mL) and the 99th percentile for trough values (52 ng/mL). There was modest residual anti-Factor Xa activity 24 hours post-dose after several days of dosing with 60 mg daily in healthy male volunteers. The onset and offset of the PD effects track with plasma levels.

PK information:

- Peak concentrations occur within 2 h of oral administration. PK is dose proportional over oral single doses in the range of 10 to 150 mg.
- Absolute bioavailability of edoxaban is 62%.
- About 60% of absorbed edoxaban is excreted renally unchanged, with a lesser extent of biliary excretion.

- Edoxaban undergoes minimal metabolism. The main metabolite, D21-2391 (which is active), is formed through hydrolysis by carboxylesterase 1 (CE-1), but exposure to this metabolite is about 10% of edoxaban levels. There is metabolism by CYP3A4/5, but exposure to hepatic metabolites is less than 5% of exposure to edoxaban, indicating that this route of elimination is not consequential.
- Edoxaban is a substrate of P-gp, but not of the OAT polypeptides or OCT2.
- Edoxaban has a terminal elimination half-life of about 9 hours and an effective half-life of about 6 hours. CL/F is ~36 L/h.
- As one would expect from the $T_{1/2}$ information above, there are wide swings from peak to trough with once daily dosing. This is discussed further below in a comment.
- Accumulation with repeated once daily administration is 10%-15% in terms of AUC, but C_{max} is increased by 70%. For twice daily dosing, analogous increases for AUC and C_{max} are 45% and 100%, respectively.
- The primary metabolite of edoxaban, D21-2393, has PK that is not notably different from the parent.
- Healthy volunteers and patients with A Fib have similar edoxaban PK. In volunteers, the inter- and intra-subject variability for clearance and volume of distribution is <30%. In patients with A Fib, intra-subject variability in clearance and volume of distribution is 14% and 22%, respectively.

5.2. Drug-drug interactions

P-gp inhibitors and inducers:

Results of studies with use of edoxaban with concomitant administration of 7 inhibitors and 1 inducer of P-gp (with or without effects on other enzymes relevant to PK) show increased edoxaban exposure (with the inhibitors) or decreased exposure (with the inducer) as follows:

Table 1 Effects of P-gp Inhibitors and Inducers on C_{max} and AUC of Oral Edoxaban

Inhibitor Drug	Effect on C_{max}, AUC (point estimate of increase, in %)	Inducer Drug	Effect on C_{max}, AUC (point estimate of decrease, in %)
Ketoconazole	89%, 87%	Rifampin	0%, 34%
Quinidine	85%, 77%		
Verapamil	53%, 53%		
Erythromycin	68%, 85%		
Cyclosporine	73%, 73%		
Dronedarone	46%, 85%		
Amiodarone	56%, 40%		

The sponsor's only current recommendation regarding drug-drug interactions based on drug metabolism is to not use edoxaban with P-gp inducers such as rifampin. P-gp inhibitors increase edoxaban exposure (see **Table 1**) but not more than about 90% in the worst case of studied interactions. The applicant now agrees with OCP that no adjustment of dose is necessary for use with P-gp inhibitors.

Esomeprazole

Coadministration with esomeprazole 40 mg QD X 5 days, with a single dose of edoxaban 60 mg 2 hr after the last dose of esomeprazole, resulted in no change in total exposure, but peak

exposure decreased by 33%. In ENGAGE, about 17% of subjects were treated with various proton pump inhibitors. Their trough edoxaban concentrations were similar across the PPIs and also similar to those not taking a PPI.

5.3. Pathways of Elimination

- About 60% of absorbed edoxaban is excreted unchanged in the urine, with a lesser extent of biliary excretion.
- In subjects with mild, moderate or severe renal impairment (creatinine clearance of >50 to 80 mL/min, 30 to 50 mL/min, or <30 mL/min, respectively) edoxaban AUC was increased by 32%, 74%, and 72% respectively, compared to subjects with normal renal function.
- Edoxaban undergoes minimal metabolism. The main active metabolite, D21-2391, is formed through hydrolysis by carboxylesterase 1 (CE-1), but exposure to this metabolite is about 10% of that of edoxaban. There is metabolism by CYP3A4/5, but exposure to hepatic metabolites of edoxaban is less than 5% of exposure to edoxaban, indicating that this route of elimination is not consequential.
- Edoxaban is a substrate of P-gp, but not of the OAT polypeptides or OCT2 (see drug-drug interactions, above.). IC_{50} values for inhibition of tested transporters were >100 µM for OAT1, OAT3, OCT1 and OCT 2 and > 50 µM for OATPB1 and OATPB2.

5.4. Demographic interactions/special populations

The most important intrinsic factor affecting edoxaban exposure and clinical effects is renal function, which is discussed at the end of this section.

Hepatic Function:

There was no effect of mild or moderate hepatic impairment on edoxaban exposure or exposure to the major metabolite. However, we typically state in labeling of novel anticoagulants that because of intrinsic coagulation abnormalities in patients with Child-Pugh Class B hepatic dysfunction (i.e., moderate impairment), dosing recommendations cannot be made, and OCP proposes such a statement for edoxaban. There is no experience in patients with severe hepatic impairment.

Age:

When weight and renal function was taken into account, there was no effect of age on edoxaban PK. OCP does not support a dose adjustment based on age.

Gender:

OCP recommends no dose adjustment based on gender because gender-related defenses in PK were not significant after other factors were taken into account.

Body Weight:

Subjects in ENGAGE AF with weight ≤60 kg, about 4% of enrolled patients, received a 50% reduction in edoxaban dose. (b) (4) However, in the final ENGAGE population PK model, body weight was not a significant predictor of edoxaban clearance. It did predict efficacy events (low body weight was associated with increased risk of efficacy events, the opposite of what one would expect if exposure was high),

but there was no effect of weight on bleeding. OCP concluded that there is no need for dose reduction in patients with weight ≤60 kg.

5.5. Thorough QT study or other QT assessment

There was no effect of edoxaban 90 or 180 mg on the QT interval in a thorough QT study in healthy men and women. Assay sensitivity was demonstrated.

5.6. Other notable issues (resolved or outstanding)

The only issue found to date that could affect approval of edoxaban or substantially affect labeling is the interaction between baseline renal function and results for the primary endpoint and ischemic stroke in ENGAGE. The most notable finding related to this interaction was decreased efficacy in the normal renal function subgroup. The clinical and OCP review teams collaborate worked separately and together on this issue. The outstanding work both teams is presented in this section.

Primary endpoint results overall and for the renal function subgroups are shown in tabular form in **Table 2** and **Figure 4**. Key findings are:

- The most favorable results for edoxaban compared to warfarin were observed in the subgroup with mildly impaired renal function in the 60/30 mg arm. One would expect patients with mild renal impairment to have higher exposure to edoxaban than those with normal renal function because of the high degree of renal excretion of edoxaban, and they did (see **Figure 6** for PK data for all renal function subgroups).

- Patients with normal renal function in the 60/30 mg arm had a reversal of the hazard ratio vs. warfarin for the primary endpoint, with results numerically favoring warfarin by a substantial margin.

- About 80% of patients with moderately impaired renal function, who would be expected to have the highest edoxaban exposure, were dose reduced, and received 30 mg or 15 mg, depending on their randomized arm. Their mean edoxaban exposure was thus substantially less than that of patients with mild renal impairment.

The two edoxaban arms had similar patterns of results across the renal function subgroups (**Figure** 4). The p value for the interaction between renal function and the primary endpoint was <0.01 for each edoxaban arm compared to warfarin. The similarity of the pattern of results in the two treatment arms and the small interaction p values suggest it is unlikely that observed reduction in efficacy of edoxaban in the normal renal function subgroups is due to chance.

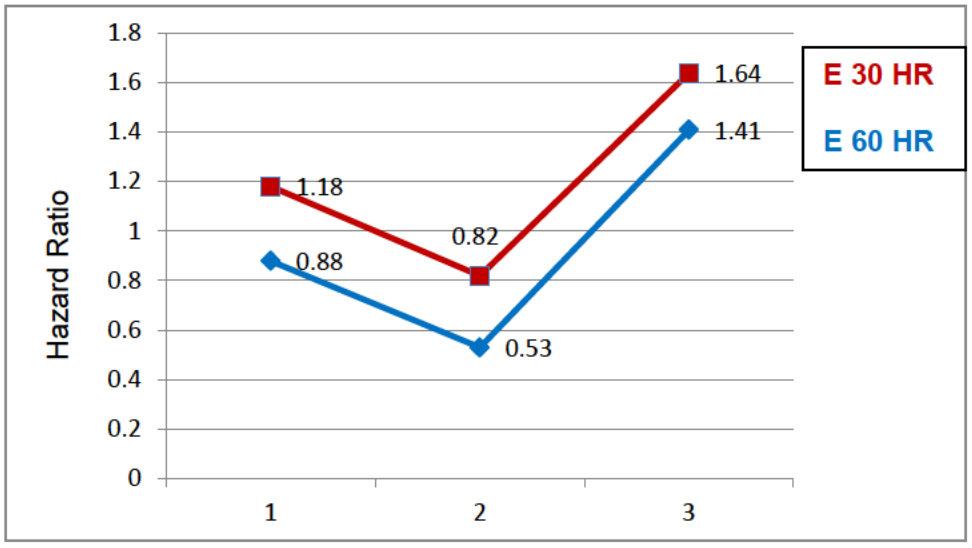
Results for ischemic stroke show a similar pattern in each edoxaban arm as the primary endpoint results (see **Table 3** and **Figure 5).** However, results in each arm for ischemic stroke are less favorable for edoxaban overall than for the primary endpoint due to the inclusion in the primary endpoint analysis of data relating to hemorrhagic stroke, which strongly favors edoxaban (and all the other NOACS) over warfarin. A p was not calculated for the interaction of renal function vs. the ischemic stroke results, but the similarity of pattern of results with the primary endpoint results suggests that it also would be quite small for each edoxaban arm vs. warfarin. Notably, the overall results favor warfarin over edoxaban 30/15 mg for ischemic stroke with a confidence interval that does not cross 1 (**Table 3**), which supports the Applicant's decision not to seek approval of this regimen.

Table 2 Primary Endpoint Results Overall and in Subgroups Based on Renal Function at Baseline
MITT Population, On Treatment

Renal Function Subgroup*	Arm	n(N)	Event Rate %/yr	HR vs. W
All patients	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 to <=50 (moderately impaired)	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 to <80 (mildly impaired)	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 (normal)	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)

Primary Endpoint: Time to stroke or systemic embolism
Reviewer's Table: Source Data: BASEGP.xpt, ADJEFFCA.xpt, modeling with Dose Adjustment, yes or no. CHADS2≤3=0, or >3=1.
* - Renal function: Estimated creatinine clearance in mL/min calculated using Cockcroft-Gault formula

Figure 4 Primary Endpoint Results in Subgroups Based on Renal Function at Baseline
MITT Population, On Treatment – Hazard Ratios for Edoxaban vs Warfarin



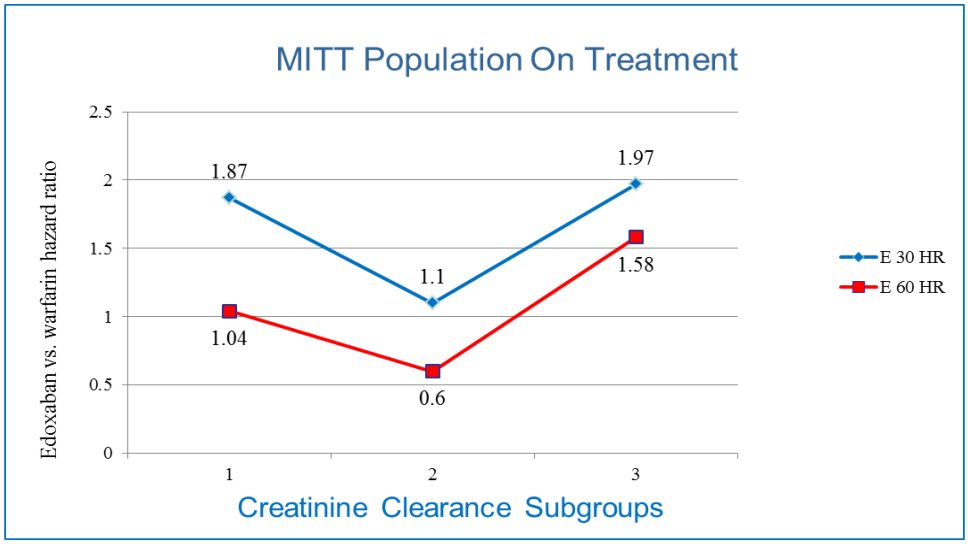
X axis markers represent renal function subgroups: 1 – moderately impaired; 2 – mildly impaired; 3 – normal
Reviewer's figure, based on data in **Table 2**

Table 3 Ischemic Stroke Results Overall and in Subgroups Based on Renal Function at Baseline
MITT Population, On Treatment

Renal Function Subgroup*	Arm	n(N)	Event Rate %/yr	HR vs. W
All patients	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 to <=50 (moderately impaired)	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 to <80 (mildly impaired)	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 (normal)	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)

Primary Endpoint: Time to stroke or systemic embolism
* Renal function: Estimated creatinine clearance in mL/min calculated using Cockcroft-Gault formula
Source: Reviewer's Table: Source Data: BASEGP.xpt, ADJEFFCA.xpt, modeling with Dose Adjustment, yes or no. CHADS2≤3=0, or >3=1.

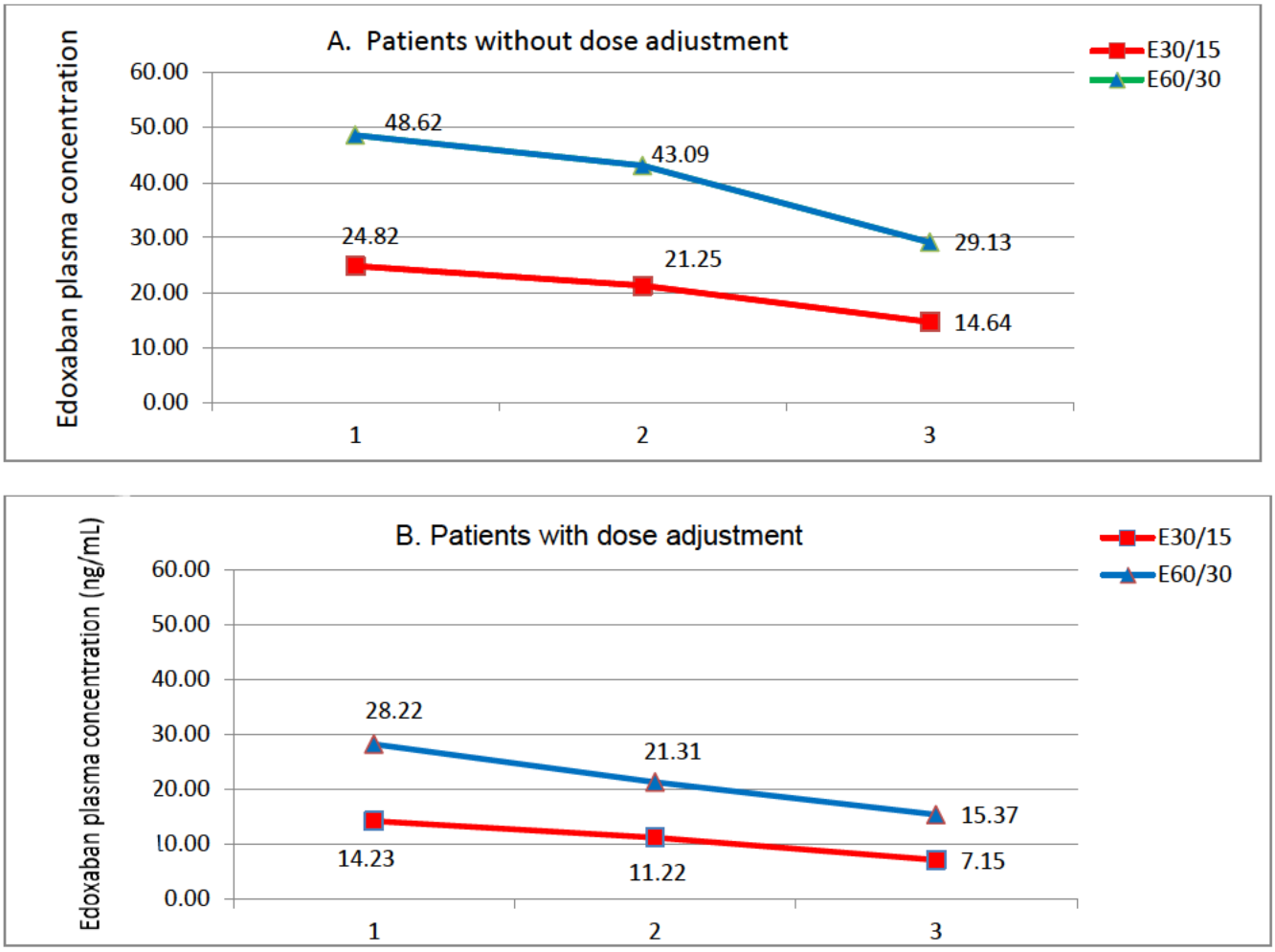
Figure 5 Ischemic Stroke Results in Subgroups Based on Renal Function at Baseline
MITT Population, On Treatment – Hazard Ratios for Edoxaban vs Warfarin



X axis markers represent renal function subgroups: 1 – moderately impaired; 2 – mildly impaired; 3 – normal
Source: Reviewer's figure, based on data Table 3

Data for geometric mean trough edoxaban concentrations in ENGAGE are provided in **Figure 6**. There data are displayed for patients in each arm who were not dose adjusted (A) and those who were dose adjusted (B). Dose adjusted patients in the edoxaban 60/30 arm received 30 mg daily and those in the 30/15 arm received 15 mg daily. The pattern of concentration values across the renal function subgroups is similar in each arm and for cohorts who were or were not dose adjusted: as renal function improves, edoxaban trough levels decrease for any fixed dose. In the edoxaban 60/30 mg arm, patients with normal renal function had similar edoxaban exposure as those in the moderately impaired group with dose adjustment, suggesting that both these subgroups may have been underdosed. About 80% of patients with moderately impaired renal function in this analysis were dose reduced, meaning that this subgroup as a whole had lower plasma concentrations and thus reduced efficacy of edoxaban compared to warfarin compared to the patients in the mild renal impairment subgroup for each edoxaban treatment arm (see note below Figure 6 for information about N for each data point).

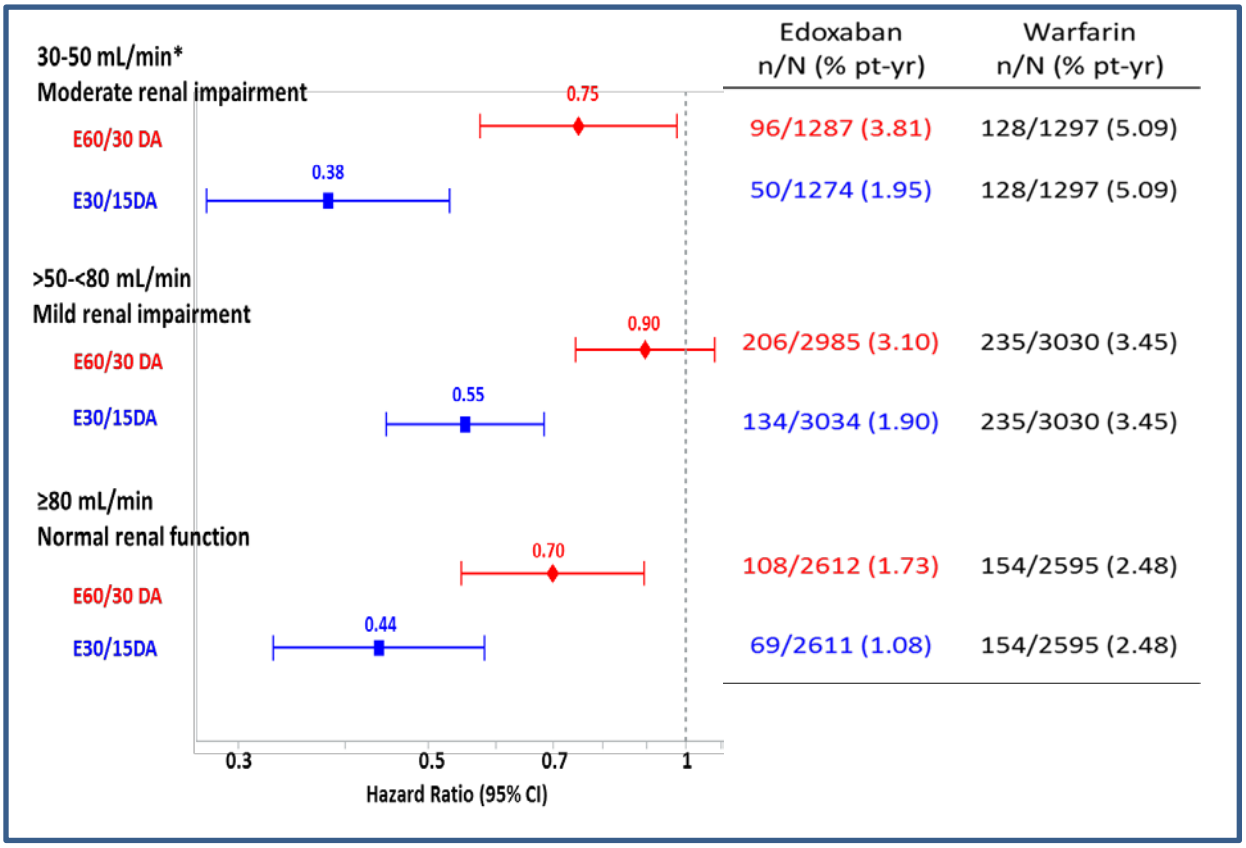
Figure 6 ENGAGE - Edoxaban Trough Plasma Concentrations) by Treatment Arm in Patients without and with Dose Adjustment



X axis markers represent renal function subgroups: 1 – moderately impaired; 2 – mildly impaired; 3 – normal.
For patients without dose adjustment, N per arm in each subgroup was about: 215 in 1; 2475 in 2, and 2500 in 3
For patients with dose adjustment, N per arm in each subgroup was about: 1070 in 1; 540 in 2; and 110 in 3
Source: Reviewer's analysis of PCANAL.xpt dataset

Finally, it should be noted that the results for the primary safety endpoint, ISTH Major Bleeding, show a pattern across the renal function subgroups that is essentially the inverse of the efficacy results pattern: for each edoxaban dose group, the subgroup with the highest edoxaban exposure and the best efficacy results compared to warfarin (i.e., the mild renal impairment subgroup), had the worst results for bleeding compared to warfarin. However, all renal function subgroups had point estimates for this endpoint that are less than 1 (**Figure 7**).

Figure 7 ENGAGE – ISTH Major Bleeding by Treatment and Renal Function Subgroup
MITT Population on Treatment



Barred lines represent 95% CI.
Source: Safety Reviewer Analysis.

Note that in **Figure 7** the color coding is reversed from the efficacy figures: here the E 60/30 mg group data are in red and the E 30/15 data are in blue. While there are differences in bleeding hazard ratios that generally vary directly with exposure (i.e., higher edoxaban results in higher bleeding rates and less favorable hazard ratios) among the subgroups of each treatment arm, the differences in hazard ratios are not as striking as for efficacy.

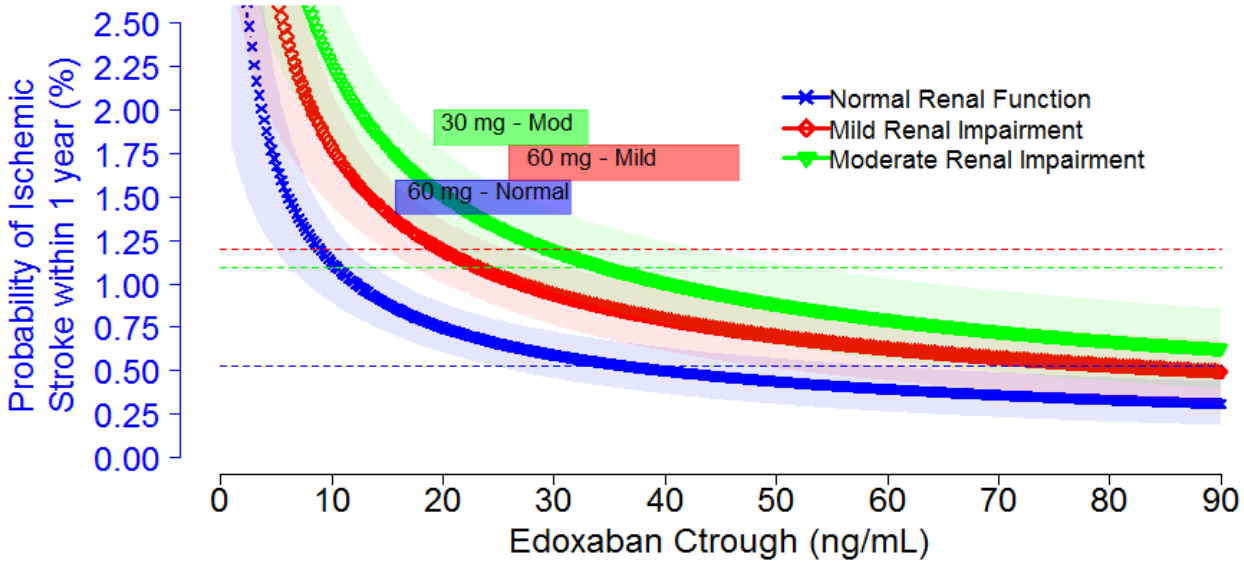
All of the above reinforces the Applicant's decision not to seek approval of the 30/15 mg regimen for the A Fib indication and also suggests that 60 mg, the highest dose studied in Phase 3, is too low a dose for patients with normal function. While exposure in the moderate renal impairment subgroup was similar to exposure in the normal renal function subgroup, the hazard ratios for the primary endpoint and ischemic stroke were more favorable for edoxaban

than those for the normal renal function subgroup. OCP agrees with the Applicant that 30 mg is an appropriate dose for subjects with moderate impairment of renal function.

Accordingly, OCP has plotted the concentration-response relationships for ischemic stroke and bleeding. They have also performed PK modeling to find a dose appropriate for the normal renal function subgroup. Their PK modeling assumes subjects with mild renal dysfunction who received edoxaban 60 in the mildly impaired renal function subgroup achieved appropriate exposure levels because they had the best efficacy results and Major Bleeding rate numerically less than warfarin. The goal of the modeling was to determine a dose for subjects with normal renal function that would result in trough edoxaban exposure that is similar to that of patients with mild renal impairment who received 60 mg.

Figure 8 is a plot of edoxaban trough plasma concentrations from the large PK subset of over 12,000 patients. Colored curves were generated for each renal function subgroup. The horizontal colored bars with the subset labels (e.g., "60 mg – Normal" in purple) represent the actual 95% range of trough concentrations for that subgroup. The dashed purple horizontal line represents the actual rate of events in eh warfarin arm in the purple (normal renal function) subgroup. The other subgroups are analogously represented and labeled. For example, when the range corresponding to the purple bar is superimposed on the purple concentration-response curve, the expected rates of ischemic stroke appear to be about 0.8% (for concentrations at the low end of the purple bar) to 0.5% (based on the high end of the purple bar). The actual rate in the warfarin arm of was 0.5%, meaning that 97.5% of subjects in the normal renal function subgroup who received 60 mg daily had edoxaban concentrations that yielded an expected rate of ischemic stroke similar or higher than the observed rate for warfarin. On the other hand the entire red bar (for mildly impaired renal function) corresponds to concentrations that would expected to be associated with rates of ischemic stroke below the observed rate for warfarin in that subgroup, about 1.2% (represented by the red dotted line).

Figure 8 Exposure Response Relationship for Ischemic Stroke
ENGAGE PK Subset



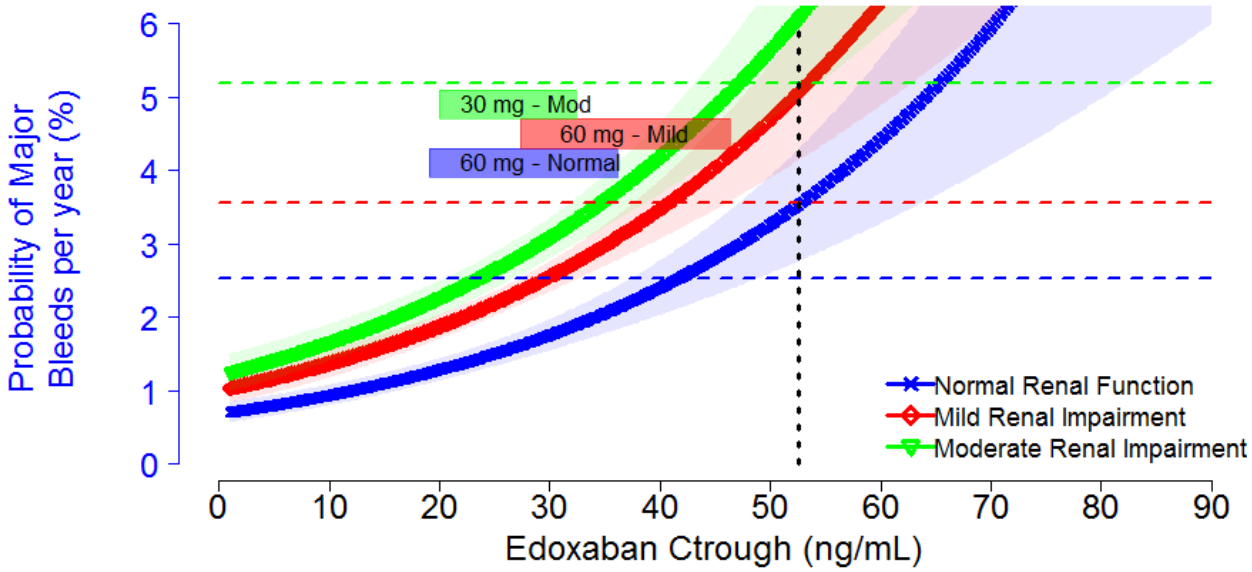
Source: OCP reviewer

An analogous plot for the primary endpoint was produced but is not shown. The plot is quite similar to the one above and yields similar conclusions, which is not surprising because most primary endpoint events are ischemic strokes.

Figure 9 is a plot for ISTH Major Bleeding that is analogous in format to the one above. Note that when the red bar (corresponding to mildly impaired renal function is superimposed on the red curved line, part of the line segment thus selected lies above the dotted red line, indicating that patients with exposures at the high end of the exposure range would be expected to have higher bleeding rates than with warfarin, while those at the lower end would have a rate less than with warfarin.

When the purple bar is superimposed on the purple curve (for the normal renal function subgroup, the entire length of the selected segment is below the purple dotted line, suggesting that expected concentrations in the expected range would be expected to produce less bleeding than warfarin, which is what occurred in ENGAGE in this subgroup. However, when the range of the red bar is superimposed on the purple curve (as would be appropriate if patients with normal renal function had exposure similar to that of patients with mildly impaired renal function), a small part of the selected segment would be above the purple dotted line, suggesting that persons at the high end of the exposure range would have a higher bleeding risk than with warfarin, but the most patients in the expected range would have a lower risk than with warfarin.

Figure 9 Exposure Response Relationship for Major Bleeding
ENGAGE PK Subset

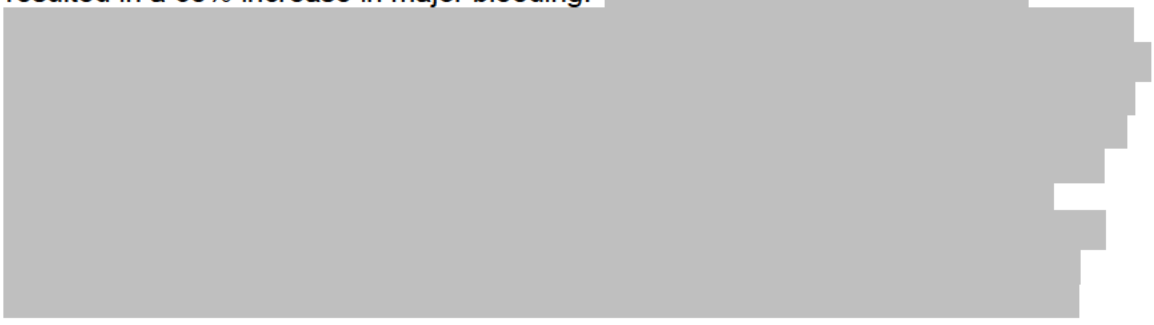


Black vertical line at 52 ng.mL represents the 99% limit of observed concentration values.
Source: OCP reviewer figure.

Thus, the exposure-response information suggest that for patients with normal renal function, exposure matching to edoxaban levels observed in patients with mild renal impairment would lower the risk of ischemic stroke without a substantial increase in the risk of having a Major Bleed. Similar plots was generated for Major GI bleeding and show a slightly larger increase in similar increase risk – to about a doubling of risk compared to warfarin with the highest exposures in the expected range – with the exposure matching strategy. The OCP review also

includes an analogous plot for life threatening bleeding, which mostly consists of intracranial bleeds. This plot shows very shallow slopes for the 3 renal function subgroups exposure-response curves, with a very small increase in risk associated with exposure matching in patients with normal renal function. The expected risk with exposure matching would remain less than the risk for warfarin at all reasonably expected concentrations of edoxaban.

- *The rate of major bleeding in patients in ENGAGE with normal renal function was only 60% higher in the 60 mg arm compared to the 30 mg arm, a proportional change in dose that is 4 X the proposed change here.* In ENGAGE very few patients with normal renal function qualified for dose reduction. Thus, most patients with normal renal function received either 30 mg or 60 mg daily. The annualized overall major bleeding rate in patients with normal renal function was increased by 60% compared to the 30 mg arm: 1.73% vs. 1.08%. Because exposure to edoxaban is dose proportional, doubling the dose results in double the systemic exposure, as well as double the exposure of the GI tract to unabsorbed drug. Here, systemic exposure that was increased by 100% resulted in a 60% increase in major bleeding. (b) (4)



- *In RE-LY, which supported approval of dabigatran for the same indication the Applicant is seeking for edoxaban, the increase in major bleeding for patients with normal renal function was 33% in the dabigatran 150 mg bid arm compared to the 110 mg bid arm, corresponding to a dose increase of 36%, substantially more than proposed for*

edoxaban. In RE-LY, patients were randomized to receive warfarin or either 110 or 150 mg dabigatran bid. The high dabigatran dose was 36% more than the low dose; exposure is dose proportional. The annualized rate of major bleeding in patients with normal renal function (defined the same way in RE-LY as in ENGAGE) was 1.40% for dabigatran 110 mg bid and 1.86% for dabigatran 150 mg bid – i.e., a 33% increase in bleeding with a 36% higher dose. (b) (4) Even a 33% percent increase in major bleeding in the normal renal function subgroup of the edoxaban 60 mg arm would yield a rate of 2.3%/year, again less than the rate in ENGAGE in the comparable renal function subgroup of the warfarin arm (2.48%).

- *Data from ENGAGE suggest that doubling the amount of unabsorbed edoxaban in the gut does not have large or directionally consistent effects on GI bleeding*. One concern with both edoxaban and dabigatran is that both drugs are poorly absorbed from the GI tract, leading some to speculate that that unabsorbed drug might be locally active in the GI tract and contribute to GI bleeding. The large PK subset in ENGAGE (>6000 patients per arm) yielded a very broad range of systemic exposure, including several thousand patients with similar systemic trough edoxaban levels despite the fact that some received a dose of 30 mg and some a dose of 60 mg (patients with normal or mildly impaired renal function), or some a dose of 15 mg and some a dose of 30 mg (patients with moderate renal impairment). OCP did an analysis of major GI bleeding in these exposure-matched patients. Results across the various subsets of renal function indicated that the is not a large or directionally consistent effect of a doubled dose of edoxaban (with double the mass of unabsorbed edoxaban in the GI tract) on the rate of GI bleeding when trough systemic exposure is similar (**Table 4**). (b) (4) However, the comparisons in **Table 4** among patients in the same renal function subgroup who received different doses are not randomized comparisons, and patients in the compared dosing groups may have differed in various factors that might affect GI bleeding risk.

Table 4 ENGAGE – Major GI Bleeding in Patients Receiving Different Oral Doses but with Similar Systemic Exposure to Edoxaban

Renal Function Category (Creatinine Clearance)	Dose/ Exposure Quartiles	Major GI Bleeds (% events/year)	n/N	Edoxaban Ctrough [min; max]
Moderate Impairment (30-50 mL/min)	15 mg, Q4	1.26 (0.46; 2.72)	6/261	[14.0; 25.0]
	30 mg, Q1,2	0.65 (0.26; 1.33)	7/533	[14.1; 25.5]
Mild Impairment (50-80 mL/min)	30 mg, Q2,3,4	1.12 (0.83; 1.47)	49/1864	[16.5; 37.1]
	60 mg, Q1,2	1.62 (1.19; 2.16)	46/1241	[16.0; 36.6]
Normal (>80 mL/min)	30 mg, Q2,3,4	0.59 (0.39; 0.85)	27/1884	[12.0; 26.6]
	60 mg, Q1,2	0.68 (0.42; 1.04)	21/1261	[10.7; 27.3]

Q1-4: Quartiles of exposure in each dosing cohort
Analyses are limited to subjects with normal/mildly impaired renal function with no dose adjustment and subjects with moderately impaired renal function with a dose adjustment

The clinical review team and the OCP review team are unanimous in concluding that edoxaban 60 mg daily is too low a dose for patients with A Fib and normal renal function. However, there was not unanimity with respect to the implications of this belief for action on the application. For further discussion of this issue, see Sec. 13.

6. Clinical

6.1 Clinical/Statistical - Efficacy

Dose Identification

There was one confirmatory trial performed for the A Fib indication, ENGAGE AF-TIMI 48, described below. The main edoxaban doses used in this study, 60 mg once daily and 30 mg once daily were based on the results of PRT-018, a Phase 2, randomized, multi-national, partially blinded, parallel study performed in over 1100 adult patients with non-valvular A Fib and $CHADS_2$ score ≥2. The goal of this study was to evaluate the safety of 4 edoxaban dosing regimens and warfarin in patients with A Fib. Bleeding events and liver function tests (transaminases and bilirubin) were the primary safety endpoints.

In PRT-018, patients were randomized to 12 weeks of treatment with:

- Edoxaban 30 mg once daily (OD)
- Edoxaban 30 mg bid
- Edoxaban 60 mg OD
- Edoxaban 60 mg bid
- Warfarin, titrated to an INR 2.0 to 3.0

Edoxaban doses used in PRT-018 were based on Phase I data and prior studies in patients with DVT. For patients randomized to edoxaban, there was a double bind with respect to dose. Warfarin was administered in an entirely open manner. Planned enrollment was about 240 subjects per arm.

Patients were treated for 3 months, with a 30 day post treatment visit. In addition to the safety data already described, MACE events were captured. These were defined as stroke of any kind, SEE, CV death, and hospitalization for any cardiac condition. There was a fully blinded CEC to adjudicate events. PD sampling was performed on Day 1 (randomization) and Day 28 (1 and 3 h post dose).

At the recommendation of the DMC, the 60 mg bid arm was terminated early due to excess bleeding after 180 subjects had enrolled in that arm. The other 4 arms were fully enrolled, with a mean enrollment of 242 subjects per arm.

Safety data, copied from the clinical review, are shown below:

Table 5: Incidence of Bleeding in PRT-018 during the treatment period

	Edoxaban Dose					
	Any Dose	**30 mg qd (N = 235)**	**30 mg bid (N = 244)**	**60 mg qd (N = 234)**	**60 mg bid (N = 180)**	**Warfarin (N = 250)**
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

The 60 mg bid arm had the highest rate of bleeding, and the 30 mg OD arm had the lowest rate. Bleeding was more frequent in the 30 mg bid arm than with 60 mg OD. Bleeding with 60 mg OD was similar to bleeding with warfarin. Largely on the basis of the bleeding data above, 60 mg once daily and 30 mg once daily were selected for evaluation in Phase 3.

Data for MACE events in PRT-018 is shown in the following table. Note that while the rate of stroke and systemic embolism was low with 60 mg OD, this arm had the highest rate of MACE events.

Table 6: Major Adverse Cardiovascular Events in Study PRT-018

	Edoxaban Daily Dose				
	30 mg qd (N = 235)	**30 mg bid (N = 244)**	**60 mg qd (N = 234)**	**60 mg bid (N = 180)**	**Warfarin (N = 250)**
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]

Source: PRT-018 CSR

The Applicant cites PRT-018 as the major study contributing to the selection of doses for ENGAGE. Their intent was to select doses of edoxaban that would have less bleeding risk than warfarin. Both 30 mg OD and 60 mg OD appeared to meet that test in PRT-018. PD testing in PRT-018 indicated that edoxaban 60 mg was associated with similar reductions in fibrin split products as warfarin (data not shown), suggesting that the drugs might have similar antithrombotic effects.

Of note, the quality of anticoagulation in the warfarin arm was not good. Over 90% of subjects were from eastern Europe, an area that has sometimes performed poorly in terms of time in therapeutic range (TTR) for INR in anticoagulant studies. At baseline, 57% to 68% of subjects in each of the 5 arms were warfarin naïve, meaning that about 30% to 40% came into the study on warfarin. However, only 7% were in range for INR at baseline in the warfarin arm. By the end of the study the TTR in the warfarin ARM was 50%. About 80% of the time out of range was time below range (i.e., a 40% absolute rate of time below range). If TTR was similar to the excellent TTR obtained in ENGAGE (about 65%), one would expect patients in the warfarin arm to have bled more. A comment in the clinical review suggests that a higher rate of bleeding in the warfarin arm in PRT-018 might have induced the Applicant to choose a higher edoxaban dose for evaluation in Phase 3. However, it is impossible to know whether better control of INR would have affected the Applicant's choice of dose for Phase 3.

Design and results of the pivotal efficacy study:

In support of the proposed indication, the applicant conducted one trial: the ENGAGE AF-TIMI 48 study, a large (21,000+ subjects) trial comparing wo dosing regimens of edoxaban to warfarin to reduce the rate of stroke and systemic embolism.

ENGAGE was an international, randomized, double- blind, double-dummy, event-driven, non-inferiority study comparing edoxaban given orally once daily to warfarin titrated to a target INR 2.0 to 3.0 except in Japan, where patients age 70 and above were titrated to an INR of 2.0 – 2.5. Two edoxaban dosing regimens were evaluated: a high exposure regimen, with most patients receiving 60 mg daily, with a reduced dose of 30 mg for patients who met any one or more of 3 dose reduction criteria: creatinine clearance 30 to 50 mL/min; body weight ≤60 kg, or use of specified p-GP inhibiting drugs (dronedarone, verapamil, quinidine); and a low exposure regimen, with most patients receiving 30 mg daily, with a reduced dose of 15 mg daily for those who met the dose reduction criteria described above. Randomization was stratified by dichotomized $CHADS_2$ score (2-3 vs. 4-6) and dose adjustment (full dose or half dose).

ENGAGE enrolled patients with non-valvular atrial fibrillation and a $CHADS_2$ score ≥ 2. This requirement produced a population at higher risk of stroke than patients in RE-LY and ARISTOTLE but at lower risk than those in ROCKET. Study exclusions included: patients who with transient A Fib with a reversible cause; moderate or severe mitral stenosis; intracardiac mass; left ventricular thrombus; a mechanical heart valve; high risk of bleeding from a list of specified causes including dual anti-platelet therapy, other anticoagulants, and use of chronic systemic NSAIDS; creatinine clearance < 30 mL/min,; transaminase ≥ 2X ULN; total bilirubin ≥ 1.5 X ULN; stroke or ACS or PCI within 30 days; and use of specified potent P-gp inhibitors, among others.

A double dummy technique was used in ENGAGE. A point of care device was used to determine INR, with provision of sham INRs to patients randomized to edoxaban. In attempt to maintain the blind, the protocol also specified that while on study drug, unblinded INR measurements were not to be performed the investigator first contacted the TIMI hotline to discuss the situation except in the setting of a medical emergency. A warfarin dosing algorithm was provided but its use was not mandatory. Intervals for INR determination were not specified; the investigator was to use "good clinical judgment" and keep the INR in the specified therapeutic range.

The trial was event-driven and was designed to establish the non-inferiority of edoxaban to warfarin for the reduction of stroke and systemic embolism. A non-inferiority margin of 1.38 was used, as is customary. Efficacy endpoints and safety endpoints of interest (i.e. bleeding and liver findings) were adjudicated by an independent blinded clinical endpoint committee.

There was a scheduled interim analysis when 50% of the target number of events had occurred, but only the result of this analysis could be dropping of a study group, so there was no reduction in the final alpha. In the final analysis, each edoxaban group was compared to warfarin at the 0.025 level (two-sided) using a Cox model with stratification covariates, assessing non-inferiority of edoxaban to warfarin win an NI margin of 1.38. A hierarchical analysis plan was specified in the event that the 60 mg group was non-inferior to warfarin for the primary endpoint with all analyses involving the comparison of edoxaban 60 mg to warfarin. In the order to be performed the analyses were:

1. superiority for the primary endpoint, p=0.01
2. superiority for time to the composite of stroke/SE/CV death, p=0.01
3. superiority for time to MACE (which includes fatal bleeding as part of CV death), p=0.01

4. superiority for time to stroke/SE/all-cause death, p=0.01

All of these analyses were conducted using a Cox model with the stratification covariates. If any of these analyses did not succeed, subsequent analyses were not to be performed.

There were two major analysis populations: the ITT population (all patients randomized), and the MITT population (all patients who received at least one dose of study drug). There were two major analysis periods: the "overall study period," defined as randomization or first dose of study drug (as specified in the analysis plan) to the CSED visit, and the "on-treatment period," defined as first dose to last dose + 3 days or the CSED, if the patient took study drug up to the CSED.

There was also a per-protocol population, which consisted of MITT patients without major protocol violations. Inclusion in this population was made on the basis of a blinded assessment of whether a major protocol violation occurred. However, this population was not analyzed in any of the analyses in the hierarchy described above.

The primary analysis of NI was determined in the MITT population on-treatment. All the superiority analyses in the hierarchy above were made using the ITT population in the overall study period.

An overview of ENGAGE's design is shown in **Figure 10** ENGAGE Design, along with some relevant data on enrollment, TTR, and endpoints reported:

Figure 10 ENGAGE Design

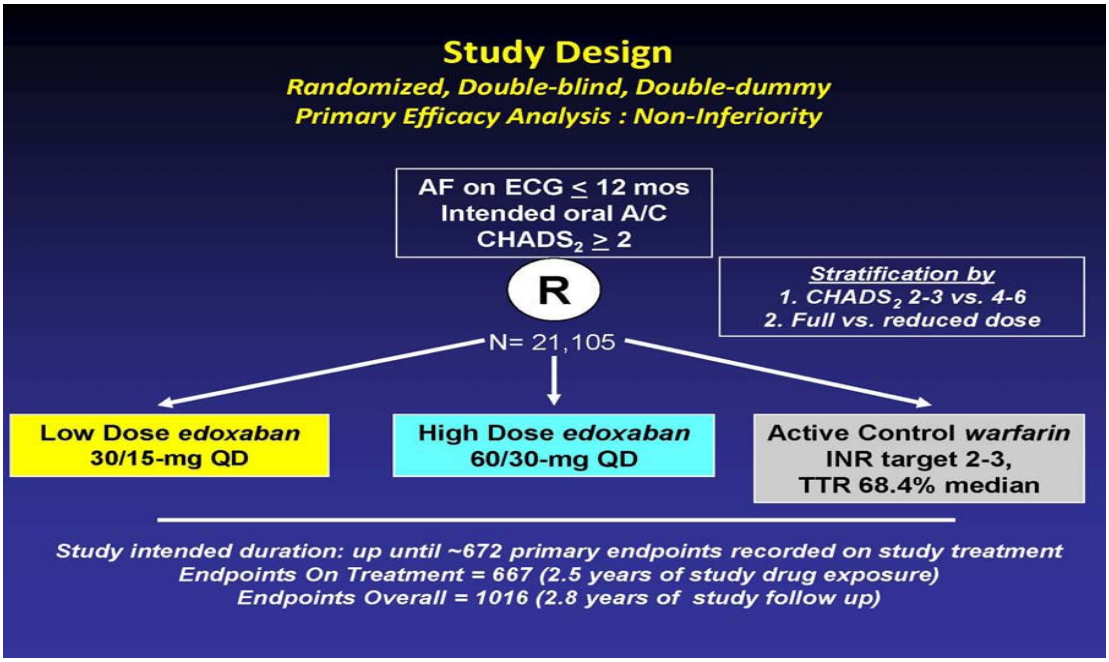


Table 7 is a display the study analysis populations and disposition. The study was well run with a low rate of loss to follow-up for vital status (0.2%).

Table 7 ENGAGE Analysis Populations and 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 d (2.5 yr)	904 d (2.5 yr)	904 d (2.5 yr)	
Subject-year Exposure	15,840	15,471	15,569	
Median Study Follow-up	1023 d (2.8 yr)	1023 d (2.8 yr)	1021 d (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%)	
Reasons for Not Completing				
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

Study arms were well-balanced for demographic and risk-related features. The average $CHADS_2$ score was 2.8 in subjects who received the full dose of study drug and 3 in those who received a reduced dose. About 40% of subjects were 75 years old or older, and 38% were women. About 25% were dose-adjusted at randomization. About 18%, 43% and 37% were in the moderate renal impairment, mild renal impairment, and normal renal function subgroups, respectively. About 1% had creatinine clearance < 30 mL/min. In the clinical review, Dr. Blank noted that the constancy assumption was satisfied by ENGAGE when trial conduct and patient characteristics were compared to the placebo controlled trials of warfarin, meaning that the non-inferiority results can be interpreted. Time in therapeutic range of INR as good as or better than any of the other confirmatory trials for the approved NOACs: the mean time in range was 64.9% and the median was 68.4%. Mean time below range was 22.8%.

Table 8 is a display of the main efficacy outcome analyses of ENGAGE. Both edoxaban arms were non-inferior to warfarin for the primary endpoint using the pre-specified NI margin of 1.38, and the 60 mg arm came close to succeeding in the pre-specified superiority analysis. However, the primary endpoint results favored *warfarin* over the edoxaban 30 mg arm, and the difference came close to being statistically significant. Other findings of note were:

- Ischemic stroke results favored edoxaban 60 mg over warfarin slightly, but favored warfarin over edoxaban 30 mg by a wide margin with nominal statistical significance.
- Hemorrhagic stroke rates favored both edoxaban arms over warfarin, with the hazard ratios being nominally significant in each case. A dose response was observed here, with edoxaban 30 mg having a lower rate than edoxaban 60 mg, unlike the findings in RE-LY where there was no evident dose response for the effect of dabigatran on hemorrhagic stroke.
- Disabling stroke favored warfarin over edoxaban 30 mg.
- There was no signal of MI risk with edoxaban 60 mg.
- Both edoxaban arms had fewer CV deaths and all-cause deaths than warfarin. For the edoxaban 30 mg arm, the advantage over warfarin was nominally significant for CV death.
- The results for MACE (defined as MI, stroke, CV death, fatal bleeding) favored edoxaban 60 mg over warfarin with nominal statistical significance.
- Results for the per-protocol, on-treatment analysis were very similar to the MITT, on-treatment results, and support non-inferiority of edoxaban 60 mg to warfarin.

Table 8 ENGAGE – Major Efficacy Outcome Analyses

Endpoint	Edoxaban 30 mg (15mg DA) (N=7002)		Edoxaban 60 mg (30 mg DA) (N=7012)		Warfarin (N=7012)		E 30 vs. W HR (97.5% CI) p	E 60 vs. W HR (97.5% CI) p
	# of events	KM Event Rate (%/yr)	# of events	KM Event Rate (%/yr)	# of events	KM Event Rate (%/yr)		
Primary Endpoint / Non-inferiority mITT Analysis Set On Treatment Period	253	1.61	182	1.18	232	1.50	1.07 (0.87, 1.31) --	0.79 (0.63, 0.99) --
Primary Endpoint / Superiority ITT Analysis Set Overall Study Period	383	2.04	296	1.57	337	1.80	1.13 (0.96, 1.34) 0.10 *	0.87 (0.73, 1.04) 0.08 *
Other Endpoints (considered separately) mITT Analysis Set On Treatment Period							**HR (95% CI) p**	**HR (95% CI) p**
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
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
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
Disabling Stroke	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
SEE	11	0.07	8	0.05	13	0.08	0.83 (0.37, 1.85) 0.65	0.62 (0.26, 1.50) 0.29
MI	120	0.76	88	0.27	105	0.68	1.12 (0.86, 1.46) 0.38	0.84 (0.64, 1.120) 0.24
CV Death	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 Death	221	1.39	234	1.51	258	1.65	0.84 (0.70, 1.01) 0.06	0.89 (0.74, 1.07) 0.32
MACE	546	3.48	449	2.92	530	3.43	1.02 (0.90, 1.14) 0.82	0.85 (0.75, 0.97) 0.012

DA: Dose adjusted
SEE: Systemic embolic event
Primary Endpoint: Time to first event of composite of stroke (any type) or systemic embolism
Disabling Stroke: Rankin score of 3 to 5 on a scale of 0 to 6 (does not include fatal strokes)
MACE: MI, stroke, CV death, bleeding death
* $p<0.01$ required to show superiority for the primary endpoint
Source: ENGAGE CSR Tables 11.2, 11.4, 11.7, 11.9, 11.11

An examination of the primary endpoint results by quartiles of center-based TTR was performed by the Applicant. In the 3 lowest quartiles of INR control, with TTR up to 73.9%, the HR for the primary endpoint ranged from 0.73 to 0.80 for the edoxaban 60 mg arm. In the fourth quartile, with sites with TTR >73.9%, TTR was 1.02 (data not shown).

Overall, the efficacy findings support approval of the edoxaban 60 mg regimen. Because this regimen came close to being superior to warfarin for the primary endpoint, and warfarin was nearly superior to edoxaban 30 mg, one can infer that edoxaban 60 mg is superior to edoxaban 30 mg for reducing the rate of the primary endpoint of time to stroke and systemic embolism. One can also infer that edoxaban 60 mg was superior to edoxaban 30 mg for ischemic stroke (the event we are hoping to prevent with anticoagulation in patients with A Fib) because warfarin was shown to be superior to edoxaban 30 mg and edoxaban had numerically better results for this endpoint than warfarin. The superiority of dabigatran 150 mg bid over dabigatran 110 mg bid was a factor in our decision to approve only the higher dose, even though the lower dose was non-inferior to warfarin. The ENGAGE data support the Applicant's decision to not seek approval of the 30 mg regimen, and there is precedent for not approving the less effective dose in this situation.

Other than the interaction between renal function and efficacy (discussed in Sec. 5), there are no other issues relating to efficacy that would stand in the way of approving edoxaban for the A Fib indication.

6.2 Safety

General safety considerations:

All data discussed in this section are from the ENGAGE trial unless otherwise specified. Total exposure to study drug in ENGAGE was quite extensive and is displayed in **Table 9**Error! Reference source not found. Median exposure to study drug was more than 900 days in each arm and total exposure in each arm was more than 15,000 patient-years. Note that the headings below refer to randomized treatment arms, not dose as-treated.

Table 9 Study Drug Exposure in ENGAGE

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.

Information regarding discontinuations of study treatment for AEs and other reasons is provided in **Table** 10 by study arm and by dose adjustment status. Note that patients who were dose adjusted discontinued study drug at substantially higher rates overall than patients who were not dose adjusted. Dose adjustment criteria (based on renal function, weight, and use of P-gp inhibitors) yielded a population that would be expected to be older and frailer than those who were not dose adjusted. Notably, the highest discontinuation rate was in "dose-adjusted" patients in the warfarin arm, who were not actually dose adjusted because all warfarin arm patients were titrated to an INR target of 2.0 to 3.0.

Table 10 Study Drug Discontinuation

	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 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)

Adj: Dose adjustment
Reviewer's Table. Applicant's datasets: DM, EX.

The overall number of discontinuation for AEs that were not efficacy events was lowest in the edoxaban 30 arm (1110, 15.9%) and highest in the edoxaban 60 mg arm (1268, 18.1%), with 1226 (17.5%) in the warfarin arm, including dose adjusted patients (DA) and not dose adjusted patients (NDA) in each randomized arm. Of note, NDA patients in the 30 mg edoxaban arm received the same dose as DA patients in the 60 mg arm (i.e., 30 mg), but the AE discontinuation rate in the two groups was 13% and 24%, respectively. This suggests that DA cohorts may have been quite different from the NDA cohorts. Death rates were also higher across the table in the DA patients compared to their NDA counterparts in the same arm. Bleeding/Surgery was the most common specified AE leading to discontinuation in each arm.

Death

Death on treatment is discussed in Sec. 6.2, regarding efficacy. Death during the overall study period is shown in **Table 11**. For death in the overall study period, the treatment arms are ordered in the same way as for death on-treatment: from fewest to most deaths the arms are edoxaban 30 mg (731 deaths), edoxaban 60 mg (769), and warfarin (836). Because total N in each arm is similar, I will focus on the number of deaths. The count of death due to malignancies was 93, 94, and 84 in the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively. The Yates chi square p for edoxaban 60 mg vs. warfarin is 0.5 and is even higher for the both edoxaban arms pooled vs. warfarin. This is not a signal of harm. Note that in **Table 12**, with results for deaths by MedDRA SMQ, the results for malignancy-related deaths for the 3 arms are even more similar to each other than in **Table 11**. In addition, the overall count of SAEs in the Neoplasms Benign, Malignant and Unspecified SOC was lower for both edoxaban arms than for warfarin: 261, 264, and 283 in the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively.[1]

For non-CV, non-malignant deaths, the count was 116, 148, and 144 in the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively. The lower rate in the edoxaban 30 mg arm was driven by the results for deaths due to infection, which were 69, 94, and 92 in the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively. One possible explanation for this pattern was that the increased rate of bleeding with edoxaban 60 mg and warfarin led to more hospitalizations and subsequent serious infections, but this is speculative and was not explored. Less bleeding with edoxaban 30 mg also might have contributed to the results for deaths due to accidents or trauma: 5, 10, and 10 in the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively.

[1] There was no notable excess with edoxaban for any of the many reported solid malignancies in the Applicant's table of SAEs, including (in order of prevalence, starting with the most commonly reported tumor): colon cancer, prostate cancer, basal cell carcinoma, breast cancer, 2 terms for bladder cancer, "lung neoplasm malignant", lung adenocarcinoma, rectal cancer, and squamous cell carcinoma, which constituted 10 of the 12 most common tumors. Two of the 12 most common had results notably favoring warfarin: myelodysplastic syndrome (9th most common, 1, 6, and 1 cases in the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively) and prostatic adenoma (10th most common, 1, 6, and 0 cases in the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively. However, there was no signal for either acute myeloid leukemia (which may follow myelodysplastic syndrome) or prostate cancer with edoxaban. None of this belongs in labeling.

Table 11 Summary of Adjudicated Deaths- overall study period

	Edoxaban 30mg (15mg DosAdj) (N=7002)	Edoxaban 60mg (30mg DosAdj) (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

Dr. McDowell performed an analysis of deaths associated with MedDRA SMQs (**Table 12**). She examined all SMQs, but only those of special interest and those with unexpected findings are shown in the table.

Table 12 Incidence of Death by MedDRA SMQs
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 most notable finding is for the Interstitial lung disease SMQ, with 5, 8, and 0 deaths associated with the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively. This finding is discussed further below. Notably, the malignancies SMQ showed similar rates of death in the 3 arms, and the rates are fairly similar to the ones in **Table 11**.

Bleeding:

Bleeding events were blindly assessed by the CEC. Bleeding was characterized as major (using the ISTH definition[2]), clinically relevant non-major (CRNM), or minor. Major bleeding was subdivided into life-threatening and non-life-threatening. Life-threatening bleeds were intracranial bleeds and other bleeds that resulted in hemodynamic compromise requiring intervention (i.e., GUSTO severe bleeding).

CRNM bleeding was non-major bleeding that required medical attention beyond a simple dressing or an outpatient visit. A long list of medical interventions that qualified a bleed for CRNM status was provided. In addition to physical measures to control bleeding, tactics such as discontinuing or changing a medication at the request of a physician to reduce bleeding were sufficient to classify a bleed as CRNM.

Bleeds that were not major bleeds or CRNM bleeds were classified as minor.

[2] ISTH Major bleeding is defined as an overt bleeding event that is fatal, intracranial, pericardial, or into one of several other critical spaces, or causes a 2g/dL reduction in hemoglobin, with adjustment for transfused blood products (1 u blood or packed RBC=1 g/dL reduction in hemoglobin).

Table 13 is a display of various classifications and anatomic locations of bleeding in ENGAGE. The results for ISTH Major bleeding, the primary safety endpoint, favored each edoxaban regimen over warfarin with nominal statistical significance, but there is a clear dose-response for bleeding with edoxaban. All comparisons for edoxaban 30 mg vs. warfarin favored edoxaban 30 mg numerically. All comparisons for edoxaban 60 mg vs. warfarin favored edoxaban 60 mg except several comparisons of GI bleeding. However, the more serious cases of GI bleeding, classified as TIMI major or GUSTO severe, were not more frequent with edoxaban 60 mg than with warfarin (highlighted in blue).

Table 13 ENGAGE – Adjudicated Bleeding Results

	Edoxaban 30 mg N = 7002 n (per 100 pt-year)	**Edoxaban 60 mg** N = 7012 n (per 100 pt-year)	**Warfarin** N = 7012 n (per 100 pt-year)	**Edoxaban 30mg vs. W** HR (95% CI)	p value	**Edoxaban 60 mg vs. W** HR (95% CI)	p value
ISTH 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
-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)	<0.0001
-Non ICH	65 (0.40)	104 (0.66)	127 (0.80)	0.50 (0.37-0.68)	<.00001	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
CRNM Bleeding	965 (1.44)	1210 (8.32)	1390 (9.65)	0.66 (0.61-0.71)	<0.0001	0.86 (0.80-0.93)	0.0002
Major + CRNM Bld.	1161 (7.68)	1528 (10.64)	1761 (12.39)	0.62 (0.58-0.67)	<0.0001	0.86 (0.80-0.92)	<0.0001
Minor Bleeding	533 (3.52)	604 (4.12)	714 (4.89)	0.72 (0.65-0.81)	<0.0001	0.84 (0.76-0.94)	0.0023

ENGAGE CSR Table 12.6; 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

The above tables count hemorrhagic strokes as major intracranial bleeds. However, hemorrhagic strokes are also counted as primary endpoint events. To avoid double counting of these events, Dr. McDowell performed an analysis of major bleeding without

hemorrhagic stroke (**Table 14**). Results favor each edoxaban regimen over warfarin for each category of bleeding. Notably, even without counting hemorrhagic strokes, there is a 3 per thousand rate of intracranial hemorrhage with warfarin, several-fold higher than with edoxaban at either dose. Fatal bleeding without hemorrhagic stroke also favors each edoxaban dose over warfarin. GI bleeding rates and other rates of non-ICH bleeding are not included because they would not be expected to change with exclusion of hemorrhagic stroke events.

Table 14 ENGAGE – Adjudicated Major Bleeding Results without Hemorrhagic Stroke

Name	*Edoxaban 30 mg N = 7002* *n (per 100 pt-year)*	*Edoxaban 60 mg N = 7012* *n (per 100 pt-year)*	*Warfarin N = 7012* *n (per 100 pt-year)*	*Edoxaban 30mg vs. W* *HR (95% CI)*	Edoxaban 60 mg vs. W HR (95% CI)
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.

Anemia and Hemoglobin

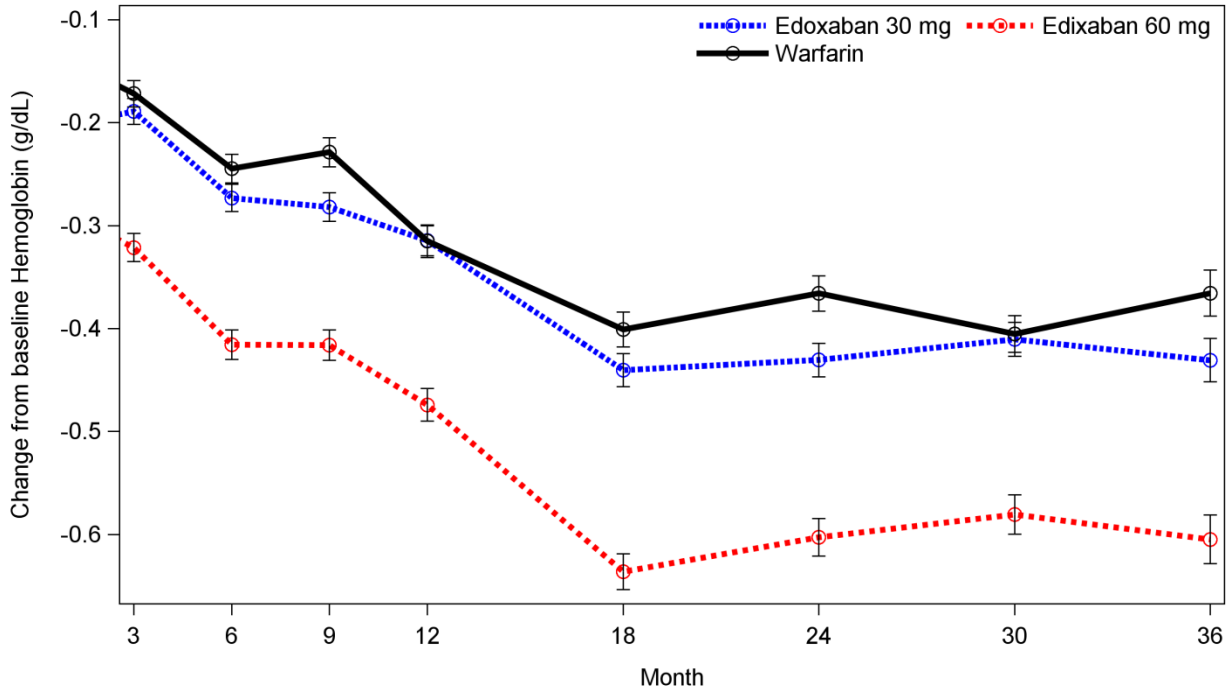
Oddly, although observed bleeding was more frequent with warfarin, anemia was more frequent with edoxaban 60 mg than with warfarin (**Table 15**). There was also a higher incidence of anemia-related conditions in the edoxaban 60 mg group compared with the warfarin group among subjects who did not report any bleed in the study (4.9% vs. 3.1%). Likewise, reductions in hemoglobin were more frequent with edoxaban 60 mg than with warfarin (**Figure 11, Table 16**). The warfarin and edoxaban 30 mg arms were similar for these parameters. Finally, , a more in the edoxaban 60 mg group compared with the warfarin group had ≥ 2 units of transfusion (5.4% vs. 4.9%, respectively). Dr. McDowell speculated that, "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." This thought is reasonable, but we can't be sure about the cause of the excess anemia with edoxaban 60 mg, which was not explored further. However, the finding should be included in labeling in Sec. 6.

Table 15 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

Figure 11 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 16 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.

NON-BLEEDING ADVERSE FINDINGS:

Hepatic Injury:

Because of medically important hepatic toxicity of ximelagatran, it has become routine to carefully asses the hepatic toxicity of new anticoagulants. It appears that edoxaban, like the 3 NOACs approved since 2010, does not share this significant drawback.

Careful reviews of the pattern of transaminase and bilirubin elevations were performed by Dr. McDowell as well by our hepatic consultant, Dr. Senior. These were similar in the three study arms. Medical histories of all potential Hy's Law cases were reviewed by Dr. Senior. Dr. Senior concluded that there was no signal of hepatic toxicity in the A Fib or VTE Phase 3 studies.

Interstitial Lung Disease:

As noted above (**Table 12**), the interstitial lung disease (ILD) SMQ had more fatal events with edoxaban than warfarin. There were also more ILD SAEs in the ILD SMQ with edoxaban: 4, 8, and 0 cases in the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively, after exclusion of cases that appeared not to be true ILD (such as associated with acute respiratory distress or use of amiodarone). The median time to onset of the ILD SAE was 292 days (range 59 to 744 days). Half of the ILD cases with edoxaban occurred in patients with a baseline history of ILD (6 of 124, (5%)) compared to 6 cases in the 13,890 patients with no history of ILD (0.04%). Of note, ILD has been reported with rivaroxaban, but that finding seemed largely limited to Japanese patients, and is not mentioned in US labeling. However, in ENGAGE most of the cases of ILD SAEs involved Caucasians and were not reported from Japan. This finding should be mentioned in Sec. 6.

Macular Degeneration:

Late in the review cycle Dr. Unger notified us that he had seen a signal for macular degeneration and related terms (MD): 6 cases in the edoxaban 30 mg arm (4 of these patients

received 15 mg, 3 in the edoxaban 60 mg arm (all received 60 mg), and 1 in the warfarin arm. If the edoxaban arms are pooled, this is a 4.5:1 signal. There seems to be no dose response.

Dr. McDowell followed up with her own evaluation. She found 10 SAEs of MD during the overall study period. Four of these were on treatment, and 3 more occurred within 30 days of the last dose. These 7 cases are highlighted in the table below.

Table 17 SAEs of Macular Degeneration or Related Terms

USUBJID	ACTARM	DOSE	AGE	SEX	AEDECOD	AESEV	ONTRT	ON30TRT	Outcome	Baseline
DU176b-17590020	Edoxaban 60mg (30mg DosAdj)	60 mg	80	M	MACULAR OEDEMA	MODERATE	1	1	Recovered/ Resolved	0
DU176b-19100061	Edoxaban 30mg (15mg DosAdj)	15 mg	79	F	MACULAR DEGENERATION	MODERATE	.	.	Recovered/ Resolved	0
DU176b-33040023	Edoxaban 60mg (30mg DosAdj)	60 mg	78	M	AGE-RELATED MACULAR DEGENERATION	SEVERE	.	.	Not Recovered/ Not Resolved	0
DU176b-33130006	Edoxaban 30mg (15mg DosAdj)	30 mg	82	M	MACULAR FIBROSIS	MILD	1	1	Recovered/ Resolved	0
DU176b-42070002	Edoxaban 30mg (15mg DosAdj)	30 gm	79	M	MACULAR FIBROSIS	MODERATE	.	1	Recovered/ Resolved	0
DU176b-49060011	Edoxaban 60mg (30mg DosAdj)	60 gm	75	M	AGE-RELATED MACULAR DEGENERATION	MODERATE	.	1	Recovered/ Resolved	1
DU176b-50220004	Warfarin	-	81	M	MACULAR DEGENERATION	MODERATE	.	.	Recovered/ Resolved with Sequelae	0
DU176b-58030001	Edoxaban 30mg (15mg DosAdj)	15 mg	73	F	MACULOPATHY	MODERATE	.	1	Recovered/ Resolved	0
DU176b-61570002	Edoxaban 30mg (15mg DosAdj)	15 mg	79	M	AGE-RELATED MACULAR DEGENERATION	MODERATE	1	1	Recovered/ Resolved	1
DU176b-61640009	Edoxaban 30mg (15mg DosAdj)	15 mg	62	M	MACULAR HOLE	MODERATE	1	1	Recovered/ Resolved	0

ACTARM: As treated; DosAdj: Dose adjusted DJ
ONTRT: On treatment; ON30TRT: On treatment + 30 days; Baseline: Macular degeneration resent at baseline; 1: Y 1: YES; 0: NO
Highlighted cases occurred on treatment or within 30 days of the last dose of study drug.

Note that when cases with onset outside of last dose of study drug + 30 days are excluded, the count is 7 for edoxaban and 0 for warfarin. Only 2 cases occurred in a patient with MD at baseline. Of the 7 cases that occurred in the on treatment + 30 day period, all but one occurred after at least one year of treatment with edoxaban. The exception was patient no. 33130006. This was an incident case of "mild" macular fibrosis in an 82 year old man that was picked up after 50 days of treatment with edoxaban 30 mg (not dose adjusted). The timing suggests the possibility that macular fibrosis may have been present at baseline and not picked up. If this patient is excluded, the imbalance would be 6 vs. 0 serious AEs of macular degeneration or related conditions in the pooled edoxaban arms vs. warfarin.

At baseline, there was an imbalance of patients with MD, with a higher rate for warfarin: 62, 63, and 75 patients in the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively. However during the study, the number of AEs (serious + non-serious) was 31, 43, and 28 in the edoxaban 30 mg, edoxaban 60 mg and warfarin arms respectively. By the end of the study, the count of patients with a history of MD (including baseline cases and new cases arising during the study) was 86, 96 and 101. While this type of analysis may or may not be valid, the difference in the number new cases is not very unlikely to be due to chance. The number of

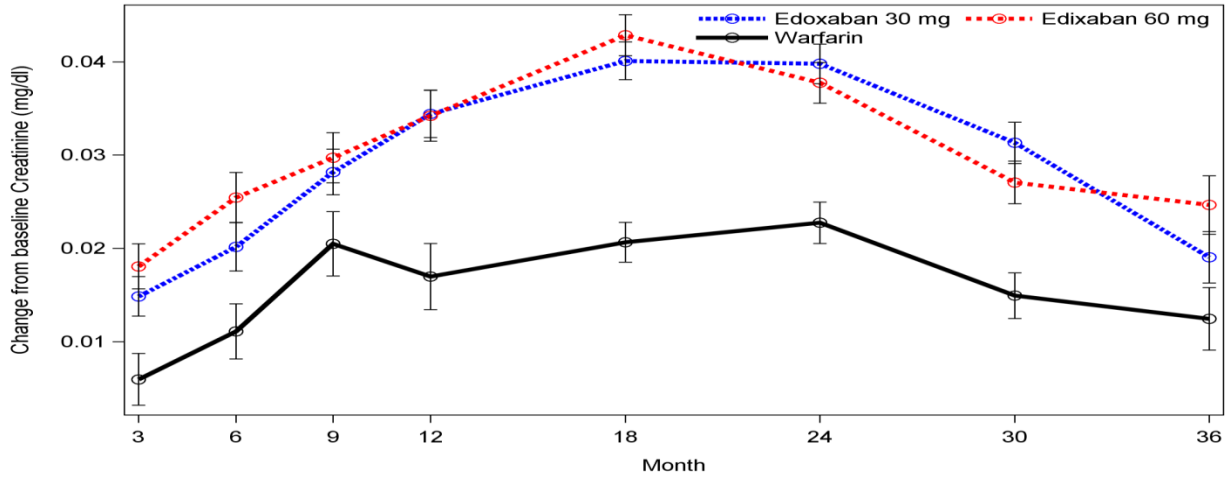
incident cases during the study (regardless of end of treatment) was 23, 33 and 26 in the placebo and vorapaxar arms, respectively. There is little difference between warfarin and the edoxaban 60 mg arm. However, the imbalance in serious AEs on treatment suggests that this AE should be flagged for post marketing follow-up.

Increased Serum Creatinine

Clinical laboratory data show that compared to warfarin, patients in both edoxaban arms had similar (i.e., there was no dose response), consistent and small increases in serum creatinine concentration from baseline compared to warfarin, on the order of 0.01 to 0.02 mg/dL, starting at month 3 (the first on-treatment blood draw for creatinine) and lasting until the end of the study (**Figure 12**). At month 18, the 95% CI of the increase from baseline was 0.036 to 0.044 mg/dL. The resulting decrease from baseline in creatinine clearance (Cockcroft-Gault) compared to warfarin was about 1.0 to 1.5 mL/min (data not shown). There are insufficient data to determine whether this change in serum creatinine compared to warfarin resolved after study drug was discontinued.

Shift tables for serum creatinine showed slightly more upward shifts for the 2 edoxaban arms than for warfarin, but again with no edoxaban dose response (**Table 18**). However, there was no AE signal indicating an increased risk of renal failure.

Figure 12 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 18 Changes from Baseline 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.

The mechanism for the increase in serum creatinine levels is not known, but the observed pattern is consistent with inhibition of active creatinine transport in renal tubular cells. A recent publication indicates that the transporters OAT2, OAT3, OCT2, OCT3, MATE1 and MATE2-K are involved in the active transport of creatinine into the urine.(2) Dr. Yang's preclinical review indicates that edoxaban does not produce meaningful inhibition of OCT2, but its effects on the other transporters listed above were not assessed.

The small upper limit of the 95% CI for change from baseline in serum creatinine (0.044 mg/dL) and the minimal difference from warfarin in terms of categorical increases in serum creatinine suggests that this finding is not medically important and should not be mentioned in labeling.

8. Advisory Committee Meeting

A meeting of the CRDAC was held on October 30, 2014 regarding edoxaban. The focus of the meeting was the interaction of efficacy and renal function. The Applicant argued for approval based on their proposed labeling, with dosing instruction nearly identical to those for patients randomized to the 60 mg arm, i.e., 60 mg OD for all except those who qualified for dose reduction. The Applicant argued that the reduced efficacy observed in patients with normal renal function was a chance result. We made arguments consistent with the views expressed in this review. We indicated our belief that the only issue complicating approval was the renal subgroup findings, and if not for that issue, we would support approval with dosing recommendations that were similar to the Applicant's recommendations for patients with normal or mildly impaired renal function

Regarding the key discussion items and vote for approval, the AC members had the following views:

- 3 AC members thought the reduced efficacy in patients with normal renal function was due to chance, while 6 did not.

- Most AC members were not comfortable with exposure matching in patients with normal renal function, which would result in a dose higher than any dose used in Phase 3.
- The vote regarding approval was 9 in favor, and 1 against. The No vote came from Dr. Rich, who seemed most concerned about selecting a dose for a patient with fluctuating renal function.
- Members who voted to approve were asked to select options regarding dosing as follows:
    (a) Approval of the 60-mg dose for patients with normal or mildly impaired renal function. (5 in favor)
    (b) Approval of a dose higher than 60 mg for patients with normal renal function. (2 in favor)
    (c) Approval only for patients with mild and moderate renal impairment. (2 in favor)

  The most frequent pick was (a), but most and perhaps all members who selected (a) later added that labeling should describe the results of the renal function subgroup analysis.

9. Other Regulatory Issues

(b) (4)

10. Financial Disclosure

No issues.

11. Labeling:

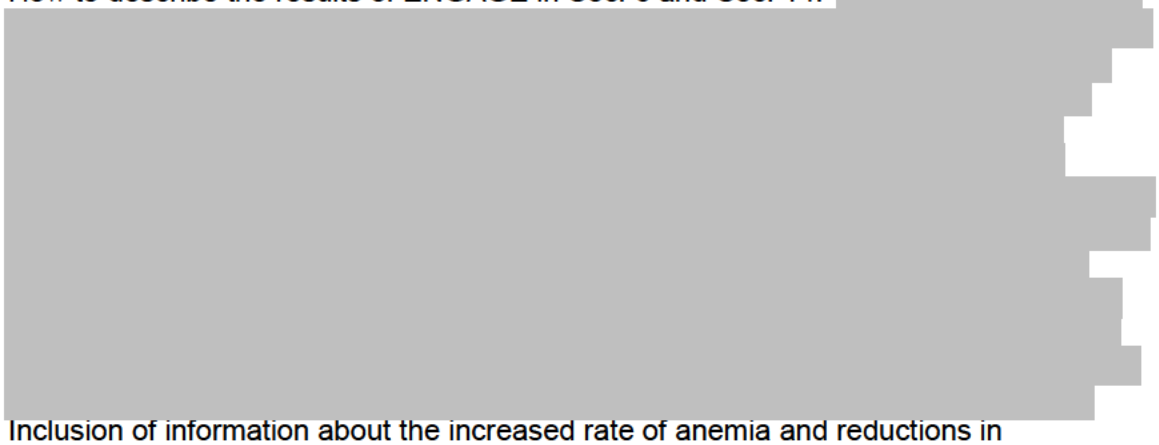
The Applicant, (b) (4)

(b) (4)

OCP is taking the lead in responding to the Applicant on this issue.

Additional labeling issues are:

1. Whether and how to communicate the increased risk of ischemic stroke associated with use of 60 mg daily (b) (4)

2. How to describe the results of ENGAGE in Sec. 6 and Sec. 14. (b) (4)

3. Inclusion of information about the increased rate of anemia and reductions in hemoglobin with edoxaban 60 mg compared to warfarin. This, along with the issue immediately above, may affect how the comparison to warfarin in the rate of major bleeding is described in Sec. 6.
4. Inclusion of information relating to inhibition of thrombin activity in the description and possibly elsewhere
5. Labeling changes requested by Dr. Yang in 8.1 (Pregnancy), 8.2 (Labor and Delivery), and 8.4 (Pediatric Use).

12. DSI Audits

There are no issues barring approval relating to DSI audits.

Sites to be audited by DSI were based on relatively high enrollment and several other factors, including high favorable effect size, high or low rate of death, high or low rate of discontinuation, and high or low bleeding or AE rates. Five clinical sites were inspected. The Oct. 28 review from Dr. Gershon indicates that all inspected sites were NAI or preliminary NAI.

The sponsor was inspected as well. The results were VAI. A 3 items 483 was issued for the following:

1) Failure to ensure the study is conducted in accordance with the protocol and investigational plan.
   a) The sponsor failed to follow the Clinical Events Committee (CEC) Charter, Data Monitoring Committee (DMC) Charter, and Academic Contract Research Organization (ACRO) agreement during the adjudication process. The issue was that copies of all the independent adjudications were not retained – only the final form with the adjudications final decision. We told DSI this was non-significant. DS will revise their procedures to keep all adjudication forms.
   b) The Sponsor failed to ensure the CEC organizational meeting was held, as required by the protocol and CEC Charter. The Sponsor indicated that the meeting was held but that no minutes were taken.
   c) The Sponsor failed to ensure all CEC members updated their financial disclosure agreements annually, as required. The Sponsor later indicated that through an oversight updated forms were not collected in 2010, but were collected in other years.

2) Failure to notify FDA of the termination, for-cause, of an investigator's participation in an investigation. This involved one site with "serious GCP non-compliance issues." All other closures were reported.

3) Lack of records covering receipt, shipment to investigators, and disposition of investigational drug. This involved 3 known sites. The sponsor indicated that they would change their Scope of Work templates to assure future compliance.

However, Dr. Gershon states that "data from this site appear acceptable." I agree.

13. Recommended Regulatory Action

I recommend approval, with recommended doses of 30, 60 (b) (4) once daily for subjects with creatinine clearance of 15 to 50 mL/min, > 50 to < X, (b) (4) respectively, where X is to be determined but is in the range of 80 to 90 mL/min. (b) (4)

Labeling for the most important risk of edoxaban, pathological bleeding, should be similar in style that of other NOACs. There should be prominent language regarding the renal function subgroup findings (b) (4)

(b) (4)

(b) (4)

(b) (4)

No REMS or post-marketing studies are envisioned at this time. However, OSE should be asked to assess post-marketing reports and possibly observational data regarding the rate of macular degeneration in patients taking edoxaban compared to control agents.

Reference List

1. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am.J.Cardiol. 2013 Oct 15;112(8):1142-7

2. Lepist EI, Zhang X, Hao J, Huang J, Kosaka A, Birkus G, Murray BP, Bannister R, Cihlar T, Huang Y, et al. Contribution of the organic anion transporter OAT2 to the renal active tubular secretion of creatinine and mechanism for serum creatinine elevations caused by cobicistat. Kidney Int. 2014 Aug;86(2):350-7. PMCID:PMC4120670

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/s/

MARTIN ROSE
12/09/2014