CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206316Orig1Orig2s000

MEDICAL REVIEW(S)

Division of Cardiovascular and Renal Products

Addendum to Clinical Review (Efficacy section): Additional Analyses

NDA: 206316

Drug: Edoxaban

Applicant: Daiichi Sankyo

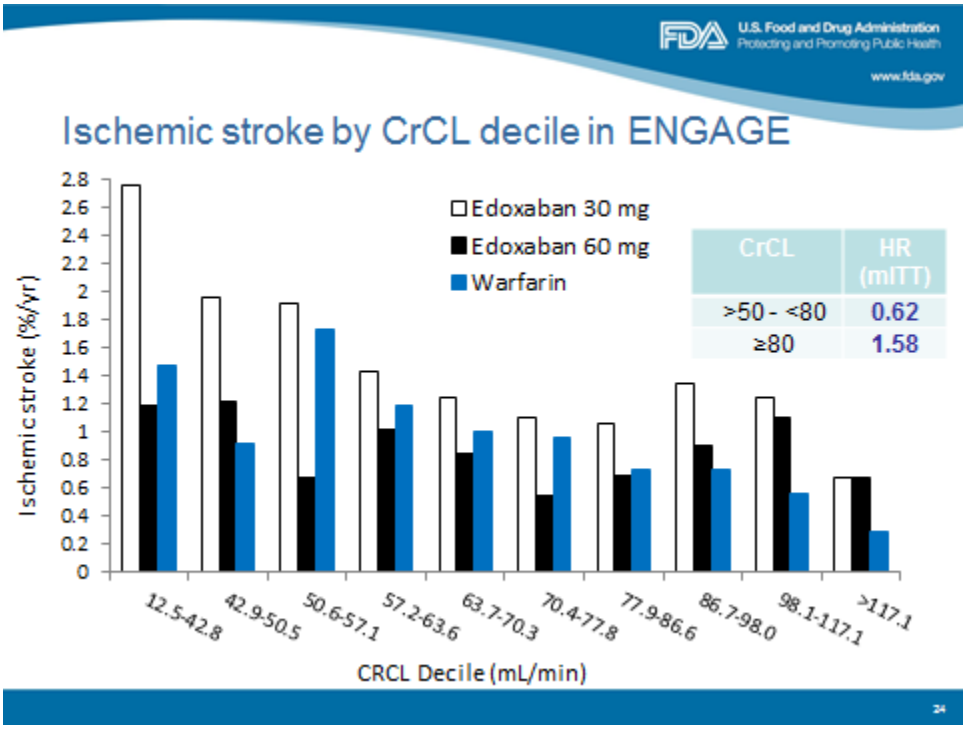
Clinical Reviewers: Melanie J. Blank, MD, and Tzu-Yun McDowell, PhD

Team Leader: Martin Rose, MD

Date: 1/13/2015

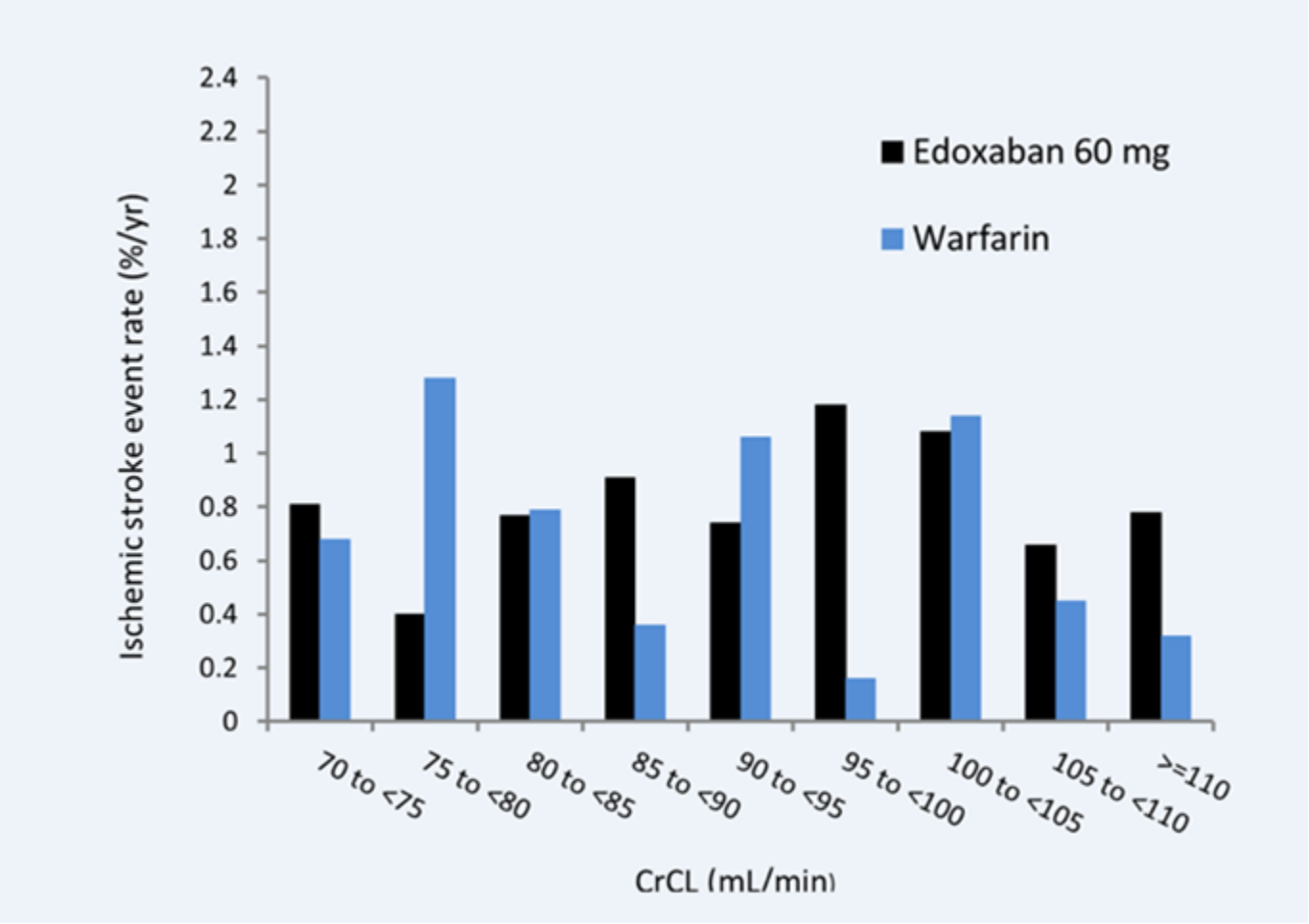
In order to further our understanding of the decline in efficacy of edoxaban relative to warfarin for prevention of ischemic stroke as renal function improved in ENGAGE AF-48-TIMI, we calculated the ischemic stroke event rate by renal function decile. The analysis which is shown in figure 1 was done in the mITT population on treatment [to Clinical Study End Date (CSED) or last day of drug + 3 days]. It is apparent from the figure that the ischemic stroke rate for edoxaban was higher than for warfarin once the CrCL increased over 86.7 mL/min.

Figure 1: Ischemic Stroke by CrCL decile in ENGAGE AF-48-TIMI (mITT, on Treatment)



Displayed in Figure 2 is a similar analysis except that CrCLs were divided by increments of 5 mL/min. Here the ischemic stroke rate starts to look worse than warfarin at a CrCL of ~ 95 mL/min.

Figure 2: Ischemic Stroke by 5 mL/min increments in CrCL in ENGAGE AF-48-TIMI (mITT, on Treatment)



The applicant claimed that warfarin performed exceptionally well in those subjects and that accounts for the pattern. This was not the case, as shown in Table 1. Notice that when comparing ITT populations (overall study period), the warfarin stroke/SEE event rate was approximately 1.0%/year in all trials except ROCKET AF, which enrolled a sicker population than other pivotal NOAC trials.

Table 1: Warfarin Stroke/SEE event rate in the normal renal function subgroups in pivotal NOAC trials

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Warfarin Stroke/SEE event rates in the normal renal function subgroup in pivotal NOAC trials

	Warfarin stroke/SEE rate (%/yr)		
Trial	Normal Renal Function A	Mild renal impairment B	Decrease in event rate from B to A
RE-LY; dabi vs. warfarin (ITT, overall study period)	1.03	1.87	45%
ROCKET AF; riva vs. warfarin (per-protocol, on-treatment)	1.42	2.41	41%
ARISTOTLE; apix vs. warfarin (ITT, overall study period)	1.12	1.69	34%
ENGAGE AF; edox vs. warfarin (mITT, on-treatment)	**0.76**	2.01	62%
ENGAGE AF; edox vs. warfarin (ITT, overall study period)	**0.98**	2.19	55%

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The above analyses together supported the decision to approve edoxaban (Savaysa) only for patients with CrCL < 95 mL/min.

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/s/

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01/13/2015

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01/15/2015

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS AND OFFICE OF DRUG EVALUATION I

Memorandum

NDA: 206316 Edoxaban tosylate (Savaysa) and others

Review date: 13 November 2015

From: Norman Stockbridge, M.D., Ph.D., Director, DCaRP
Mary Ross Southworth, Pharm.D., Deputy Director for Safety, DCaRP
Robert Temple, M.D., Deputy Director, ODE-I
Ellis Unger, M.D., Director, ODE-I

Regarding: Potential for anticoagulant, antiplatelet, and angiotensin receptor blocking (ARB) drugs to cause cancer.

On 12 December 2014, Dr. Thomas Marciniak filed a 347-page review to the following applications:

Application	Brand	Drug	Application	Brand	Drug
NDA 009218	Coumadin	Warfarin	NDA 202155	Eliquis	Apixaban
NDA 20839	Plavix	Clopidogrel	NDA 202439	Xarelto	Rivaroxaban
NDA 21686	Exanta	Ximelagetran[1]	NDA 204866	Zontivity	Vorapaxar
NDA 22307	Effient	Prasugrel	NDA 206316	Savaysa	Edoxaban
NDA 22433	Brilinta	Ticagrelor	TSI 1361		Clopidogrel
NDA 22512	Pradaxa	Dabigatran			

In addition to the above applications, the entire 347-page review is appended to a review that Dr. Marciniak filed to NDA 206143 (Corlanor; ivabradine) on 17 December 2014, and elements of this review appear in a review that Dr. Marciniak filed to NDA 207620 (Entresto; sacubitril plus valsartan) on 28 December 2014.

Dr. Marciniak's review concludes that anti-platelet drugs (clopidogrel, prasugrel, ticagrelor, vorapaxar) and newer anticoagulant drugs (dabigatran, apixaban, rivaroxaban, edoxaban) all potentially cause cancer. It also repeats assertions from a previous review that ARBs cause cancer. Before discussing the specific content of his review, let us note some unusual features related to process:

1. With rare exception, Division reviews are performed on assigned work. This review is unusual in that none of the applications to which it was originally filed was assigned to Dr. Marciniak.
2. Most reviews address a specific application before the Agency—a New Drug Application (NDA), a Biologics License Application (BLA), an Investigational New Drug exemption (IND), or a Tracked Safety Issue (TSI)—so this review is unusual in pertaining to numerous drugs spanning several pharmacological classes.
3. Most reviews involve a collaborative effort among staff members with specialized expertise relevant to the material at hand. As needed, this specialized expertise might include a pharmacologist or toxicologist to review carcinogenicity, a medical

[1] *Never approved.*

officer (like Dr. Marciniak) to review clinical findings, and a statistician or pharmacometrician to explore relationships between exposure to a drug and clinical events. This review was unusual in its lack of involvement or collaboration with other staff with potentially critical expertise.

4. Reviews of this magnitude almost always involve discussions with more senior managers, intended to enrich the perspectives on the work through constructive feedback and dialog. This review was unusual in that no one senior to Dr. Marciniak in either the Division or ODE-I was given the opportunity to discuss the review with Dr. Marciniak in advance of, or subsequent to, its being finalized and filed. We wish to emphasize that, in bypassing management in this manner, Dr. Marciniak was not avoiding censure or being ordered to desist. As Dr. Marciniak knew well, he had the right to present his own perspectives on the matter at hand, and, if he were unhappy with management's opinions or handling of his concerns, he knew he had the opportunity to appeal the Division's decision to ODEI, ODEI's decision to OND, and OND's decision to the CDER Center Director. We note, too, that scientific disagreements within the Office of New Drugs are not unexpected, and the normal review and appeal process ensures that each professional viewpoint has been fully developed, understood, and considered.

5. Because the new drug applications to which he filed his review were not assigned to him, his review was unexpected, and in many cases filed without knowledge of the team actually assigned to review the new drug.

6. Important endpoints in clinical trials are often adjudicated, typically by a committee of experts who make judgments based on standard criteria defined in a manual. For example, judgments on whether a patient had a heart attack, stroke, or a hospitalization for a particular medical condition, are often adjudicated by a committee of experts. CDER policy[2] is that reviewers should survey the adjudication process to form an opinion as to the reliability of the process and the conclusions reached. Reviewers are strongly discouraged, however, from undertaking the wholesale readjudication of data as Dr. Marciniak did here, but particularly in an unblinded fashion. When problems are uncovered, the matter is expected to be referred back to the applicant to have blinded readjudication performed by experts, based on pre-defined criteria.

   Much of Dr. Marciniak's review is based on his view as to whether particular adverse events reported in clinical trials constituted evidence of cancer progression. Dr. Marciniak made such decisions by himself, with full knowledge of treatment assignment (i.e., without blinding). We have not been able to verify the particular counts of cancer events that Dr. Marciniak reported.

What then is Dr. Marciniak's thesis? The review consists of 347 pages as follows:

Pages 1-63	Body of the review
Pages 64-250	Slides produced by HCRI with preliminary analyses of the DAPT study, dated 22 August, 5 September, 17 September, and 24 October 2014
Pages 251-290	A review filed to TSI 935 by Dr. Marciniak of ARBs and cancer, dated 7 March 2013
Pages 291-346	Dr. Marciniak's analysis plan for ARBs and cancer, dated 18 August

[2] *MaPP 6010.3, published in 2010 and available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM229716.pdf.*

	2012.
Page 347	Electronic signature

Dr. Marciniak summarizes his concerns in the paragraph preceding his recommendations:[3]

> *"I conclude that the totality of evidence strongly supports that prolonged thienopyridine use is associated with increased rates of solid cancers, at least in patients undergoing invasive procedures. The evidence also suggests that the association is not limited to inhibition of the $P2Y_{12}$ receptor but extends to the PAR-1 receptor. The totality of evidence also supports that excess bleeding from higher anticoagulant dosing also increases the risk of solid cancers. Hence the increased solid cancer risk appears to be related to inhibition of coagulation and not inhibition of a particular receptor or use of a particular drug, i.e., it is a "class" effect. I provide recommendations below based on these conclusions as well as my observations regarding trial conduct problems in the 23 trials analyzed."*

As background, we note that Dr. Marciniak's reviews focus mainly on two distinct types of drugs: anti-platelet drugs and anti-coagulants. Thienopyridines (clopidogrel, prasugrel) are anti-platelet drugs of a particular structural class; they block the $P2Y_{12}$ receptor in platelets. In so doing, they have benefit in preventing blood clots leading to heart attacks, but they also exacerbate bleeding. Vorapaxar is a different type of anti-platelet drug that blocks the PAR-1 platelet receptor. Although voraxapar differs in structure from the thienopyridines and blocks a different platelet receptor, it has a similar indication and similar effects on bleeding.

Anticoagulants are entirely distinct from anti-platelet drugs, both structurally and functionally. They interfere with the non-cell-based blood coagulation process. They fall into several structural classes, and, among other things, are approved to prevent strokes in patients with non-valvular atrial fibrillation. Despite the marked differences between anti-platelet drugs and anti-coagulants, they share the propensity to worsen bleeding.

In brief, his thesis is that drugs that worsen bleeding somehow worsen the risk of cancer—not a specific type of cancer or a related group of cancers, but all types.

In addition, Dr. Marciniak holds the belief that angiotensin receptor blockers (ARBs), a completely unrelated class of drugs, increase the risk of cancer.

Here we will address most of the issues Dr. Marciniak raises with regard to the potential for antiplatelet drugs, anticoagulants, and ARBs to increase the risk of cancer.

In the quoted paragraph, Dr. Marciniak refers to "23 trials analyzed." The body of the memo discusses his findings from the following studies:

Study	**Comparison**
ACTIVE-A	Clopidogrel vs. aspirin
ACTIVE-W	Clopidogrel vs. warfarin
APPRAISE	Apixaban vs. warfarin

[3] *Page 8.*

ARISTOTLE	Apixaban vs. warfarin
ATLAS	Rivaroxaban vs. placebo
AVERROES	Apixaban vs. aspirin
CAPRIE	Clopidogrel vs. aspirin
CHARISMA	Clopidogrel vs. placebo
CREDO	Clopidogrel vs. placebo
CURE	Clopidogrel vs. placebo
DAPT	Clopidogrel or prasugrel vs. placebo
ENGAGE	Edoxaban vs. warfarin
J-ROCKET	Rivaroxaban vs. warfarin
PLATO	Ticagrelor vs. clopidogrel
PRoFeSS	Clopidogrel vs. aspirin
RE-LY	Dabigatran vs. warfarin
ROCKET	Rivaroxaban vs. warfarin
SPORTIF III	Ximelagatran vs. warfarin
SPORTIF V	Ximelagatran vs. warfarin
SPS3	Clopidogrel vs. placebo
TRA2P	Vorapaxar vs. placebo
TRACER	Vorapaxar vs. placebo
TRILOGY	Prasugrel vs. clopidogrel
TRITON	Prasugrel vs. clopidogrel

The Marciniak review was filed shortly before the Division Director memo (22 December 2014) and Office memo (8 January 2015) documenting the action for edoxaban. His review was not expected and went unnoticed by the review team. Thus, his review was not discussed in our memos documenting our regulatory decision on that application. Before discussing Dr. Marciniak's general concern about cancer in patients treated with anti-platelet and anticoagulant drugs, we briefly address edoxaban, which is mentioned in the first summary paragraph of Dr. Marciniak's review:

> *The most recent submission for a new anticoagulant, edoxaban, is typical in providing, by itself, suggestive but not conclusive evidence for the association [with cancer].*[4]

The "suggestive" data are further described in Table 15[5] (reproduced below), which gives Dr. Marciniak's estimated relative risk estimate from his counts of cancers in ENGAGE, a study that compared edoxaban (two dose levels) and warfarin. The data show [6] (RR) =

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[4] *Page 1.*

[5] *Page 37.*

[6] *"Relative risk", i.e., how many times more likely some experimental intervention is to cause an event (in this case, cancer) than is some control.*

1.0 with 95% confidence interval (CI) of 0.9-1.1; i.e., there is no evidence of any overall effect on cancer in ENGAGE, at least compared with warfarin.

Warfarin is an anticoagulant that causes at least as much bleeding as edoxaban does, so that there is no plausible reason, given Dr. Marciniak's hypothesized relationship, to expect a higher rate of cancer with edoxaban; indeed, the rate should be lower. As Table 15[7] clearly shows, solid cancer rates were not increased compared with warfarin for any of the newer anticoagulants.

Table 15: New Oral Anticoagulant Outcome Trials 2

New oral anticoagulant	rivaroxaban	dabigatran	edoxaban	ximelagatran	
Trial	J-ROCKET	RELY	ENGAGE	SPORTIF III	SPORTIF V
Dates randomized	06/07-11/08	12/05-12/07	11/08-11/10	08/00-09/01	08/00-12/01
Population	afib	afib	afib	afib	afib
N	1,280	18,113	21,105	3,407	3,922
Age, median y	72	72	72	71	73
Male	80%	64%	62%	69%	69%
Invasive	NA	NA	NA	NA	NA
Control	warfarin	warfarin	warfarin	warfarin	warfarin
Clopidogrel use	NA	6%	2.3%	0%	o%
Aspirin use	38%	40%	30%	12%	18%
Follow-up, median m	19	24	34	15	20
New drug discontinuation	26%	24%	34%	18%	37%
Complete follow-up	90%	91%	90%	88%	83%
Died	1.8%	7.6%	10.8%	4.4%	6.1%
Major/severe bleed RR	0.9	0.9	0.7	0.7	0.7
95% CI	0.5-1.4	0.8-1.0	0.6-0.8	0.5-1.1	0.5-1.0
Solid cancer RR	0.9	1.1	1.0	1.0	0.8
95% CI	0.5-1.7	0.9-1.3	0.9-1.1	0.7-1.5	0.6-1.1
Solid ca/100 PEY (control)	1.9	2.1	1.7	1.8	2.7
Non-CV death RR	0.3	1.0	1.0	0.7	0.7
95% CI	0.1-1.4	0.8-1.2	0.9-1.2	0.4-1.3	0.5-1.1
Died with solid ca RR	1.0	0.9	1.1	1.3	0.7
95% CI	0.1-16	0.7-1.2	0.9-1.4	0.6-3.2	0.4-1.3
Died %, solid ca pts (control)	5%	32%	30%	21%	30%

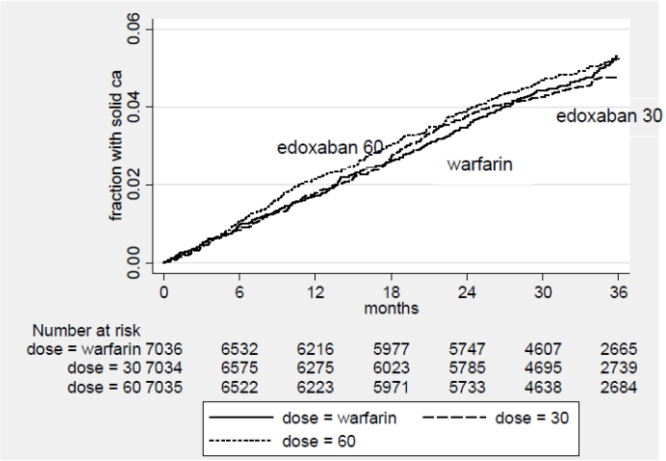
PEY = person exposure year; RR = risk ratio new drug/control; CI = confidence interval

Despite there being no overall effect, Dr. Marciniak goes on to analyze the two doses of edoxaban in ENGAGE separately in Figure 28[8] (reproduced below), which again shows no evidence of a difference.

[7] *Page 37.*

[8] *Page 53.*

Figure 28: Solid Cancer Event Incidence in ENGAGE



Having found no effect for pooled doses and no effect by dose, Dr. Marciniak finds four specific cancer types (colon, esophageal, lung, and pancreas) whose analyses by dose "appear to be informative."[9] He does not list all cancers and does not give p-values for any of the 8 comparisons (two doses and four cancer types) he finds "informative." He also tells us nothing about other cancer types, so you cannot tell whether these trends are likely to be chance. Nor does he mention other cancers for which there were trends for lower rates on edoxaban (which there surely were, given the overall RR of 1.0).

Dr. Marciniak does not mention the detailed clinical review[10] of record for edoxaban by Drs. Blank and McDowell. This review was considered in the approval of Savaysa, and it was available to Dr. Marciniak, too. Drs. Blank and McDowell looked specifically at malignancy in the edoxaban development program, both as adverse events specific to cancer types as reported by the investigator and through broader groupings called Standardized MedDRA Queries. For the most part, the reviewers saw the absence of risk overall as reassuring, but they did tabulate cancers by type, and we show the complete list of cancer event rates from that review[11] below:

[9] *Page 53.*

[10] *Dated 10 October 2014*

[11] *Page 210 of NDA Clinical Review by Drs. Blank and McDowell, dated 10 October 2014*

Table 96 Investigator Reported Clinically Evident Post Randomization Malignancies by Location, overall study period

Malignancies Category/Location	Edoxaban 30mg (15mg DosAdj) (N=7002)		Edoxaban 60mg (30mg DosAdj) (N=7012)		Warfarin (N=7012)	
	n	Event Rate (%/yr)	n	Event Rate (%/yr)	n	Event Rate (%/yr)
Any Location	463	2.50	494	2.68	485	2.64
Skin[a]	150	0.80	178	0.95	163	0.87
Small or Large Bowel	51	0.27	52	0.27	60	0.32
Lung	44	0.23	50	0.26	40	0.21
Prostate	48	0.41	48	0.41	53	0.45
Bladder	29	0.15	32	0.17	29	0.15
Breast	21	0.11	25	0.13	27	0.14
Stomach	15	0.08	19	0.10	20	0.11
Other	23	0.12	17	0.09	17	0.09
Pancreatic	16	0.08	16	0.08	10	0.05
Esophageal	13	0.07	14	0.07	4	0.02
Multiple	3	0.02	13	0.07	11	0.06
Liver, Gall Bladder, or Bile Ducts	18	0.09	10	0.05	17	0.09
Lymphoma	6	0.03	10	0.05	8	0.04
Lip, Oral, Pharynx	15	0.08	9	0.05	9	0.05
Uterine	7	0.09	8	0.11	6	0.08
Leukemia	12	0.06	6	0.03	13	0.07
Renal	8	0.04	6	0.03	12	0.06
Thyroid	1	0.01	6	0.03	2	0.01
Brain	6	0.03	5	0.03	8	0.04
Genital	3	0.02	3	0.02	8	0.04
Other Respiratory (Excluding Lung)	1	0.01	2	0.01	1	0.01
Unspecified	8	0.04	2	0.01	4	0.02

Source: CSR Table 12.25

We see confirmation that the overall event rates are similar on warfarin and edoxaban, at about 2.6%/year. Of the cancer types Dr. Marciniak highlighted, we see similar rates on warfarin and edoxaban for small and large bowel cancer (0.3%/year), lung (0.2%/year), pancreas (<0.1%/year), and esophagus (<0.1%/year). While some of these cancers trend higher on edoxaban than warfarin, both doses of edoxaban look better than warfarin for prostate, breast, stomach, leukemia, renal, brain, and genital cancers. Dr. Marciniak not remark upon these trends that appear to favor edoxaban and run contrary to his thesis. In our view, these data are all consistent with there being no overall effect of edoxaban on cancer. With no difference overall between edoxaban and warfarin, in order to believe that edoxaban causes certain cancers (compared to warfarin), one would have to believe that edoxaban prevents other cancers, or that edoxaban causes some cancers and warfarin causes others. Clearly, this is not plausible or rational.

Moreover, as noted, if one's theory was that cancer risk related to bleeding, then it is not clear to us why one would expect there to be any increased risk of a novel anticoagulant compared with warfarin, because warfarin and these other anticoagulants cause similar rates of bleeding.

We conclude there is no evidence for an increased risk of cancer with edoxaban. Dr. Marciniak's basis for finding the evidence "suggestive" is not apparent to us.

Dr. Marciniak's recommendations

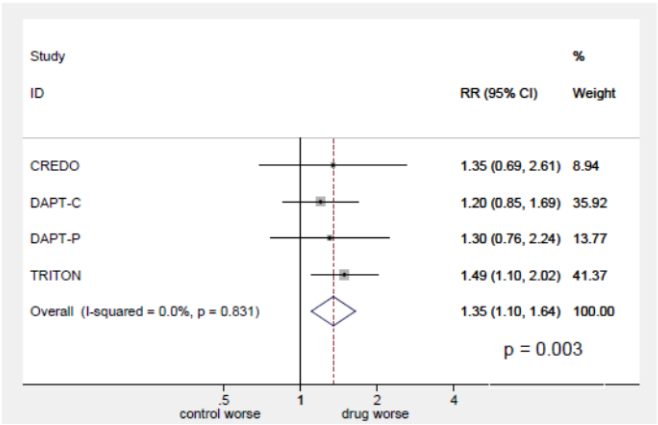
Dr. Marciniak makes a series of specific recommendations[12] reflecting his conclusions about drugs that increase the risk of bleeding and cancer, and we address below the arguments he poses in support of those recommendations:

1. *"The FDA should provide practitioners and patients with the data regarding the association between bleeding and solid cancers as soon as possible."* He goes on (his item 2) to suggest methods of communication, including a safety communication, posting his review, and holding an Advisory Committee meeting covering this topic and ARBs and cancer (see below). All of his recommendations depend on a conclusion that the data do indeed suggest that the bleeding/cancer relationship is credible. We address "bleeding and solid cancers" first, and then discuss "ARBs and cancer."

   Although one might reasonably address such a hypothesis by looking at all relevant studies of antiplatelet and anticoagulant drugs together, Dr. Marciniak does not do that. He first discussed the antiplatelet drugs, so we do too.

   With regard to thienopyridines and cancer, Dr. Marciniak provides this meta-analysis:[13]

Figure 1: Meta-Analysis of Solid Cancer Events in the Thienopyridine Trials with Substantial Invasive Approach and for Which the FDA Has Cancer Data



   Although there are many other thienopyridine studies, Dr. Marciniak opted to show pooled data representing only four comparisons from three studies: clopidogrel vs. placebo in CREDO, 12- vs 30-month treatment in the clopidogrel subset of DAPT, 12- vs. 30-month treatment in the prasugrel subset of DAPT, and clopidogrel vs. prasugrel in TRITON. Note that in TRITON, we are comparing two drugs with quite similar rates of bleeding, so, if the bleeding were predictive of cancer, the rates of cancer should be most similar for this study.

   His decision to limit his meta-analysis to studies for which data were available might have been reasonable and unbiased, but he stated that he restricted his analysis to studies "with substantive invasive approach." Such a restriction is odd, and does not seem relevant to his hypothesis. Here is how he explains it:[14]

   > *"The results of the antiplatelet drug trials without a substantial invasive approach contrast with those shown in Figure 2. The older*

[12] *Pages 8-10.*

[13] *Page 2.*

[14] *Page 5*

> *non-invasive clopidogrel trial results do not support a relationship between clopidogrel use or bleeding and solid cancers. All trials had study limitations that I discuss in the Clopidogrel and Cancer section that limit their validity. Prasugrel TRILOGY in medically managed ACS is similarly negative, although TRILOGY, like PLATO, had serious conduct problems. Vorapaxar TRA2P, a very large trial in high risk patients, was neutral for solid cancers and non-CV deaths despite substantially higher bleeding in the vorapaxar arm. However, TRA2P had a design flaw similar to the ones in the two large clopidogrel studies (CAPRIE and CHARISMA) that also produced neutral results: CAPRIE did not count adverse events (AEs) more than 28 days after study drug discontinuation; CHARISMA defined AEs as occurring within 28 days of treatment discontinuation; and TRA2P did not solicit AEs that occurred more than 60 days after the last dose."*

We note that the Figure 2[15] to which Dr. Marciniak refers shows nothing relevant to this question, nor does any other figure in this review. Instead we see a series of excuses for excluding studies for a variety of reasons—perceived "study limitations," design, conduct, or analysis issues—none of which have anything to do with an "invasive approach" and none of which bias against finding an effect of treatment on cancer. All share the common feature of failing to support his hypothesis—the purported association with cancer. We note that, with the nominal results at his disposal, Dr. Marciniak knew the implications of his decisions to include or exclude various studies on the results of his meta-analyses. We describe below the cancer findings for the 5 studies mentioned above that Dr. Marciniak specifically discounts as not being credible—TRILOGY, PLATO, TRA2P, CAPRIE, and CHARISMA.

TRITON vs. TRILOGY

Three of the comparisons incorporated in Figure 1 are against placebo, but TRITON compared prasugrel with clopidogrel. Because prasugrel and clopidogrel caused similar rates of bleeding, one might have expected similar rates of bleeding-related cancer. However, of the studies Dr. Marciniak utilized for the analysis in Figure 1, TRITON shows the greatest relative risk, with prasugrel worse than clopidogrel. The Division's assessment of TRITON is in the Deputy Division Director's memo.[16] There was no signal in non-clinical carcinogenicity assessments for prasugrel, and the Division and ODE-I concluded the signal was likely chance or driven by bleeding that led to cancer discovery. The approved labeling says:

> *"During TRITON-TIMI 38, newly diagnosed malignancies were reported in 1.6% and 1.2% of patients treated with prasugrel and clopidogrel, respectively. The sites contributing to the differences were primarily colon and lung. It is unclear if these observations are causally-related or are random occurrences."*

A subsequent study—TRILOGY—was getting underway as prasugrel was approved, and, to follow up on TRITON, the sponsor was asked to assess cancer as an event of special interest in that study. Dr. Marciniak's analyses of TRILOGY revealed no increased risk of cancer with prasugrel, but he reiterated his concerns about the interpretation of cancer data in TRILOGY,[17] although he failed to name concerns

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[15] *Page 3. The figure is entitled "Meta-Analysis of Solid Cancer Events in the Antiplatelet and Anticoagulant Trials with Substantial Invasive Approach and Having a Major Bleed RR ≥ 1.2 and for Which the FDA Has Cancer Data", and we show it below.*

[16] *NDA 22307, CDTL review dated 9 January 2009.*

[17] *Page 24-26.*

that would lead to bias. He described small sample size, loss to follow-up, and low cancer incidence rates as problems, but we note that these factors do not lead to bias.

In fact, TRILOGY compared prasugrel and clopidogrel in 9326 subjects over 14 months. It was carefully designed to assess new cancers, in part to fulfill the post-marketing requirement by FDA. The results from a total of 11718 patient-years of exposure were about 14 new cancers per 1000 patient-years, the same on prasugrel and clopidogrel. Dr. Marciniak's review counts fewer cancer events, but found fewer events on prasugrel than on clopidogrel, the opposite of the finding in the earlier TRITON study. The Division's conclusions[18] from TRILOGY were that the data were reassuring and no less likely to be correct than were the findings of TRITON.

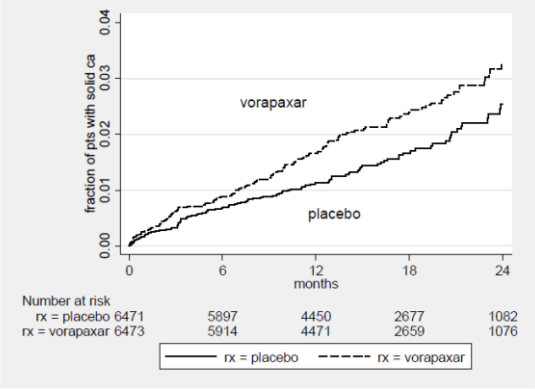
PLATO

PLATO compared ticagrelor and clopidogrel in 18624 subjects over a median of 10.5 months. By Dr. Marciniak's counts, there were 15 cancers per 1000 patient-years on clopidogrel and about 13 per 1000 patient-years on ticagrelor—about the same rates reported in TRILOGY. Dr. Marciniak discounts this reassuring finding[19] because of its "short duration and incompleteness of follow-up," neither of which introduces bias.

TRACER vs. TRA2P

TRACER compared vorapaxar with placebo in 12944 subjects followed for a median of about 15 months. Dr. Marciniak's counts of events in this study are reproduced below:

Figure 10: Solid Cancer Event Incidence in TRACER



TRACER was stopped early for futility, so it has *lots* of missing data, yet here Dr. Marciniak did not consider the missing data to be a deficiency. He did note that the curves diverge before any new cancer could grow large enough to be discovered, which he attributes to "detection bias," bleeding that leads to earlier discover of pre-existing cancer. We agree. A much larger study of vorapaxar, TRA2P, strongly suggests that the TRACER finding is a chance occurrence and not a drug effect at all. TRA2P compared vorapaxar with placebo in 26449 subjects followed for a median of about 2.5 years. Twice as large and twice as long as TRACER, TRA2P included ~4 times as many patient-years of experience. According to Dr. Rose's clinical review,[20] there were about 14.8 cancer events per 1000 patient-years on

[18] *NDA 22307 Division Director memo dated 15 October 2013.*

[19] *Page 32.*

[20] *Page 123 of a review dated 16 December 2013 and co-signed by Dr. Marciniak as team leader.*

placebo and 14.4 per 1000 patient-years on vorapaxar. Dr. Marciniak dismisses TRA2P in a paragraph[21] without saying more than it is discrepant with TRACER. Why? "*Its one identified design flaw is that the protocol specified phone contacts for patients who had discontinued treatment....*" We understand how incompleteness of follow-up might have led to missing events, but not how such missingness could have biased one group over another in TRA2P. We also cannot understand why missingness rendered TRA2P uninterpretable but did not impede TRACER's interpretation, given that the extent of missing data was greater in TRACER.

All in all, we conclude that the placebo-controlled data on vorapaxar do not suggest any increase in cancer risk; Dr. Marciniak's omission of TRA2P was not scientifically justifiable. In this placebo-controlled trial where there was unequivocally more bleeding in the voraxapar group than the placebo group, Dr. Marciniak rejected use of the data, presumably because they rebutted his assertion that bleeding causes cancer.

CAPRIE

CAPRIE compared clopidogrel and aspirin in 19185 subjects followed for 23 months. By Dr. Marciniak's counts, there were 14 cancers per 1000 patient-years on aspirin and 14 per 1000 patient-years on clopidogrel. Dr. Marciniak discounted CAPRIE because its analysis only included events identified within 28 days of study drug discontinuation; whether optimal for capturing cancer events or not, this rule was applied to both treatment groups. This is certainly not biased to hide events on clopidogrel, and, once again, Dr. Marciniak rejected data that rebutted his assertion that bleeding causes cancer.

CHARISMA

CHARISMA compared clopidogrel and placebo in 15603 subjects followed for 28 months. By Dr. Marciniak's counts, there were 10 cancers per 1000 patient-years on placebo and 9 per 1000 patient-years on clopidogrel. Dr. Marciniak discounts CHARISMA for the same reason as he does CAPRIE.

In each of these cases—TRILOGY, PLATO, TRA2P, CAPRIE, and CHARISMA—the studies were as large or larger than the studies Dr. Marciniak included in his meta-analysis. In three cases, the findings are inconsistent with studies of the same drug that Dr. Marcinak included, and all five of these studies show no evidence for a cancer signal. Three of these studies—TRA2P, CAPRIE, and CHARISMA—compared a drug with placebo or aspirin, settings where the any cancer-promoting potential should have been clearer than in comparisons with another antiplatelet medication. We conclude that there was no reasonable basis for excluding the studies that failed to sustain Dr. Marciniak's hypothesis.

DAPT

Dr. Marciniak did include two subgroup analyses of DAPT. DAPT was a randomized comparison of 12 months and 30 months on aspirin plus thienopyridine (clopidogrel or prasugrel at the investigator's discretion) following placement of a drug-eluting or bare-metal coronary artery stent. Dr. Marciniak's description of this study's results[22] was based upon *"preliminary results to the FDA in four PowerPoint presentations"* and one publication. The Agency's assessment of DAPT is available in a Drug Safety Communication,[23] but it is unclear how these results met Dr.

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[21] *Page 32.*

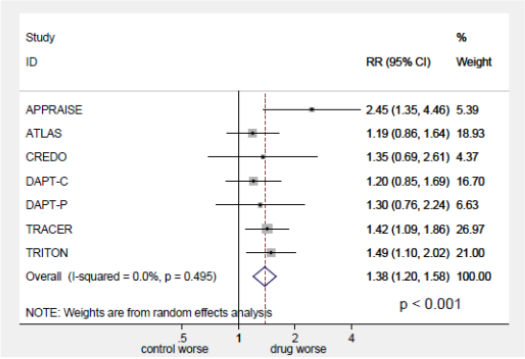
[22] *Pages 10-17.*

[23] *http://www.fda.gov/drugs/drugsafety/ucm471286.htm*

Marciniak's inclusion criteria for studies for his meta-analysis. He stated that he included studies *"for which the FDA has cancer data,"* but he did not have access to the DAPT data.

After presenting his analysis of antiplatelet drugs alone, Dr. Marciniak presented his more integrated analysis of antiplatelet and anticoagulant drugs and risk of cancer, shown in Figure 2:[24]

Figure 2: Meta-Analysis of Solid Cancer Events in the Antiplatelet and Anticoagulant Trials with Substantial Invasive Approach and Having a Major Bleed RR ≥ 1.2 and for Which the FDA Has Cancer Data



Of various candidates, he included selected placebo-controlled studies in acute coronary syndrome (ACS)—APPRAISE (apixaban; 7392 subjects followed for 8 months), ATLAS (rivaroxaban, 15526 subjects followed for 14 months), and TRACER. But note that we are now looking at a further subgrouping—not just *"trials with a substantial invasive approach"* and *"for which the FDA has cancer data,"* but also trials *"having a major bleed RR ≥ 1.2."* This additional selection criterion has some plausibility as a factor in bringing to light latent cancers, especially GI cancers, but that does not lead to any ominous conclusions regarding the suspect drugs.

Dr. Marciniak acknowledges the possibility that early separations in event rates for particular cancers (whether or not nominally significant) may represent bleeding leading to discovery;[25] he thinks that cases where the separation appears late (whether or not nominally significant) represent true promotion.[26] Tabulated,[27] but not included in the presented meta-analysis are results for ARISTOTLE (apixaban vs. warfarin, n=18201, RR for cancer of 0.9), AVERROES (apixaban vs. aspirin, n=5598, RR for cancer of 1.1), ROCKET (rivaroxaban vs. warfarin, n=14264, RR for cancer of 1.1), J-ROCKET (rivaroxaban vs. warfarin, n=1280, RR for cancer of 0.9), RELY (dabigatran vs. warfarin, n=18113), ENGAGE (edoxaban vs. warfarin, n=21105, RR for cancer of 1.0), SPORTIF III (ximelagatran vs. warfarin, n=3407, RR for cancer of 1.3) and SPORTIF V (ximelagatran vs. warfarin, n=3992, RR for cancer of 0.7).

What was wrong with them? According to Dr. Marciniak's review, ARISTOTLE,[28] AVERROES,[29] and ROCKET[30] failed the test for 20% worse bleeding. (That did not

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[24] *Page 3.*

[25] *E.g., comment on page 41.*

[26] *E.g., comment on page 44.*

[27] *Pages 36 and 37.*

[28] *Page 41.*

[29] *Page 44.*

prevent Dr. Marciniak from pointing out a few adverse trends among cancer types.) ATLAS[31] had problems with follow-up, but that did not prevent inclusion in the meta-analysis nor did it prevent description of selected adverse cancer findings. No reason is given for excluding J-ROCKET.[32] RELY[33] had 20% lower bleeding on the 110-mg dose than on warfarin, but no difference from warfarin on cancers that Dr. Marciniak counts;[34] it gets discounted *"because dabigatran [110 mg only?] caused a different pattern of bleeding than [did] warfarin."* He excluded ENGAGE because it had incomplete follow-up (but 34 months of it), markedly less bleeding on edoxaban than on warfarin, and no difference he could identify in cancers. Likewise, SPORTIF III and V both showed less bleeding on ximelagatran than on warfarin with no difference in cancers identified by Dr. Marciniak.

Also unmentioned are numerous trials of reasonable size and duration supporting the use of anticoagulant drugs in settings of deep venous thrombosis and shorter-term studies of these drugs for a period following joint surgery.

Finally, none of these drugs has any non-clinical signal for new cancers or for tumor promotion in animal life-time carcinogenicity studies.[35]

ARBs and cancer

With regard to ARBs and cancer, Dr. Marciniak asserts[36] that FDA *"suppressed the evidence associating ARBs with lung cancer: Almost five years after the association of ARB use with cancer was first published (Sipahi, Debanne et al. 2010), the FDA still has not released the evidence that the risk of lung cancer with ARB use is real."* Dr. Marciniak's accusation is completely without merit. This matter was reviewed in TSI #935. The findings of thus safety review were announced to the public in a Drug Safety Communication[37] on 2 June 2011. We concluded that there was nothing to "suppress," and we are puzzled by Dr. Marciniak's ignorance of this response.

2. *"The FDA should review all of the data regarding duration of dual antiplatelet therapy post-stenting and integrate it with these data regarding bleeding and cancer. Based on this review the FDA should recommend changes to the labels of antiplatelet drugs to include warnings regarding solid cancers and recommendations for duration of antiplatelet therapy and for investigating possible cancer signals. The FDA should also recommend changes to the labels of anticoagulants noting the data regarding anticoagulants and cancer and including recommendations for investigating possible cancer signals."*

   Despite many discussions with each of us and others at FDA during his tenure at FDA, Dr. Marciniak has failed to produce plausible evidence of a risk for any of the named drug classes or specific members thereof. His choices of which studies to include and which analyses to do or show appear to select studies for analysis and presentation that support the signal he expects to see. He denigrates or ignores

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[30] *Page 47.*

[31] *Page 44.*

[32] *Page 47.*

[33] *Page 48.*

[34] *Pages 48-49, Table 19.*

[35] *Apixaban NDA 202155, Pharmacology/toxicology review dated 21 February 2012, page 70ff; rivaroxaban NDA 202439, pharmacology/toxicology review dated 1 August 2011, page 60ff; vorapaxar NDA 204866, pharmacology/toxicology review dated 17 December 2013, page 124ff.*

[36] *Page 8.*

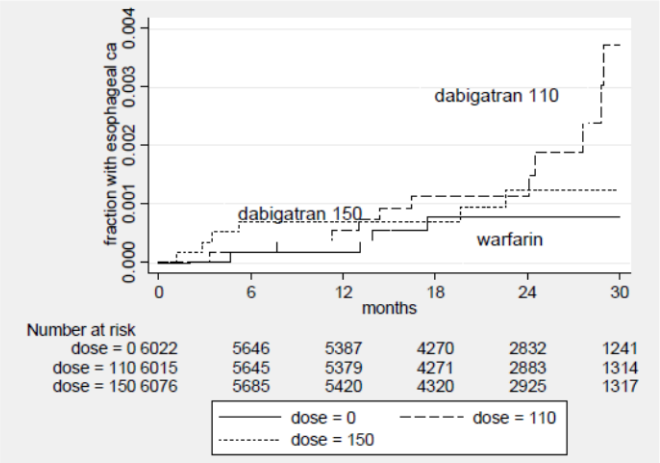
[37] http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm

good quality studies whose findings do not support his thesis, finding them all flawed without really providing support for those conclusions. We reject as without support the hypothesis that bleeding or drugs that cause bleeding cause cancer or lead to cancer promotion. We therefore do not believe that we have cause for amending labels for antiplatelet drugs, anticoagulants, or ARBs. While FDA will, of course, continue to monitor emerging safety signals in new studies with these drugs and in the post-marketing setting, we lack any case for directing more active surveillance.

3. *"The FDA should inform the sponsors about the signal for esophagus cancers with NOACs, request their proposals for elucidating it, and design or commission drug surveillance database studies to address the signal."*

   Dr. Marciniak finds the following data supportive of an association between dabigatran and esophageal cancer:[38]

Figure 25: Esophagus Cancer Event Incidence in RELY



These results are described as follows:[39]

> *"The breast and esophagus cancer incidence curve suggest similar, higher rates than warfarin for both doses. Whether these are real differences or chance variation cannot be distinguished definitively from this size study. The esophagus cancer increase late appears relevant because one established dabigatran adverse effect is GI irritation. If this increase in esophagus cancer is real the late disparity between the doses would likely be the result of chance."*

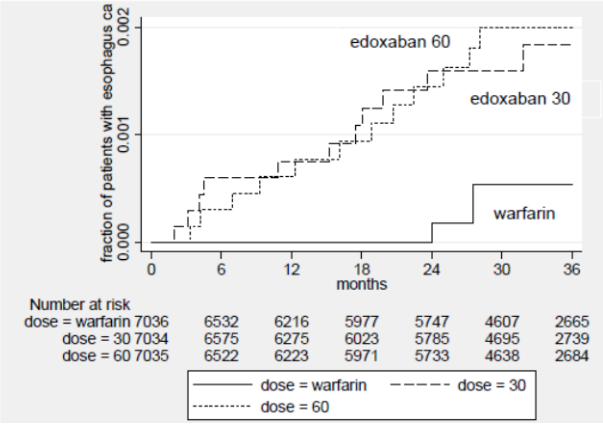
Although he selectively provided a nominal p-value for some other associations he described, he did not provide a p-value for this. We suspect this finding was not close to being statistically significant, even before considering multiplicity adjustment for 25 categories of solid cancer types he described in the RELY database. He concluded that the disparity of the effect of the two doses is likely the result of chance. We would conclude that the inconsistency in the findings between the lower and higher doses of dabigatran strongly suggests that the 'finding' with the lower dose is due to chance. With the higher dose of dabigatran, the dose that is marketed in the U.S., there is no finding whatsoever.

[38] *Page 51.*

[39] *Page 52.*

Here are the data Dr. Marciniak found suggestive of risk of esophageal cancer on edoxaban from the ENGAGE study:[40]

Figure 30: Esophagus Cancer Event Incidence in ENGAGE



Dr. Marciniak's description of this result was as follows:

> *"Esophagus cancer incidence was much higher and similar in both edoxaban arms. The incidence curves start diverging early from warfarin's. While one would be tempted to dismiss the differentiation as chance, the fact that both edoxaban arms are similar and the differentiation of esophagus cancer with dabigatran (although with a difference time course), suggests that we shouldn't dismiss this finding."*

This apparent association looks more plausible than the association with dabigatran, but again no p-value is provided, and we cannot even guess at the magnitude of multiplicity problem here, because of the myriad of types of solid tumors analyzed. This is one of four cancer types subjected to time-to-event analyses from ENGAGE, but we cannot determine how many others were performed. In addition, warfarin causes at least as much bleeding as edoxaban does or the other non-vitamin K-dependent oral anticoagulants (NOACs) do, so these data hardly support an effect of bleeding per se.

Dr. Marciniak found an association between ximelagatran and esophageal cancer: 3 cases vs 0 on warfarin in the SPORTIF III study and 2 vs 0 in SPORTIF V. Again, it is difficult to assess the multiplicity problem, but he does, for SPORTIF V, tabulate[41] more cancers on warfarin overall, with trends for breast (11 on warfarin vs. 2 on ximelagatran) and melanoma (8 on warfarin vs 4 on ximelagatran). Although these are more impressive than any adverse trends with ximelagatran, they go without much comment by Dr. Marciniak.[42]

The associations of esophageal cancer with edoxaban, dabigatran, and ximelagatran are all weak. What about the associations with other NOACs? By Dr. Marciniak's counts, there was one case in each of the two rivaroxaban arms in ATLAS, one on apixaban in APPRAISE, and 3 on apixaban vs 2 on warfarin in ARISTOTLE. Thus, these do not show much of a signal, either. We cannot determine why Dr. Marciniak excluded data from other large studies of these drugs.

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[40] *Page 54.*

[41] *Pages 58-59.*

[42] *Page 61.*

Although we do not believe there is any evidence that NOACs, individually or as a class, cause esophageal cancer, we would not have been surprised to see some association resulting from cancer discovery precipitated by esophageal bleeding events. In fact there is scant evidence for NOACs in general to predispose to esophageal cancer:[43]

NOAC	Study	RR for hemorrhage	Esophageal cancer cases	
			Control	NOAC
Apixaban	ARISTOTLE	0.6	2	3
Edoxaban	ENGAGE	0.7	N/A	N/A
Ximelagatran	SPORTIF III	0.7	0	3
Ximelagatran	SPORTIF V	0.7	0	2
Rivaroxaban	J-ROCKET	0.9	N/A	N/A
Dabigatran	RELY	0.9	3	8
Rivaroxaban	ROCKET	1.0	N/A	N/A
Apixaban	AVERROES	1.1	N/A	N/A
Rivaroxaban	ATLAS	2.3	0	1
Apixaban	APPRAISE	2.6	0	1

We conclude that there is an inadequate basis for any of Dr. Marciniak's recommendations with regard to NOACs and an association with esophageal cancer.

4. *"Vital status ascertainment in trials should be > 99% of all randomized subjects. All trials should capture the identifiers needed for national death registry indexing. If regions refuse to allow passive follow-up of vital status for trial subjects, e.g., registry access, then the trial sponsor should not conduct trials for U.S. registration in those regions."*

   The impact of missing data, particularly for mortality, is universally appreciated, and we believe that we generally get good ascertainment. As Dr. Marciniak surely knew, at least for major outcome studies with some expectation of mortality, the Division has long been routinely recommending studies be conducted in regions where follow-up for vital status is possible through passive means.

5. He recommends that studies generally should assess events of particular interest (death, cancer, MIs, stroke, and major thrombotic events) at the end of study, preferably at a final visit. He also suggests that "…[case report forms] for visits should be recorded and submitted in real time…."

   We believe that we get reasonable assessment of adverse events of special interest. In addition, we believe there is little potential for bias from cases missed because of loss to follow-up (which is not generally related to cancer) or incomplete ascertainment of events.

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[43] *RR for major/severe bleeding come from Dr. Marciniak's Tables 14 and 15 (pages 36-37). Where available, counts of events come from his review, too. Studies with two doses of a NOAC are the mean of the two doses. Dr. Marciniak's review does not have counts of esophageal cancer events for ENGAGE (edoxaban), and they are not in the primary clinical review of ENGAGE.*

We regard the request for real-time submission of case report forms (CRFs) to be unreasonable. First, the sponsor invests considerable effort in the quality control of data we receive. We share Dr. Marciniak's interest in understanding the effect of quality assurance processes, but we as an agency are ill-equipped to review CRFs in real time. Moreover, companies typically find errors in CRFs, and query investigators with respect to missing data, incomplete data, data that appear erroneous, etc. In other words, CRFs are subjected to auditing and quality control prior to submission to FDA (the audit trail is available to FDA, if needed).

6. He recommends good quality data collection regarding cancer events. We agree and think that generally we get good quality reporting and response to requests for additional follow-up.

We began by outlining some unusual and inefficient aspects of Dr. Marciniak's work on this problem. Most troubling among these was the failure to involve colleagues and supervisors. Dr. Marciniak did not involve pharmacologists or toxicologists, who have uniformly concluded there is a lack of non-clinical evidence for carcinogenic potential for any of these drugs. He did not consult statisticians who might have alerted him regarding the hazards of cherry-picking studies to pool for an analysis when you know how the choices will affect the results, because you know the effect in each of the trials one has. He also ignored the statistical problem of multiplicity—choosing to focus on 'findings' for particular tumor types, while ignoring other tumor types that failed to support his view. He ignored all of the relevant reviews by these staff and fellow medical officers.

Dr. Marciniak also failed to justify his determinations of cancer cases over the applicants', which is contrary to CDER policy, and failed to show the impact of his attributions on the final results. Moreover, when reviewers have attempted to verify the numbers of cancer-related adverse events that Dr. Marciniak found in various trials, they have been unable to corroborate his findings.

With respect to integration of data across multiple studies, Dr. Marciniak failed to justify his inclusion of some studies and rejection of others. He names factors in his decisions to exclude some studies that are highly unlikely to bias the results, giving the strong impression that he simply cherry-picked studies that supported his preferred conclusion.

Dr. Marciniak lists his own component reviews[44] of some of these studies, so we, his supervisors, were well aware of his interests in cancer-causing potential of various drug classes. We have discussed these matters with him on numerous occasions over the years, just not this final summary review. Dr. Marciniak had opportunities, therefore, to convey his point of view, and to hear and to respond to many of the criticisms we provide here, so we are puzzled that he provides so little insight into these other points of view. We also know that, having failed to convince us of a problem, Dr. Marciniak knew about the CDER appeal process, but he failed to avail himself of it. Instead, Dr. Marciniak ignored his colleagues and normal processes and planted this poorly argued case in various applications.

[44] *Page 62.*

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/s/

NORMAN L STOCKBRIDGE
11/13/2015

MARY R SOUTHWORTH
11/13/2015

ROBERT TEMPLE
11/13/2015

ELLIS F UNGER
11/13/2015

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date:	December 12, 2014
Reviewer:	Thomas A. Marciniak, M.D. Medical Team Leader
NDAs:	20-839, 22-307, 22-433, 204-886, 9-218, 21-686, 22-512, 202-155, 202-439, and 206-316
TSI:	1361
Drugs:	Antiplatelet and anticoagulant drugs (clopidogrel, prasugrel, ticagrelor, vorapaxar, warfarin, ximelagatran, dabigatran, apixaban, rivaroxaban, and edoxaban)
Subject:	Cancer risk

Summary

The large outcome trial supporting the approval of prasugrel, the first new antiplatelet drug approved in more than 10 years, raised the issue of whether use of a drug inhibiting coagulation could be associated with an increased risk of solid cancers. (Marciniak 2009) Subsequent trials of antiplatelet and anticoagulant drugs provided both supportive and neutral evidence for this association. The most recent submission for a new anticoagulant, edoxaban, is typical in providing, by itself, suggestive but not conclusive evidence for the association. (See **ENGAGE** below.) However, the most recently reported trial, the Dual Antiplatelet Therapy (DAPT) Study, provides strong evidence that the association of use of drugs inhibiting coagulation with an increased risk of solid cancers is real.

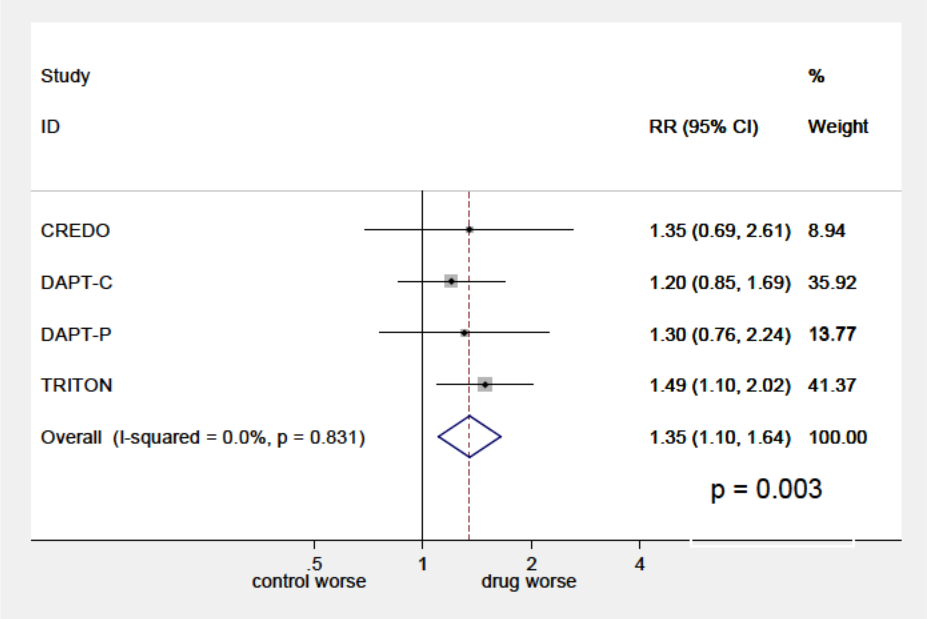
DAPT is a large (N = 11,648), randomized, placebo-controlled trial comparing 30 vs. 12 months of dual antiplatelet therapy in coronary stented patients. In August 2014 the principal investigators shared with the FDA the preliminary results: While the 30-month arm did have lower rates for the primary death, myocardial infarction (MI), or stroke (MACCE) endpoint and for stent thromboses, it had a higher rate of all cause mortality in the drug-eluting stent subgroup (hazard ratio (HR) (b) (4) p = 0.04) and had higher rates of cancer (HR (b) (4)) and cancer deaths (b) (4) in the whole study. (See Attachment 1.) The latter findings, both the mortality and the cancer results, have generated considerable concern among the investigators, the sponsors, and the FDA. The Division Deputy Director for Safety filed a memo concluding that the finding of increased mortality is reliable and that "the number of non-

cardiovascular deaths are also certain." (Southworth 2014) Regarding cancers the memo states that "Cause of death may be less certain and therefore some thought must go into how/if the cancer and trauma death findings would be represented in the [safety] communication." Because I have analyzed cancer and non-CV death findings in all large antiplatelet and anticoagulant studies submitted to the FDA, I am filing this review to record the cancer findings for edoxaban and to provide data-based recommendations for addressing the serious issue of cancer risk with all drugs that inhibit coagulation.

DAPT results support an increased risk of solid cancers with thienopyridine use, at least in the setting of invasive percutaneous procedures. The DAPT results look like an extension of the prasugrel TRITON study, the index study that raised the issue of whether the thienopyridine prasugrel increases solid cancer rates. In TRITON, like in DAPT, the arm with greater thienopyridine effect had more bleeding, more solid cancers, and more non-CV deaths.

The consistency of these relationships is shown well by a meta-analysis of solid cancer events in the thienopyridine outcome trials with substantial invasive approach in which cancer data were collected and for which the FDA has the trial data. I show the meta-analysis results in Figure 1.

Figure 1: Meta-Analysis of Solid Cancer Events in the Thienopyridine Trials with Substantial Invasive Approach and for Which the FDA Has Cancer Data



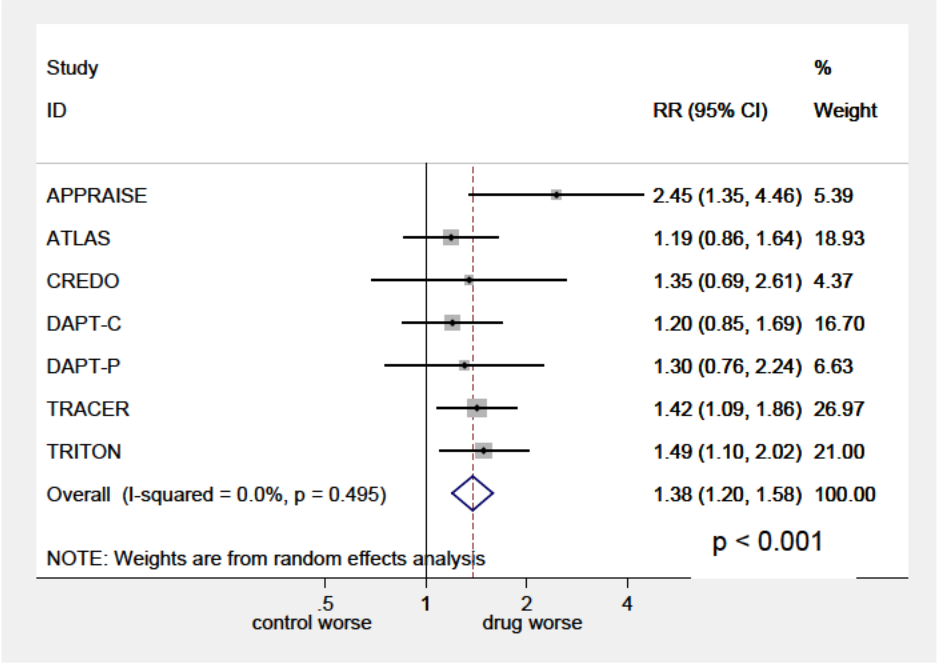
DAPT-C in Figure 1 is the clopidogrel substudy of DAPT and DAPT-P is the prasugrel substudy. All four studies are remarkably consistent for solid cancer risks.

In addition to the thienopyridine trials, there have been two recent large outcome trials in predominantly invasive ACS patients of non-thienopyridine antiplatelet drugs: PLATO for the non-thienopyridine $P2Y_{12}$ receptor inhibitor ticagrelor and TRACER for the PAR-1 receptor inhibitor vorapaxar. The TRACER results are very similar to those shown in Figure 1; including them changes the RR minimally (1.37) but reduces the p value to < 0.001. PLATO did not show an increased rate of solid cancers with ticagrelor but its bleeding RRs are close to 1, study

duration was relatively short, and it had serious conduct problems that challenge its validity. Including both TRACER and PLATO in the meta-analysis produces a pooled RR estimate of 1.24 and a p value of 0.002.

There have also been two recent large, placebo-controlled outcome trials of new oral anticoagulants (NOACs) in predominantly invasive ACS patients: APPRAISE for the factor Xa inhibitor apixaban and ATLAS for the factor Xa inhibitor rivaroxaban. Both of these NOAC outcome trials in ACS support an association between increased bleeding and solid cancers. The solid cancer results in APPRAISE, which had substantially higher bleeding rates in the apixaban arm, are statistically significant ($p = 0.003$) for APPRAISE alone. In rivaroxaban ATLAS the solid cancer results are not statistically significant. However, ATLAS tested two doses and there is a strong suggestion for a dose-response both for bleeding and for solid cancers. I performed a random effects meta-analysis of solid cancer events combing these two NOAC trials and the invasive antiplatelet drug trials (all of which have major bleed risk ratios ≥ 1.2). I show the results in Figure 2.

Figure 2: Meta-Analysis of Solid Cancer Events in the Antiplatelet and Anticoagulant Trials with Substantial Invasive Approach and Having a Major Bleed RR ≥ 1.2 and for Which the FDA Has Cancer Data



The p value for the DerSimonian-Laird random effects meta-analysis in Figure 2 is <0.001. If PLATO (which has a lower major bleed RR as well as conduct problems) is included in the meta-analysis, the p value is 0.004.

Survival following a solid cancer event was typically poor in all studies and similar between the drug and control arms. In the DAPT the difference in malignancy deaths was high enough to result in an appreciable difference in non-CV deaths. I show in Figure 3 a meta-analysis of non-CV mortality for the same trials include in Figure 2 and in Figure 4 a meta-analysis of deaths in patients with solid patients with solid cancers.

Figure 3: Meta-Analysis of Non-CV Mortality in the Antiplatelet and Anticoagulant Trials with Substantial Invasive Approach and Having a Major Bleed RR ≥ 1.2 and for Which the FDA Has Cancer Data

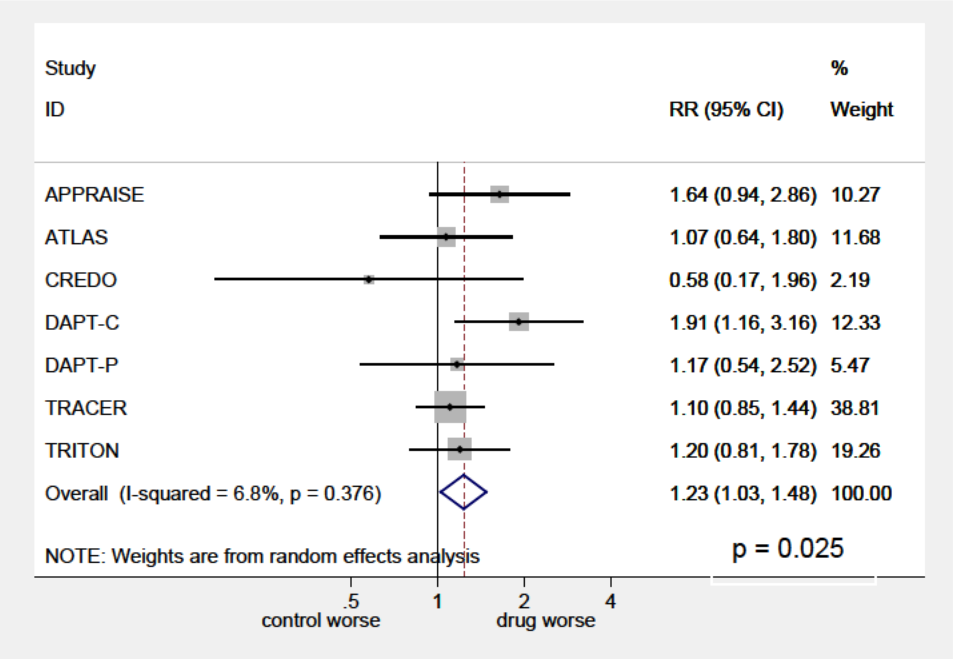
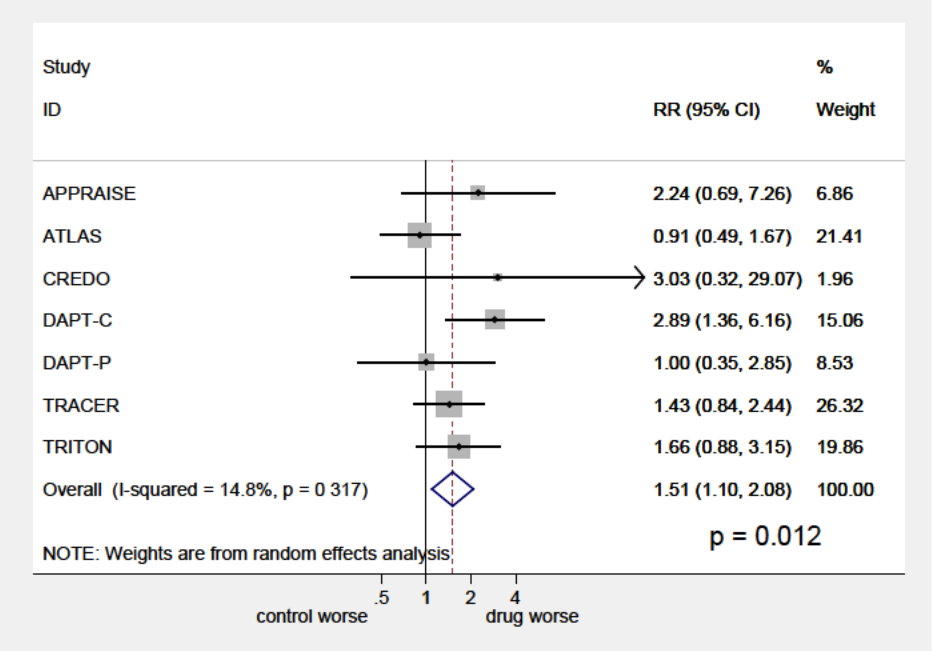


Figure 4: Meta-Analysis of Deaths in Patients with Solid Cancers in the Antiplatelet and Anticoagulant Trials with Substantial Invasive Approach and Having a Major Bleed RR ≥ 1.2 and for Which the FDA Has Cancer Data



The trials statistics used to produce Figure 4 for all trials except DAPT are the deaths during the trial ITT period for all patients having a solid cancer event reported during the ITT period. (In the tables of trials at the start of each drug and cancer section below the rows "Died %, solid ca pts (control)" provides this statistic for the control arms.) For DAPT they are the adjudicated malignancy deaths because that is the statistic reported. Both figures confirm that the increased solid cancers observed in the trials result in more deaths. The variability is higher for these cause-specific mortality statistics than for solid cancer rates because the numbers of cause-specific deaths are lower than the numbers of solid cancers. The mortality rates in the patients with solid cancers range from about 3- (in a short study) to 8-fold higher than the mortality rates in patients who didn't experience a solid cancer event. Because solid cancers are deadly, I advocate analyzing deaths in patients with solid cancers to avoid the problems of adjudication and arbitrary decisions about the underlying causes of deaths.

The results of the antiplatelet drug trials without a substantial invasive approach contrast with those shown in Figure 2. The older non-invasive clopidogrel trial results do not support a relationship between clopidogrel use or bleeding and solid cancers. All trials had study limitations that I discuss in the **Clopidogrel and Cancer** section that limit their validity. Prasugrel TRILOGY in medically managed ACS is similarly negative, although TRILOGY, like PLATO, had serious conduct problems. Vorapaxar TRA2P, a very large trial in high risk patients, was neutral for solid cancers and non-CV deaths despite substantially higher bleeding in the vorapaxar arm. However, TRA2P had a design flaw similar to the ones in the two large clopidogrel studies (CAPRIE and CHARISMA) that also produced neutral results: CAPRIE did not count adverse events (AEs) more than 28 days after study drug discontinuation; CHARISMA defined AEs as occurring within 28 days of treatment discontinuation; and TRA2P did not solicit AEs that occurred more than 60 days after the last dose. While these restrictions may not appear to be too limiting, I have a well-documented experience with another outcome trial that suggests that their impact may be critical:

> The LIFE study was a large trial of losartan vs. atenolol in hypertensive patients with left ventricular hypertrophy. The sponsor of LIFE counted AEs only until 14 days after study drug discontinuation (although they collected AEs throughout the trial.) Applying the 14 day limit atrial fibrillation (afib) SAEs were similar in the two arms (2.0% vs. 2.1%, atenolol vs. losartan) and numerically higher with losartan. However, I demonstrated that AE rates did not return to a stable level until about 90 days after study drug discontinuation. Counting AEs until 90 days after study drug discontinuation I could document a small difference in afib AE rates between the two arms (7.9% vs. 6.8%, atenolol vs. losartan), higher with atenolol. While this small difference in afib rates would not appear to be critical, Minnesota coding of annual ECGs collected in LIFE confirmed a difference in afib rates favoring losartan (7.9% vs. 5.7%). These differences, again not alarming, were impactful: Losartan was superior to atenolol in LIFE for stroke rates. The detected difference in afib rates accounted for half of this difference in stroke rates.

I have concerns that investigators interpreted limits on AEs such as 28 days or 60 days after treatment as indicating that only AEs clearly related to the study drug should be collected—and investigators would not consider cancer to be related to these drugs. I suspect that the neutral results in CHARISMA and TRA2P may be related to their AE collection specifications.

That how AEs are or are not collected can affect cancer findings is demonstrated well by analyses of the angiotensin receptor blocker (ARB) trials for cancer. (Marciniak 2013) Because the analyses are extensive and highly relevant to this review, I have included the ARB trials analyses as Attachment 5. Please see Appendix 1 of that attachment for a detailed discussion of trials for which AE collection deficiencies led to inadequate cancer ascertainment. Please see Attachment 6 the pre-specified methodology that I used for the analyses of cancer in the ARB, antiplatelet, and anticoagulant trials. (Marciniak 2012) For both ARBs and drugs inhibiting coagulation, the trials having reasonably complete AE collection show an association between drug use and cancer risk. (For ARBs the risk is for lung cancer, not all solid cancers.) The trials with incomplete AE collection frequently fail to show the association.

We should also consider possible mechanistic differences between invasive and non-invasive of trials. One possibility is the use of drug eluting stents (DES) in the invasive trials. DAPT may raise this issue because the differences in non-CV deaths and adjudicated malignancy deaths (per the preliminary presentations) occur only in the DES subgroup—these statistics in the bare metal stent (BMS) subgroup are similar between arms. However, the BMS subgroup is about $1/6^{th}$ the size of the DES group so its event rates are low and hence their confidence intervals are wide. The older trials do not support an effect of DES on solid cancer rates. CREDO was conducted prior to the introduction of DES. The trials with DES use (TRITON, ATLAS, APPRAISE, and TRACER) do not show an increased risk of solid cancers with DES use or an interaction between DES and drug for solid cancer incidence. Furthermore, for the trials including more balanced numbers of invasive and medically managed patients (ATLAS, APPRAISE, and TRACER), there are no significant differences in cancer risk between the invasive and medically managed patients nor is there a significant interaction between invasive management and drug use for cancer risk.

There could be other biologic mechanistic differences between the two sets of trials (e.g., radiation exposure from cardiac fluoroscopy in the invasive trials?) but my suspicion remains that the different solid cancer findings in the two sets of trials are related to cancer ascertainment limitations in the noninvasive trials. I do not know of a method for proving that hypothesis with the existing data (but I do recommend changes for future trial conduct in the next subsection.) I remain highly concerned about the bleeding and cancer associations in the invasive trials and the mortality findings in SPS3, the NIH trial of clopidogrel and aspirin vs. aspirin alone in recent stroke. Unfortunately we do not have cancer data for SPS3. SPS3 again suggests that clopidogrel can produce more bleeding and more non-CV mortality. While our expectation is that the high non-CV mortality in SPS3 is related to cancer (the publication states that it is not related to bleeding), confirmation of that would be informative.

The anticoagulant trials provide some additional insights: Apixaban APPRAISE in ACS provides an informative comparison to apixaban ARISTOTLE in afib. While in APPRAISE there was more bleeding with apixaban (because it was administered on a background of DAPT) and more solid cancers, in ARISTOTLE there was less bleeding with apixaban and fewer solid cancers. In ARISTOTLE warfarin showed a higher rate of solid cancers. The difference in cancers is borderline significant ($p = 0.052$ by log rank) for the ITT period and nominally significant ($p=0.024$) for all cancers reported. The ximelagatran SPORTIF V trial also shows higher bleeding rates and higher solid cancer rates with warfarin. ARISTOTLE and SPORTIF V demonstrate that the cancer increases appear to be related to inhibition of the coagulation system,

not strictly related to a particular receptor or to platelet inhibition, and that warfarin is implicated as well as the NOACs.

Other anticoagulant trials suggest another complexity: The cancer effects may be related to specific tissue concentrations and not systemic blood levels. Many of the NOACs show increased GI bleeding rates despite having overall bleeding rates lower than warfarin's. While colon cancer[1] has variable results in the trials, four of the trials show increased rates of esophagus cancer in the NOAC arms: dabigatran RELY; edoxaban ENGAGE; and ximelagatran SPORTIF III and V. (Rivaroxaban ATLAS also reported esophagus cancers in its two rivaroxaban arms, but only one in each of the arms.) Many of these esophagus cancers were reported late, suggesting that an early detection bias was not the mechanism. There are other variations in specific cancer site incidences between arms in the NOAC studies but, given that any specific site has small numbers of cancers reported for a given study, most of the variations are remote from statistical significance and impossible to sort out from chance variations.

For the NOACs, as for the antiplatelet drugs, the two studies (APPRAISE and ATLAS) with the highest bleed RRs and showing an association of bleeding with increased solid cancers were ACS studies with a substantial invasive component. These studies were also the placebo-controlled studies with the NOAC administered typically in addition to dual antiplatelet therapy, the latter contributing to the high bleed RRs. Only AVERROES (apixaban vs. aspirin) showed a slightly higher bleed RR for the NOAC and little difference in solid cancer rates. The other NOAC trials were warfarin-controlled and reported lower bleeding RRs for the NOACs than for warfarin, with only SPORTIF V suggesting an association between overall bleeding and overall solid cancer rates. The threshold for observing an increase in solid cancer rates in the NOAC trials of these sizes appears to be at least a major bleeding RR of 1.4 (the RR for warfarin/NOAC in SPORTIF V.)

I have mentioned an "early detection" effect or bias several times. Some have tried to explain the prasugrel TRITON and other trial results as totally the result of early detection resulting from investigations of bleeding. However, several observations argue against that conclusion:

- Survival after a solid cancer event is typically poor and equally poor regardless of the imbalance in events. If there were a detection bias, we would expect at least a lead-time bias because of the earlier detection and hopefully improved survival—the latter is why we advocate cancer screening! That survival may be worse is shown in DAPT by the fact that the statistically significant signal is for non-CV mortality rather than for solid cancer incidence.
- The overall solid cancer incidence curves do not typically diverge immediately but only after a delay of several months. They also typically diverge for the duration of the studies.

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[1] [1] In this review I refer to "colon cancer". I include rectal carcinomas with colon carcinomas in the term "colon cancer."

- For some sites for which bleeding is a telltale sign (e.g., colon, other GI, bladder), we do see an initial diagnosis of a few cases immediately after randomization. The initial high rate of diagnosis is not typically sustained beyond a few months.
- DAPT provides the strongest argument against an early detection bias. DAPT randomized patients at one year after initiating thienopyridine treatment, after the time we would expect an early detection bias to have dissipated. The early high detection rates for the incidence curves suggesting a detection bias typically last only a few months.

I conclude that the totality of evidence strongly supports that prolonged thienopyridine use is associated with increased rates of solid cancers, at least in patients undergoing invasive procedures. The evidence also suggests that the association is not limited to inhibition of the $P2Y_{12}$ receptor but extends to the PAR-1 receptor. The totality of evidence also supports that excess bleeding from higher anticoagulant dosing also increases the risk of solid cancers. Hence the increased solid cancer risk appears to be related to inhibition of coagulation and not inhibition of a particular receptor or use of a particular drug, i.e., it is a "class" effect. I provide recommendations below based on these conclusions as well as my observations regarding trial conduct problems in the 23 trials analyzed.

Recommendations

1. The FDA should provide practitioners and patients with the data regarding the association between bleeding and solid cancers **as soon as possible**. The increased deaths and solid cancers in DAPT, consistent with other antiplatelet trials with a predominantly invasive approach, justify immediate action. The FDA safety communication from November 16, 2014, that advises patients and practitioners to continue DAPT bases that advice on flawed logic: It reports that more patients on extended DAPT died, the outcome of prime importance, but concludes that the benefit-risk for extended DAPT is still favorable. (FDA 2014) The current FDA plan for resolving the DAPT cancer risk issue, outlined in minutes from an internal meeting, has a proposed schedule that is completely inappropriate for the seriousness of this issue: "The goal date for CDER's review will be 6 months from the time the data from DAPT are submitted." (Wachter and Southworth 2014) The FDA plan appears to be dismissing cancer risk with antiplatelet drugs as unimportant just as it suppressed the evidence associating ARBs with lung cancer: Almost five years after the association of ARB use with cancer was first published (Sipahi, Debanne et al. 2010), the FDA still has not released the evidence that the risk of lung cancer with ARB use is real.
2. There are at least two possible approaches for conveying this critical information regarding the risks of long term DAPT:
    a. The issuance of a safety communication summarizing the findings in this review along with the posting of this review on the FDA website.
    b. The holding of an advisory committee meeting on this topic and the related topic of angiotensin receptor blockers (ARBs) and cancer, with the usual public posting

of this review and all of the ARBs and cancer documents immediately prior to the meeting.

3. The FDA should review all of the data regarding duration of dual antiplatelet therapy post-stenting and integrate it with these data regarding bleeding and cancer. Based on this review the FDA should recommend changes to the labels of antiplatelet drugs to include warnings regarding solid cancers and recommendations for duration of antiplatelet therapy and for investigating possible cancer signals. The FDA should also recommend changes to the labels of anticoagulants noting the data regarding anticoagulants and cancer and including recommendations for investigating possible cancer signals.
4. The FDA should inform the sponsors about the signal for esophagus cancers with NOACs, request their proposals for elucidating it, and design or commission drug surveillance database studies to address the signal.
5. Our confidence in the trial results and our understanding of the differing results between the invasive and non-invasive trials is reduced by trial conduct issues, particularly incomplete follow-up and limitations in adverse event reporting. These trial conduct issue are not limited to the question of bleeding and cancer but are pervasive for all recent trials and for all issues. The FDA should inform sponsors about the following expectations:
    a. Vital status ascertainment in trials should be > 99% of all randomized subjects. All trials should capture the identifiers needed for national death registry indexing. If regions refuse to allow passive follow-up of vital status for trial subjects, e.g., registry access, then the trial sponsor should not conduct trials for U.S. registration in those regions.
    b. The FDA should inform sponsors that knowing subjects didn't have certain events by the end of the study—not the end of treatment or the end of treatment plus an finite period—is as critical as knowing that subjects did have certain events. Cancer is always one of these events of special interest—see the next item for specific recommendations regarding cancers. Besides deaths major cardiovascular adverse events, including MIs, strokes, and other major thrombotic events, are also always events of special interest. The sponsor should design trial procedures and case report forms (CRFs) to ensure the following:
        i. Preferably all living trial subjects should have a final site visit on or after the global trial end date, although final phone contacts may be allowed for subjects who have discontinued treatment. Site staff should follow a detailed written protocol for conducting the site visits, including the date of contact, the site staff conducting the visit or contact, whether the patient visited or was contacted, the relationship of the contact to the patient if not the patient, and specific questions regarding not only the endpoint events but all adverse events of special interest. The CRFs for visits should be recorded and submitted in real time, not days or weeks later.

ii. The completion rate for subjects with a well-documented site visit or contact on or after the global trial end date should be > (100%-1% x years from randomization). This goal, like the >99% for vital status, is not meant to be a rejection criterion. If it is achieved, then the burden of proof will rest with the FDA to show that the study is unreliable if there is other evidence of problems, e.g., from inspections. If it is not achieved, then the burden of proof will be on the sponsor to convince the FDA that the study is reliable.

6. The FDA and sponsors must recognize that pre-clinical rodent carcinogenicity are inadequate for detecting cancer promoting drugs. One mechanism for understanding better the cancer promotion potential of drugs having large outcome trials is to record malignancies accurately and completely in such trials. Hence malignancies, other than basal cell and squamous cell skin cancers, should be considered events of special interest to be captured for the entire duration of such trials regardless of treatment discontinuation. The protocol and site manuals should specify following up on all potential malignancy events (e.g., unexplained GI bleeds, lung nodules) until the malignancy status of them is determined. For all malignancies the protocol and site manuals should specify collecting the operative report for the diagnosis, the histopathology report for the diagnosis, the presumed primary site (if the operative report and the histopathology report were not done or are not available or do not identify the primary site), the date of first clinical diagnosis of the malignancy event, and (for the patients with malignancy events) the identities of all malignancies diagnosed prior to randomization, and the current statuses of all know malignancies.

DAPT Study Results

The principal investigators published the rationale and design for the DAPT study. (Mauri, Kereiakes et al. 2010) They stated that the study was sponsored by Harvard Clinical Research Institution and they acknowledged four drug eluting stent (DES) manufacturers and four thienopyridine manufacturers as providing funding for the study, as well as supplemental funding from Health and Human Services. They described the aim of DAPT as ascertaining the impact of extending the duration of dual antiplatelet therapy beyond 1 year after coronary stent procedures by examining the balance of risk and benefit in a broad population of treated patients.

To achieve this aim they proposed a novel study design: Patients undergoing percutaneous coronary intervention (PCI) with stent placement (15,245 DES patients and 5,400 bare metal stent (BMS) patients) and no contraindications to long term DAPT and no current medical conditions with a life expectancy < 3 years were to be enrolled at the time of PCI. The enrolled patients were to receive 12 months of open label DAPT, with the choice and dosage of the thienopyridine (clopidogrel or prasugrel) left to local investigator choice. Aspirin dosage was to be the lowest acceptable dose per physician's discretion (75-325 mg for the first 6 months after the procedure and 75-162 mg indefinitely thereafter.) All enrolled patients who were treated for 12 months with DAPT and who were event-free (from death, MI, stroke, repeat coronary revascularization, stent thrombosis, and GUSTO moderate or severe bleeding) and who demonstrated compliance with thienopyridine therapy (defined as no interruptions > 14 days) were eligible for randomization. Eligible patients were to be randomized to continue

thienopyridine treatment (at the pre-randomization dosage of clopidogrel 75 mg or prasugrel 5 or 10 mg daily) or to placebo, while continuing aspirin, for an additional 18 months. Study drug was to be discontinued at 30 months followed by a 3-month observation period with patients on aspirin alone (to capture possible thienopyridine withdrawal rebound events.) The co-primary efficacy endpoints at 33 months were to be MACCE and stent thrombosis. The primary analyses were to be performed on the DES patients.

The investigators presented the preliminary results to the FDA in four PowerPoint presentations. (DAPT_Investigators 2014; DAPT_Investigators 2014; DAPT_Investigators 2014; DAPT_Investigators 2014)[2] and recently published the main trial results for the DES subgroup. (Mauri, Kereiakes et al. 2014) The preliminary communications and PowerPoint presentations do not provide all of the details helpful for understanding the study results, e.g., they do not include detailed reasons for enrolled patients not being randomized, dosages for prasugrel and aspirin, follow-up details, etc. The NEJM publication included statistics based on readjudication for malignancies and malignancy deaths but did not change appreciably the cancer statistics from the preliminary presentations. What has been reported remains very concerning. I summarize the data presented relevant to the mortality and cancer findings below.

I show in Table 1 the patient flow in DAPT.

Table 1: Patient Flow in DAPT

	DES		BMS	
	N	%	N	%
Enrolled	22,866		2,816	
Randomized	9,961	44%*	1,687	60%*
30m follow-up	9490	95%†	1580	94%†
33m follow-up	9390	94%†	1565	93%†

*percent of enrolled; †percent of randomized

The number enrolled is substantially higher than that projected in the 2010 article for DES but lower for BMS. Note that only about 44% of patients in the DES subgroup were randomized while only 60% of patients in the BMS subgroup were randomized. The presentation slides did not specify how the follow-up statistics count deaths but another presentation slide shows about 5% missing data, so presumably the statistics in Table 1 count deaths as non-missing.

COMMENT: How enrolled patients were selected for randomization could affect the cancer risks, but it is impossible to project how or the magnitude of any effect. Regardless, because DAPT was a large randomized trial, the initial risks should be equal in both arms. We should be aware of the unique study design, i.e., the 1-year "run-in" period with about half of patients excluded, when comparing DAPT to the typical antiplatelet study lacking the extended run-in. It is also relevant whether the randomization rates varied by thienopyridine type, i.e., clopidogrel

[2] Because the PowerPoint presentations provide the data on which I based my analyses of DAPT and because the investigators have not published many of those data, I have included the presentations as Attachments 1 to 4.

vs. prasugrel, but that information was not provided in the two preliminary communications. The rate of missing data, about 5-6%, appears to be neither great nor incomplete enough to reject the study results

Because the focus of this review is upon cancer risk and mortality, not efficacy, I will not provide details of the preliminary efficacy analyses. The presentations provide conclusions that, for the primary DES analysis, 30m DAPT was associated with reduction in both MACCE and stent thrombosis at 30 and 33m. The benefit was greater for stent thrombosis (HR 0.29) than for MACCE (HR 0.71). The MACCE benefit was driven by reduction in MI.

Despite the reported benefit for stent thrombosis and MI, all cause mortality trended (b) (4) The two preliminary presentations and the NEJM publication did not have statistics for the study as a whole but did include the following Kaplan-Meier (K-M) plot for the DES subgroup.

Figure 5:

While cardiovascular (CV) death rates were neutral, non-CV deaths (NCVD) diverged starting at about 6 months post randomization as shown in the following K-M plot.

Figure 6:

COMMENT: The cause of death (b) (4) *in non-CV deaths for a moderate-sized study such as DAPT should be obvious. I show in Table 2 the CDC's tabulation of the causes of death in the 2011 U.S. population aged 60-64 (the average age in DAPT was about 62): (CDC 2014)*

Table 2: CDC Causes of Death in the 2011 U.S. Population Aged 60-64

	Cause of death (ICD-10)	N	% NCVD
	All causes	179,043	
	All non-CV deaths (NCVD)	131,142	100%
1	Malignant neoplasms (C00-C97)	64,649	49%
2	Diseases of heart (I00-I09,I11,I13,I20-I51)	39,152	
3	Chronic lower respiratory diseases (J40-J47)	9,381	7%
4	Diabetes mellitus (E10-E14)	7,249	6%
5	Accidents (unintentional injuries) (V01-X59,Y85-Y86)	6,602	5%
6	Cerebrovascular diseases (I60-I69)	6,509	

	Cause of death (ICD-10)	N	% NCVD
7	Chronic liver disease and cirrhosis (K70,K73-K74)	4,888	4%
8	Nephritis, nephrotic syndrome and nephrosis (N00-N07,N17-N19,N25-N27)	2,857	2%
9	Septicemia (A40-A41)	2,812	2%
10	Intentional self-harm (suicide) (*U03,X60-X84,Y87.0)	2,713	2%
11	Influenza and pneumonia (J09-J18)	2,365	2%
12	Essential hypertension and hypertensive renal disease (I10,I12,I15)	1,500	
13	Viral hepatitis (B15-B19)	1,427	1%
14	In situ neoplasms, benign neoplasms and neoplasms of uncertain or unknown behavior (D00-D48)	886	1%
15	Aortic aneurysm and dissection (I71)	740	
	All other causes (Residual)	25,313	19%

Note that about 50% of the non-CV deaths were attributed to cancer while the highest percentage of another non-CV specific cause of death (lower respiratory disease) is 7%. Given that it is mechanistically improbable that a drug causes a difference in all non-CV causes of death, for a moderate-sized drug study to show a significant difference in non-CV deaths there are two possibilities: (1) Either the drug causes a moderate increase in cancer deaths or (2) the drug causes a whopping increase in another specific cause of death. For example, for the second most frequent non-CV cause of death (lower respiratory disease at 7%) we can estimate the magnitude of the increase required as follows: (b) (4)

[redacted]

That an antiplatelet drug may increase the risk of cancer is an issue that I raised based on my reviews of the prasugrel TRITON study starting in 2008. For the details please seem my review dated May 6, 2009. (Marciniak 2009) I also reviewed the cancer findings in the prasugrel TRILOGY study in my review dated September 13, 2013. (Marciniak 2013) I have summarized the findings from both studies in the ***Prasugrel and Cancer*** *section below.*

My review of cancers in TRITON was motivated by my interpretation of the prasugrel mouse carcinogenicity study that prasugrel increased frequencies of solid cancers in mice. Based on that study and the arguments presented below I pre-specified performing the primary analyses for TRITON on solid cancers excluding non-melanoma skin cancers and brain tumors. My justifications for excluding from the primary analyses hematologic malignancies, non-melanoma skin cancers, and brain tumors are the following:

- *Hematologic malignancy rates were not increased by prasugrel in the mouse carcinogenicity study. Furthermore, one possible mechanism for an antiplatelet drug promoting solid cancers is interfering with platelet aggregation and hence interfering with a potential defense mechanism against solid cancer neovascularization. Hematologic malignancies are not dependent upon neovascularization.*

- *Non-melanoma skin cancers (more accurately basal cell and squamous cell skin cancers) are much less serious than other solid tumors and rarely metastasize or cause death. They are likely underreported in clinical trials, e.g., they are the most frequent cancers in the elderly in population studies but not in clinical trials. Furthermore, the underlying etiology is predominantly solar skin damage, an etiology not operative for other solid cancers.*

- *Brain tumors are dependent upon the drug crossing the blood-brain barrier. They are not infrequently reported as "brain tumors" without a histologic diagnosis and without a confirmation of malignancy. Not uncommonly they are not distinguished as primary tumors or metastatic disease.*

I believe these exclusions are still reasonable for the primary analyses of cancers associated with drugs causing bleeding. I present the statistics from the presentations for solid cancers below as well as for my three exclusions separately.

The presentations do not identify whether the statistics are for new diagnoses or for new malignancy events, including ones in patients with a history of a malignancy at the same site. With that limitation I show in Table 3 malignancies by site and thienopyridine use in DAPT months 12 to 33 as reported in the presentations.

Table 3: Malignancies by Site and Thienopyridine Use in DAPT 12-33m

	Clopidogrel		Prasugrel		Either	
Site	30m	12m	30m	12m	30m	12m
Bladder	5	4	3	0	8	4
Bone	2	0	0	0	2	0
Breast	2	8	3	1	5	9
Colorectal	8	8	5	4	13	12
Endocrine	1	2	0	2	1	4
Esophagus	1	2	0	3	1	5
Gynecologic	1	0	1	0	2	0
Kidney/Ureter	3	3	2	1	5	4
Liver	1	0	1	2	2	2
Lung	15	12	2	2	17	14
Malignant melanoma	1	4	0	0	1	4
Metastasis, primary?	12	6	0	1	12	7
Oral Cavity/Pharynx	0	1	2	2	2	3
Other	3	0	1	0	4	0
Pancreas	2	0	3	1	5	1
Prostate	14	9	7	3	21	12
Stomach	1	1	0	1	1	2
Solid cancers N	72	60	30	23	102	83
Solid cancers RR*	1.2		1.3		1.2	

Site	Clopidogrel		Prasugrel		Either	
	30m	12m	30m	12m	30m	12m
Brain	2	0	1	0	3	0
Non-melanoma skin	6	5	0	0	6	5
Leukemia	1	2	1	1	2	3
Lymphoma	4	1	2	2	6	3
Other hematologic	2	3	0	1	2	4
All hematologic	7	6	3	4	10	10

*RR = risk ratio 30m/12m

The increased risk of solid cancers with continued thienopyridine use is consistent between clopidogrel and prasugrel (risk ratio 1.2 vs. 1.3). There are higher rates of bladder, prostate, and pancreas cancers and unknown primaries in the 30m arm. GI cancers, ones whose detection we associate with bleeding, were not increased in the 30m arm.

Brain tumors were rare but were only reported in the 30m arm. Non-melanoma skin cancers were rarely reported (and likely unreported) and evenly distributed. Hematologic malignancies were also evenly distributed between the two arms.

This point estimate of the increased risk of solid cancers is not statistically significant ($p \sim 0.19$ by Chi square statistic) in DAPT but the study is underpowered for detecting a modest difference in cancer risk. If the point estimates of the rates are the true rates, about 54,000 patients would have to be randomized in order to have 80% power of detecting a risk ratio of 1.2 at alpha = 0.05.

While the difference in solid cancer rates is not statistically significant, the investigators reported a statistically significant difference in deaths attributed to cancer (33 vs. 16, $p = 0.02$.) As noted above, cancer deaths contributed substantially to the higher rate of non-CV death in the 30m arm.

COMMENT: While the increased solid cancer incidence in the 30m arm is not statistically significant, we should interpret it in light of the statistically significant difference in cancer deaths and in light of the cancer rates in other studies of antiplatelet drugs. The supporting evidence from these latter observations suggests that the increased solid incidence is real. I summarize the evidence from other studies of antiplatelet drugs below.

I have observed in other antiplatelet and anticoagulant studies that solid cancer rates frequently are higher in the arms with higher bleeding rates. GUSTO moderate/severe bleeding was the pre-specified primary safety endpoint in DAPT. Hence I show in Table 4 the GUSTO moderate/severe bleeding rates by thienopyridine use in DAPT, DES Subgroup, months 12-30.

Table 4: GUSTO Moderate/Severe Bleeding Rates by Thienopyridine Use in DAPT, DES Subgroup, Months 12 to 30

	clopidogrel	prasugrel	either
30m	2.66%	2.28%	2.5%
12m	1.68%	1.36%	1.6%
diff	0.98%	0.92%	0.96%
RR*	1.6	1.7	1.6
p	0.01	0.048	0.001

*RR = risk ratio 30m/12m

Bleeding was moderately increased with continued thienopyridine use. The increased relative risk was similar for clopidogrel and for prasugrel.

COMMENT: The increased bleeding and solid cancer rates are consistent with the increased bleeding and solid cancer rates we have seen with other antiplatelet and anticoagulant agents. Clopidogrel and prasugrel appear to have behaved similarly for both bleeding and solid cancers in DAPT. I am not concerned that only clopidogrel appears to have shown a difference for deaths attributed to cancer or for non-CV deaths because the prasugrel subgroup was smaller and its confidence intervals for such statistics are wide.

Prasugrel and Cancer

Prasugrel has two large CV outcome trials potentially providing additional data regarding its association with solid cancers: TRITON and TRILOGY. I summarize relevant features of them in Table 5 compared to the prasugrel part of DAPT.

Table 5: Prasugrel Outcome Trials

Trial	TRITON	TRILOGY	DAPT-P
Dates randomized	11/04-01/07	01/09-9/11	08/09-04/14
Population	ACS invasive	ACS medical	stents
N	13,608	9,456	3,686
Age, average y	61	66	59
Male	74%	61%	77%
Follow-up, average m	15	17	~20
Prasugrel discontinuation	18%	24%	~25%?
Complete follow-up	94%	79%	94%
Died	2.7%	8.9%	NA
Major/GUSTO bleed RR	1.4	1.3	1.7*
95% CI	1.1-1.7	0.9-1.9	NA
Solid cancer RR	1.5	0.9	1.3
95% CI	1.1-2.0	0.6-1.3	0.7-2.2
Solid ca/100 PEY (control)	1.0	1.0	NA
Non-CV death RR	1.2	1.0	1.2

95% CI	0.8-1.8	0.7-1.4	0.5-2.5
Died with solid ca RR	1.7	0.7	NA
95% CI	0.9-3.2	0.4-1.3	NA
Died %, solid ca pts (control)	22%	46%	NA

*GUSTO bleed RR DES subgroup; NA = not available currently to FDA; PEY = person exposure year; RR = risk ratio prasugrel/clopidogrel; CI = confidence interval

*COMMENT: What appears striking to me in Table 5 is the similarity in the bleeding, cancer, and non-CV death findings between TRITON and DAPT-P. All three adverse events are increased in the prasugrel arms of both studies with not too dissimilar point estimates and overlapping confidence intervals. TRILOGY appears to be the odd study out with dissimilar results, although its confidence intervals are still overlapping. I believe that the difference in TRILOGY may be the result of conduct issues, e.g., incomplete follow-up, that I document below. Another possibility is the differing results for studies in patients managed invasively compared to studies in patients managed medically. I discuss the latter in the **Anticoagulant Drugs and Cancer** section below.*

I have reviewed cancer findings from TRITON in my review from 2009 (Marciniak 2009) and from TRILOGY in my review from 2013. (Marciniak 2013) I summarize the most relevant findings from those reviews below.

TRITON

TRITON was a trial in ACS patients managed invasively of prasugrel vs. clopidogrel. TRITON is my index study for my concerns about CV drugs increasing cancer risk. I analyzed solid cancer rates in TRITON because my interpretation of the prasugrel 24-month mouse carcinogenicity study was that prasugrel may be a tumor promoter for a wide variety of solid cancers (excluding skin cancers.)

COMMENT: While the preclinical carcinogenicity studies have been interpreted as negative by the usual criteria, the sizing of the studies is inadequate for statistical confirmation of modest cancer promotion effects. Furthermore, the usual criteria (analyzing tumor incidences by site and sex) are inappropriate for analyzing an effect upon a wide range of solid tumors. My analyses of the prasugrel carcinogenicity studies did not follow the usual criteria but analyzed groups of solid cancers and suggested that prasugrel was promoting the growth of many solid cancers. Please see my 2009 review for the details (Marciniak 2009) but I have included my conclusions below:

> *"Because of the highly significant difference in hepatic adenomas, the moderately suggestive trend in hepatic cancers, the weakly suggestive trends in intestinal and lung cancers, the supportive data of the altered cell foci, and the absence of any tumors showing a clear reverse trend, I would still interpret the mouse study as suggestive of a carcinogenic effect of prasugrel in one species."*

Regardless, negative preclinical carcinogenicity studies do not rule out a drug being a cancer promoter in humans. The TSI memo's author has made this mistake previously: She rejected the possibility that ARBs are associated with increased rates of lung cancer in her memo dated 15 April 2013 (Southworth, Stockbridge et al. 2013) because "there is no evidence from nonclinical

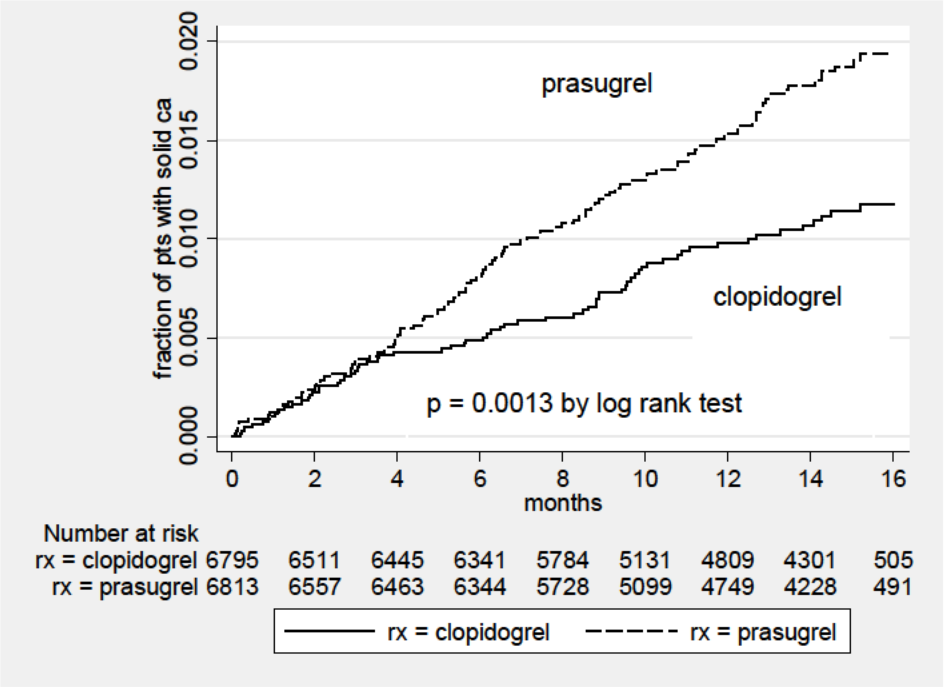
assessments of any of the ARBs that they are carcinogenic" and "we know of no case of specific lung-cancer promotion or true carcinogenesis for an orally administered agent" and concluding that "We regard it as implausible that ARBs somehow cause or accelerate cancer without a reasonable precedent or proposed mechanism . . ." Orally administered beta carotene is a recognized risk factor for lung cancer per the National Cancer Institute. (NCI 2012) The NCI bases its conclusion on the results of two large randomized controlled trials that document beta carotene as a risk factor or cancer promoter for lung cancer in humans, particularly smokers. (ATBCCP_Study_Group 1994; Omenn, Goodman et al. 1996) Beta carotene appears to be a cancer promoter despite negative carcinogenicity studies (Heywood, Palmer et al. 1985) and preclinical and epidemiologic evidence suggesting that beta carotene may prevent cancer. (Peto, Doll et al. 1981)

I have proposed a mechanism for how drugs that increase bleeding may increase solid cancer rates: Solid cancers are dependent upon neovascularization for their growth. If one of the body's defense mechanism is clotting to inhibit the neovascularization and the tumor growth, then drugs inhibiting clotting may promote solid cancer growth. That the coagulation system plays a role in malignancy is demonstrated by the well established observation that malignancy is frequently associated with a hypercoagulable state. (De Cicco 2004) While one hypothesis has been that the malignancy is inducing the hypercoagulable and there is evidence supporting that hypothesis, I advocate that the hypothesis that the coagulation system is also a defense mechanism against solid cancers should be explored.

There is another possible mechanism for how antiplatelet drugs may increase solid cancer rates: It is well established that platelets function in immunity as well as coagulation. (Morrell, Aggrey et al. 2014) While the immune functions of platelets have been studied predominantly regarding body defenses against microorganisms, I believe that the possibility that platelets play a role in immune defense against solid cancers should also be explored. It is also well established that many carcinogenic drugs impair immune surveillance. (Rubin 1964) Hence antiplatelet drugs such as clopidogrel and prasugrel impairing platelet-mediated cell immunity and promoting cancer growth is a possibility. This mechanism may not be shared with other drugs increasing bleeding, the oral anticoagulants, and could be platelet receptor specific. Because anticoagulants also appear to be associated with increased solid cancer rates, I judge that the data support better the coagulation defense mechanism than an immune surveillance mechanism.

The solid cancer (excluding non-melanoma skin and brain) event rates by arm in TRITON showed the strikingly different incidence curves shown in Figure 7.

Figure 7: Solid Cancer Event Incidence in TRITON



The solid cancer rates[3] begin to diverge at about 4 months and continue to diverge throughout 16-months of follow-up. The hazard ratio estimated by Cox regression is about 1.6 (95% CI 1.2-2.2). The absolute risk difference at 16 months is about 0.8%. Figure 7 includes recurrent cancers as well as new cancers, the results limited to new solid cancers are similar although of lower statistical significance (p = 0.024). I show the sites of the solid cancers in TRITON in Table 6.

Table 6: Solid Cancer Sites in TRITON

	clopidogrel	prasugrel
bladder	10	8
breast	1	6
carcinoid	1	0
cervix	1	1
colon	8	18

[3] In this document I refer to "cancer rates" and "cancers" for brevity. However, unless I specifically comment otherwise, the rates are fractions of patients with at least one cancer adverse event during the ITT trial period rather than rates or incidence of newly diagnosed cancers. Clinical trials do not always capture complete histories of cancers, so in some cases we cannot determine whether a cancer event is a newly diagnosed cancer or a recurrence. Regardless, because most cancer deaths result from the progression or recurrence of the cancer rather than the primary tumor, I recommend analyzing cancer events regardless of novelty. In CV trials the vast majority of first cancer events are newly diagnosed cancers and multiple cancers in one patient are uncommon. For this review I based site-specific cancer rates on the tabulations of first solid cancers and did not add in second cancers, if any.

	clopidogrel	prasugrel
esophagus	2	5
gi other	1	0
head & neck	2	1
kidney	2	3
liver	0	2
lung	14	19
melanoma	2	3
mesothelioma	0	1
other	1	0
pancreas	3	2
prostate	10	17
sarcoma	0	2
stomach	8	8
thyroid	1	0
unknown	1	7
uterus	1	0
total	69	103

The sites with higher rates in the prasugrel arm are mainly the more common sites, i.e., breast, colon, lung, and prostate. Unknown primaries (frequently lung or GI) also had a higher rate with prasugrel. Esophagus, a site perhaps detected because of bleeding, also had a higher rate although stomach and bladder, other sites detected because of bleeding, were balanced between the two arms.

COMMENT: I believe that the cancer results in TRITON are very well validated. They have been scrutinized both internally within the FDA and with the sponsor. The disagreements have predominantly been regarding whether to include other neoplasms such as skin cancers, whether to count both new and recurrent disease, and whether the differences represent a cancer promotion or early detection effect rather than regarding the identities of the solid cancers. I have detailed my reasons for excluding skin cancers, and brain tumors and hematologic malignancies, in my review and summarize them in the ***DAPT Study Results*** *section.*

DAPT provides additional evidence that the increase in solid cancer rates in TRITON are not the result of early detection in patients who bled. While I have argued that the continued divergence of the curves in Figure 7 and the similar survival rates after a solid cancer event for prasugrel and clopidogrel suggest tumor promotion rather than early detection, the facts that in DAPT the solid cancer increases occurred despite the 1-year run-in period and that mortality was increased due to the solid cancer increases provide compelling support for cancer promotion.

The solid cancer results in TRITON are solid: They support a statistically (p = 0.0013) and clinically (HR 1.6, absolute risk difference 0.8% at 16 months) significant increase in solid cancers with prasugrel vs. clopidogrel when prasugrel is dosed per the TRITON protocol.

Mortality rates after a solid cancer event in TRITON were high and similar in both arms, about 30% at 9 months. Because assigning a single cause of death (other than the cancer) is problematic in cancer patients and because the mortality rate following a solid cancer event is substantially higher than the late mortality rate in ACS patients without cancer, I analyzed deaths in cancer patients rather than deaths attributed to cancer (and I recommend primarily analyzing deaths in cancer patients rather than deaths attributed to cancer or non-CV deaths in all studies.) I show in Table 7 the numbers of cancer patients who died in TRITON.

Table 7: Deaths in Cancer Patients in TRITON

	Through end of study			With additional follow-up	
	Clopidogrel	Prasugrel	RR†	Clopidogrel	Prasugrel
New solid cancers*	14	22	1.6	22	36
Treatment emergent solid cancer* AEs	15	26	1.7	24	42
New malignancies	14	23	1.6	24	37
Treatment emergent malignancy AEs	16	27	1.7	28	43

*excluding non-melanoma skin and brain; †RR = risk ratio prasugrel/clopidogrel

The sponsor for TRITON acquired additional follow-up on the cancer patients. Regardless of whether one ignores or counts this additional follow-up, the relative risk of dying with cancer was about 1.5-1.7 fold higher in the prasugrel arm than in the clopidogrel arm.

All cause mortality was virtually identical in the two arms at the end of TRITON. However, because there was an early mortality benefit with prasugrel particularly in the STEMI substudy, mortality at the end of TRITON was trending unfavorably for prasugrel. I show the incidence curves for all cause mortality in Figure 8 and for non-CV mortality in Figure 9.

Figure 8: All Cause Mortality Incidence in TRITON

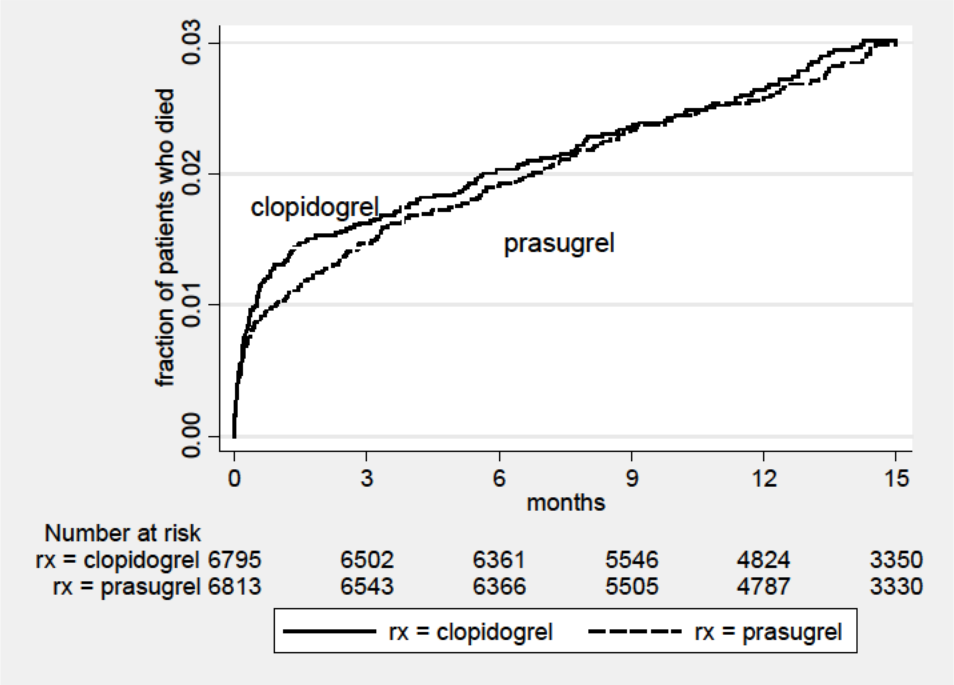
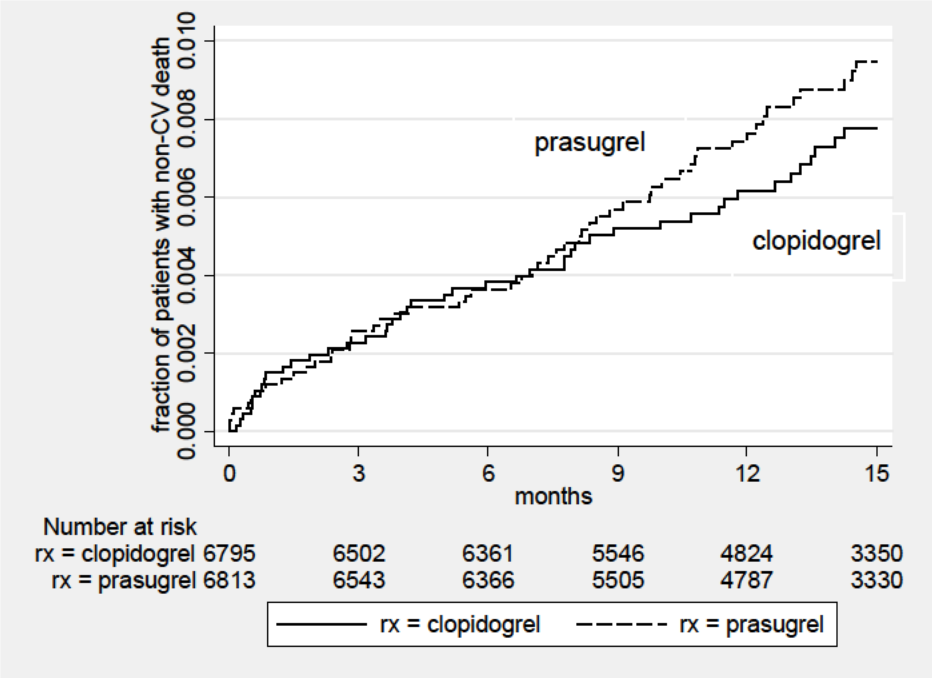


Figure 9: Non-CV Mortality Incidence in TRITON



While the separation of the non-CV death curves is not statistically significant by usual tests, the separation at about 9 months is striking and consistent with the increased cancer rates in the prasugrel arm.

COMMENT: In TRITON prasugrel produced about a 30% higher rate of major or minor TIMI bleeding than clopidogrel. The TRITON results are consistent with DAPT overall results in that the arms with greater platelet inhibition and more bleeding led to higher rates of solid cancers and solid cancer deaths and non-CV mortality. DAPT looks like an extension of TRITON.

As I discuss in the **Summary** section above, the antiplatelet drug trials in patients with substantial management by an invasive approach appear to show an association between bleeding and solid cancers while the non-invasive trials do not. We need to consider possible mechanistic differences between the two types of trials. One possibility is the use of drug eluting stents (DES) in the invasive trials. TRITON had substantial use of both types of stents, with about 47% of patients receiving at least one DES at the index PCI. There is no interaction between prasugrel and DES use in TRITON for solid cancers (RR for interaction term 1.0, $p > 0.8$) or for the primary MACE endpoint, for deaths, or for CV deaths. The simplest Cox regression model of non-CV mortality including only prasugrel, DES, and their interaction has hazard ratios (HRs) of about 2 for both prasugrel and DES use and an HR for the interaction of 0.35, with all terms significant (p's ≈ 0.015). However, in more comprehensive Cox models the interaction is not significant. I show one such model in Table 8.

Table 8: Cox Regression of Non-CV Mortality in TRITON

```
Cox regression -- Breslow method for ties

No. of subjects =        13608                     Number of obs   =     13608
No. of failures =           99
Time at risk    =  174264.8667
                                                   LR chi2(7)      =     84.92
Log likelihood  =   -883.98458                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.083262   .0108698     7.97   0.000     1.062166    1.104777
        male |   1.421757   .3313628     1.51   0.131     .9004082    2.244974
    prasugrel |   1.883072   1.112817     1.07   0.284     .5913464    5.996416
         des |   1.110573   .5305733     0.22   0.826     .4353993    2.832738
des#prasugrel |   .3822446   .2405797    -1.53   0.127     .1113285     1.31243
         bms |    .392559   .1950346    -1.88   0.060      .148253    1.039456
bms#prasugrel |   1.220962   .7806721     0.31   0.755     .3486999    4.275163
------------------------------------------------------------------------------
```

While both prasugrel use and DES use alone were associated with higher non-CV mortality, patients receiving prasugrel with a DES experienced lower non-CV mortality. The prasugrel-DES interaction for deaths in solid cancer patients is similar.

COMMENT: The TRITON data do not strongly support a prasugrel-DES interaction and the observed interaction is in the wrong direction for explaining why the invasive trials appear to show an association between bleeding and solid cancers while the noninvasive trials don't. I suspect the borderline interaction is a chance variation. However, I do think we should examine other trials including DES for effects upon cancer and other disorders, e.g., infections.

TRILOGY

TRILOGY was a failed trial of prasugrel vs. clopidogrel in ACS patients managed medically (as opposed to the TRITON invasively managed ACS patients.) It failed to demonstrate superiority of prasugrel to clopidogrel regarding its primary endpoint of reducing CV death, MI, and stroke in such patients.

Because of the prasugrel cancer results, I had recommended that the sponsor examine cancer rates in an adequately sized study to have 90% power of detecting a 50% increase in the rate of development of new solid cancers. For cancer rates similar to those in TRITON, i.e., a control rate of about 1% per year, the number of events needed is about 279. A large trial is needed, e.g. a 22,000 patient trial with mean follow-up of a year and minimum follow-up exceeding 8 months is an example.

We (the FDA) did not require an adequately sized study but recommended that the sponsor capture cancer events in TRILOGY. Despite this recommendation, cancer event capture appears to have been problematic in TRILOGY. I summarize below the many problems with TRILOGY:

- TRILOGY was underpowered for cancer analyses. Rather than the 279 new solid cancers needed for adequate power, it reported 138 new solid cancers, 147 solid cancers including recurrent. TRILOGY was half the size needed.

- Study drug discontinuation rates were high. Per the NEJM article 24% of prasugrel and 22% of clopidogrel patients discontinued study drug during the study period. Working from the exrxendt ("Exposure Prescribed End Date ") variable in the NDA submission, I calculated that about 30% of patients had discontinued study drug more than 30 days prior to death or study end. By 120 days (the time at which the cancer rates started to diverge in TRITON) about 15% of prasugrel patients had already discontinued study drug. Study drug discontinuations are particularly problematic in TRILOGY because of the protocol specification regarding adverse event (AE) reporting—see next bullet.

- The protocol specified collecting adverse events only until 30 days after the last dose of study drug unless the investigator "feels the events were related to either study drug or a protocol procedure." While the protocol does state that cancers should be reported through study end, cancer events were adverse events. The statistics on cancer rates that I present below suggest that cancer events were underreported.

- Follow-up was incomplete. The NEJM article reported that about 6% of patients did not complete the study. However, from the data sets submitted to the NDA I can verify only that about 80% of the patients died or had a last contact on or after the study end date (or maximum treatment duration) and only about 70% of patients died or had a visit with vital signs on or after the end date.

- Solid cancer rates were low in TRILOGY. In TRILOGY the solid cancer rate was about 0.92 per 100 person exposure years (PEY) while in TRITON it was about 1.28 per 100 PEY (for both arms combined). Yet TRILOGY had a higher median age (66) than TRITON (61) and age is one of the most predictive risk factors for cancer rates. However, the differences in overall solid cancer rates are not as prominent as the differences in cancer rates in some geographic regions—see next bullet.

- Asian and Eastern European sites appear to have underreported cancers in TRILOGY. About 21% of randomized patients were from Asia in TRILOGY while none were from Asia (excluding Israel) in TRITON. Reported solid cancer rates in Asian patients in TRILOGY were very low, about 0.15 per 100 PEY, or more than 10-fold lower than in the US (1.7) and Western Europe (2.0). Cancer rates in Asia as reported in international statistics are 2 to 3 fold lower in Asia than in the Western world. Cancer rates in Asia in the apixaban ARISTOTLE trial were about half of Western rates. Ten-fold lower suggests underreporting. About 35% of randomized patients were from Eastern Europe in TRILOGY while 24% were from Eastern Europe in TRITON. Reported solid cancer rates in Eastern European patients in TRILOGY were low, about 0.68 per 100 PEY compared to 1.14 in TRITON and 1.17 in ARISTOTLE. Hence there also appears to be underreporting of solid cancers from Eastern Europe in TRILOGY.

- Cancer results were only favorable in the second half of the trial. The solid cancer results were unfavorable for prasugrel in patients enrolled in the first half of the trial (RR about 1.07) becoming favorable in patients enrolled in the second half (RR about 0.7) as shown in Table 9.

Table 9: Solid Cancer rates for Patients Enrolled by Half in TRILOGY

	half 1		half 2	
	rate*	RR†	rate*	RR†
clopidogrel	0.93		0.99	
prasugrel	0.99	1.07	0.69	0.70

*rate per 100 PEY; †RR = risk ratio prasugrel/clopidogrel

The interaction between treatment and trial half for the solid cancer rates as reported by the sponsor is statistically significant (p = 0.033 by Cox regression). The rates above are also consistent by quarter: clopidogrel is favorable in quarters 1 and 2 patients and prasugrel in quarters 3 and 4 patients. The anomalous rate appears to be the low prasugrel rate in the second half patients.

Ignoring the limitations of the problems described above, the sponsor analyzed "all new non-benign neoplasms" and calculated a hazard ratio (HR) of 1.045 (95% confidence interval (CI) 0.767-1.425, p = 0.786.) I analyzed solid cancer events and calculated a HR of 0.96 (95% CI 0.68-1.36, p = 0.82.)

COMMENT: TRITON and TRILOGY are not absolutely inconsistent because the confidence intervals for their cancer rates overlap, but TRILOGY has been interpreted as establishing that prasugrel does not have a cancer risk. Because of the many problems with TRILOGY I judge its results to be unreliable. I believe that the DAPT results, which are more consistent with TRITON than with TRILOGY, now confirm that TRITON provides the better estimate of cancer risk and that prasugrel does increase the risk of solid cancers. DAPT also confirms that the increased risk of solid cancers with prasugrel is likely a cancer promoter effect and not a detection bias because the difference in cancer rates was manifested during the thienopyridine withdrawal period long (> 1 year) after the initiation of thienopyridine treatment.

The TRITON-TRILOGY-DAPT comparisons also confirm my belief that a confirmatory trial, one allegedly with specific directions for ascertaining the event of interest, is not necessarily more reliable than the index trial lacking pre-specifications. I believe that TRILOGY demonstrates that, by sloppy conduct, one may obscure a signal despite having a goal to clarify whether that signal exists. The TRITON-TRILOGY-DAPT comparisons have implications for our recommendations regarding how trials must be conducted to maximize confidence in their results. However, while it is clear that TRILOGY had conduct issues, it is not clear that the TRILOGY results are completely wrong. The vorapaxar TRACER-TRA2P comparison is similar to the prasugrel TRITON-TRILOGY comparison as I discuss in the ***Other Antiplatelet Drugs and Cancer*** *section below.*

Clopidogrel and Cancer

Clopidogrel has been studied in a heterogeneous set of outcome trials, many performed long ago. I show the features of the older clopidogrel trials for which we have datasets in Table 10 and the newer trials (including an NIH trial SPS3 for which we do not have datasets) in Table 11.

Table 10: Older Clopidogrel Outcome Trials

Trial	CAPRIE	CURE	CREDO	CHARISMA
Dates randomized	03/92-02/95	12/98-09/00	06/99-04/01	10/02-11/03
Population	high risk	ACS	PCI	high risk
N	19,185	12,562	2,116	15,603
Age,average y	63	65	62	64
Male	72%	62%	71%	70%
Control	ASA	placebo	clopidogrel 28d	placebo
ASA - clopidogrel	0	75-325 mean 170-150	325 28d then 81-325	75-162
ASA - control	325			
Follow-up, average m	23	10	12	28
Clopidogrel discontinued	24%	20%	37%	20%
Complete follow-up	87%	77%	91%	86%
Died	5.9%	6.0%	2.0%	4.8%
Major/severe bleed RR	0.9	1.4	1.3	1.25
95% CI	NA	1.1-1.7	1.0-1.8	1.0-1.6
Solid cancer RR	1.0	1.0	1.4	0.9
95% CI	0.8-1.2	0.7-1.5	0.7-2.7	0.8-1.1
Solid ca/100 PEY (control)	1.4	1.0	1.4	1.0
Non-CV death RR	1.0	1.1	0.6	1.0
95% CI	0.8-1.3	0.7-1.6	0.2-2.0	0.8-1.2
Died with solid ca RR	1.1	0.8	3	0.8
95% CI	0.8-1.5	0.4-1.6	0.3-29	0.6-1.1
Died %, solid ca pts (control)	33%	39%	7%	34%

NA = not available currently to FDA; PEY = person exposure year; RR = risk ratio clopidogrel/control; CI = confidence interval

Table 11: Newer Clopidogrel Outcome Trials

Trial	ACTIVE-W	ACTIVE-A	PRoFESS	SPS3	DAPT-C
Dates randomized	06/03-12/04	06/03-05/06	09/03-07/06	03-11	08/09-04/14
Population	afib	afib	hx of stroke	recent stroke	stents
N	6,706	7,554	20,332	3,020	7,962
Age, average y	71	72	66	63	63
Male	66%	58%	64%	63%	74%

Trial	ACTIVE-W	ACTIVE-A	PRoFESS	SPS3	DAPT-C
Control	warfarin	placebo	ASA+ dipyridamole	placebo	placebo
ASA - clopidogrel	75-100	75-100	1st 2027	325	75-325 6m 75-162 >6m
ASA - control	12%		50		
Follow-up, average m	15	43	30	41	~20
Clopidogrel discontinued	14% @ 18m	16% @ 1y 39% @ 4y	23%	30%	~25%?
Complete follow-up	94%	82%	96%	87%	94%
Died	4.7%	21.8%	7.1%	6%	NA
Major/severe bleed RR	1.1	1.6	0.9	2.0	1.6
95% CI	0.8-1.5	1.3-1.9	0.8-1.0	1.4-2.7	NA
Solid cancer RR	0.9	1.1	1.0	NA	1.2
95% CI	0.7-1.2	0.9-1.3	0.9-1.2	NA	0.8-1.7
Solid ca/100 PEY (control)	2.2	1.6	1.2	NA	NA
Non-CV death RR	0.7	0.9	1.0	1.3	1.9
95% CI	0.5-1.1	0.8-1.1	0.8-1.2	0.8-2.1	1.1-3.1
Died with solid ca RR	0.7	1.0	1.1	NA	NA
95% CI	0.4-1.3	0.8-1.3	0.9-1.4	NA	NA
Died %, solid ca pts (control)	28%	56%	45%	NA	NA

NA = not available currently to FDA; PEY = person exposure year; RR = risk ratio clopidogrel/control; CI = confidence interval

I did not include COMMIT and CLARITY in the tables because of their short follow-up durations, too short to be informative regarding cancer development. As can be judged from the tables, the trials are heterogeneous regarding years conducted, populations studied, ages, the use of aspirin, control, clopidogrel discontinuation rates, duration of follow-up, completeness of follow-up, and results.

COMMENT: Of the nine trials, only CREDO and DAPT-C have a signal for higher solid cancer rates with clopidogrel (but we don't have cancer data for SPS3) while only SPS3 and DAPT have a signal for increased non-CV death rates with clopidogrel. However, most of the trials have significant limitations that I discuss below.

CAPRIE

CAPRIE was a trial in high CV risk patients of clopidogrel vs. aspirin 325 mg. CAPRIE was neutral for bleeding, solid cancers and non-CV deaths. Because bleeding was about the same in the two arms, I consider the results to be consistent. The completeness of follow-up was not good and incomplete follow-up appears to be a limitation of many of the trials (with the exception of the early-terminated ACTIVE-W trial) conducted by the clopidogrel innovator.

CAPRIE also illustrates what may be the most serious limitation of cancer ascertainment in some CV trials: In CAPRIE "Adverse experiences of patients were recorded for the duration of their

follow-up, except in those patients who permanently discontinued study drug early; for these patients adverse experiences were counted up to 28 days after discontinuation." Yet we might expect a patient to develop an initial, vague symptom of cancer and discontinue study drug, but not be diagnosed until weeks later. In CAPRIE 24% of patients discontinued clopidogrel prematurely so we may be missing many cancers.

CURE

CURE was a trial in ACS patients of clopidogrel vs. placebo with background aspirin. About 18% of the patients underwent PCI or CABG. CURE showed neutral solid cancer and non-CV death results despite a substantially higher rate of bleeding in the clopidogrel arm. However, treatment duration could be as short as 3 months, the median follow-up duration was too short (10 months) and the completeness of follow-up too low (77%) to have any confidence that the results are accurate and complete.

CREDO

CREDO was a factorial trial in PCI patients of a pre-procedural clopidogrel loading dosing vs. none and then 3 vs. 12 months of clopidogrel. I doubt that the loading dose is relevant to cancer rates so I do not analyze that randomized comparison in this review. The CREDO 3 vs. 12 months comparison does appear to support the hypothesis that higher bleeding rates are associated with higher solid cancer rates, although the difference in solid cancer rates is not even nominally statistically significant. The low point estimate for the non-CV death RR (0.6) is not inconsistent because there were few non-CV deaths in CREDO (4 vs. 7) so the confidence interval is wide. Lung cancers were 5 clopidogrel vs. 0 control, nominally statistically significant, but not greatly concerning given the small number. CREDO was a relatively small, shorter duration trial that started with clopidogrel use in both arms for the first 28 days. While I believe it supports the hypothesis, the support by the study alone is weak.

CHARISMA

CHARISMA was a trial in high CV risk patients of clopidogrel vs. placebo against a background of aspirin. CHARISMA was similar to CAPRIE except that, because clopidogrel was added to aspirin rather than aspirin serving as the control, bleeding rates were higher in the clopidogrel arm. Despite that, solid cancer and non-CV death rates were similar. Like CAPRIE, the completeness of follow-up was not good. Also like CAPRIE, CHARISMA had a limitation regarding reporting adverse events (AEs): For CAPRIE, AEs were not to be reported >28d after drug discontinuation while for CHARISMA treatment-emergent AEs were defined as occurring on-treatment or within 28d of treatment discontinuation. The solid cancer rates in CHARISMA per 100 PEY were lower in CHARISMA than in comparable trials, suggesting underreporting in CHARISMA, although cross-trial comparisons are not reliable. Within these limitations CHARISMA is suggestive that clopidogrel does not increase solid cancer or non-CV death rates.

ACTIVE-W

ACTIVE-W was one of the trials of the ACTIVE program in atrial fibrillation (afib) patients. ACTIVE-W randomized afib patients to clopidogrel+aspirin vs. warfarin. (ACTIVE patients could also be randomized to irbesartan vs. placebo in a factorial design, but I do not discuss the

irbesartan findings here. Please see my review of angiotensin receptor blockers and cancer.) ACTIVE-W had a small difference in bleeding and solid cancer rates between its clopidogrel+aspirin arm and its warfarin arm. There were more lung cancers (21:13) and prostate cancers (19:13) in the warfarin arm. While the non-CV death difference appears favorable to clopidogrel, there was no difference in all-cause mortality. ACTIVE-W supports little difference in bleeding associated with little difference in solid cancer rates.

ACTIVE-A

ACTIVE-A randomized afib patients intolerant of warfarin to clopidogrel vs. placebo with a background of aspirin. ACTIVE-A results are a variation on CHARISMA: The major bleed RR in ACTIVE-A was higher than that in CHARISMA and in ACTIVE-A, unlike CHARISMA, there is a hint of a higher solid cancer rate. Bladder, esophagus and stomach, and prostate cancer rates were substantially higher in the clopidogrel arm. The non-CV death rates in ACTIVE-A were not differentiated. Completeness of follow-up was not high. ACTIVE-A results don't rule out an effect of clopidogrel on solid cancer rates but neither are they suggestive of one.

PRoFESS

PRoFESS was another factorial trial. PRoFESS randomized patients with a history of ischemic stroke randomizing to clopidogrel vs. aspirin plus dipyridamole and telmisartan vs. placebo. I do not discuss the telmisartan randomized comparison here. PRoFESS was neutral for bleeding, solid cancer, and non-CV death rates. Discontinuation of clopidogrel was high, follow-up completeness was not great, and only serious AEs were captured. PRoFESS supports no difference in bleeding associated with no difference in solid cancers..

SPS3

SPS3 was an NIH-sponsored trial of clopidogrel and aspirin vs. aspirin alone in recent stroke. We do not have data sets or a detailed study report with cancer data for it. I abstracted its information from its publication. Noteworthy is that the clopidogrel arm had about a 2-fold higher "major hemorrhage" and a higher non-CVD death rate, the latter not attributed to bleeding deaths. While the non-CV death difference is not statistically significant, the difference in all cause mortality is (hazard ratio 1.5, $p = 0.004$). We do not currently have cancer statistics for SPS3. However, per its protocol SPS3 only required "scrupulous standardized documentation" for "nine categories of events", i.e., ones believed to be related to antiplatelet drugs and not including cancer. SPS3 may not have complete cancer ascertainment. SPS3 is another trial that suggests that clopidogrel is associated with higher bleeding rates and higher non-CV mortality.

SUMMARY COMMENT FOR CLOPIDOGREL TRIALS: Considering the results of the older clopidogrel trials at face value, it is not surprising why I concluded in 2009 that those trials suggested that clopidogrel is not associated with an increased risk of solid cancers. The later trials, with the possible exception of SPS3, also do not suggest a risk. Currently we do not have the cancer data for SPS3—and what was collected regarding events may not be adequate for ascertaining cancer rates accurately—but its non-CV mortality results are concerning.

One possibility for the neutral results in the vast majority of the clopidogrel trials may be incomplete follow-up and cancer ascertainment. While I have summarized above the statistics

*suggesting the problems with incomplete follow-up, I do not know of any way of verifying that cancer ascertainment was incomplete. I discussed in the **Summary** section above one adverse event collection limitation of two of the trials, CAPRIE and CHARISMA.*

*There is another possibility for the neutral results: Solid cancer rates have been differentiated predominantly in trials with an invasive management component, like DAPT. I discuss this possibility in the **Other Antiplatelet Drugs and Cancer** section below.*

Other Antiplatelet Drugs and Cancer

There are two other new antiplatelet drugs studied recently in large outcome trials: ticagrelor and vorapaxar. Ticagrelor is a reversible $P2Y_{12}$ receptor inhibitor. Vorapaxar (unlike clopidogrel, prasugrel, and ticagrelor) is an inhibitor of the PAR-1 receptor rather than the $P2Y_{12}$ receptor. Ticagrelor has one large, clopidogrel-controlled outcome trial (PLATO) and vorapaxar has two large, placebo-controlled outcome trials (TRACER and TRA2P.) I summarize relevant features of them in Table 12.

Table 12: Ticagrelor and Vorapaxar Outcome Trials

New antiplatelet drug	ticagrelor	vorapaxar	
Trial	PLATO	TRA2P	TRACER
Dates randomized	10/06-07/08	09/07-11/09	12/07-11/10
Population	ACS	High risk	ACS
N	18,624	26,449	12,944
Age, median y	62	61	64
Male	72%	76%	72%
PCI	55%	8%*	58%
Clopidogrel use	(control)	62%	92%
Aspirin use	97%	94%	99%
Follow-up, median m	10.5	30	16
Drug discontinuation	23%	24%	28%
Complete follow-up	86%	96%	94%
Died	4.8%	4.3%	4.8%
TIMI major bleed RR	1.0	1.5	1.5
95% CI	0.8-1.2	1.2-1.8	1.2-1.9
Solid cancer RR	0.9	1.0	1.4
95% CI	0.7-1.2	0.9-1.1	1.1-1.9
Solid ca/100 PEY (control)	1.5	1.4	1.0
Non-CV death RR	0.9	1.0	1.1
95% CI	0.6-1.2	0.8-1.2	0.8-1.4
Died with solid ca RR	0.7	1.0	1.5
95% CI	0.4-1.4	0.8-1.2	0.8-2.4
Died %, solid ca pts (control)	23%	30%	26%

PEY = person exposure year; RR = risk ratio new drug/control; CI = confidence interval

I comment on the trial results below.

PLATO

PLATO was a trial in both invasively and medically managed ACS patients of ticagrelor vs. clopidogrel. PLATO had serious conduct issues as I detailed in my review of it. It had a short median follow-up (10.5 months), a substantial (although not unusual) rate of drug discontinuation (23%), and incomplete follow-up (about 86% complete). It can be interpreted as consistent with the hypothesis that neutral bleeding is associated with neutral solid cancer rates because overall TIMI major bleeding was neutral as were solid cancer rates and non-CV death rates. While overall TIMI major bleeding was neutral, non-CABG-related TIMI major bleeding rate was higher in the ticagrelor arm (hazard ratio about 1.2), so one could argue that PLATO is not supportive. However, given the short duration and incompleteness of follow-up, I judge PLATO to be neutral or uninterpretable.

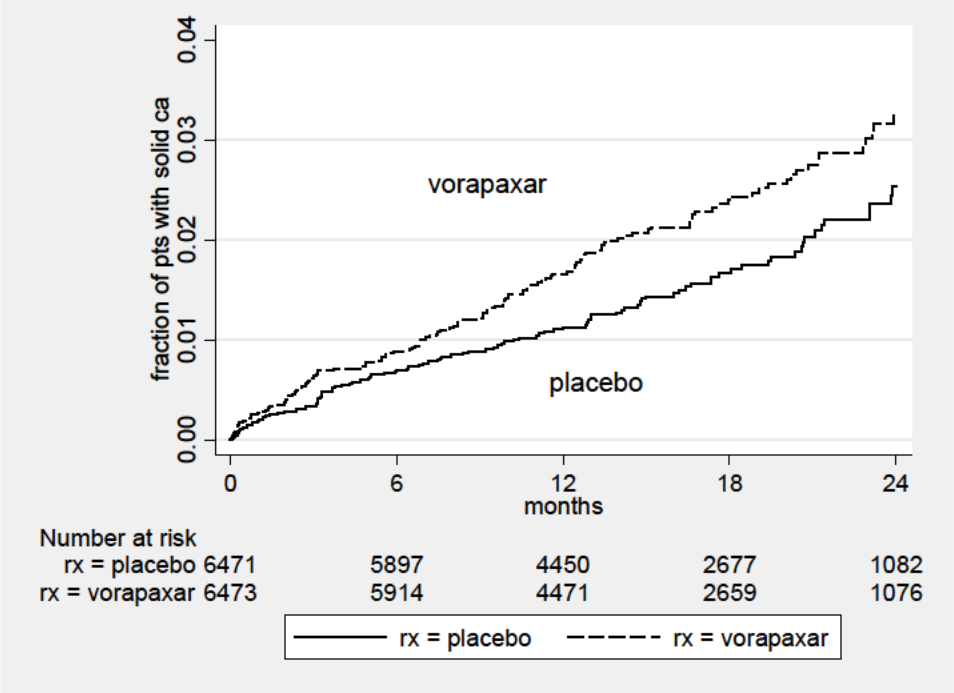
TRA2P

TRA2P was a trial in high CV risk patients of vorapaxar vs. placebo. TRA2P is the largest of the long term antiplatelet and anticoagulant drug trials. About 94% of patients received aspirin and 78% a thienopyridine, usually clopidogrel. It showed a moderately higher rate of TIMI major and other bleeding in the vorapaxar arm but solid cancer and non-CV mortality rates comparable to placebo. Its one identified design flaw is that the protocol specified phone contacts for patients who had discontinued treatment but stated that "During these telephone contacts, the investigator/qualified designee will also collect information about any serious adverse event that occurred up to 60 days after the last dose of study treatment." I discussed above regarding CAPRIE how such an instruction may hinder complete capture of cancer events. Within this limitation TRA2P does not support an association between bleeding and solid cancers but it is inconsistent with TRACER.

TRACER

TRACER was a study in ACS patients of vorapaxar added to standard therapy, usually aspirin (99%) and clopidogrel (92%). About 58% of patients underwent PCI and 10% CABG. About 31% of patients had a DES inserted. TRACER terminated early because of excessive bleeding without an offsetting benefit. TRACER showed significantly higher rates of bleeding and of solid cancer events in the vorapaxar arm (RR or hazard ratio for solid cancers 1.4, 95% CI 1.1 to 1.9, $p \approx 0.01$). Non-CV mortality was only slight higher in the vorapaxar arm (RR 1.1) while deaths in solid cancer patients were about 50% higher with vorapaxar but not statistically significantly increased. I show the incidence curves for solid cancer events in Figure 10.

Figure 10: Solid Cancer Event Incidence in TRACER



The solid cancer event incidence curves diverge early and then almost converge at 6 months, suggesting an early detection bias in the vorapaxar arm. They then continue to diverge for most of the study. The convergence near the end may reflect fewer numbers of patients at risk near the end and hence higher variability in the rate point estimates.

About 57% of TRACER patients had a PCI within 7 days and 31% of TRACER patients had a DES inserted early. Neither early invasive approach nor DES insertion are significant factors or interact with vorapaxar for solid cancer incidence.

The sites responsible for the divergence in the first 3 months were colon (12 vs. 3), lung (10 vs 6) and prostate (4 vs. 0). I show the incidence curves for colon cancer in Figure 11 and for lung cancer in Figure 12.

Figure 11: Colon Cancer Event Incidence in TRACER

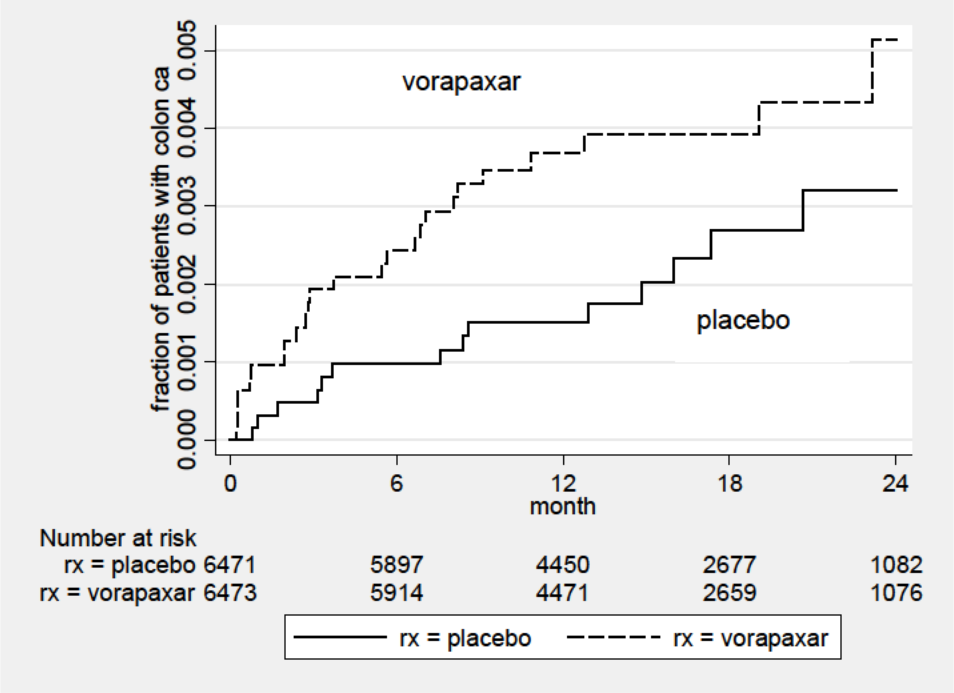
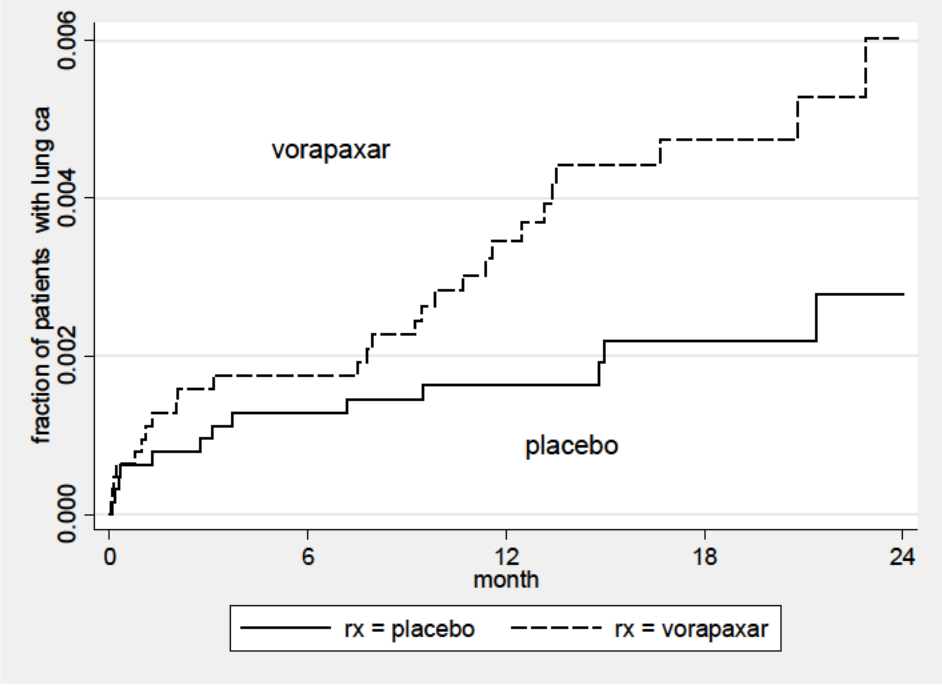


Figure 12: Lung Cancer Event Incidence in TRACER



The incidence curves for the two cancers differ: The colon cancer curves diverge immediately but then almost converge late (18-24m). The lung cancer curves both show an early steeper slope, vorapaxar greater than placebo, but then they diverge starting about 8 months and continue to diverge.

COMMENT: I interpret the colon cancer curves as suggesting an early detection bias for colon cancer in the vorapaxar arm because of higher bleeding. There appears to be catch-up later in the placebo arm. For lung cancer the early steeper slopes in both arms are likely due to detection during the x-rays and fluoroscopy performed during the index hospitalization. The later divergence may be due to cancer promotion with vorapaxar.

I show the sites of the solid cancers during the entire ITT period of TRACER in Table 13.

Table 13: Solid Cancer Sites in TRACER

	placebo	vorapaxar
bile duct	3	1
bladder	11	18
breast	3	4
colon	13	24
esophagus	3	3
head & neck	4	4
kidney	8	6
liver	2	1
lung	12	23
melanoma	6	9
other	1	0
ovary	3	1
pancreas	1	3
prostate	9	14
sarcoma	0	2
stomach	8	5
testes	1	0
thyroid	0	2
unknown	1	3
uterus	1	5
total	90	128

The sites with substantially higher rates in the vorapaxar arm are bladder, colon, lung, prostate, and uterus.

COMMENT: TRACER appears to show some evidence for a detection "bias", or earlier detection of cancers that bleed in the vorapaxar arm due to more bleeding with vorapaxar than with placebo. This bias likely is more prominent particularly for GI cancers with vorapaxar because vorapaxar is not a prodrug like clopidogrel and prasugrel and hence is active in the gut.

While this mechanism should also be operative for TRA2P, patient scrutiny during the initial hospitalization for ACS in TRACER was likely much higher than during the outpatient initiation of vorapaxar in TRA2P.

I am impressed by the similarities between the prasugrel trials and the vorapaxar trials: Both of the ACS, largely early invasive trials (TRITON and TRACER) showed statistically significant increases in solid cancers in the arms with more bleeding. And both of the noninvasive, predominantly medical management trials (TRILOGY and TRA2P) showed no differences in solid cancer rates. This distinction is also apparent for the clopidogrel trials, with the one invasive trial CREDO showing an effect upon cancer rates and the other noninvasive cardiac trials being negative. The cerebrovascular trial SPS3 may be the exception.

Because there appears to be an association between bleeding and cancer rates, a good question is whether anticoagulant drugs show this association like the antiplatelet drugs. Hence I compared cancer rates in all recent trials of new oral anticoagulant (NOAC) drugs. I present and discuss the results for the anticoagulants next.

Anticoagulant Drugs and Cancer

I show selected characteristics and results for the large outcome trials of NOACs in Table 14 and Table 15.

Table 14: New Oral Anticoagulant Outcome Trials 1

New oral anticoagulant	apixaban			rivaroxaban	
Trial	APPRAISE	ARISTOTLE	AVERROES	ATLAS	ROCKET
Dates randomized	03/09-11/10	12/06-02/10	09/07-12/09	11/08-01/11	12/06-06/09
Population	ACS	afib	afib	ACS	afib
N	7,392	18,201	5,598	15,526	14,264
Age, median y	67	70	70	61	73
Male	68%	65%	59%	75%	60%
Invasive	50%	NA	NA	60%	NA
Control	placebo	warfarin	aspirin	placebo	warfarin
Clopidogrel use	81%	2%	1%	93%	2.5%
Aspirin use	97%	31%	(control)	99%	36%
Follow-up, median m	8	21	13	14	22
New drug discontinuation	24%	25%	22%	28%	24%
Complete follow-up	98%	85%	86%	80%	78%
Died	4.3%	7.0%	4.7%	3.3%	8.6%
Major/severe bleed RR	2.6	0.6	1.1	2.3	1.0
95% CI	1.5-4.5	0.5-0.7	0.7-1.8	1.6-3.2	0.9-1.2
Solid cancer RR	2.5	0.9	0.9	1.2	1.1
95% CI	1.4-4.5	0.7-1.0	0.6-1.4	0.9-1.6	0.9-1.4
Solid ca/100 PEY (control)	0.6	1.7	1.5	0.8	1.5
Non-CV death RR	1.6	0.9	0.7	1.1	1.0

New oral anticoagulant	apixaban			rivaroxaban	
Trial	APPRAISE	ARISTOTLE	AVERROES	ATLAS	ROCKET
95% CI	0.9-2.9	0.8-1.1	0.5-1.0	0.6-1.8	0.8-1.2
Died with solid ca RR	2.2	0.8	0.5	0.9	1.2
95% CI	0.7-7	0.6-1.0	0.2-1.2	0.5-1.7	0.9-1.7
Died %, solid ca pts (control)	27%	31%	28%	30%	32%

PEY = person exposure year; RR = risk ratio new drug/control; CI = confidence interval

Table 15: New Oral Anticoagulant Outcome Trials 2

New oral anticoagulant	rivaroxaban	dabigatran	edoxaban	ximelagatran	
Trial	J-ROCKET	RELY	ENGAGE	SPORTIF III	SPORTIF V
Dates randomized	06/07-11/08	12/05-12/07	11/08-11/10	08/00-09/01	08/00-12/01
Population	afib	afib	afib	afib	afib
N	1,280	18,113	21,105	3,407	3,922
Age, median y	72	72	72	71	73
Male	80%	64%	62%	69%	69%
Invasive	NA	NA	NA	NA	NA
Control	warfarin	warfarin	warfarin	warfarin	warfarin
Clopidogrel use	NA	6%	2.3%	0%	o%
Aspirin use	38%	40%	30%	12%	18%
Follow-up, median m	19	24	34	15	20
New drug discontinuation	26%	24%	34%	18%	37%
Complete follow-up	90%	91%	90%	88%	83%
Died	1.8%	7.6%	10.8%	4.4%	6.1%
Major/severe bleed RR	0.9	0.9	0.7	0.7	0.7
95% CI	0.5-1.4	0.8-1.0	0.6-0.8	0.5-1.1	0.5-1.0
Solid cancer RR	0.9	1.1	1.0	1.0	0.8
95% CI	0.5-1.7	0.9-1.3	0.9-1.1	0.7-1.5	0.6-1.1
Solid ca/100 PEY (control)	1.9	2.1	1.7	1.8	2.7
Non-CV death RR	0.3	1.0	1.0	0.7	0.7
95% CI	0.1-1.4	0.8-1.2	0.9-1.2	0.4-1.3	0.5-1.1
Died with solid ca RR	1.0	0.9	1.1	1.3	0.7
95% CI	0.1-16	0.7-1.2	0.9-1.4	0.6-3.2	0.4-1.3
Died %, solid ca pts (control)	5%	32%	30%	21%	30%

PEY = person exposure year; RR = risk ratio new drug/control; CI = confidence interval

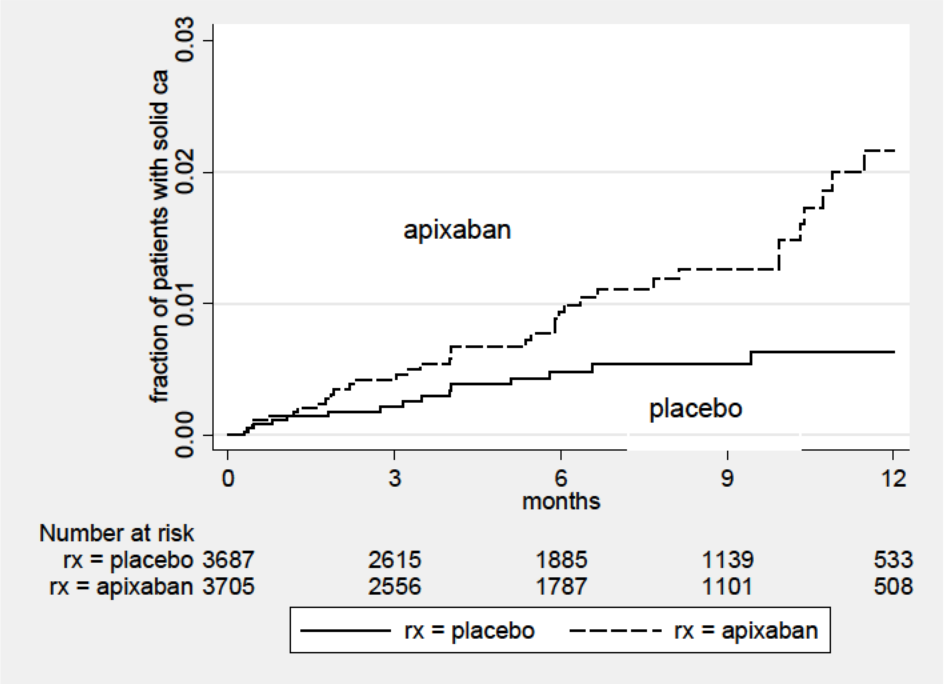
I provide additional data regarding the trials below.

APPRAISE

APPRAISE (APPRAISE-2) was a trial of apixaban vs. placebo on top of standard antiplatelet therapy in patients with a recent (within 7 days) ACS episode. APPRAISE terminated early because of an increase in bleeding with apixaban without an offsetting decrease in ischemic

events. Both bleeding and solid cancer rates were dramatically higher in the apixaban arm. I show the solid cancer event incidence in APPRAISE in Figure 13.

Figure 13: Solid Cancer Event Incidence in APPRAISE



The increased incidence of solid cancers with apixaban in APPRAISE was statistically significant: hazard ratio (HR) 2.5 (95% CI 1.4-4.6, p=0.002). Non-CV deaths were also more frequent (although not quite nominally statistically significantly) with apixaban: HR 1.6 (95% CI .94-2.9, p = 0.079). There were no interactions between apixaban use and invasive approach or DES use for either solid cancer incidence or non-CV mortality.

I show the sites of the solid cancer in APPRAISE in Table 16.

Table 16: Solid Cancer Sites in APPRAISE

	placebo	apixaban
anus	1	0
bile duct	0	1
bladder	0	5
breast	0	1
colon	5	4
esophagus	0	1
gi other	0	1
head & neck	1	0
kidney	0	2
lung	2	8
ovary	0	1

	placebo	apixaban
pancreas	1	3
prostate	2	1
stomach	2	6
testes	0	1
unknown	1	1
uterus	0	1
total	15	37

The cancer sites with higher incidence and higher rates in the apixaban arm were bladder, lung, and upper gastrointestinal (UGI – esophagus and stomach). Kidney and pancreas cancer sites were also more frequent with apixaban but few in number. The incidence curves for the higher incidence sites should be informative so I show bladder cancer incidence in Figure 14, lung cancer incidence in Figure 15, and upper GI cancer incidence in Figure 16.

Figure 14: Bladder Cancer Event Incidence in APPRAISE

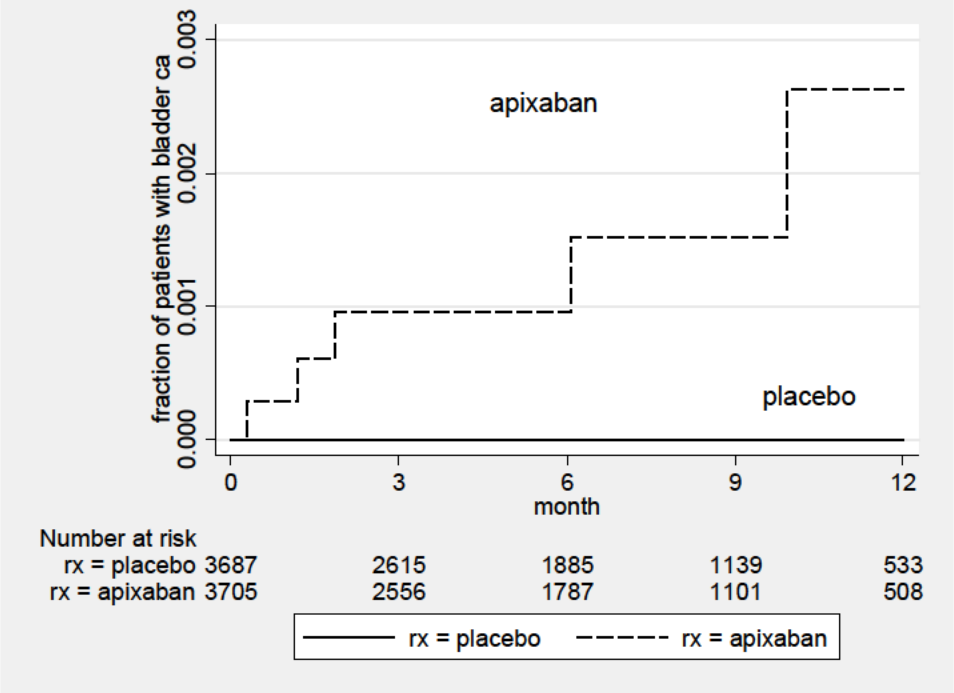


Figure 15: Lung Cancer Event Incidence in APPRAISE

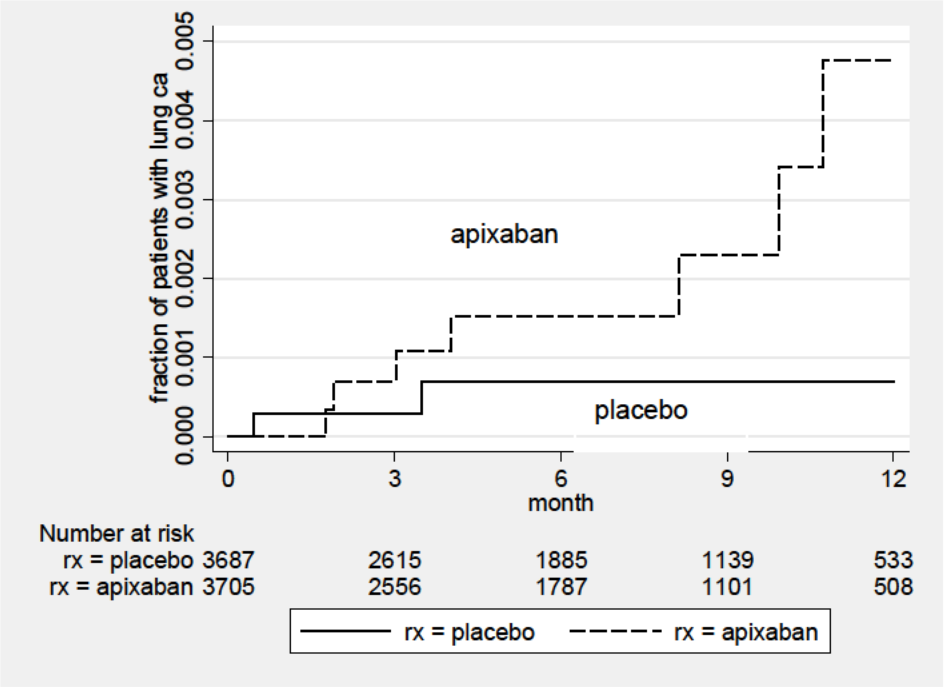
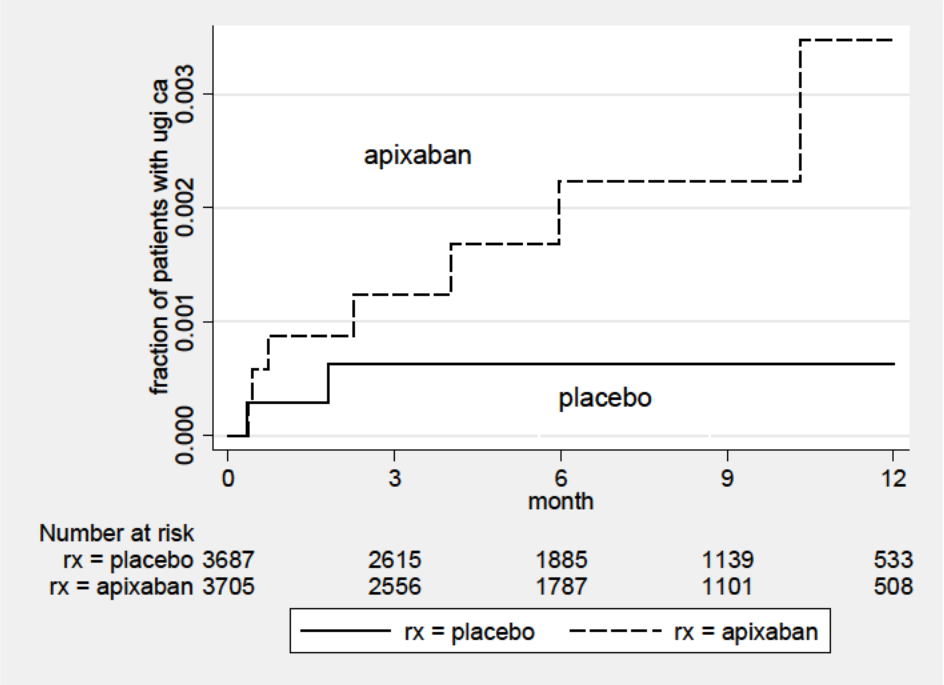


Figure 16: Upper GI Cancer Incidence in APPRAISE



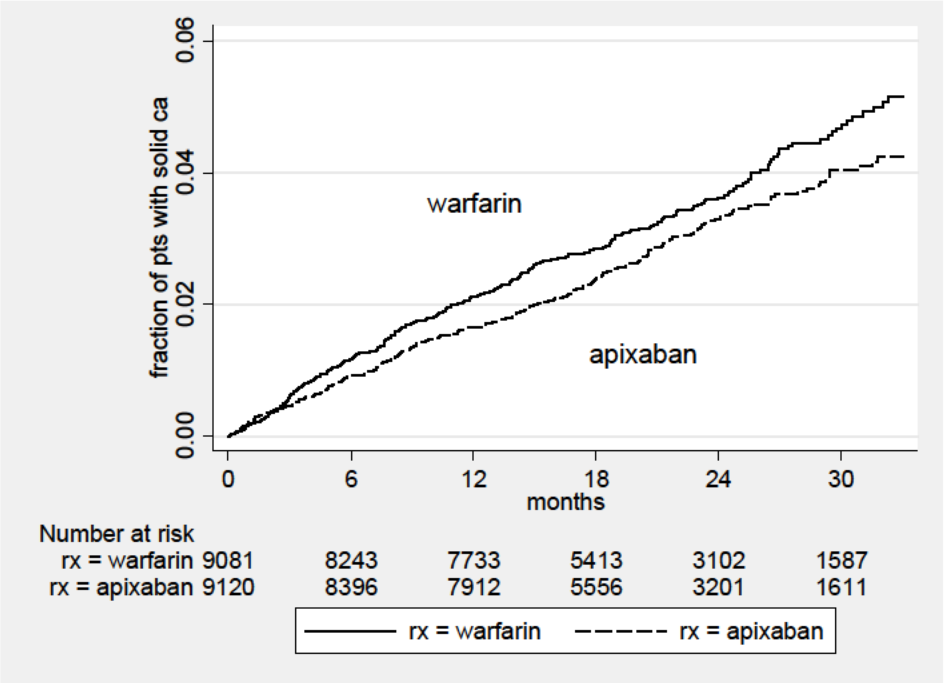
Bladder cancer detection began early in the apixaban arm, suggesting a detection effect rather than tumor promotion. They were not found in the placebo arm, and similarly lung and UGI cancers were rare in the placebo arm, with a low solid cancer incidence rate in APPRAISE compared to many other studies. While rates for these three cancer sites all diverged early they continued to diverge for the duration of the study and lung cancer rate divergence appeared to accelerate.

COMMENT: The APPRAISE solid cancer results do suggest an early detection effect because of bleeding. Because of its short duration, APPRAISE is not optimal for discriminating between an early detection effect only and the addition of a cancer promotion effect. Regardless, APPRAISE does support an association between bleeding and cancer, particularly considering the ARISTOTLE results I present next.

ARISTOTLE

ARISTOTLE was a trial of apixaban vs. warfarin in atrial fibrillation (afib) patients. Because apixaban was not added to standard antiplatelet therapy as in APPRAISE, bleed rates in ARISTOTLE were higher in the warfarin arm than in the apixaban arm. Correspondingly solid cancer rates were higher in the warfarin arm. I show the solid cancer event incidence curves for ARISTOTLE in Figure 17.

Figure 17: Solid Cancer Event Incidence in ARISTOTLE



While the divergence of the curves may not be extreme, the difference is borderline statistically significant for the ITT period (HR 0.85, 95% CI 0.72-1.00, p = 0.052) and is nominally significant for all reported cancers (p = 0.034).

I show the solid cancer sites in ARISTOTLE in Table 17.

Table 17: Solid Cancer Sites in ARISTOTLE

	warfarin	apixaban
anus	1	0
bile duct	5	4
bladder	34	25
breast	23	24
carcinoid	2	0
cervix	3	0
colon	45	47
esophagus	2	3
gi other	2	0
head & neck	9	8
kidney	12	9
liver	3	4
lung	39	36
melanoma	17	17
mesothelioma	0	1
other	1	0
ovary	3	2
pancreas	16	10
prostate	47	41
sarcoma	4	2
stomach	11	10
thyroid	4	2
unknown	13	8
uterus	5	6
vulva	0	1
total	301	260

The sites that are most differentiated between the two arms are bladder and pancreas. I show the incidence curves for bladder cancer events in Figure 18 and for pancreas cancer events in Figure 19.

Figure 18: Bladder Cancer Event Incidence in ARISTOTLE

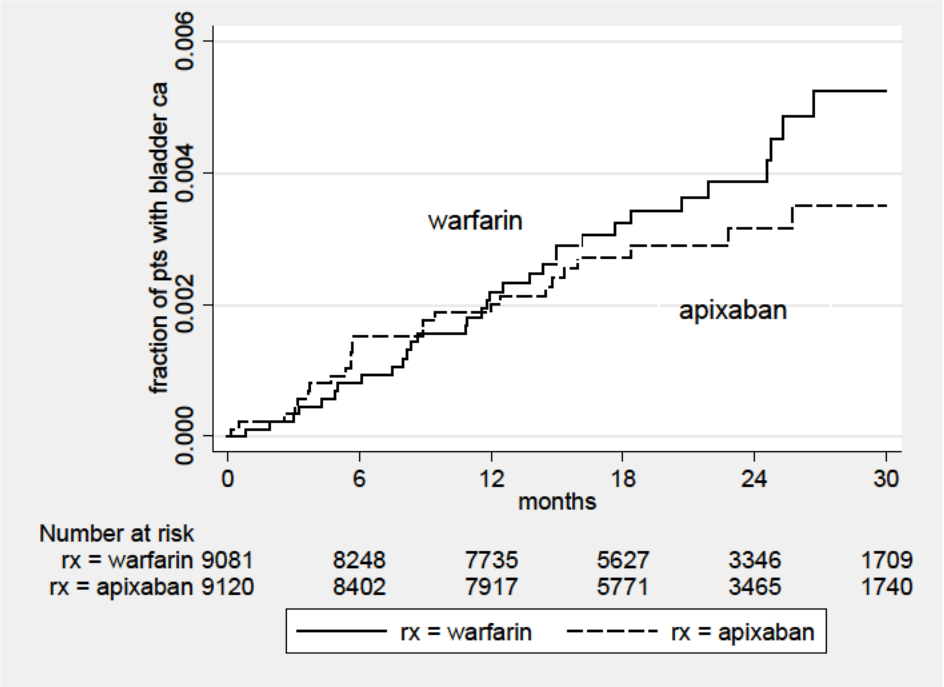
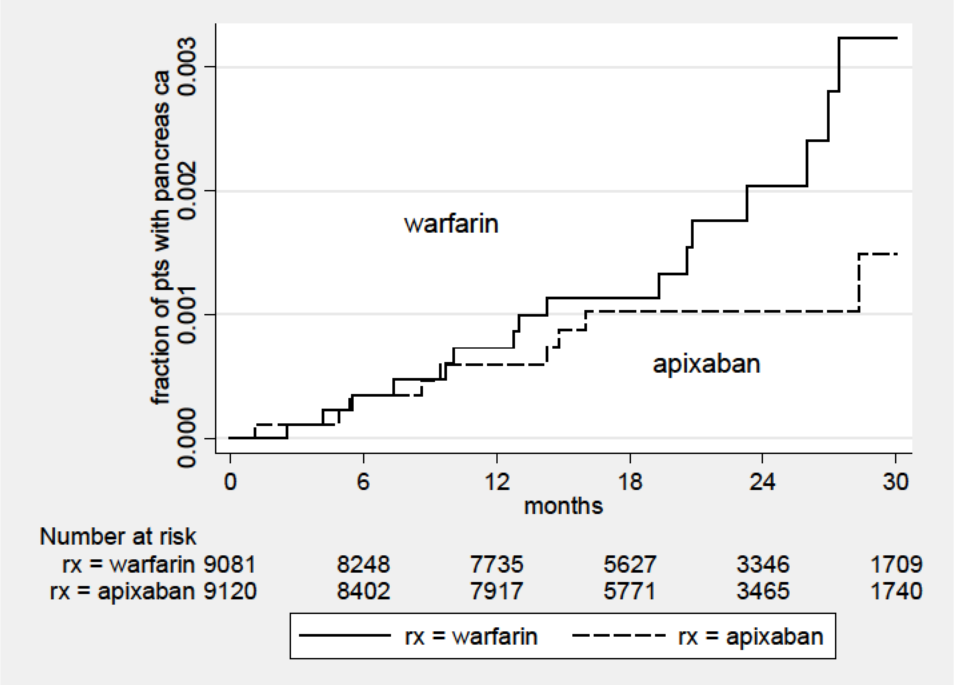


Figure 19: Pancreas Cancer Event Incidence in ARISTOTLE



Both curves diverge late, about 18 months.

COMMENT: The late divergence of the bladder and pancreas curves in ARISTOTLE suggest that the etiology is not an early detection bias but a real cancer promotion. The comparison of the APPRAISE and ARISTOTLE results suggest that the cancer promotion is related to inhibition of coagulation, rather than inhibition of a specific receptor.

AVERROES

AVERROES was a trial in afib patients of apixaban vs. aspirin. Major bleeding was little different between the two arms and solid cancer rates were little different between the two arms. Non-CV mortality was lower in the apixaban arm. AVERROES is consistent with no difference in bleeding associated with no difference in solid cancers but otherwise does not appear informative for this issue.

ATLAS

ATLAS was a trial in ACS patients of rivaroxaban vs. placebo added on to standard antiplatelet therapy. ATLAS had three arms for two dosages of rivaroxaban (2.5 or 5 mg BID) and placebo, with 1:1:1 randomization. Hence there were about 5,000 patients per arm.

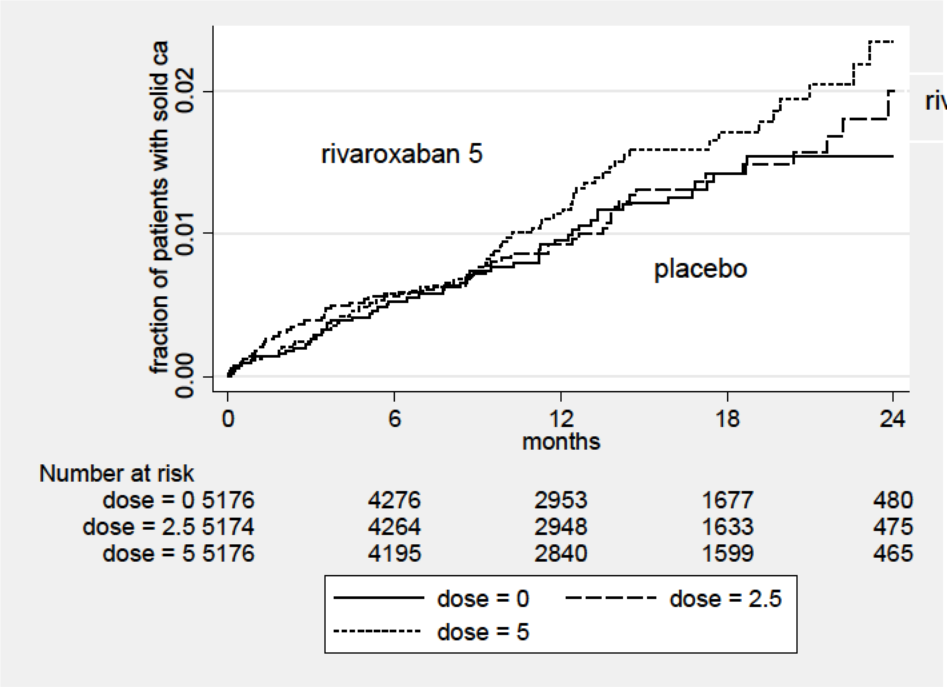
ATLAS had study conduct problems as detailed in my review of it. Follow-up was incomplete and mortality was lowest in the 2.5 mg arm but similar in the placebo and the 5 mg arms. Despite the conduct problems ATLAS had a higher rate of major bleeding in the rivaroxaban arms associated with higher rates of solid cancers and CV mortality in those arms compared to the placebo arm, although the differences in solid cancers and CV mortality are not statistically significant.

The two rivaroxaban dosages show an apparent dose-response for bleeding and solid cancers: The RRs for major bleeding were 2.1 and 2.5 respectively for the low and high dosages. The RRs for solid cancers were 1.1 and 1.3 respectively. There may also be a dose-response for non-CV mortality with RRs of 0.6 and 1.4 respectively. Note that the all-cause mortality was exceptionally low in the low dose (2.5 mg BID) group and appears anomalous as discussed in my review of ATLAS.

About 60% of patients in ATLAS had an initial invasive strategy, the vast majority being PCIs. There was no interaction between treatment or dose and an initial invasive strategy for solid cancers. The subgroup of patients managed medically actually had a higher RR point estimate for solid cancers than the invasive group (1.3 vs. 1.1), although all point estimates have wide confidence limits.

I show the solid cancer event incidence curves for ATLAS in Figure 20.

Figure 20: Solid Cancer Event Incidence in ATLAS



The solid cancer event incidence curves for placebo and rivaroxaban 2.5 mg are virtually superimposed (except at study end when numbers of patients at risk are low) while the curve for 5 mg starts to diverge at about 9 months and continues to separate for the rest of the study. I show the solid cancer sites in Table 18.

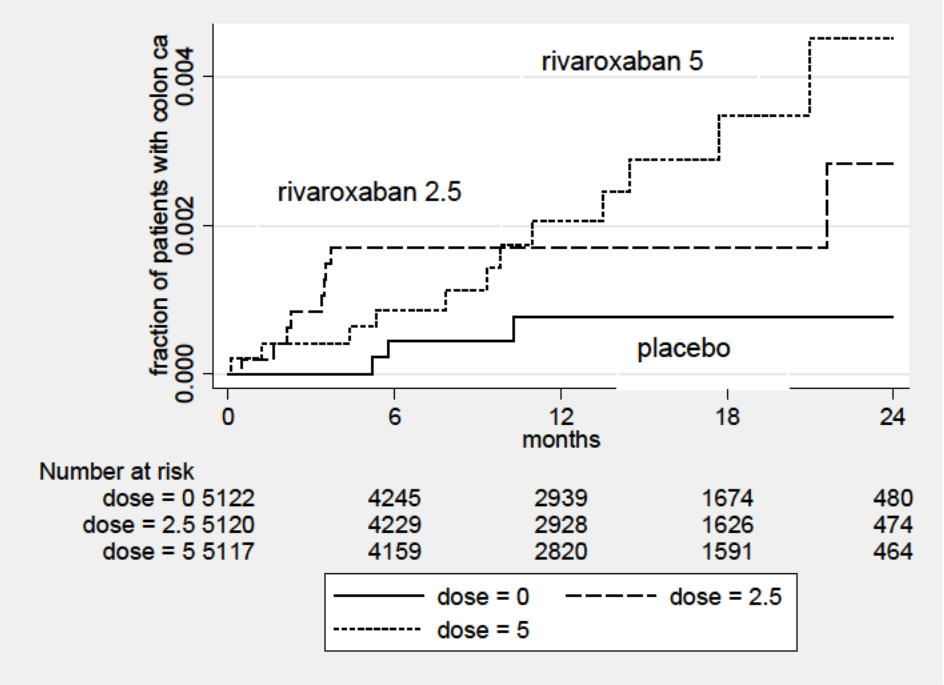
Table 18: Solid Cancer Sites in ATLAS

	placebo	rivaroxaban		
		2.5	5	any/2
bile duct	0	0	2	1
bladder	6	10	6	8
breast	3	5	5	5
cervix	2	0	0	0
colon	4	9	14	11.5
esophagus	0	1	1	1
head & neck	3	2	0	1
kidney	4	1	1	1
liver	1	0	1	0.5
lung	10	8	12	10
melanoma	0	2	3	2.5
mesothelioma	0	2	0	1
other	1	1	0	0.5
ovary	1	0	1	0.5

	placebo	rivaroxaban		
		2.5	5	any/2
pancreas	2	4	4	4
prostate	5	4	9	6.5
sarcoma	0	1	0	0.5
stomach	6	1	5	3
testes	0	0	1	0.5
thyroid	1	0	0	0
unknown	1	3	3	3
uterus	3	2	0	1
vagina	0	2	0	1
total	53	58	68	63

The cancer site that shows the greatest differentiation between rivaroxaban and placebo and dose-response is colon. I show the incidence curves for colon cancer events in Figure 21.

Figure 21: Colon Cancer Event Incidence in ATLAS



Particularly the 2.5 mg arm appears to show an early detection effect for colon cancers while the incidence curve for the 5 mg arm diverges more from the placebo curve starting about 9-10 months and diverges greatly thereafter.

COMMENT: While the solid cancer differences in ATLAS are not statistically significant, directionally they and the bleeding differences are consistent with those seen in APPRAISE, the other ACS trial of an anticoagulant added to standard antiplatelet therapy. APPRAISE may

show a more pronounced difference in cancer rates because of the older ages enrolled in APPRAISE compared to ATLAS (median age 67 vs. 61). The bleeding/cancer association of APPRAISE/ATLAS also is consistent with that seen in the antiplatelet ACS trials TRITON/TRACER and the clopidogrel trial CREDO in PCI. In fact, among the six trials with a majority (or close to majority) invasive component, only PLATO does not show an association of increased bleeding with increased solid cancers arguably because PLATO did not show much difference in bleeding rates between its arms—and its study conduct issues also may have obscured a small association and ticagrelor is not a thienopyridine. TRILOGY is the one ACS trial that does not confirm a bleeding-cancer association despite having higher somewhat higher major bleeding in its prasugrel arm but TRILOGY, like PLATO, also had serious conduct problems.

TRA2P, while not an ACS trial, is the one recent large cardiac outcome trial that does not demonstrate an association between bleeding and solid cancer. While apparently discordant with the invasive ACS trials, its results are consistent with the older, non-ACS cardiac outcome trials of clopidogrel having differentiated bleeding rates, i.e., CHARISMA, CURE, and ACTIVE-A. (See Table 10*.) I do not have a validated explanation for why the TRA2P and CHARISMA results for bleeding and solid cancers are quite different from those for CREDO, TRITON, TRACER, APPRAISE, and ATLAS. I can speculate that one possibility is the radiation exposure with the fluoroscopy during cardiac angiography and angioplasty. While it is not high relative to the levels required for DNA damage associated with initiation of carcinogenesis, I don't think we know whether it can affect immune function—and cardiac fluoroscopy irradiates the entire blood volume as well as the thymus. Do the antiplatelet drugs require a two-hit mechanism (irradiation and their inhibition) to achieve cancer promotion? Currently this latter mechanism is speculative. Another possible explanation is more mundane: Do the invasive trials have more complete solid cancer ascertainment, possibly from more chest imaging detecting more lung cancers and cancers metastatic to the lung?*

ROCKET

ROCKET was a trial in afib patients of rivaroxaban vs. warfarin. Its results are neutral for major bleeding, solid cancers, and non-CV mortality. These results support the hypothesis that the critical mechanism for cancer promotion is an effect upon coagulation rather than some other off-target effect.

J-ROCKET

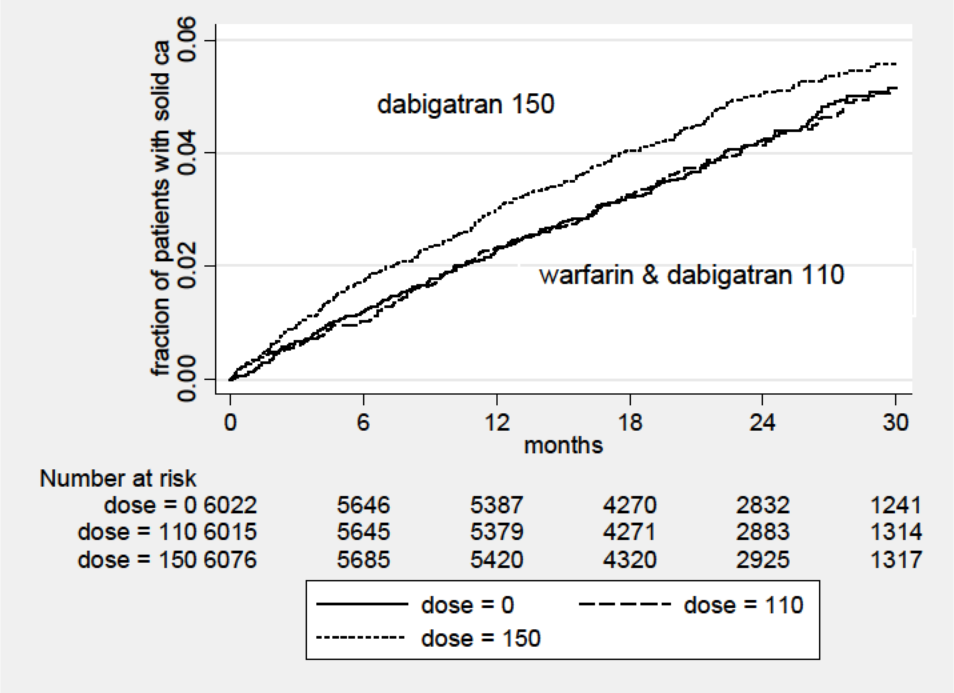
J-ROCKET was the Japanese version of ROCKET. I interpret it as similar to ROCKET. While the point estimate for the non-CV death RR looks impressive (0.3), it is based on a total of 9 non-CV deaths so its confidence interval is extremely wide. Note that J-ROCKET was performed in an elderly Asian population and did report a substantial rate of solid cancers (1.9/100 PEY.) The sites with highest incidence were colon and stomach and accounted for 57% of the first solid cancer events. Compare the 1.9/100 PEY incidence in J-ROCKET to the 0.2/100 PEY incidence in the Asian subgroup of TRILOGY.

RELY

RELY was a trial in afib patients of two doses of dabigatran (110 and 150 mg BID blinded) vs. open label warfarin. The combined doses had slightly less major bleeding than warfarin and slightly more solid cancers. However, the statistics in Table 15 do not convey all of the specific findings in RELY both because they aren't differentiated by dose and because dabigatran caused a different pattern of bleeding than warfarin.

Major bleeding was lower in the 110 mg arm (RR 0.8) than in the 150 mg arm (RR 0.9). However, GI bleeding was higher with dabigatran than with warfarin, slightly for GI bleed SAEs in the 110 mg arm (RR 1.1) and significantly higher in the 150 mg arm (RR 1.5). Solid cancer events were similar in frequency to warfarin in the 110 mg arm (RR 1.0) but more frequent in the 150 mg arm (RR 1.2).

Figure 22: Solid Cancer Event Incidence in RELY



The 150 mg arm had a higher rate of solid cancers than either the 110 mg arm or the warfarin arm, but there appears to be some convergence of the rates late.

I show the solid cancer sites in Table 19.

Table 19: Solid Cancer Sites in RELY

	warfarin	dabigatran		
		110	150	any/2
anus	0	0	2	1
bile duct	2	2	8	5
bladder	32	17	31	24

	warfarin	dabigatran		
		110	150	any/2
breast	17	21	27	24
carcinoid	1	0	0	0
cervix	1	1	0	0.5
colon	32	45	51	48
esophagus	3	10	6	8
gi other	1	1	2	1.5
head & neck	7	12	9	10.5
kidney	11	8	11	9.5
liver	6	1	3	2
lung	37	36	37	36.5
melanoma	14	15	17	16
mesothelioma	0	0	1	0.5
ovary	1	2	2	2
pancreas	10	9	8	8.5
penis	1	1	1	1
prostate	45	41	43	42
sarcoma	2	0	0	0
stomach	6	7	6	6.5
testes	0	0	1	0.5
thyroid	1	1	3	2
unknown	5	4	8	6
uterus	2	3	3	3
total	237	237	280	258.5

The sites that were more frequent in the dabigatran arm were bile duct, breast, colon, and esophagus while bladder and liver were more frequent in the warfarin arm. I show the breast cancer event incidence curves in Figure 23, the colon cancer event incidence curves in Figure 24, the esophagus event incidence curves in Figure 25, the bladder cancer event incidence curves in Figure 26, and the liver/bile duct cancer incidence curves in Figure 27. (Liver and bile duct cancers were rare and are frequently lumped in analyses, so I did so for the incidence curves.)

Figure 23: Breast Cancer Event Incidence in RELY

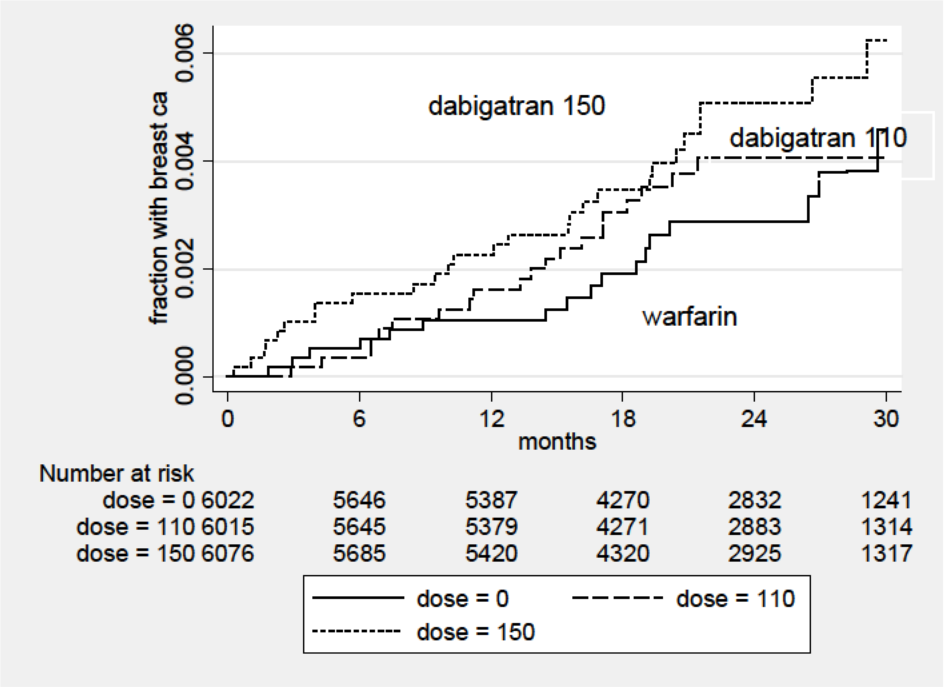


Figure 24: Colon Cancer Event Incidence in RELY

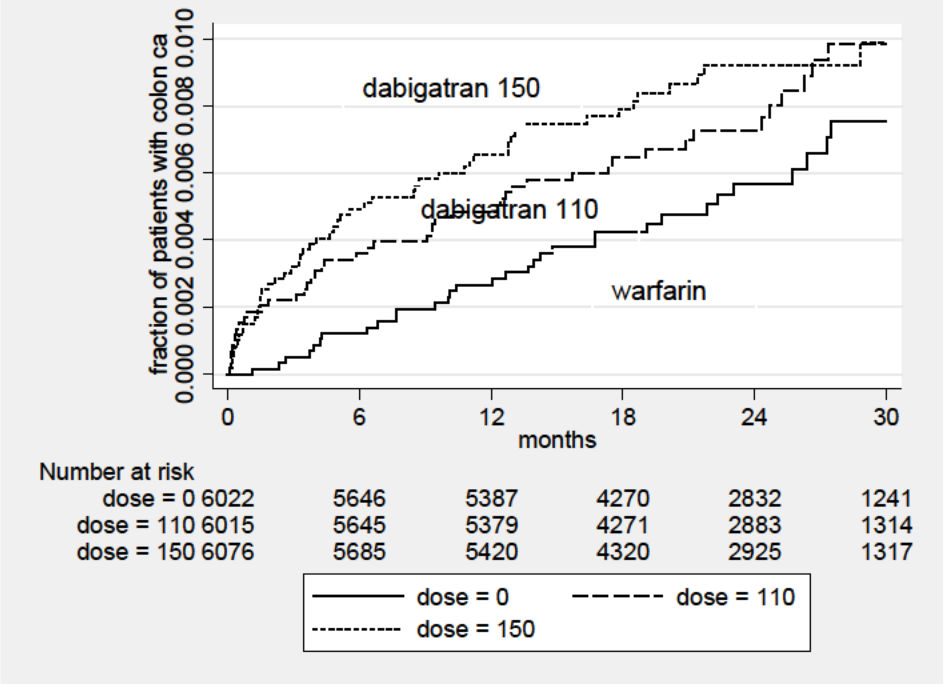


Figure 25: Esophagus Cancer Event Incidence in RELY

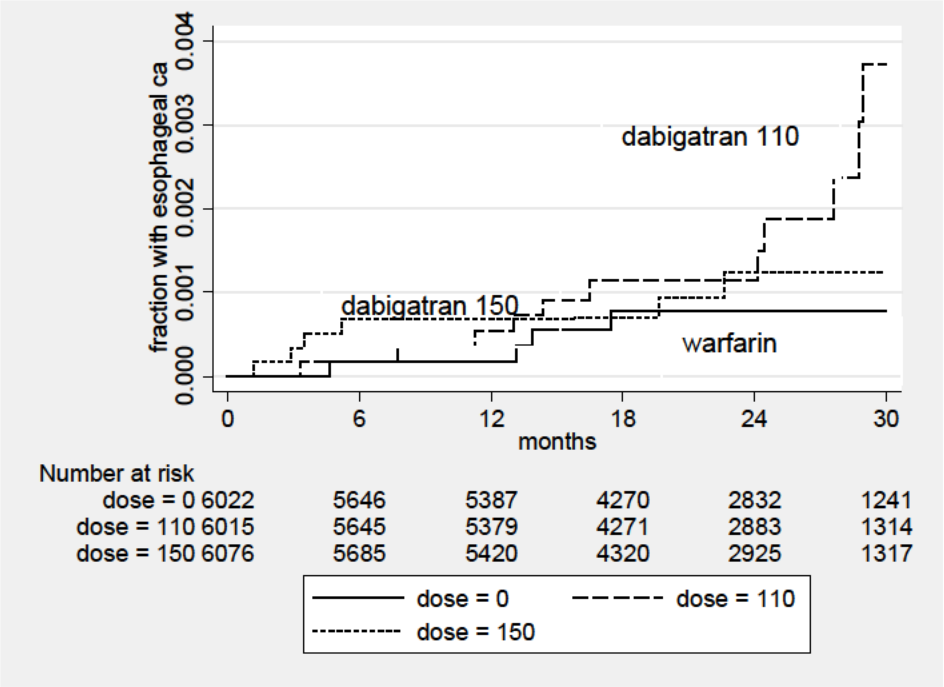


Figure 26: Bladder Cancer Incidence in Rely

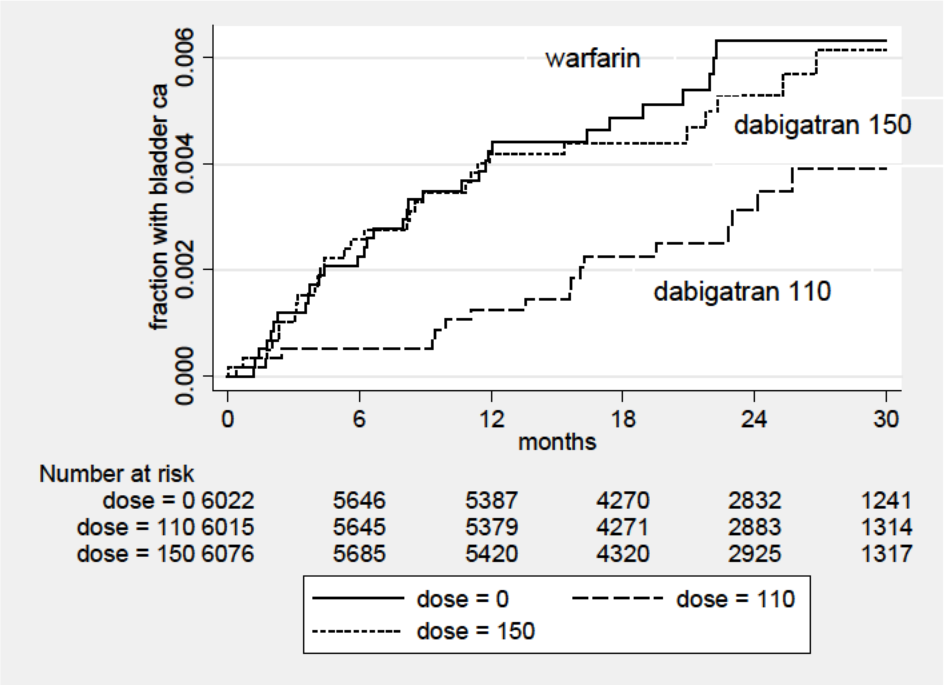
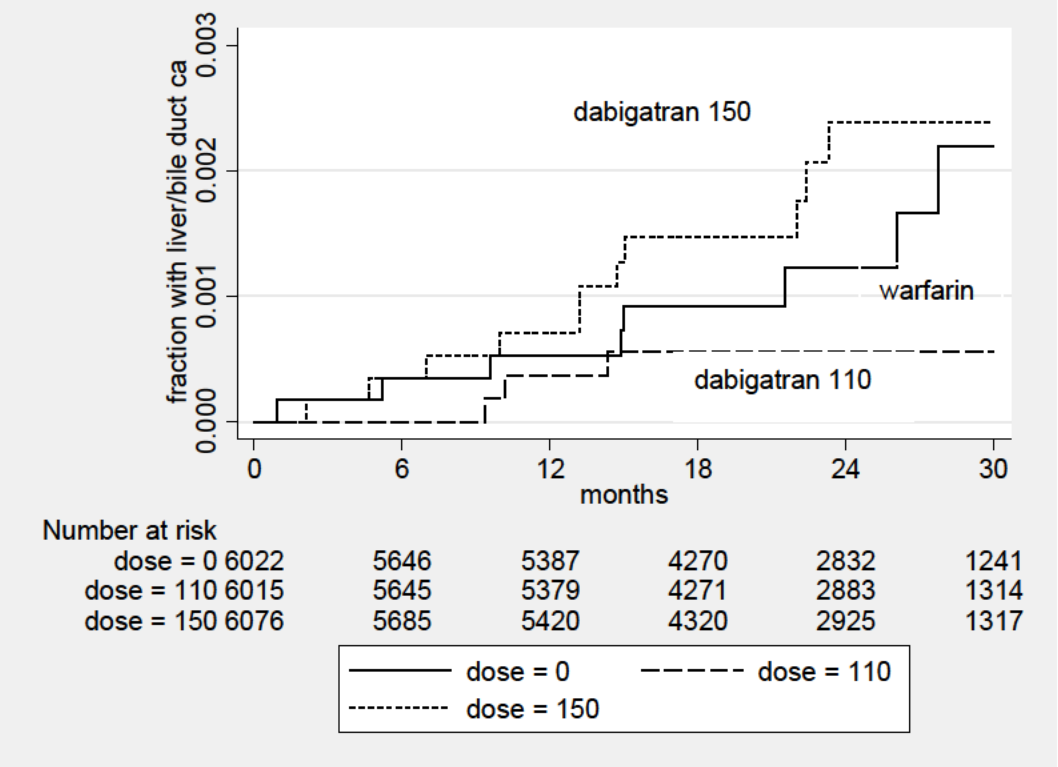


Figure 27: Liver/Bile Duct Cancer Incidence in RELY



While the site-specific cancer incidence curves have the limitation that the numbers are so and variability is high, there do appear to be several patterns:

- The breast and esophagus cancer incidence curve suggest similar, higher rates than warfarin for both doses. Whether these are real differences or chance variation cannot be distinguished definitively from this size study. The esophagus cancer increase late appears relevant because one established dabigatran adverse effect is GI irritation. If this increase in esophagus cancer is real the late disparity between the doses would likely be the result of chance.

- The colon cancer incidence curves for both doses diverge early, show greater effects at the higher dose, and converge somewhat with each other and warfarin at about 24 months. The early divergence and later convergence suggest that the colon cancer effects are detection biases resulting from the increased GI bleeding with dabigatran, likely do to active dabigatran in the gut (while warfarin's site of action is the liver.)

- Warfarin and the high dose share similar incidence curves for bladder and liver/bile duct cancer. They also share similar overall bleeding profiles (excluding the increased GI bleeding with dabigatran.) The bladder cancer incidence curves also suggest an early detection effect.

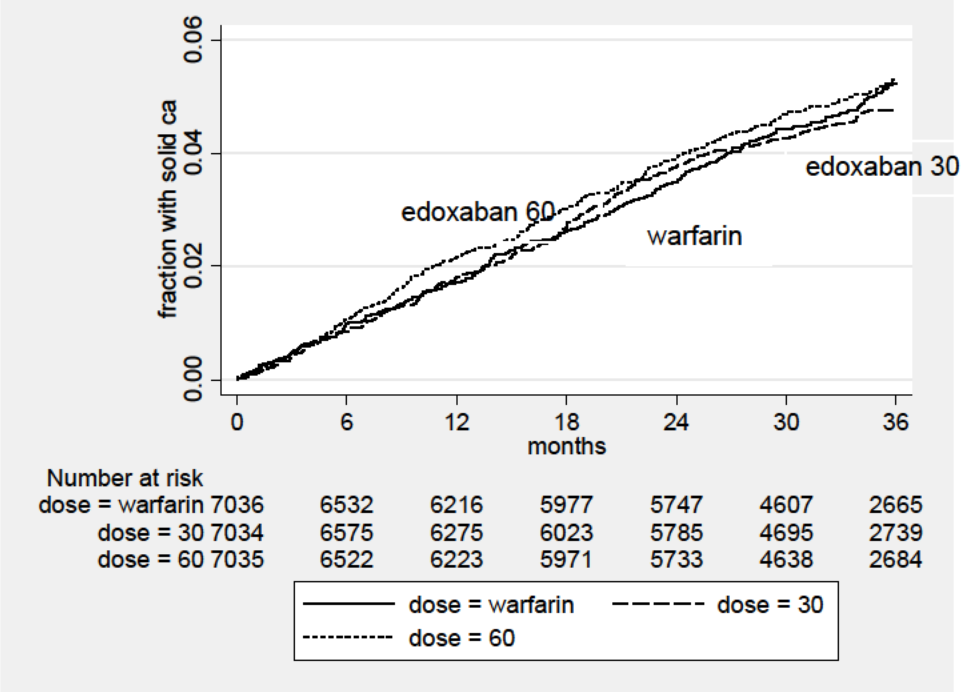
COMMENT: RELY supports both an early detection effect and increased solid cancers with increased bleeding. It also suggests that some drugs may have additional mechanisms operative, e.g., the possible increase in esophagus cancer with dabigatran.

ENGAGE

ENGAGE was a trial in afib patients of two dosages of edoxaban (30 and 60 mg QD) vs. warfarin. Hence, as for RELY, the statistics in Table 15 do not convey completely the ENGAGE findings. Furthermore, the median duration of follow-up was long (34 months) but edoxaban premature discontinuation was high (34%) and completeness of follow-up was marginal (90%). These latter two statistics limit the validity of ENGAGE for informing regarding cancer associations.

ENGAGE, also like RELY, had less overall bleeding in the new drug arms (RRs 0.5 and 0.8) than in the warfarin arm. GI bleeding in ENGAGE was a variation on the RELY rates: the 30 mg arm had less bleeding (RR 0.7) than the warfarin arm but the 60 mg arm had slightly more bleeding (RR 1.2) than the warfarin arm. Solid cancer rates were not differentiated by arm, as shown by the incidence curve in Figure 28.

Figure 28: Solid Cancer Event Incidence in ENGAGE



There are some site-specific incidence curves that appear informative. I show the cancer event incidence curves for colon cancer in Figure 29, for esophagus cancer in Figure 30, for lung cancer in Figure 31, and for pancreas cancer in Figure 32.

Figure 29: Colon Cancer Event Incidence in ENGAGE

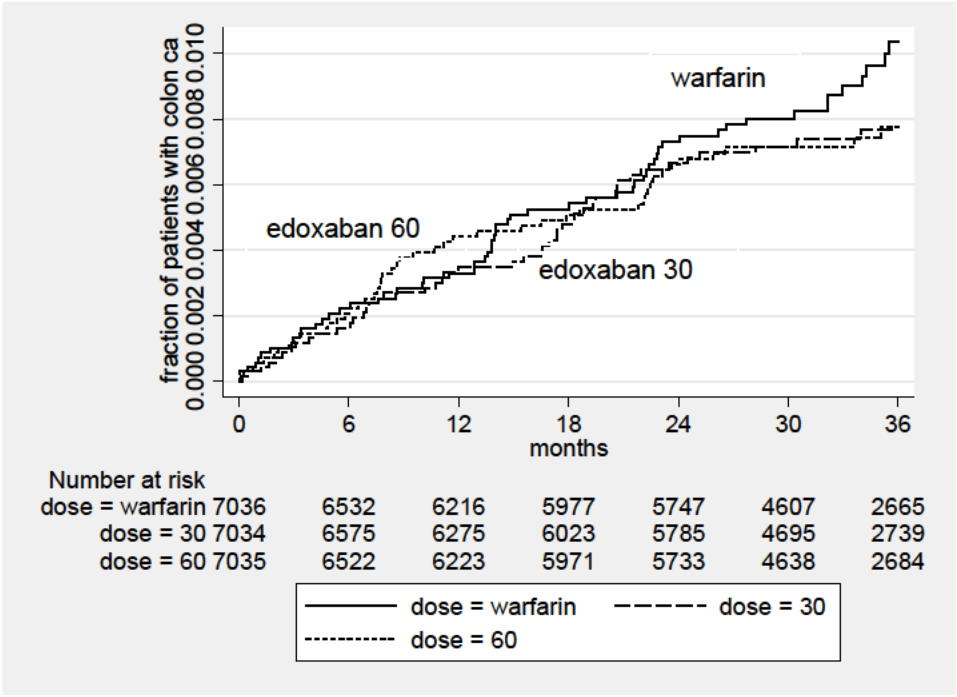


Figure 30: Esophagus Cancer Event Incidence in ENGAGE

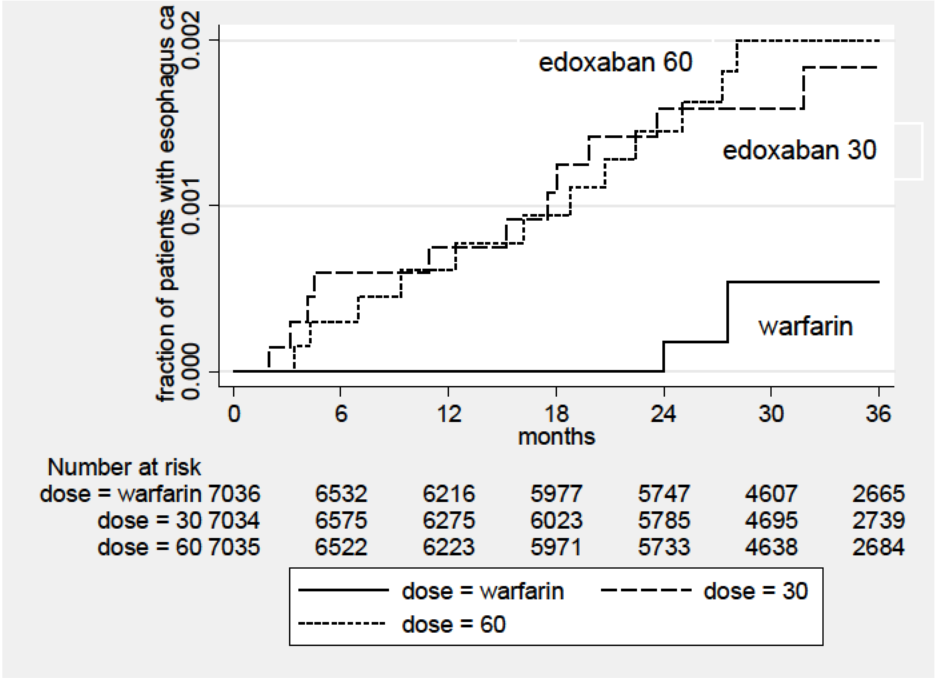


Figure 31: Lung Cancer Event Incidence in ENGAGE

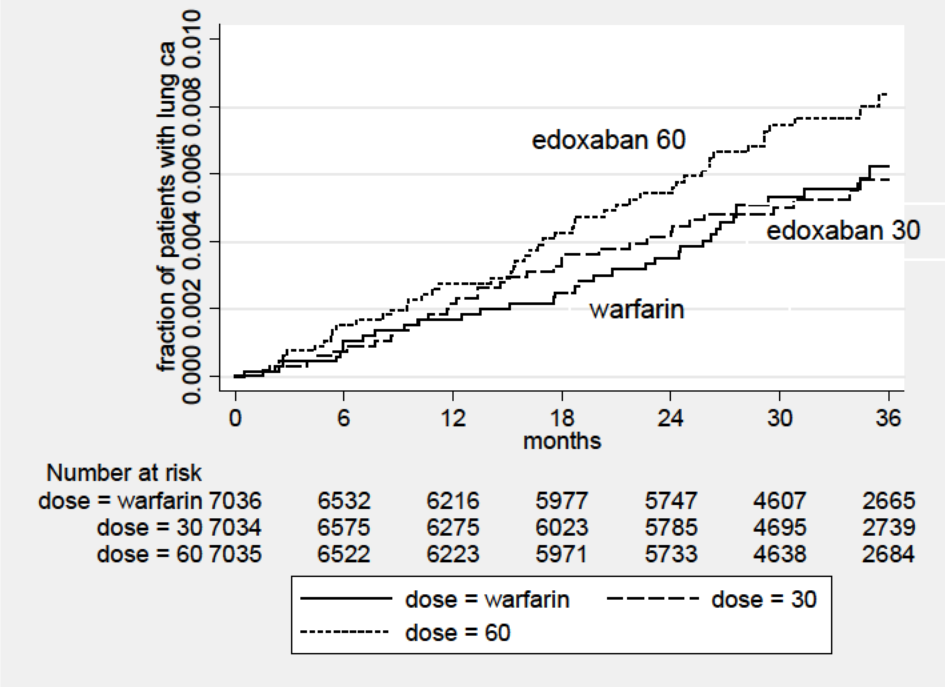
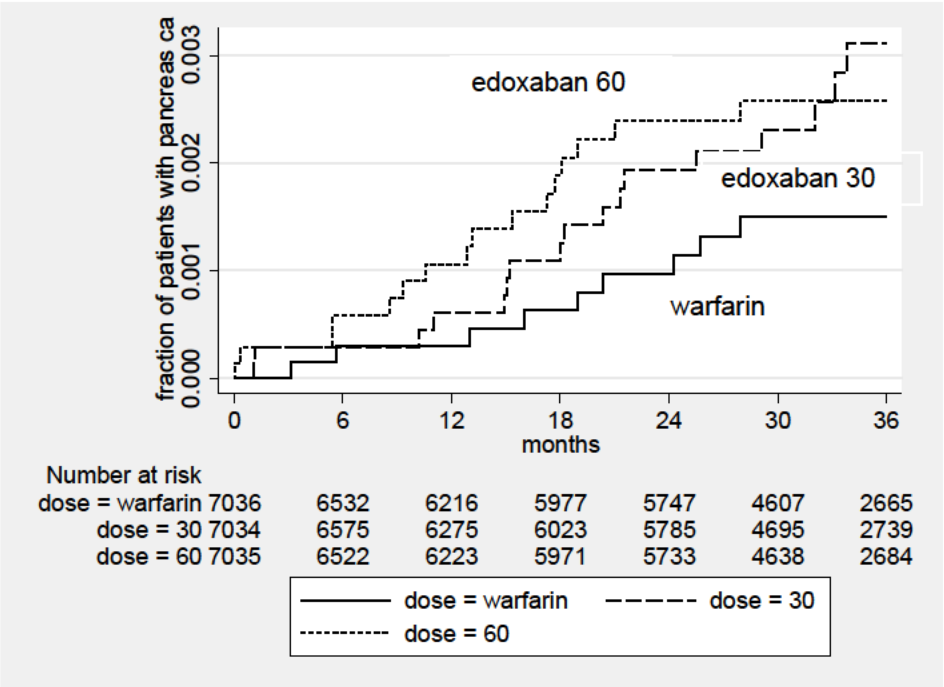


Figure 32: Pancreas Cancer Event Incidence in ENGAGE



I have the following observations about the site-specific cancer incidence curves:

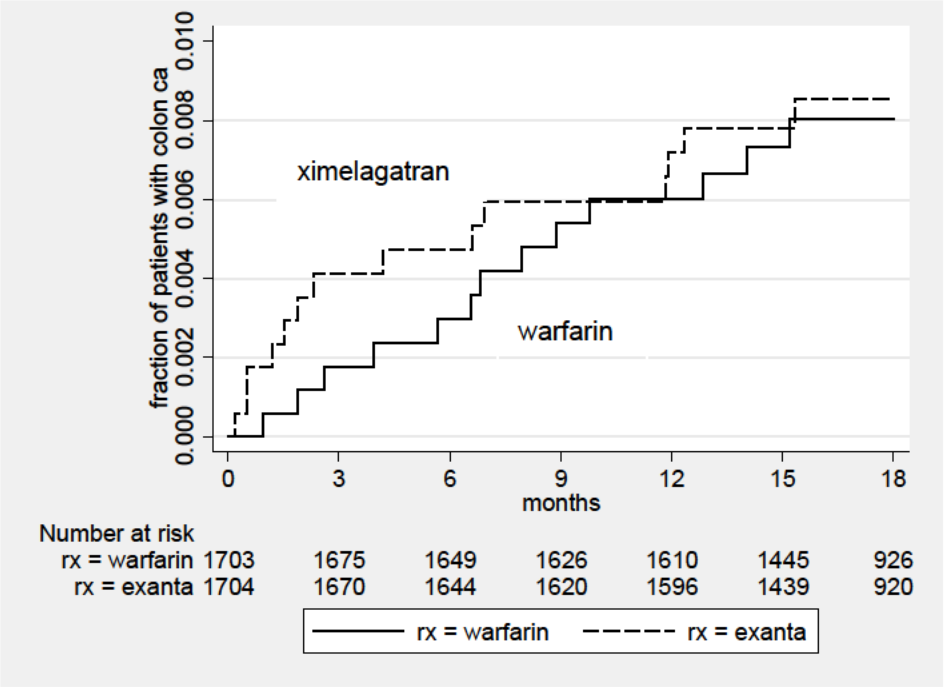
- Colon cancer was not differentiated by arm, despite the differences in GI bleeding. However, there was also no suggestion of an early detection bias.
- Esophagus cancer incidence was much higher and similar in both edoxaban arms. The incidence curves start diverging early from warfarin's. While one would be tempted to dismiss the differentiation as chance, the fact that both edoxaban arms are similar and the differentiation of esophagus cancer with dabigatran (although with a difference time course), suggests that we shouldn't dismiss this finding.
- Lung and pancreas cancer incidence is differentiated from warfarin with edoxaban, although the higher lung cancer incidence is only for the 60 mg arm. These two sites have also shown high rates with other NOACs.

COMMENT: The ENGAGE cancer results by themselves are not impressive. However, some differences appear consistent with other NOACs. ENGAGE raises the question of how much of the effect upon cancers is dependent upon local levels of the drug or transport into cells rather than measured plasma drug levels. ENGAGE suggests it is possible for the comparison of two anticoagulants to have one promote cancers at some sites and the other promote cancers at other sites depending upon different drug activations and distributions.

SPORTIF III

SPORTIF III was an unblinded trial in afib patients of ximelagatran (Exanta), a direct thrombin inhibitor, vs. warfarin. SPORTIF III was conducted outside of the U.S. while its sister trial, SPORTIF V, was conducted double-blind in the U.S. In SPORTIF III major bleeding was lower in the ximelagatran arm, as were non-CV deaths, while solid cancer event rates were similar in the two arms. While overall solid cancer events were evenly distributed between the two arms, there are two notable imbalances in specific sites: bladder cancers were reported only in the warfarin arm (5 vs. 0) while esophagus cancers were only reported in the ximelagatran arm (3 vs. 0). Colon cancers events were evenly balanced between the two arms with incidence curves as shown in Figure 33.

Figure 33: Colon Cancer Event Incidence in SPORTIF III



SPORTIF III appears to show an early detection bias in the ximelagatran arm despite GI bleeds reported as balanced between the two arms.

COMMENT: Figure 33 provides an estimate of how long an early detection bias may suggest an imbalance in cancer rates. By 9 months the colon cancer rates were equalized. However, SPORTIF V gives a different picture of colon cancer (see Figure 35) in a ximelagatran vs. warfarin study. The difference may be due to the long duration and higher cancer rates in SPORTIF V. On the other hand, the differences in small numbers of bladder cancers, with opposite directions in SPORTIF III and SPORTIF V would appear to be the play of chance. The difference in esophagus cancers, while also small, seems more suggestive because of the esophagus cancer findings in SPORTIF V and with dabigatran and edoxaban.

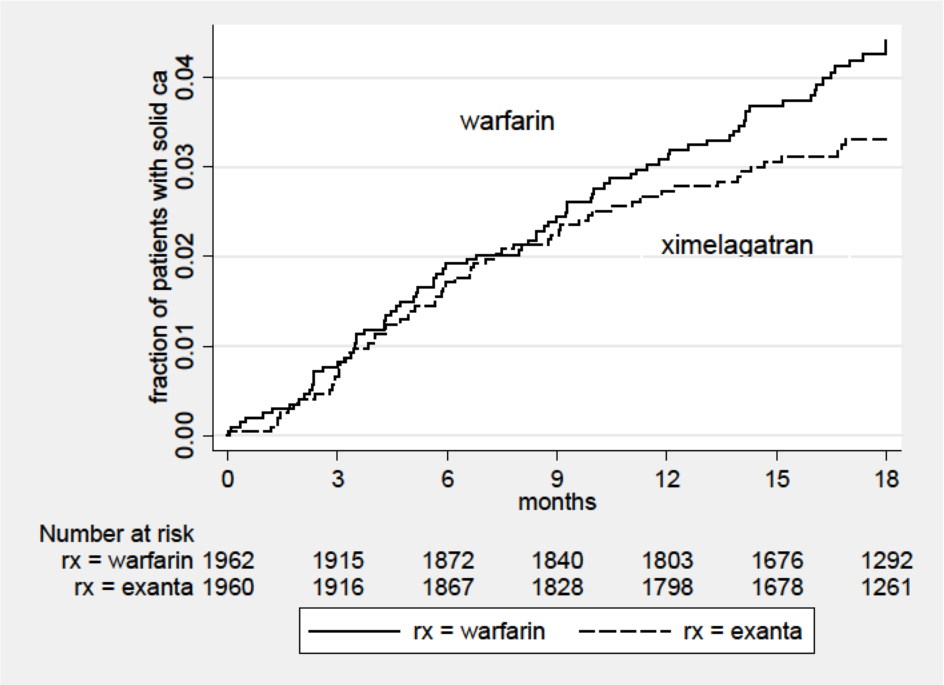
SPORTIF V

SPORTIF V was the double-blind, U.S. and Canada trial in afib patients of ximelagatran, a direct thrombin inhibitor, vs. warfarin. SPORTIF V is the sister trial to the unblinded SPORTIF III trial outside the U.S. SPORTIF V and SPORTIF III had nearly identical protocols with similar eligibility criteria. However, although not a topic for this review, SPORTIF V (the unblinded trial) produced a point estimate for the primary endpoint (stroke plus systemic embolic events) favorable to ximelagatran while SPORTIF III (the blinded trial) produced a primary endpoint point estimate unfavorable to ximelagatran. For purposes of evaluating cancers SPORTIF V had higher enrollment, higher cancer rates, and a longer duration of follow-up than SPORTIF III, resulting in more cancer events in SPORTIF V than in III.

SPORTIF V, like III, reported fewer major bleeds and non-CV deaths with ximelagatran (RR about 0.7 for each). SPORTIF V, however, reported slightly more GI bleeds with ximelagatran

(RR about 1.1) and a slightly lower solid cancer event incidence with ximelagatran (RR 0.8). I show the solid cancer event incidence curves for SPORTIF V in Figure 34.

Figure 34: Solid Cancer Event Incidence in SPORTIF V



While not statistically significant by the usual tests, the curves start to diverge at about 8 months and continue to diverge until the end of study. There were several sites with substantial differences by arm as show in Table 20.

Table 20: Solid Cancer Sites in SPORTIF V

	warfarin	ximelagatran
bladder	5	9
breast	11	2
carcinoid	1	0
cervix	0	1
colon	8	15
esophagus	0	2
head & neck	3	1
kidney	2	2
liver	1	0
lung	14	14
melanoma	8	4
mesothelioma	1	0
pancreas	1	1

	warfarin	ximelagatran
prostate	21	13
sarcoma	2	1
stomach	1	2
thyroid	1	0
unknown	2	0
uterus	1	1
vagina	1	0
total	84	68

The cancer sites with substantial differences by arm in SPORTIF V were bladder, breast, colon, melanoma, and prostate. Because bladder cancer went in opposite directions in SPORTIF III and SPORTIF V, I will not comment further regarding it. While not substantial, it is worth noting that esophagus cancer was only reported in the ximelagatran arm, as in SPORTIF V. Regarding the other sites with differences I show the cancer event incidence curves for colon cancer in Figure 33, for breast cancer in Figure 36, for melanoma in Figure 37, and for prostate cancer in Figure 38.

Figure 35: Colon Cancer Event Incidence in SPORTIF V

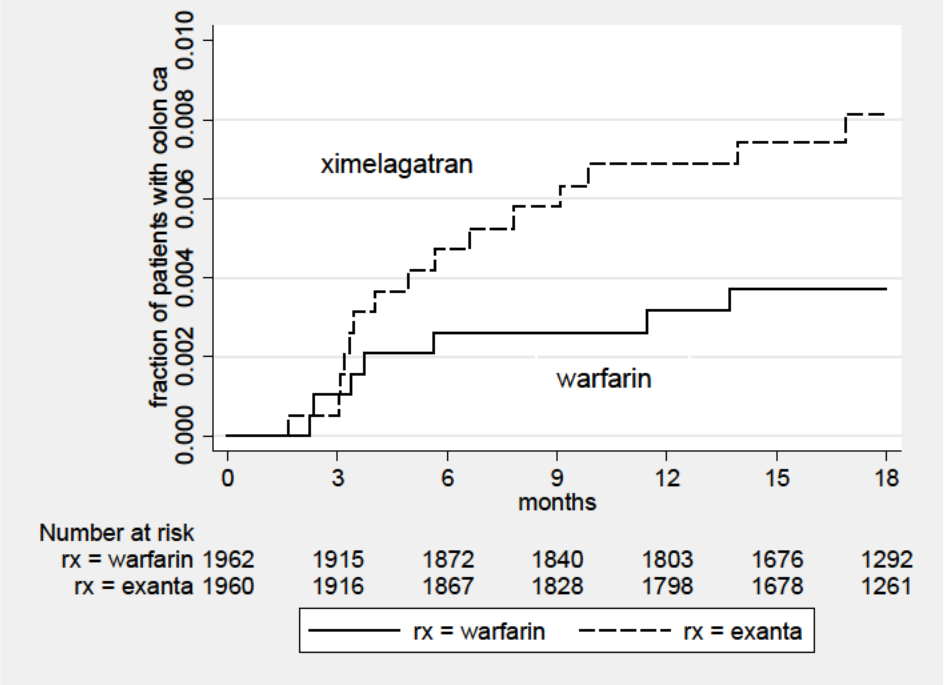


Figure 36: Breast Cancer Event Incidence in SPORTIF V

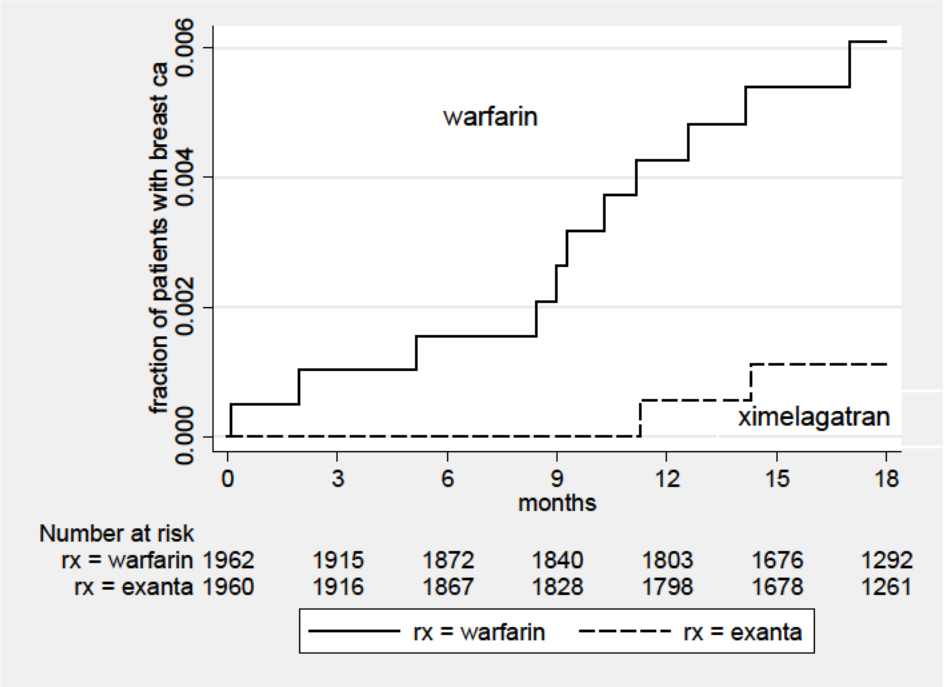


Figure 37: Melanoma Event Incidence in SPORTIF V

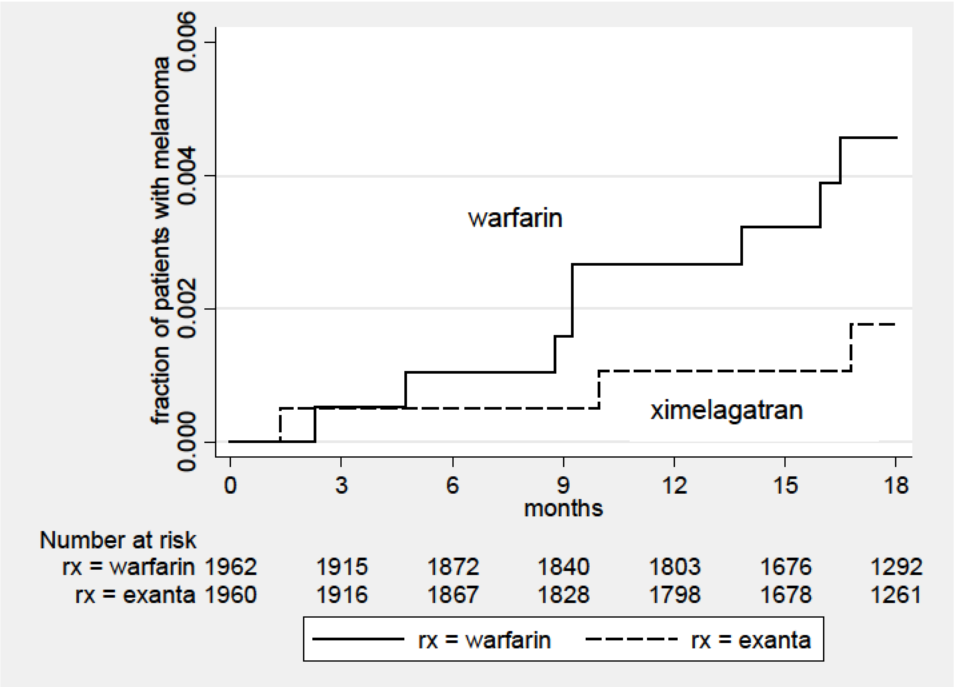
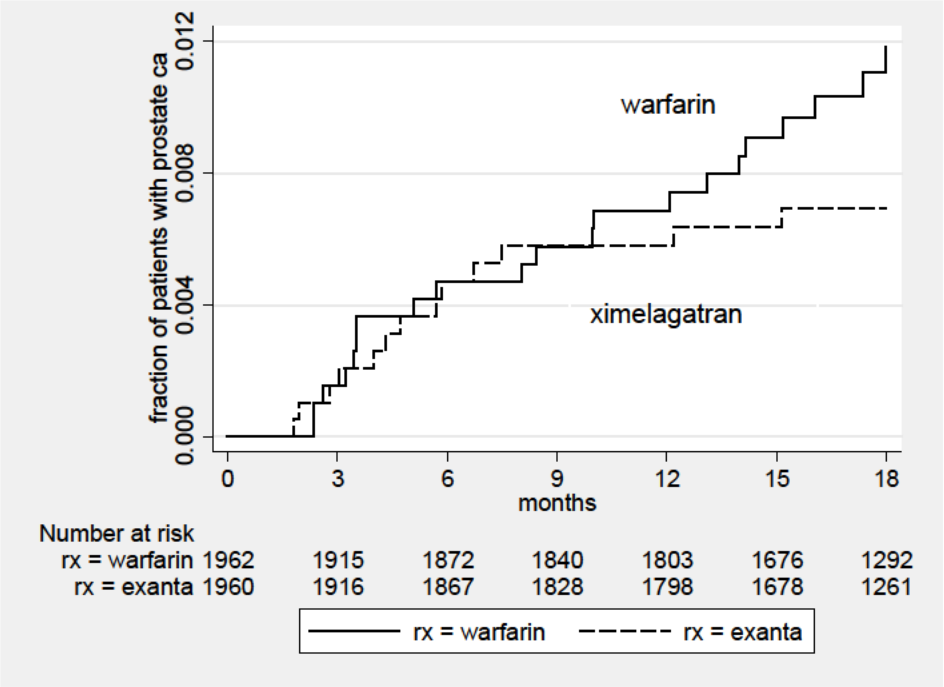


Figure 38: Prostate Cancer Event Incidence in SPORTIF V



I have the following observations regarding the site-specific cancer incidence curves:

- Colon cancer was more frequent with ximelagatran in SPORTIF V as it was initially in SPORTIF III, but the catch-up in the warfarin arm is incomplete in SPORTIF V.
- Breast cancer diverges quickly in the warfarin arm (3 cases), suggesting the random variation, but it also continues to diverge throughout the rest of the study.
- Prostate cancer and melanoma both have delayed divergences, more frequent with warfarin, after about 9 months. Because melanoma showed a nominal difference, I also examined non-melanoma skin cancer rates. Non-melanoma skin cancers were unusually highly reported, with more patients with non-melanoma skin cancers than with all other solid cancers combined. Non-melanoma skin cancers were slightly less frequent with ximelagatran (RR 0.86)—more frequent with warfarin—but not statistically significantly so. The incidence curves are more variable, i.e., diverging at 5 months, converging and 10 months, and then diverging slightly for the rest of the study.

COMMENT: SPORTIF V again demonstrates that, when warfarin produces more bleeding, it also is associated with more solid cancers. Of note is that ximelagatran in SPORTIF V produced more GI bleeding and is associated with more GI cancers (esophagus, stomach, and colon) than warfarin. While some of the latter difference may be early detection, the incidence curves diverge throughout the duration of the study.

References

ATBCCP_Study_Group (1994). "The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group." N Engl J Med **330**(15): 1029-35.

CDC (2014). LCWK1. Deaths, percent of total deaths, and death rates for the 15 leading causes of death in 5-year age groups, by race and sex: United States, 2011.

DAPT_Investigators (2014). DAPT Study Update 5Sep14, PowerPoint presentation.

DAPT_Investigators (2014). DAPT Study Update 17Sep14, PowerPoint presentation.

DAPT_Investigators (2014). DAPT Study Update 22Aug14, PowerPoint presentation.

DAPT_Investigators (2014). DAPT Study Update 24Oct14, PowerPoint presentation.

De Cicco, M. (2004). "The prothrombotic state in cancer: pathogenic mechanisms." Crit Rev Oncol Hematol **50**(3): 187-96.

FDA (2014). FDA Drug Safety Communication: FDA reviews long-term antiplatelet therapy as preliminary trial data shows benefits but a higher risk of non-cardiovascular death, 16Nov14.

Heywood, R., A. K. Palmer, et al. (1985). "The toxicity of beta-carotene." Toxicology **36**(2-3): 91-100.

Marciniak, T. A. (2009). Secondary Review of Cancer Adverse Events and Risk/Benefit, NDA 22-307, Prasugrel.

Marciniak, T. A. (2012). Analysis Plan for ARBs and Cancer.

Marciniak, T. A. (2013). Clinical Review Updated, Cancer in TRILOGY, NDA 22-307 S008, Prasugrel.

Marciniak, T. A. (2013). TSI 935 Clinical Review: Angiotensin receptor blockers (ARBs) Risk of cancer.

Mauri, L., D. J. Kereiakes, et al. (2010). "Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions." American Heart Journal **160**(6): 1035-1041.e1.

Mauri, L., D. J. Kereiakes, et al. (2014). "Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents." New England Journal of Medicine **23**(371): 2155-66.

.

Morrell, C. N., A. A. Aggrey, et al. (2014). "Emerging roles for platelets as immune and inflammatory cells." Blood **123**(18): 2759-67.

NCI. (2012). "Lung Cancer Prevention (PDQ®)." Retrieved May 1, 2013, from http://www.cancer.gov/cancertopics/pdq/prevention/lung/Patient/page3/print.

Omenn, G. S., G. E. Goodman, et al. (1996). "Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial." J Natl Cancer Inst **88**(21): 1550-9.

Peto, R., R. Doll, et al. (1981). "Can dietary beta-carotene materially reduce human cancer rates?" Nature **290**(5803): 201-8.

Rubin, B. A. (1964). "Carcinogen-induced tolerance to homotransplantation." Prog Exp Tumor Res **5**: 217-92.

Sipahi, I., S. M. Debanne, et al. (2010). "Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials." Lancet Oncol **11**(7): 627-36.

Southworth, M. R. (2014). TSI 1361 Clopidogrel and prasugrel and increased mortality Dual Antiplatelet Therapy Trial Results.

Southworth, M. R., N. Stockbridge, et al. (2013). TSI 935 Risk of cancer with angiotensin receptor blockers, Decisional Memo

.

Wachter, L. A. and M. R. Southworth (2014). TSI 1361 Meeting Memo 7Nov14.

DAPT
STUDY

STUDY UPDATE

22 August 2014

Agenda

1. Review of DAPT Stakeholder collaboration
2. Timeline
3. Communications
4. Confidentiality
5. Primary results (DES)
6. Ongoing analysis
7. Summary and discussion

Attendees

Study Leadership: Laura Mauri, MD, *PI,* Dean Kereiakes, MD, *co-PI*

HCRI: Priscilla Driscoll Shempp, *DAPT Study Project Director*

FDA

- **CRDH**: Andy Farb, MD, *Senior Medical Reviewer,* Bram Zuckerman, MD, *Director, FDA Division of Cardiovascular Devices*
- **CDER**: Mary Ross Southworth, PharmD, *Deputy Director of Safety, Division of Cardiovascular and Renal Products*

Device Manufacturers

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- **Boston Scientific**: Peter Maurer, MPH *Director of Clinical Trials*
- **Cordis**: Patti Schleckser, *Director of Clinical Research*
- **Medtronic**: Sandeep Brar, MD, *Director of Clinical Research*

Pharmaceutical Manufacturers

- **Bristol-Myers Squibb**: Charlotte Jones-Burton, MD, *Director, CV Medical Strategy*
- **Daiichi Sankyo**: Elizabeth da Silva, MSc PhD, *Executive Director of Regulatory Affairs*
- **Eli Lilly**: LeRoy LeNarz, MD, *Sr. Medical Director – Cardiovascular*
- **Sanofi**: William Daley, MD, *VP of Business Development & Licensing*

REVIEW OF DAPT STAKEHOLDER COLLABORATION

Dual Antiplatelet Therapy Study

- Manufacturers recognized that a definitive trial would necessarily be large
- The FDA request resulted in a unique public-private collaboration among 4 manufacturers of DES and then current manufacturers of thienopyridine/antiplatelet medications
- June 2008 AdvaMed facilitated a proposal process from academic CROs along the parameters of basic trial specifications from FDA and industry
- July 2008 Harvard Clinical Research Institute submitted an operational plan and trial design to AdvaMed that was accepted
- September 2008 Harvard Clinical Research Institute submitted IDE
- October 2008 IDE approved
- August 2009 trial began enrollment
- July 2011 trial completed enrollment of 26,000 subjects worldwide
- Results to be presented November 2014

TIMELINES

Key Activities Up Through AHA

Key Dates	Milestone
August 22	Primary Endpoint Review with FDA
August 29	Product specific study data provided to each device manufacturer
September 17	Circulate manuscript drafts to manufacturers and FDA
September 29	Deadline for comments
October 1	Submit manuscripts for publication
November 16	“LBCT Presentation” : DES 30m vs 12m DAPT Primary Analysis
November 18	“Update on Randomized Trials”” DES vs BMS, and BMS 30m vs 12m DAPT

COMMUNICATIONS

DAPT Study Final Results Communications Goals

- Harvard Clinical Research Institute (HCRI), as the sponsor of the DAPT Study, is responsible for ensuring that all communications regarding the DAPT Study and its final results:
  - Meet all FDA guidelines
  - Are consistent, accurate and equitable across all involved parties
  - Are ethically and responsibly managed and effectively communicated to the interventional cardiology community

- Details of the Communications Plan were issued by email on August 19

CONFIDENTIALITY

Terms of Confidentiality

DAPT STUDY

- As outlined in the confidentiality agreements:
  - All study results are strictly confidential and shall not be disclosed even internally within your organizations
  - The manuscripts are expected to be circulated for review on or around September 18, 2014, at which time up to 3 additional non-marketing individuals may sign CDAs and be allowed to review the study results, for purposes of assessing the publications.
  - Use of study results is restricted for internal evaluation only. They cannot be used in any way relating to marketing of the device or drug.
  - Terms of confidentiality are in force until the publication date, expected to be November 16, 2014

DAPT STUDY

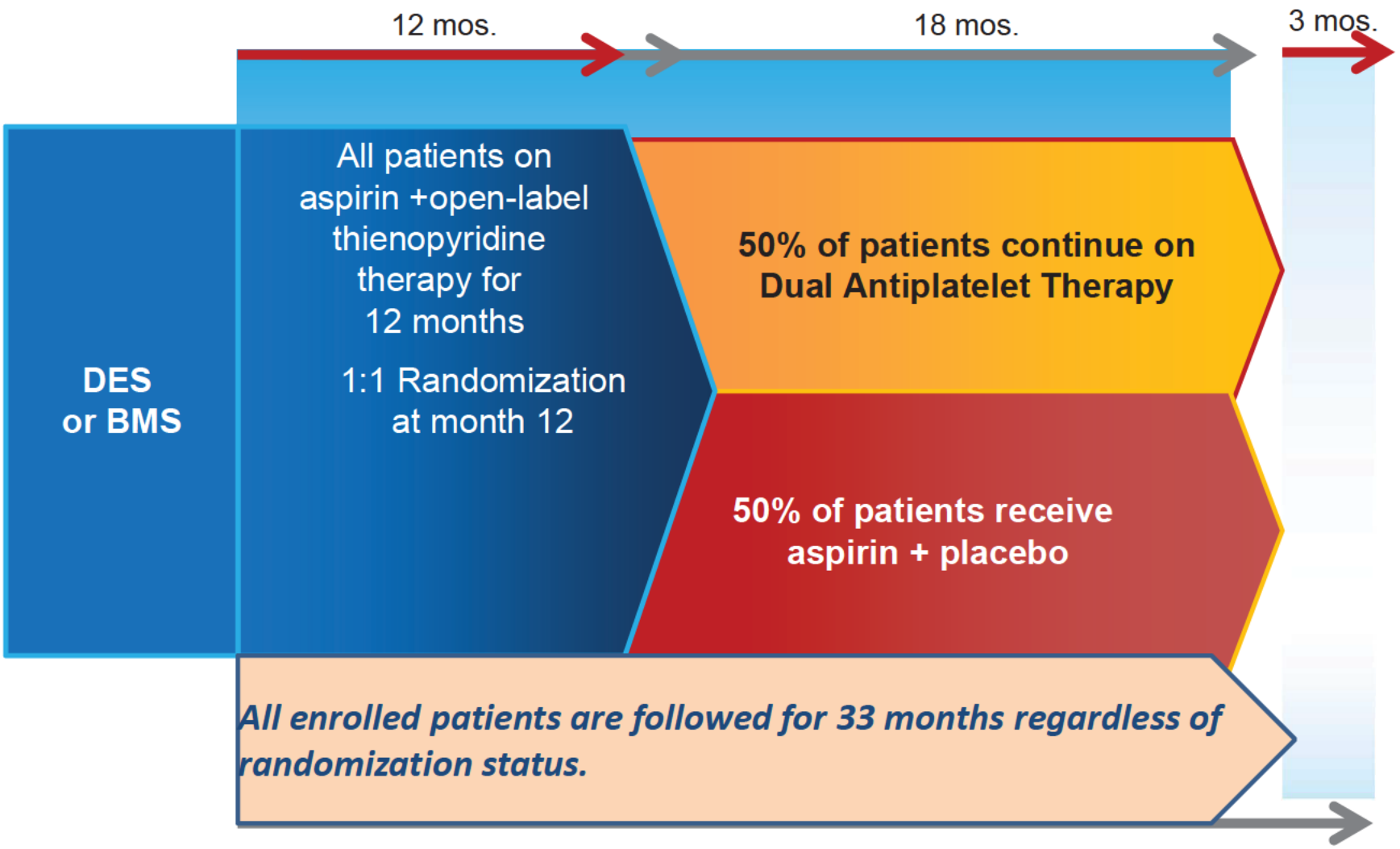
Primary Endpoint Results: DES

Objectives

The DAPT Study was designed as a multicenter, international randomized placebo-controlled trial to compare 30 versus 12 months of dual antiplatelet therapy in a broadly inclusive subject population treated with coronary stents with the objectives of:

- Determining whether dual antiplatelet therapy beyond 12 months is associated with reduction in MACCE (death, myocardial infarction or stroke) and/or stent thrombosis
- Determining the impact of dual antiplatelet therapy beyond 12 months on major bleeding

Design



Total 33 month patient evaluation including additional 3-month follow-up off study drug

Mauri, Kereiakes et al AHJ 2010; 160(6): 1035-1041

ClinicalTrials.gov number NCT00977938

Design

DAPT STUDY

Primary analysis of DES-treated subjects, randomized to 12 vs. 30 months of dual antiplatelet therapy

- Operator selection of stent and thienopyridine type from those approved by FDA at enrollment
- Site enrollment by HCRI or from 1 of 4 stent-manufacturer sponsored studies – each with uniform randomization criteria, end point definition, and follow-up as specified by overall DAPT Study
- Randomization stratified according to site, thienopyridine drug type, and by presence of risk factors for stent thrombosis
- All potential endpoint events adjudicated by one CEC, blinded to treatment
- Safety monitored by an independent overall DSMB
- No formal interim efficacy analysis was specified to stop the study or adapt the design

Mauri, Kereiakes et al AHJ 2010; 160(6): 1038-1041

Study Endpoints

Two powered co-primary effectiveness endpoints

- Academic Research Consortium (ARC) definite/probable stent thrombosis (ST) at 12-30 months post-procedure
- MACCE (death, MI or stroke) at 12-30 months post-procedure

Powered primary safety endpoint

- Major bleeding, defined as “moderate” or “severe” by Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) classification at 12-30 months post-procedure

Co-Primary Effectiveness Hypotheses

DAPT STUDY

30m DAPT increases survival free from MACCE (vs. 12m DAPT) over the 12-30m period after stent treatment:

H_o: $\lambda_{12m\text{-}DAPT} = \lambda_{30m\text{-}DAPT}$

H_A: $\lambda_{12m\text{-}DAPT} \neq \lambda_{30m\text{-}DAPT}$

where λ is hazard rate of MACCE over12-30m period.

30m DAPT increases survival free from ST (vs. 12m DAPT) over the 12-30m period after stent treatment:

H_o: $\gamma_{12m\text{-}DAPT} = \gamma_{30m\text{-}DAPT}$

H_A: $\gamma_{12m\text{-}DAPT} \neq \gamma_{30m\text{-}DAPT}$

where γ is hazard rate of stent thrombosis over 12-30m period

Use of Benjamini-Hochberg approach to control multiple comparisons:

(1) p<0.05 on both endpoints and HRs favor 30 m DAPT => 30m DAPT superior to 12m DAPT on both; IF NOT

(2) p<0.025 on one endpoint and HR favors 30m DAPT => 30m DAPT superior to 12m DAPT on that endpoint

Primary Safety Hypothesis

DAPT STUDY

Non-inferiority: 30m DAPT is associated with major bleeding rates at 12-30m post-stenting that does not exceed that of control arm by δ = 0.008 (0.8%) or more:

$$H_o: \pi_{30m\text{-}DAPT} \geq \pi_{12m\text{-}DAPT} + \delta$$

$$H_A: \pi_{30m\text{-}DAPT} < \pi_{12m\text{-}DAPT} + \delta$$

where π30m-DAPT is true major bleed rate for 30m DAPT arm and π12m-DAPT is true major bleed rate for control arm

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Partnership, Sponsorship and Funding

- Public-private partnership involving:
  - US FDA
  - Harvard Clinical Research Institute (HCRI, Boston, MA) as the study sponsor
  - 8 funding stent and pharmaceutical manufacturers
    - Abbott Vascular
    - Boston Scientific Corp.
    - Bristol-Myers Squibb Co./Sanofi Pharmaceuticals Partnership
    - Cordis Corp.
    - Daiichi Sankyo Co. Limited
    - Eli Lilly & Co.
    - Medtronic Vascular
  - With additional funding provided by grant from US DHHS (1RO1FD003870-01)

Study Administration

DAPT STUDY

Co-Principal Investigators

Laura Mauri, Dean Kereiakes

Study Statistician

Joseph Massaro

Executive Committee

Laura Mauri, Dean Kereiakes, Donald Cutlip, Sharon-Lise Normand, P. Gabriel Steg, Robert Yeh, Theodora Cohen, Priscilla Driscoll-Shempp

Advisory Committee

Eugene Braunwald (Chair), Ralph Brindis, David Cohen, Anthony Gershlick, Paul Gurbel, David Holmes, Alice Jacobs, Michael Linkoff, Daniel Simon, Jean-François Tanguay, Douglas Weaver, Stephan Windecker, Steve Wiviott

Data Monitoring Committee

Robert Bonow (Chair), Charles Davidson, James Neaton, William Wijns, Eric Bates, Clyde Yancy (ex officio)

Clinical Events Committee

Donald E. Cutlip

National Coordinating Investigators

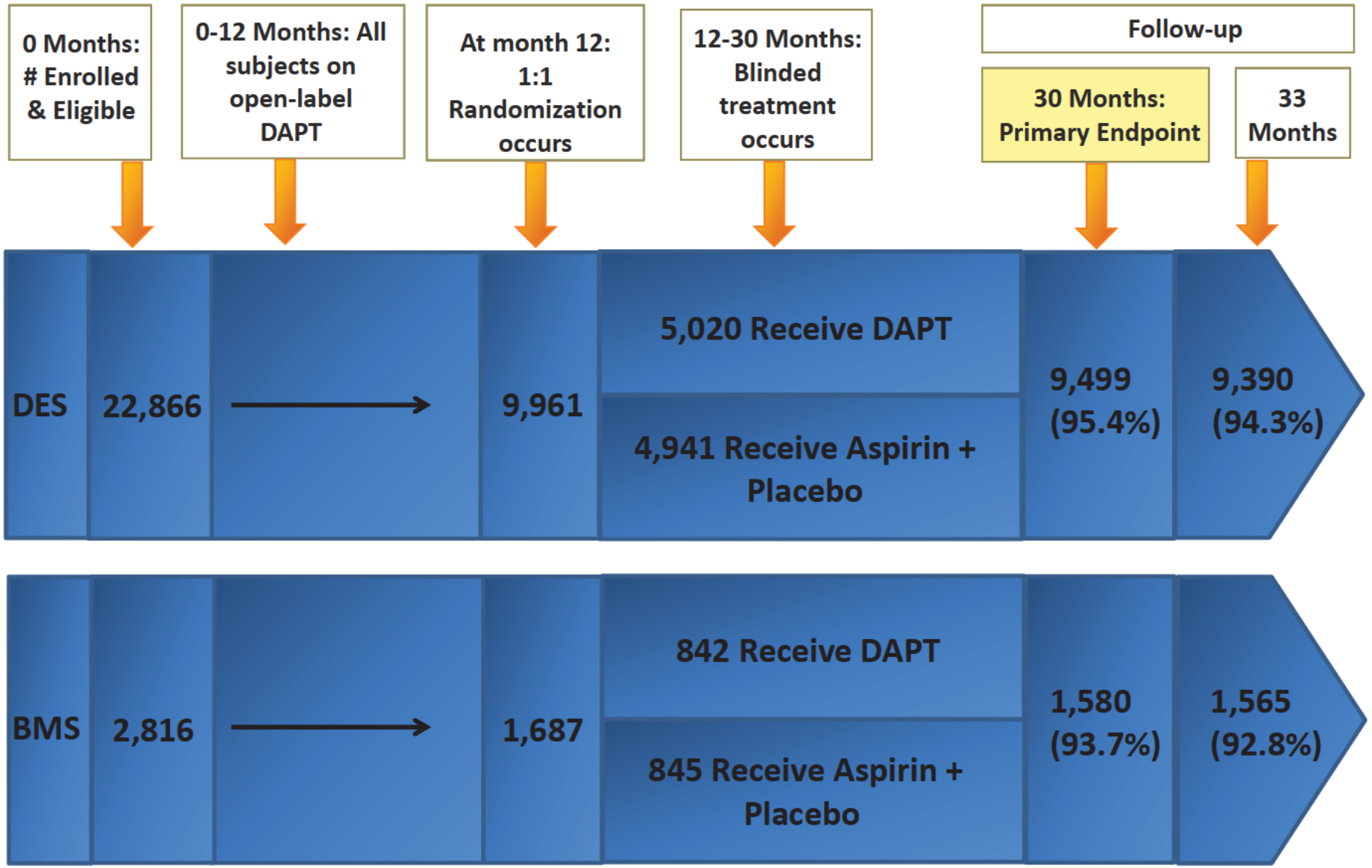
P. Gabriel Steg (France), Ian Meredith (Australia), John Ormiston (New Zealand), Harold Darius (Germany), Anthony Gershlick (United Kingdom), Wojciech Wrobel (Poland), Laura Mauri & Dean Kereiakes (United States)

Enrolling Sites

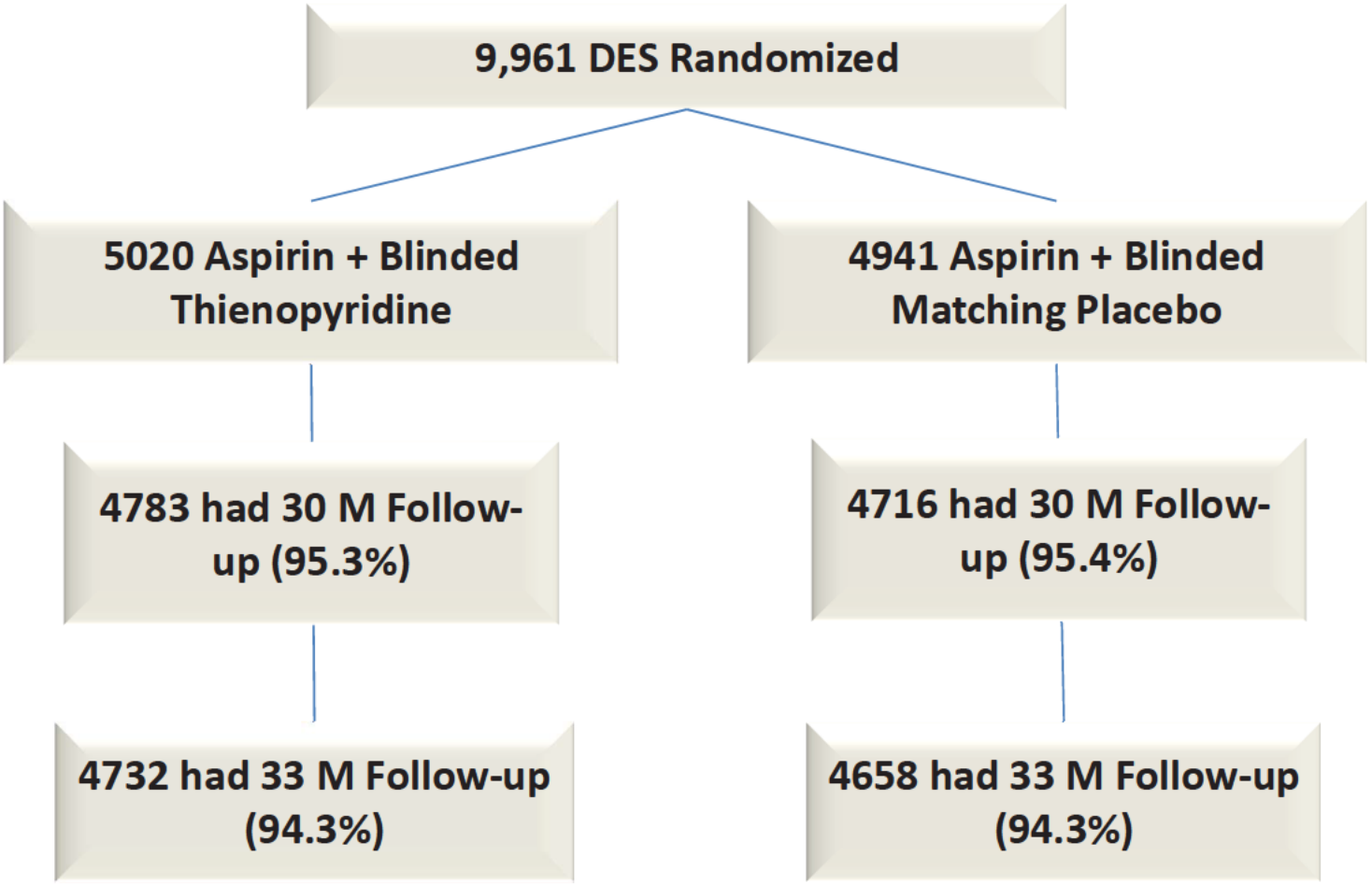
DAPT STUDY

452 Sites in 11 Countries

Subject Flow



Subject Flow: Randomized DES



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Baseline Demographics
DES ITT

DAPT STUDY

	30 Month DAPT N=5020	12 Month DAPT N=4941	P-value
Age (years)	61.8	61.6	0.24
Female	24.7%	26.0%	0.15
Race – Non White	8.9%	8.6%	0.69
Ethnicity-Hispanic or Latino	3.2%	3.3%	0.91
Weight – kg	91.5	91.5	0.93
BMI	30.5	30.6	0.92
Diabetes Mellitus	31.1%	30.1%	0.28
Hypertension	75.8%	74.0%	0.03
Cigarette Smoker	24.6%	24.7%	0.91
Prior PCI	30.4%	31.0%	0.50
Prior CABG	11.3%	11.8%	0.49
NSTEMI	15.5%	15.5%	0.93
STEMI	10.6%	10.3%	0.65

ST Risk Factors at Index Procedure, DES ITT

DAPT STUDY

	30 Month DAPT N=5020	12 Month DAPT N=4941	P-value
ACS (NSTEMI or STEMI)	26.1%	25.9%	0.80
Renal insufficiency/failure	4.5%	4.0%	0.27
LVEF < 30%	1.7%	1.5%	0.40
> 2 vessels stented	0.4%	0.6%	0.15
> 2 lesions per vessel	1.9%	1.9%	0.88
Lesion length ≥ 30 mm	10.0%	10.2%	0.87
Bifurcation lesion	6.5%	6.5%	0.97
ISR of DES	3.1%	3.2%	0.86
Vein bypass graft	2.5%	3.1%	0.09
Unprotected left main	0.4%	0.5%	0.54
Thrombus-containing lesion	11.8%	11.7%	0.87
Prior brachytherapy	0.3%	0.3%	1.00
Any Risk Factor	50.7%	51.0%	0.81

Lesion and Procedure Characteristics, DES ITT

DAPT STUDY

	30 Month DAPT N=5020 (6594 Lesions)	12 Month DAPT N=4941 (6413 Lesions)	P-Value
Number of Treated Vessels (per subject)	1.1	1.1	0.60
Number of Stents (per subject)	1.5	1.5	0.23
Minimum Stent Diameter (mm, per subject)	2.9	2.9	0.86
Total Stent Length (mm, per patient)	27.7	27.4	0.43
Native Coronary	97.1%	96.8%	0.36
Left Main	0.8%	0.9%	0.92
LAD	41.2%	40.4%	0.33
Circumflex	22.4%	23.5%	0.12
RCA	32.7%	32.1%	0.49
Venous Graft	2.34%	2.70%	0.20
Arterial Graft	0.55%	0.47%	0.54
Modified ACC/AHA Lesion Class B2 or C	43.5%	43.1%	0.65

Study Update

CONFIDENTIAL

17 September 2014

Agenda

1. Review of DES 30 vs 12m primary results
2. Update on DES vs BMS propensity analysis, and BMS 30 vs 12m RCT results
3. Update on NCVD analyses and case review plan
4. Update regarding inquiry from CDER regarding early safety release
5. DMC meeting Sept 9, 2014
6. FDA Comments
7. Manufacturer Comments
8. Communication Strategy and Timeline

Attendees

Study Leadership: Laura Mauri, MD, *PI,* Dean Kereiakes, MD, *co-PI*

HCRI: Priscilla Driscoll Shempp, *DAPT Study Project Director*

FDA

- **CRDH**:
  - Andy Farb, MD, *Senior Medical Reviewer, Division of Cardiovascular Devices*
  - Bram Zuckerman, MD, *Director, Division of Cardiovascular Devices*
- **CDER**:
  - Mary Ross Southworth, PharmD, *Deputy Director, Safety, Division of Cardiovascular and Renal Prod*
  - Karen Hicks, MD, *Medical Officer, Division of Cardiovascular and Renal Prod*
  - Bob Temple, MD, *Deputy Director for Clinical Science*
  - Ellis Unger, MD, *Director, Office of Drug Evaluation I/Office of New Drugs*

Device Manufacturers

- **Abbott**: Charles Simonton, MD, *Chief Medical Officer, Divisional VP, Med. Affairs*
- **Boston Scientific**: Keith Dawkins, MD, *Global Chief Medical Officer*
- **Cordis**: Patti Schleckser, *Director of Clinical Research*
- **Medtronic**: Sandeep Brar, MD, *Director of Clinical Research*

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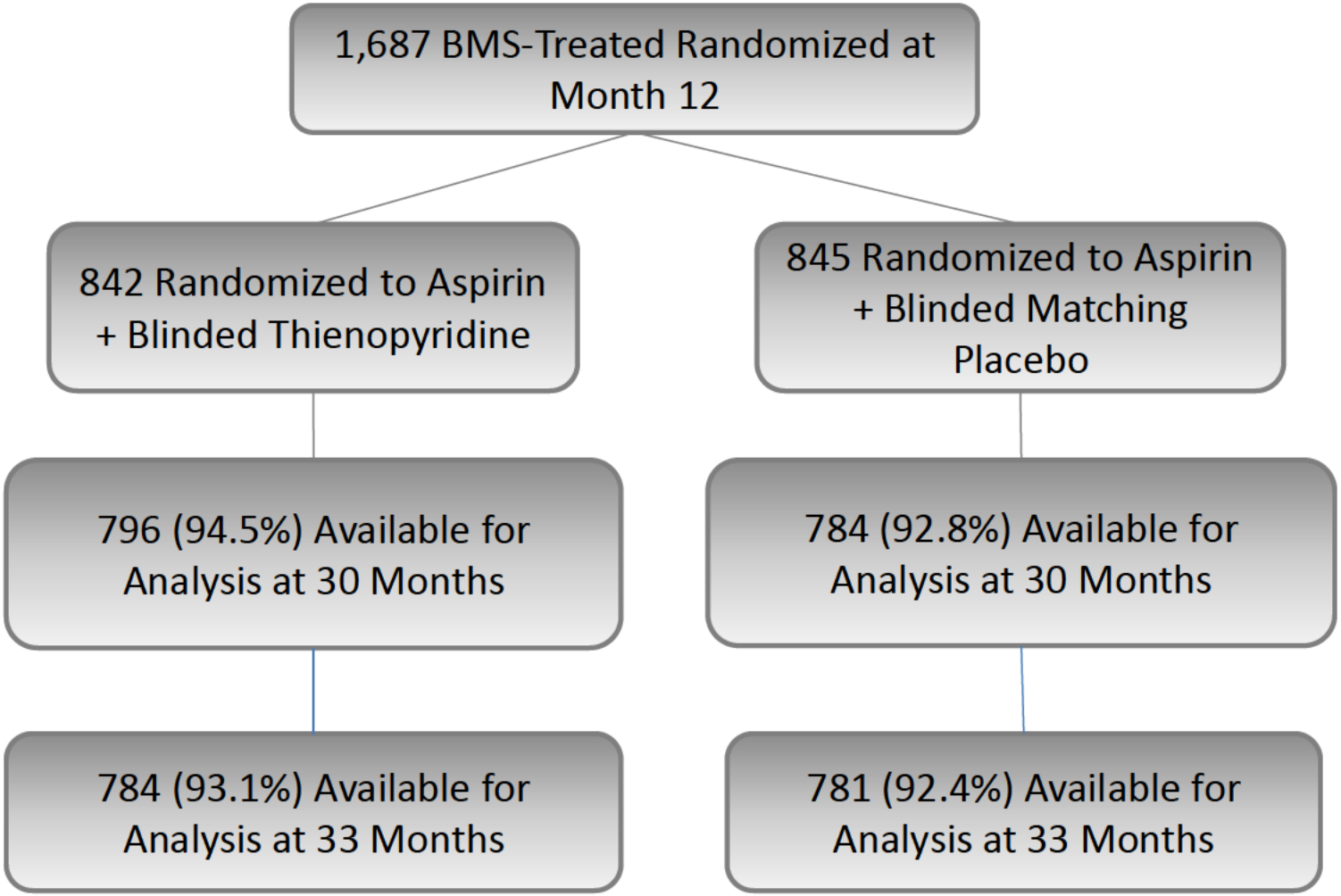
Pharmaceutical Manufacturers

- **Bristol-Myers Squibb**: Charlotte Jones-Burton, MD, *Director, CV Medical Strategy*
- **Daiichi Sankyo**: Dmitry Zamoryakhin MD, *Director, Cardiovascular Clinical Development*
- **Eli Lilly**: LeRoy LeNarz, MD, *Sr. Medical Director – Cardiovascular*
- **Sanofi**: William Daley, MD, *VP of Business Development & Licensing*

MacDougall Biomedical Communications: Kari Watson, *Senior Vice President*

BMS ITT 12 VS. 30 MONTH ANALYSIS

Subject Flow: Randomized BMS



Primary Effectiveness Outcomes, BMS ITT, 12-30 Months F/U

DAPT STUDY

Outcome	30 Month DAPT N=842	12 Month DAPT N=845	Stratified HR, 95% CI	Stratified Log-rank P-Value
Stent Thrombosis ARC Definite/Probable	**4 (0.5%)**	**9 (1.1%)**	**0.49 (0.15-1.64)**	**0.24**
ARC Definite	4 (0.5%)	9 (1.1%)	0.49 (0.15-1.64)	0.24
ARC Probable	0 (0.0%)	0 (0.0%)	-- (--, --)	
MACCE (Death, MI, Stroke)	**33 (4.0%)**	**38 (4.7%)**	**0.92 (0.57-1.47)**	**0.72**
Death	8 (1.0%)	10 (1.2%)	0.90 (0.35-2.33)	0.83
Cardiac	4 (0.5%)	5 (0.6%)	1.03 (0.26-4.12)	0.97
Vascular	0 (0.0%)	0 (0.0%)	-- (--, --)	
Non-Cardiovascular	4 (0.5%)	5 (0.6%)	0.79 (0.21-2.96)	0.73
MI	22 (2.7%)	25 (3.1%)	0.91 (0.51-1.62)	0.74
Stroke (total)	6 (0.7%)	5 (0.6%)	1.22 (0.37-4.01)	0.74
Ischemic stroke	4 (0.5%)	5 (0.6%)	0.82 (0.22-3.05)	0.77
Hemorrhagic stroke	1 (0.1%)	0 (0.0%)	-- (--, --)	0.32
Type Uncertain	1 (0.1%)	0 (0.0%)	-- (--, --)	0.32

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ACS for ST and MACCE, BMS ITT; 12-30 Months F/U

	30 Month DAPT N (%)	12 Month DAPT N (%)	HR (95% CI)	P Value for Interaction
ARC Definite/Probable ST				
No ACS Within 72 Hours	2 (0.6%)	1 (0.3%)	2.04 (0.18-22.47)	0.14
ACS Within 72 Hours	2 (0.4%)	8 (1.7%)	0.24 (0.05-1.14)	
MACCE				
No ACS Within 72 Hours	17 (5.0%)	17 (5.0%)	1.02 (0.52-2.00)	0.50
ACS Within 72 Hours	16 (3.3%)	21 (4.5%)	0.74 (0.39-1.42)	

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DAPT STUDY

Study Update

24 October 2014

Agenda

1. Brief Review of Primary Results
2. Adjudication Analysis Results
3. Meta-analysis of Published Data
4. Communication Plan
5. Questions and Discussion

Attendees

Study Leadership: Laura Mauri, MD, *PI,* Dean Kereiakes, MD, *co-PI*

HCRI: Priscilla Driscoll Shempp, *DAPT Study Project Director*

- **MacDougall Biomedical Communications**: Kari Watson, *Senior Vice President*
- **CardioMed:** Semih Oktay, *President*

FDA

- **CDRH**:
  - Andy Farb, MD, *Medical Officer, Division of Cardiovascular Devices*
  - Bram Zuckerman, MD, *Director, Division of Cardiovascular Devices*
- **CDER**:
  - Mary Ross Southworth, PharmD, *Deputy Director, Safety, Division of Cardiovascular and Renal Prod*
  - Karen Hicks, MD, *Medical Officer, Division of Cardiovascular and Renal Prod*
  - Norman Stockbridge, MD, PhD, Director, Division of Cardiovascular and Renal Products
  - Robert Temple, MD, *Deputy Director for Clinical Science (tentative)*
  - Douglas Throckmorton, *MD, Deputy Director of the Center for Drug Evaluation and Research*

Device Manufacturers

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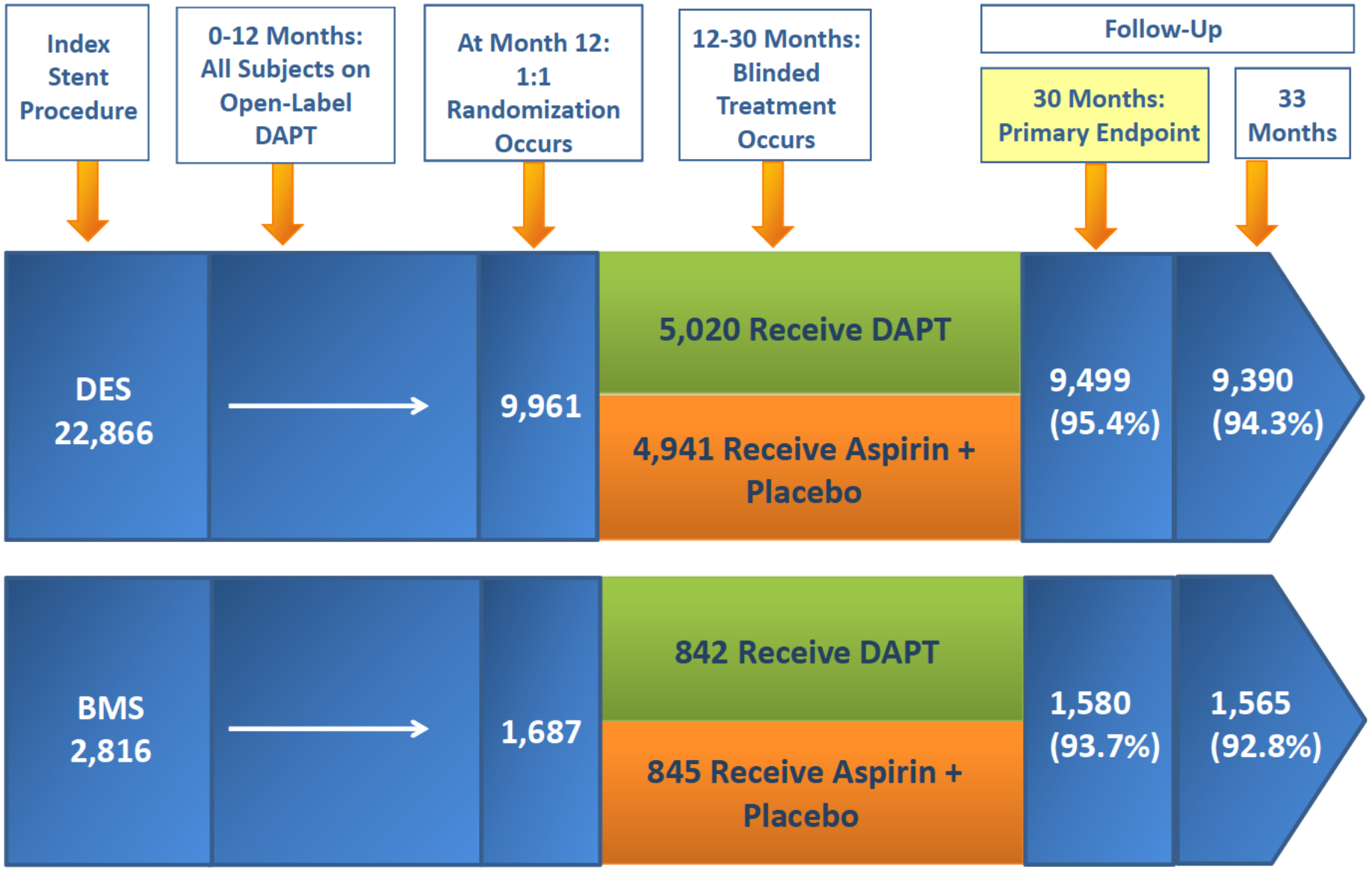
- **Eli Lilly**: LeRoy LeNarz, MD, *Sr. Medical Director – Cardiovascular*
- **Sanofi**: William Daley, MD, *VP of Business Development & Licensing (on behalf of Sanofi/BMS JV)*

DAPT STUDY

Summary of Primary Results

Subject Flow: All



Co-Primary Effectiveness Endpoints & Components, BMS ITT: 12-30 Months F/U

DAPT STUDY

Outcome	Thienopyridine N=842	Placebo N=845	Stratified HR, 95% CI	Stratified Log-rank P-Value
Stent Thrombosis ARC Definite/Probable	**4 (0.5%)**	**9 (1.1%)**	**0.49 (0.15-1.64)**	**0.24**
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MI	22 (2.7%)	25 (3.1%)	0.91 (0.51-1.62)	0.74
Stroke (total)	6 (0.7%)	5 (0.6%)	1.22 (0.37-4.01)	0.74
Ischemic stroke	4 (0.5%)	5 (0.6%)	0.82 (0.22-3.05)	0.77
Hemorrhagic stroke	1 (0.1%)	0 (0.0%)	-- (--, --)	0.32
Type Uncertain	1 (0.1%)	0 (0.0%)	-- (--, --)	0.32

DAPT
STUDY

Questions and Discussion

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 7, 2013

Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

TSI: 935

Drugs: Angiotensin receptor blockers (ARBs)

Subject: Risk of cancer

Summary

BACKGROUND: A published meta-analysis raised the question of whether use of angiotensin receptor blockers (ARBs) is associated with an increased risk of cancer.

METHODS: To identify all malignancy adverse events I followed a pre-specified analysis plan to analyze the raw data from all 16 large ARB clinical outcomes trials submitted to the FDA. Using the malignancy determinations I performed pre-specified patient-level meta-analyses of incidences of lung, prostate, and hematologic malignancy events and Kaplan-Meier analyses and Cox regressions (stratified by trial and including baseline cofactors) of incidence rates and of survival after malignancy diagnosis.

RESULTS: I excluded five trials from the primary analyses because they failed the pre-specified criteria for completeness of follow-up and malignancy reporting. The pooled risk ratio for lung cancer comparing the ARB arms to the control arms in the 11 trials with adequate data was 1.24 (95% confidence interval 1.08-1.43, p = 0.003). The increased risk of lung cancer with ARBs was robust to meta-analyses excluding the index trial, including all four of the excluded trials that had malignancy site reporting, and analyzing new diagnoses alone. Kaplan-Meier analyses estimated about 0.8 excess lung cancer cases per year per 1,000 patients treated. Cox regressions estimated about a 4-fold higher risk in ex-smokers and an 11-fold higher risk in current smokers

compared to non-smokers regardless of ARB use. Survival after a lung cancer event was dismal, about 34 percent at one year regardless of initial ARB use. The meta-analyses for prostate and hematologic malignancies were inconclusive. Solid cancer rates (excluding non-melanoma skin cancers and brain tumors) were slightly but not significantly increased with ARB use.

CONCLUSION: ARB use is associated with an increased risk of lung cancer.

Introduction

In 2010 a meta-analysis published by Sipahi *et al.* raised the question of whether use of angiotensin receptor blockers (ARBs) is associated with an increased risk of cancer. (Sipahi, Debanne et al. 2010) Sipahi *et al.* analyzed cancer data from publications and from the FDA website for 61,590 patients from five trials and observed that patients randomized to ARBs had a significantly increased risk of new cancers (risk ratio (RR) 1.08, 95% confidence interval (CI) 1.01-1.15). They also analyzed specific solid cancer sites and found that only new lung cancers were significantly more frequent in the ARB arms (RR 1.25, 95% CI 1.05-1.49). They concluded that their findings warranted further investigation.

The Sipahi *et al.* meta-analysis stimulated other meta-analyses and observational studies addressing similar issues. Bangalore *et al.* analyzed 70 antihypertensive trials with 324,168 patients. (Bangalore, Kumar et al. 2011) Regarding ARBs they found no difference in cancer risk, although they observed an increased cancer risk with the combination of ARBs with angiotensin converting enzyme inhibitors (ACEI) by a fixed effect meta-analysis but not by a random effects one. The ARB Trialists Collaboration analyzed 15 ARB trials with 138,769 patients and found no excess cancer risk with ARB use. (ARB Trialists Collaboration 2011) The FDA conducted a trial-level meta-analysis of 31 trials and approximately 156,000 patients and concluded that ARB treatment does not increase the risk of cancer. (FDA 2011)

All of the published meta-analyses have severe limitations regarding trials included and the information available on cancer cases in publically available trial data. For example, regarding trials included, the ARB Trialists Collaboration analyzed only the LIFE trial for losartan, omitting three other major losartan trials because they were not able to obtain the data. Regarding information on cancer cases, Bangalore *et al.* counted seven cancer cases for the losartan RENAAL trial and referenced the main RENAAL publication. (Brenner, Cooper et al. 2001) However the main RENAAL publication does not include statistics on cancer cases. I queried the meta-analysis authors and they confirmed that they had obtained the RENAAL cancer incidences from a 2008 meta-analysis. (Coleman, Baker et al. 2008) The latter meta-analysis also referenced only the main RENAAL publication. Upon query the author of the 2008 meta-analysis quoted the source as a RENAAL substudy publication. (Remuzzi, Ruggenenti et al. 2004) However, the RENAAL substudy publication tabulated cancer cases only for adverse events leading to patient withdrawal. Because cancer is not a reason for withdrawing ARB

treatment, counting only withdrawals grossly underestimates cancer incidence (as confirmed by the RENAAL data submission to the FDA.)

The FDA meta-analysis did not correct the flaws present in the meta-analyses using published data. The FDA requested summary trial data from the drug companies but did not specify details on how to classify incident cases, ambiguous cases, or censoring periods and did not mandate submission of data for all relevant trials. Furthermore, the FDA meta-analysis of lung cancers was seriously flawed in that it did not count lung carcinomas as lung cancers but was inappropriately limited to lung cancers coded as "malignant lung neoplasm".

Sipahi was unaware of these flaws in the FDA meta-analysis but publically criticized it for not exploring exposure-risk relationships in a patient-level analysis. (Wood 2011) I agree with Sipahi that as serious a question as whether widely-used antihypertensives increase cancer risk deserves the most discriminating analysis possible. I proceeded with a patient-level meta-analysis of the raw data in long-term ARB trials submitted to the FDA as recommended in an editorial on the Sipahi *et al.* meta-analysis. (Nissen 2010)

My experience with ARBs and cancer predates the Sipahi *et al.* meta-analysis: I had performed the primary clinical review of the losartan LIFE trial submitted to the FDA in 2002. (Marciniak 2003) I observed then that there was a numeric but not statistically significant excess of lung cancers in the losartan arm in that trial. I also observed that there was a less prominent numeric excess of prostate cancers in the losartan arm. Re-examining the LIFE data after the publication of the Sipahi *et al.* meta-analysis I observed additionally that hematologic malignancies were less frequent in the losartan arm. I hypothesized that the latter result, if real, might be related to the same mechanism responsible for the slight suppression of hematopoiesis observed with both ARBs and ACEIs. (Leshem-Rubinow, Steinvil et al. 2012) I hypothesized also that the excess of prostate cancers, if real, might be related to an increase in adrenal androgen levels resulting from the same mechanism responsible for aldosterone breakthrough following chronic ARB or ACEI use. (Bomback and Klemmer 2007)

Hence I targeted the following three independent hypotheses in patient-level meta-analyses:

1. That ARB use increases the risk of lung cancer. Because I had no *a priori* hypothesis that ACEIs share this effect, I pre-specified for the primary analysis of lung cancers ignoring the use of ACEIs both as controls and in the ARB arms.

2. That ARB use increases the risk of prostate cancer. For this hypothesis I pre-specified criteria for eliminating trials only with ACEI control arms or with substantial use of ACEIs during the trial. Because of resource limitations, i.e., I performed this work without official FDA support, I did not analyze the data by concomitant ACEI use in the ARB arms.

3. That ARB use decreases the risk of hematologic malignancies. Regarding ACEI use I proposed analyzing this hypothesis identically to that regarding prostate cancer.

Because previous meta-analyses had also targeted all cancers, I also analyzed all solid cancers excluding non-melanoma skin cancers and brain tumors. I excluded hematologic malignancies because I hypothesize that ARBs may decrease them, non-melanoma skin cancers because of their less serious nature compared to other solid cancers and because they are under-reported, and brain tumors because their malignancy status is frequently not reported and because most ARBs do not cross the blood-brain barrier.

Methods

Trial Selection

I adopted the same general criteria for trial size and duration used by the Sipahi *et al.* and FDA meta-analyses: randomized, placebo-and active comparator-controlled studies for the ARBs; enrolled more than 100 patients; had a mean or median follow-up longer than one year; and collected cancer data either as a prespecified endpoint or adverse event. I considered only trials for which the sponsors had submitted complete data (i.e., protocols, case report forms, and datasets) to the FDA.

Regarding trial data I looked for data on all cancer-related events, not just deaths, and for data on the primary site of the cancer, because the hypotheses involve specific sites and not all cancers. I prespecified excluding trials from the primary analyses if more than five percent of all cancers were detected only at study end or death or if the primary sites were not reported for more than five percent of the cancers (other than cancers reported explicitly as unknown primaries). Because I have concerns about the validity of any results from trials having poor follow-up and I have documented serious problems with them in previous reviews, I prespecified excluding trials from the primary analyses if completeness of follow-was less than 90 percent. For the hypotheses regarding prostate cancer and hematologic malignancies, which postulate similar effects for both ARBs and ACEIs, I prespecified excluding trials from the primary analyses if the trials had only ACEI control arms or if the concomitant use of ACEIs in the trials exceeded 10 percent.

Consulting with other FDA staff I identified 16 ARB trials with data submitted to the FDA and meeting the general criteria for trial size and duration. I excluded five of these 16 trials from the primary analyses because of incomplete follow-up or incomplete cancer ascertainment (see Appendix 1) and included 11 trials in the meta-analysis of lung cancer. I excluded six of the 11 trials from the meta-analyses of prostate and hematologic malignancies because of ACEI use. I list the trials used in the primary meta-analyses in Table 1 and those excluded in Table 2**.**

Table 1: Trials Included in the Primary Meta-Analyses

ARB	Trial	Reference	NDA	N	Prostate/heme analyses?
candesartan	Charm-Added	(McMurray, Ostergren et al. 2003)	20838 S022	2548	No, ACEI use ~100%
	Charm-Alternative	(Granger, McMurray et al. 2003)	20838 S022	2028	Yes
	Charm-Preserved	(Yusuf, Pfeffer et al. 2003)	20838 S022	3023	No, ACEI use ~20%
irbesartan	(b) (4)				
	IDNT	(Lewis, Hunsicker et al. 2001)	20757 S021	1716	Yes
losartan	LIFE	(Dahlof, Devereux et al. 2002)	20386 S032	9193	Yes
	RENAAL	(Brenner, Cooper et al. 2001)	20386 S028	1513	Yes
telmisartan	ONTARGET	(Yusuf, Teo et al. 2008)	20850 S025	25620	No, ACEI control arm
	PRoFESS	(Yusuf, Diener et al. 2008)	20850 S025	20332	No, ACEI use ~31%
	TRANSCEND	(Yusuf, Teo et al. 2008)	20850 S025	5926	Yes
valsartan	Val-Heft	(Cohn and Tognoni 2001)	20665 S016	5010	No, ACEI use ~93%

Table 2: Trials Excluded from the Primary Meta-Analyses

ARB	Trial	Reference	IND/NDA	N	Reason Excluded
irbesartan	IRMA 2	(Parving, Lehnert et al. 2001)	N20757 S021	611	Incomplete follow-up
olmesartan	(b) (4)				
valsartan					
	VALIANT	(Pfeffer, McMurray et al. 2003)	N21283 S011	14679	Incomplete cancer reporting

The 11 trials for the lung cancer meta-analysis include 85,925 patients and studied five different ARBs while the five trials for the prostate and hematologic malignancies meta-analyses include 20,376 patients and studied four ARBs. The five excluded trials total 29,832 patients and studied three ARBs. Two FDA-approved ARBs, azilsartan and eprosartan, did not have any eligible trials submitted to the FDA. The FDA approved azilsartan in 2011 and its sponsor has not conducted large outcome trials with it. (b) (4) The other FDA-approved ARB not included in the primary meta-analyses, olmesartan, had two trials with FDA data submissions meeting the general criteria but failing the criterion for completeness of follow-up.

Cancer Ascertainment

From the study protocols, case report forms (CRFs), and dataset documentation I identified all CRFs and datasets having data regarding cancers. The CRFs having cancer data included adverse event forms, serious adverse event forms, endpoint forms, procedure forms, end of treatment forms, disposition forms, and death forms depending upon the particular study. I used computer string searches to identify possible cancer cases from the investigator-reported verbatim terms in the corresponding datasets and string matches to standard cancer terms if coded terms were available. The string searches included misspellings and ambiguous terms, (e.g., "kancer", "lung mass") and I designed them to be sensitive rather than specific. Blinded to treatment assignment I manually reviewed all possible cancer cases, consulting primarily the investigator-reported verbatim terms and comments but reviewing the full case report forms for ambiguous cases. I assigned a primary cancer site, e.g., "lung", "prostate", if the case had adequate documentation of malignancy or seriousness and of the primary site. If medical histories included cancer sites I assigned cancer sites using the same approach.

For the post-randomization cancer events I assigned a date of first clinical diagnosis of the cancer or cancer recurrence. I used date of first clinical diagnosis because date of histologic diagnosis is frequently not available in trial CRFs. I identified both initial diagnoses of cancers, i.e., incident new cancers, as well as recurrences of cancers originally diagnosed prior to randomization, distinguishing the new cancers when possible. I consider cancer recurrences to be as clinically relevant as incident new cancers because cancer patients die more frequently from the local or metastatic recurrence than from the original primary.

Finally, I identified for each trial the earliest last follow-up date, e.g., the global study end date or the primary endpoint censoring date. I counted cancer events by the intent-to-treat (ITT) principle if they occurred on or after the randomization date and before or on the earliest last follow-up date. I did not attempt to censor the cancers occurring shortly after randomization despite the realization that they are highly unlikely to be related to study drug use; I do not have an *a priori* justification for a censoring date and, being infrequent, counting them does not appear to affect substantially the meta-analyses. I relied upon the incidence curves to show any differences in early vs. later rates. I favor and pre-specified the ITT approach because it is the only approach that preserves the randomization and, if the effect size is less than two-fold, the majority of cancers will be numerically unrelated to the study drug use. Furthermore, cancers frequently require weeks to diagnose but cause adverse effects leading earlier to study drug discontinuation. I would consider an on-treatment analysis allowing an adequate time for delayed diagnoses as a sensitivity analysis but, because of resource limitations, I did not assign dates of last treatment and perform on-treatment analyses.

Statistical Analysis

I performed all statistical analyses using Stata 12. For the meta-analyses I used the *metan* package. (Harris, Bradburn et al. 2008) Because I hypothesized similar effects for all ARBs, I performed fixed-effect meta-analyses of risk ratios evaluated by the Mantel-Haenszel method. I evaluated heterogeneity with the I^2 statistic.

To show the time course of cancer development I generated Kaplan-Meier plots of time to first cancer event occurrences. I also generated Kaplan-Meir plots of survival after first clinical diagnosis of a new or recurrent cancer. I used crude survival rather than cause-specific survival, i.e., deaths due to cancer, because I believe that cancer usually contributes to the demise of patients with recurrent or metastatic cancer. I estimated statistical significance of the time courses of cancer development and survival following cancer diagnosis by log rank tests stratified by study. I explored the effects of baseline factors by Cox regressions stratified by study. For the Cox regressions I tested the proportional hazards assumptions by graphs and statistics of Schoenfeld residuals produced by the Stata 12 *estat phtest* command.

Results

Lung Cancer

I identified new or recurrent lung cancer events during the censoring periods in 805 of the 85,925 patients in the eleven trials. The pooled RR comparing the ARB arms to the control arms is 1.24 (95% CI 1.08-1.43, p = 0.003). I show the forest plot of RRs by trial in Figure 1. The I^2 statistic did not suggest significant heterogeneity (p > 0.6). All of the trials except one, CHARM-Preserved, showed an excess of lung cancers in the ARB arms. The CI for the CHARM-Preserved risk ratio overlaps with the risk ratio CIs for all eleven trials and for the ten trials excluding CHARM-Preserved. Because LIFE was the index study suggesting an effect of an ARB upon lung cancer, I performed a second meta-analysis excluding LIFE. The pooled RR excluding LIFE is also 1.24 (95% CI 1.07-1.44, p = 0.005). As sensitivity analyses I performed meta-analyses including the trials excluded from the primary analyses. For a meta-analysis including the one irbesartan study excluded (IRMA 2), the pooled RR remains 1.24 and the p value is 0.003. For a meta-analysis including all 15 trials that collected the cancer sites for all malignancies, i.e., all except VALIANT, the pooled RR is 1.16 and the p value is 0.026.

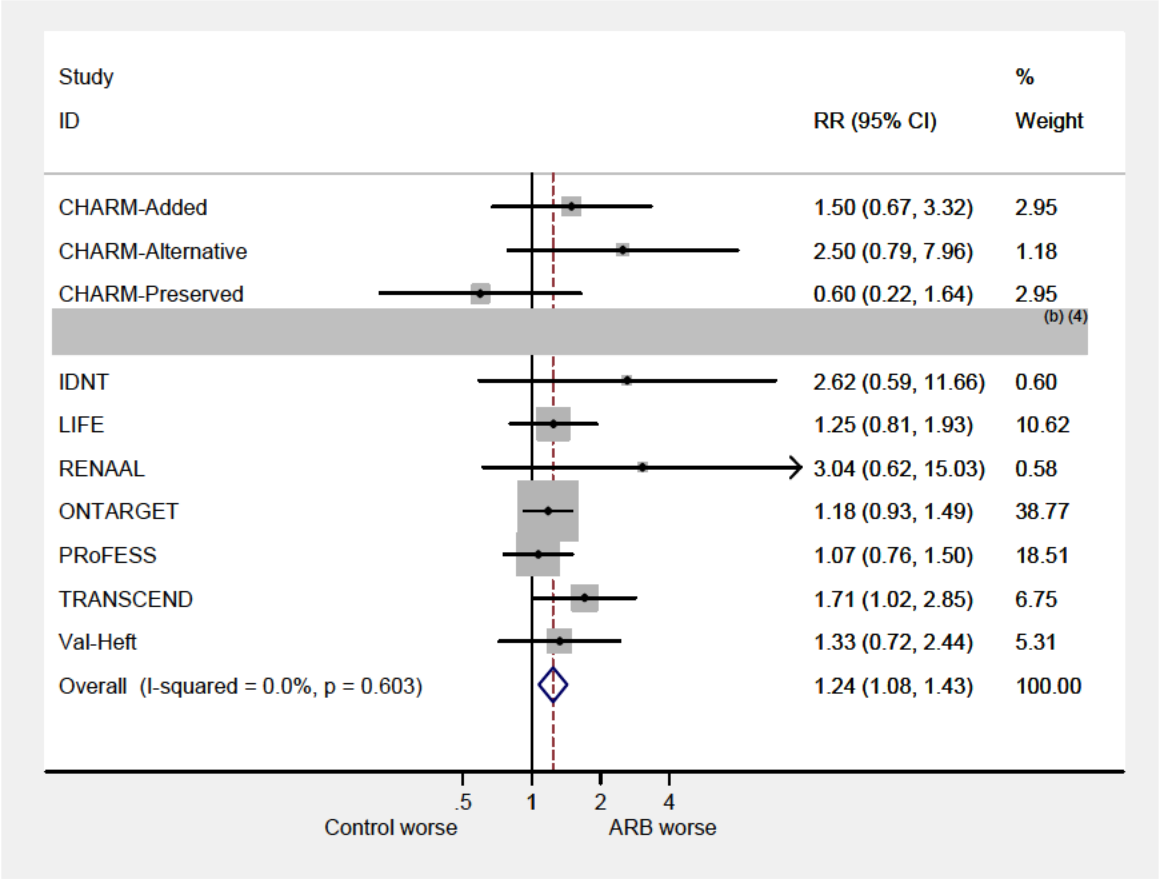
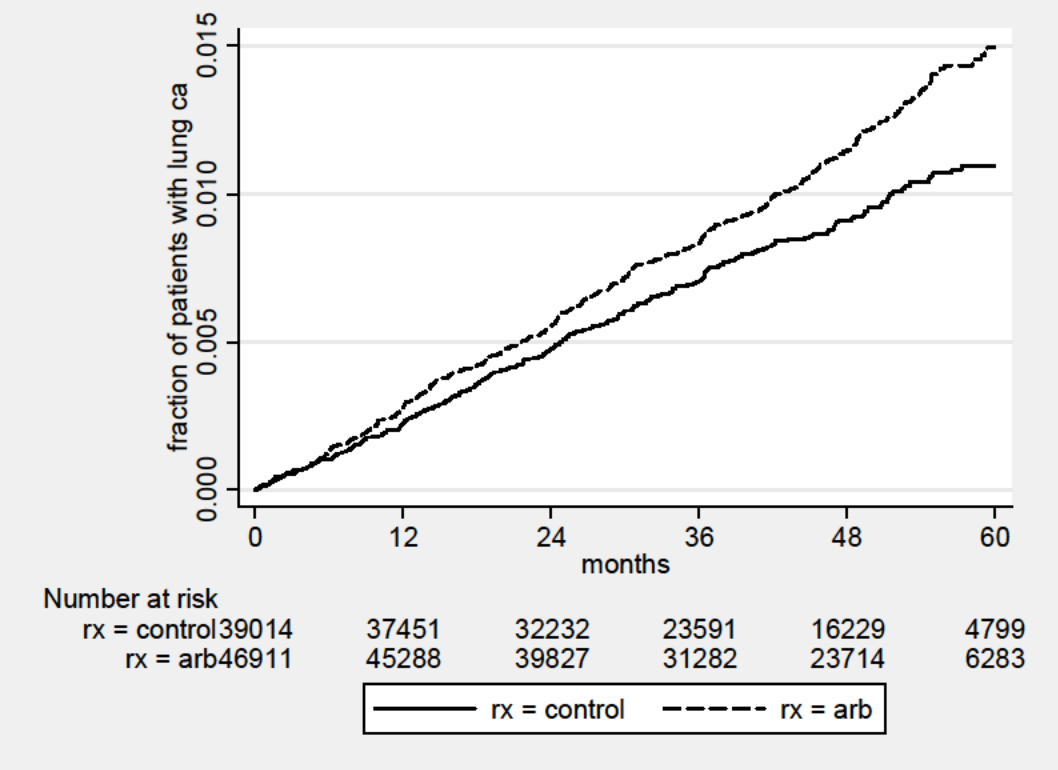


Figure 1: Risk Ratios of Patients with Lung Cancer Events by Trial

I identified new lung cancers during the censoring periods in 645 of the 63,877 patients in the nine trials that captured histories of cancer sites. (PRoFESS did not capture histories of cancer sites. IDNT may have in concomitant diagnoses but the sponsor did not submit to the FDA a dataset with them.) About 97% of the first lung cancer events were new lung cancers in these nine trials. The pooled RR is 1.32 (95% CI 1.12-1.59, p = 0.001). The pooled RR excluding LIFE is 1.33 (95% CI 1.12-1.59, p = 0.001).

I also analyzed new or recurrent lung cancer events separately for the trials excluding most ACEI use (i.e., the trials I use for the prostate cancer and hematologic malignancy meta-analyses) and for the trials including substantial ACEI use. For the five trials excluding most ACEI use the pooled RR is 1.57 (95% CI 1.16-2.13, p = 0.003). For the six trials having substantial ACEI use the pooled RR is 1.16 (95% CI 0.99-1.36, p = 0.074).

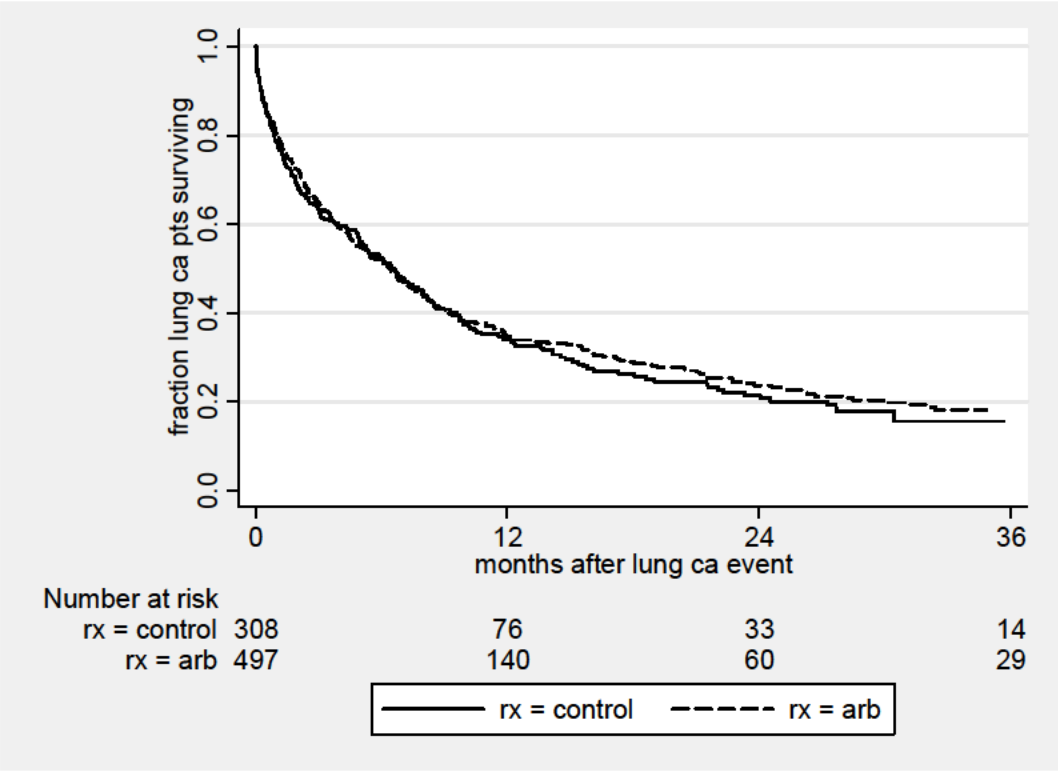
I show the Kaplan-Meier plot of times to first lung cancer events (new or recurrent) in Figure 2. The incidence curves start to diverge at about nine months and then continue to diverge throughout the five years of follow-up in the longest trials. At five years the cumulative hazard estimate is 1.5% for the ARB arms and 1.1% for the control arms, an absolute risk difference of about 0.4%, i.e., about 0.8 excess lung cancer cases per year per 1,000 patients treated.



p = 0.0033 by log rank stratified by study

Figure 2: Times to First Lung Cancer Events

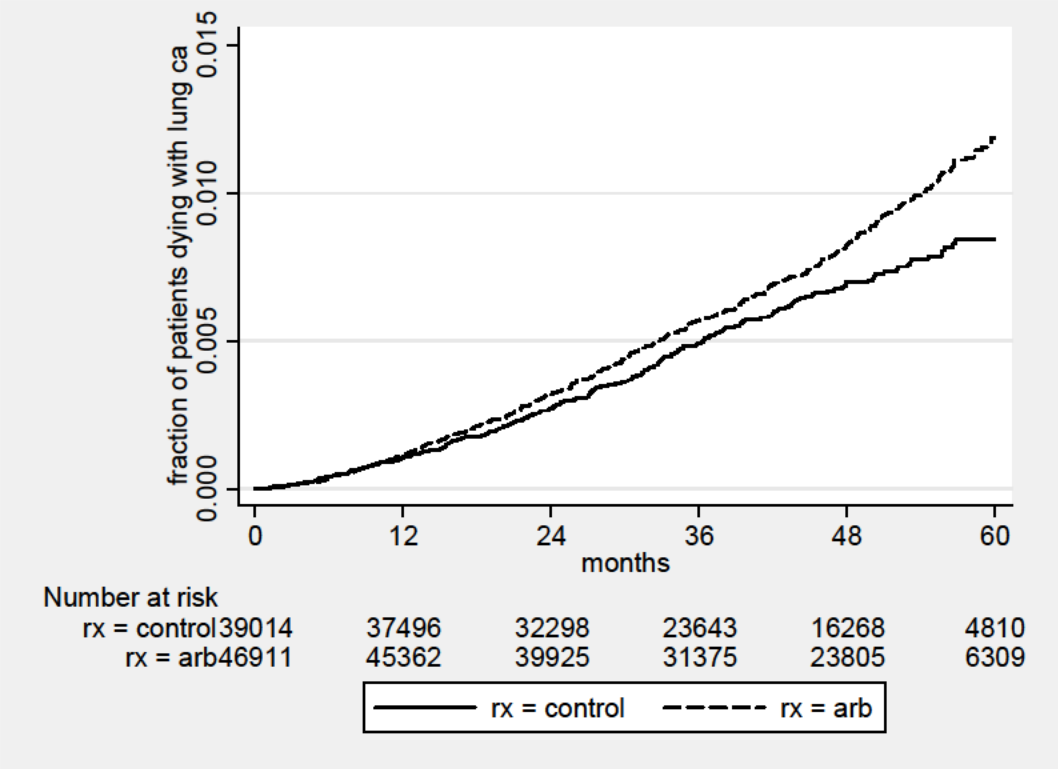
Having a lung cancer event portends a poor prognosis in these studies, similarly poor in the ARB and control arms. I show the Kaplan-Meier plots for survival after a lung cancer event in Figure 3. Survival is dismal, about 34% at one year.



p > 0.7 by log rank stratified by study

Figure 3: Survival after a Lung Cancer Event

Because lung cancer events were more frequent with ARB use while survival after a lung cancer event was similar regardless of ARB use, patients dying with lung cancer were more frequent in the ARB arms. I show the Kaplan-Meier plots for times to patients dying with lung cancer in Figure 4. The hazard ratio (HR) by Cox regression for dying with lung cancer is 1.27 (95% CI 1.08-1.51, p = 0.005).



p = 0.005 by log rank stratified by study

Figure 4: Times to Dying with Lung Cancer

I explored the effects of baseline cofactors upon lung cancer events with Cox regressions stratified by study. The Cox regression including only treatment as a factor produces results similar to the meta-analysis, HR 1.27 (95% CI 1.1-1.46, p = 0.001). For this Cox regression the proportional hazards assumption is not rejected (p > 0.3). I show the results of a Cox regression including treatment and cofactors of age, sex, and smoking status (for the 10 studies having data on smoking, i.e., except Val-Heft) in Table 3.

Table 3: Cox Regression of Times to First Lung Cancer Events

```
No. of subjects =        80915                     Number of obs    =     80915
No. of failures =          763
Time at risk    =    3526808.2                     LR chi2(5)       =    606.00
Log likelihood  =   -8097.0742                     Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         ARB |   1.256748   .0938048     3.06   0.002      1.08571    1.454731
         age |    1.06357   .0049333    13.29   0.000     1.053944    1.073283
        male |   1.332871   .1221992     3.13   0.002     1.113651    1.595245
   ex-smoker |   4.404436    .540857    12.07   0.000     3.462297    5.602945
curr. smoker |   10.59602   1.362723    18.35   0.000     8.235168    13.63369
------------------------------------------------------------------------------
                                                        Stratified by study
```

ARB use, age, male sex, and ex- or current smoking status are all associated with higher risks of lung cancer. Whether male sex is an independent risk factor is unclear because men in the trials had much higher rates of smoking than women (71% vs. 32% for any smoking). Cox regressions including interaction terms between ARB use and age, sex, and smoking status produced no statistically significant interactions (all $p > 0.4$). However, the global test for failure of the proportional hazards assumption is significant ($p = 0.003$) with age and ex-smoking status significantly contributing to the failure.

Lung cancer event rates were high for current smokers as shown in Figure 5. At five years the cumulative rate of lung cancer events in baseline current smokers in the ARB arms approaches 4%. The absolute risk difference in smokers at five years was about 1.1% and appears to be accelerating.

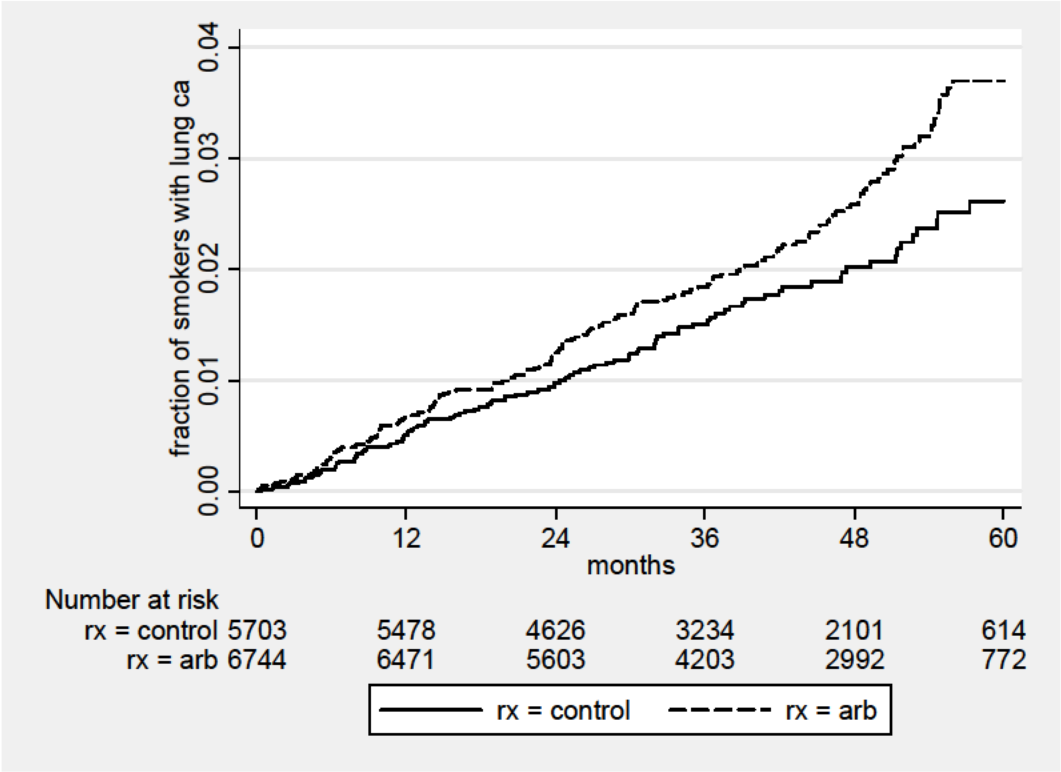


Figure 5: Times to First Lung Cancer Events for Current Smokers at Baseline

To explore age effects I analyzed separately age groups split at the median age of 65. While patients older than 65 at baseline showed proportional hazards for the treatment effect, patients aged 65 or younger showed the pattern depicted in Figure 6. There appears to be an accelerating risk for patients aged 65 or younger. In patients aged 65 or younger most lung cancer events (about 52%) occurred in current smokers while about 20% of these patients were current

smokers. However, late divergences of the curves are seen for both ex-smokers and non-smokers.

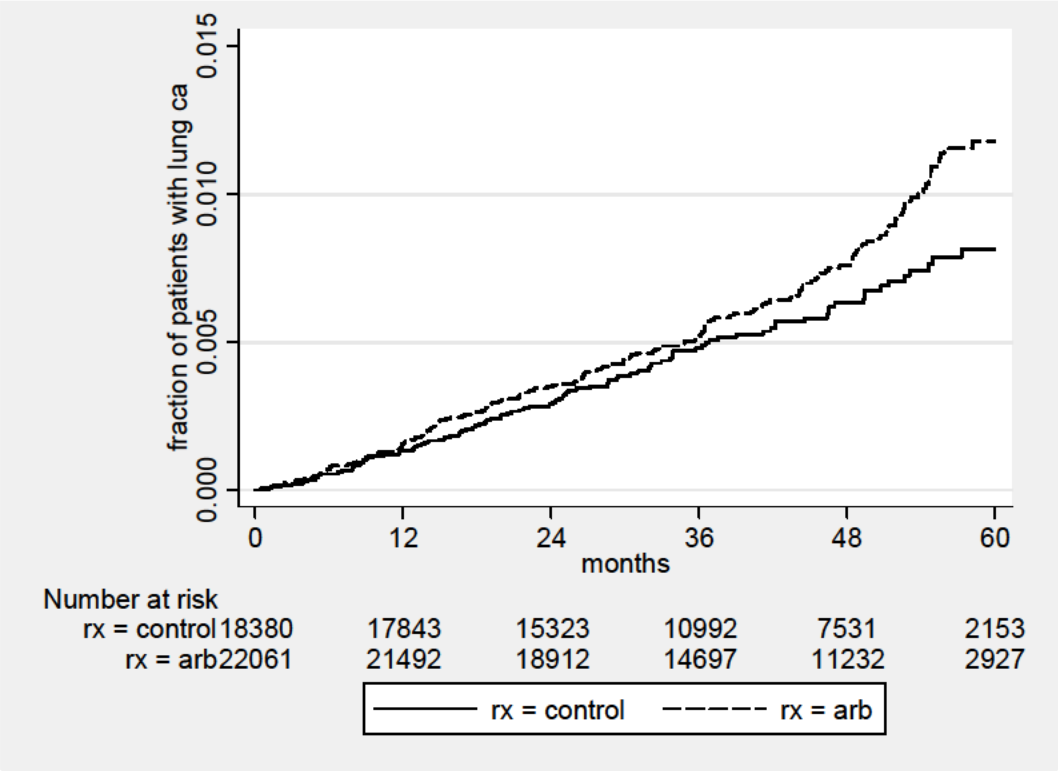


Figure 6: Times to First Lung Cancer Events for Patients 65 or Younger at Baseline

Prostate Cancer

I identified new or recurrent prostate cancer events during the censoring periods in 221 of the 11,087 men in the five trials excluding most ACEI use. The pooled RR comparing the ARB arms to the control arms is 1.23 (95% CI 0.95-1.6, p = 0.13). I show the forest plot of RRs by trial in Figure 7. The pooled RR excluding LIFE (the index study) is 1.36 (95% CI 0.88-2.1, p = 0.15). About 10% of the patients with prostate cancer events had a history of prostate cancer. The pooled RR for new prostate cancers, 1.25, is similar to that for new and recurrent prostate cancers and is also not statistically significant (p = 0.13). The pooled RR for new or recurrent prostate cancers in all 11 trials, including the ones with substantial ACEI use, is 1.04 (p > 0.6).

I show the Kaplan-Meier plot of times to first prostate cancer events (new or recurrent) in Figure 8. There is a suggestion of a slightly higher prostate cancer rate in the ARB arms beginning several months after randomization but some convergence of the curves later.

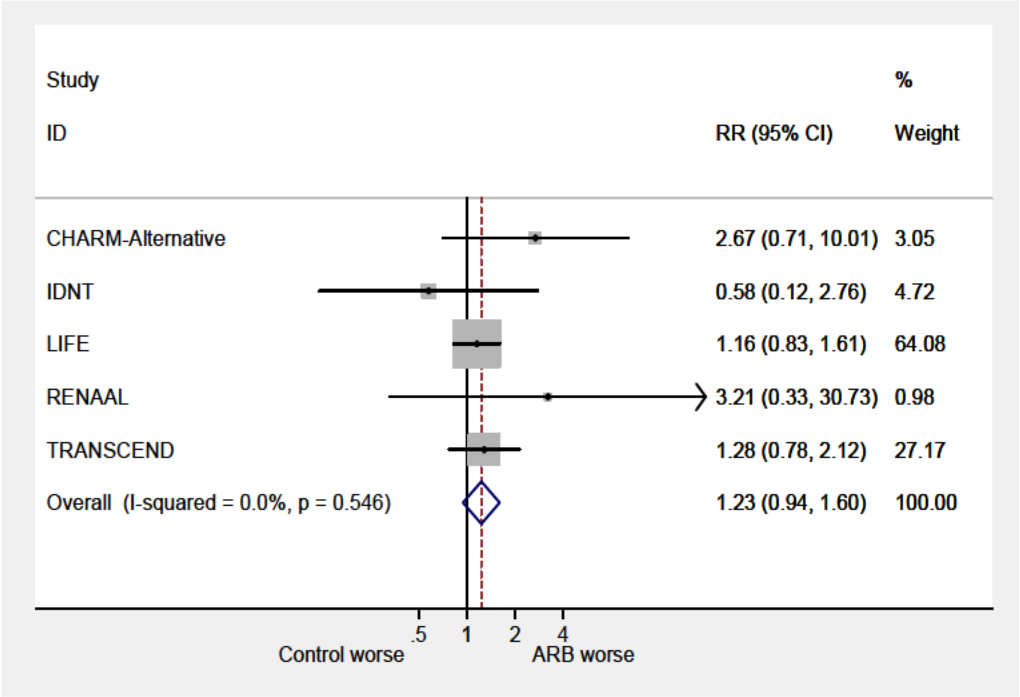
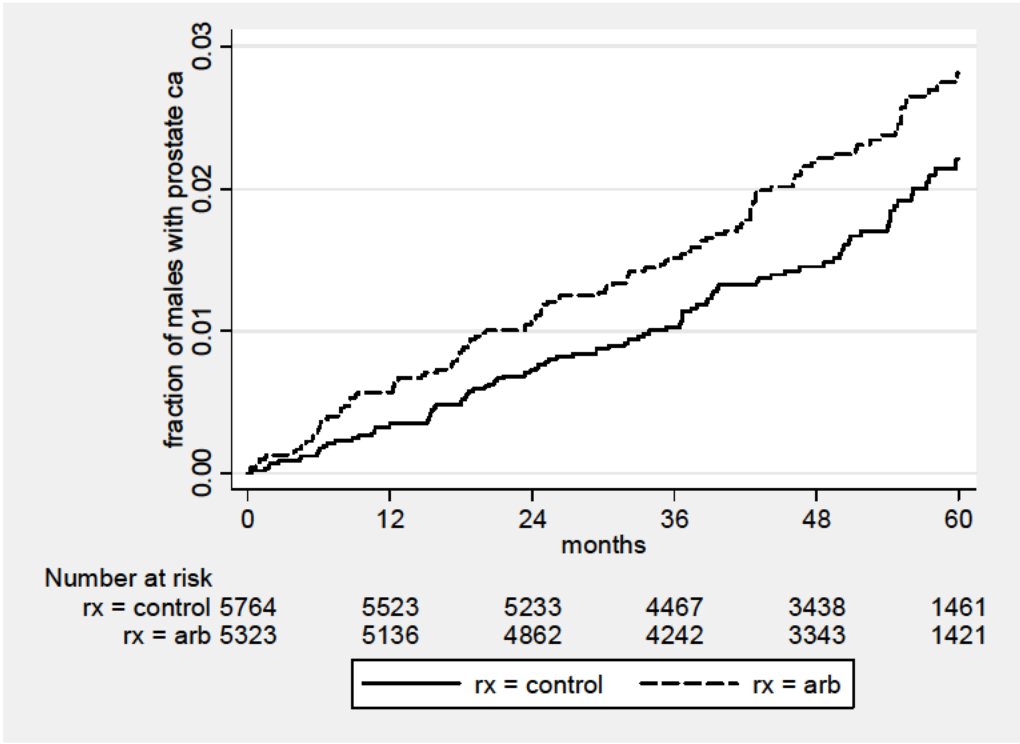


Figure 7: Risk Ratios of Patients with Prostate Cancer Events by Trial



p = 0.12 by log rank stratified by study

Figure 8: Times to First Prostate Cancer Events in Men

Survival after a prostate cancer event, about 81% at two years, was similar in the ARB and control arms. Survival from randomization was not significantly different at two years in men regardless of prostate cancer events or ARB use (about 93%).

Hematologic Malignancies

I identified new or recurrent hematologic malignancy events during the censoring periods in 98 of the 20,376 patients in the five trials excluding most ACEI use. The pooled RR comparing the ARB arms to the control arms is 0.69 (95% CI 0.46-1.03, p = 0.07). I show the forest plot of RRs by trial in Figure 9. The pooled RR excluding LIFE (the index study) is 0.83 (95% CI 0.45-1.53, p >0.5). About 6% of the patients with hematologic malignancy events had a history of hematologic malignancy. The pooled RR for new hematologic malignancies is 0.74 and less significant (p = 0.17). The pooled risk ratio for new or recurrent hematologic malignancies in all 11 trials, including the ones with substantial ACEI use, is 0.97 (p > 0.7).

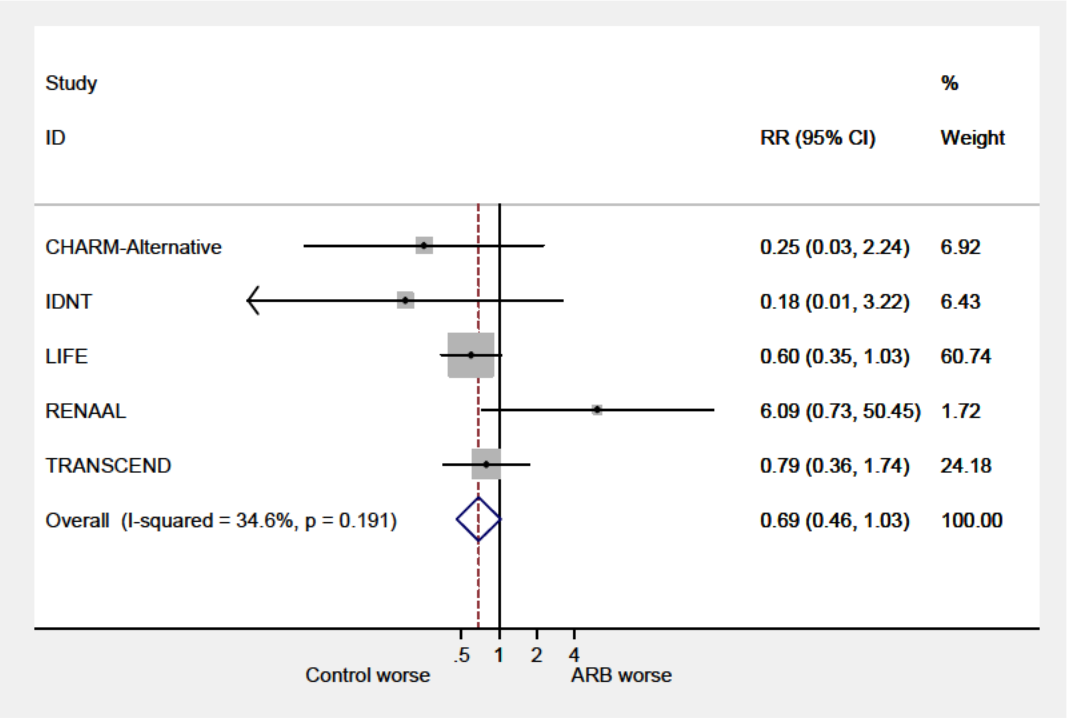
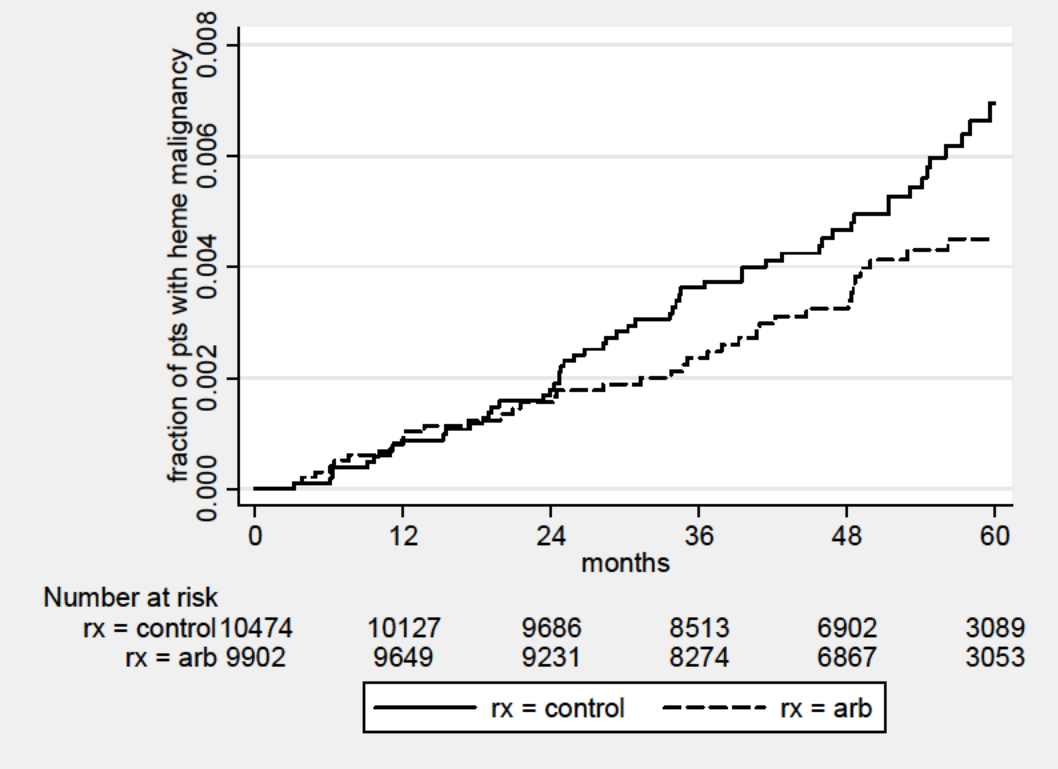


Figure 9: Risk Ratios of Patients with Hematologic Malignancy Events by Trial

I show the Kaplan-Meier plot of times to first hematologic malignancy events (new or recurrent) in Figure 10. The curves diverge after 24 months and remain apart thereafter.



p = 0.06 by log rank stratified by study

Figure 10: Times to First Hematologic Malignancy Events

Survival after a hematologic malignancy event was poor, about 48% at two years, and similar in the ARB and control arms.

Solid Cancers

I identified new or recurrent solid cancer events (excluding non-melanoma skin cancers and brain tumors) during the censoring periods in 4,459 of the 89,925 patients in the eleven trials. The pooled RR comparing the ARB arms to the control arms is 1.05 (95% CI 0.99-1.11, p = 0.10). I show the forest plot of RRs by trial in Figure 11. The pooled RR for all fifteen trials is also about 1.05 (95% CI 0.99-1.11, p = 0.093).

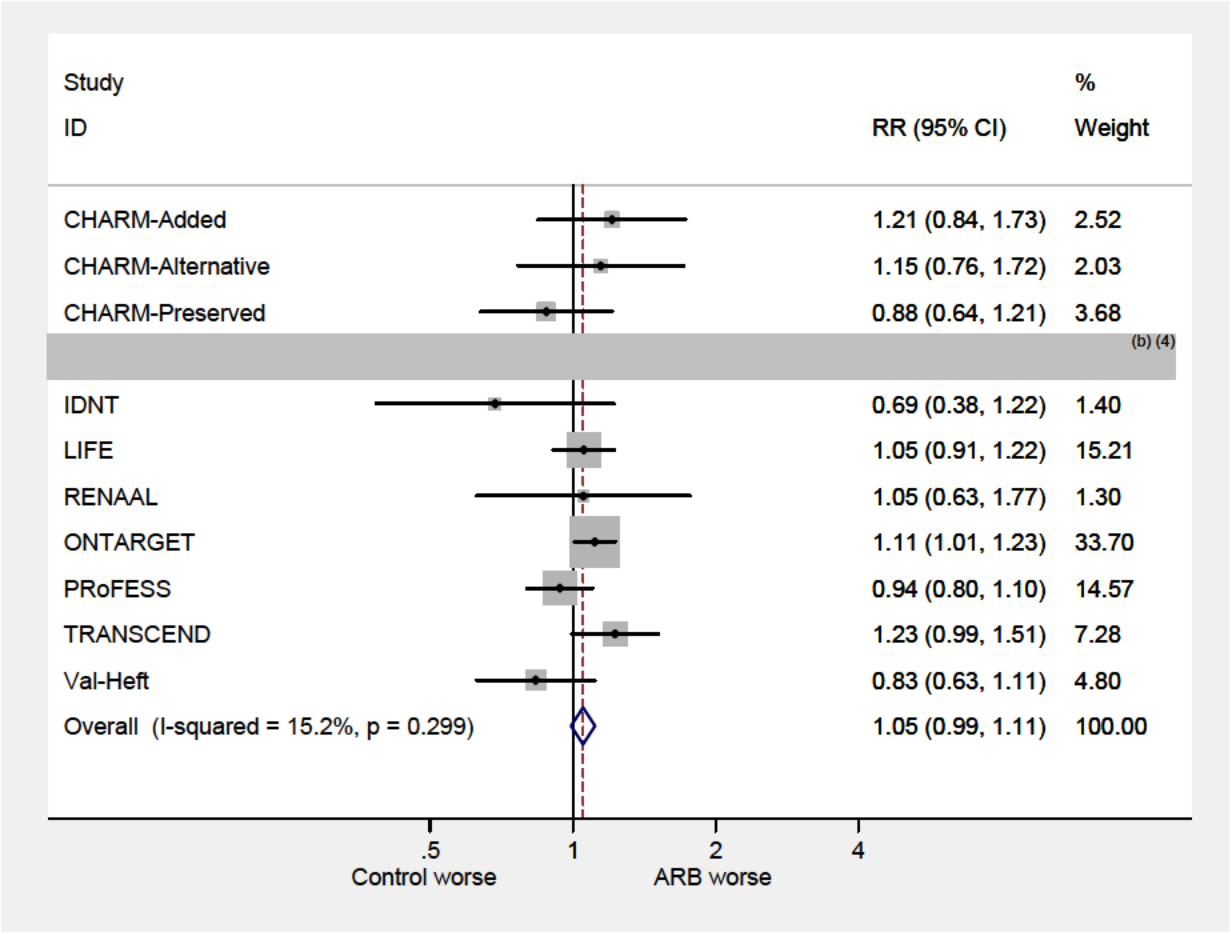
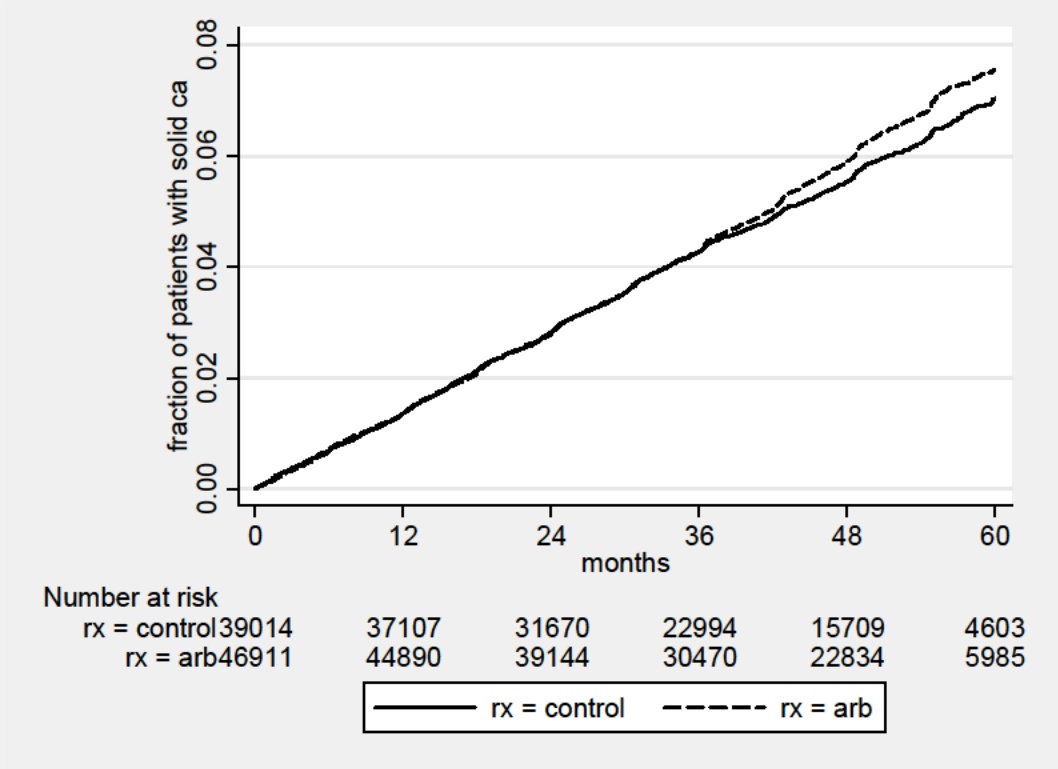


Figure 11: Risk Ratios of Patients with Solid Cancer Events by Trial

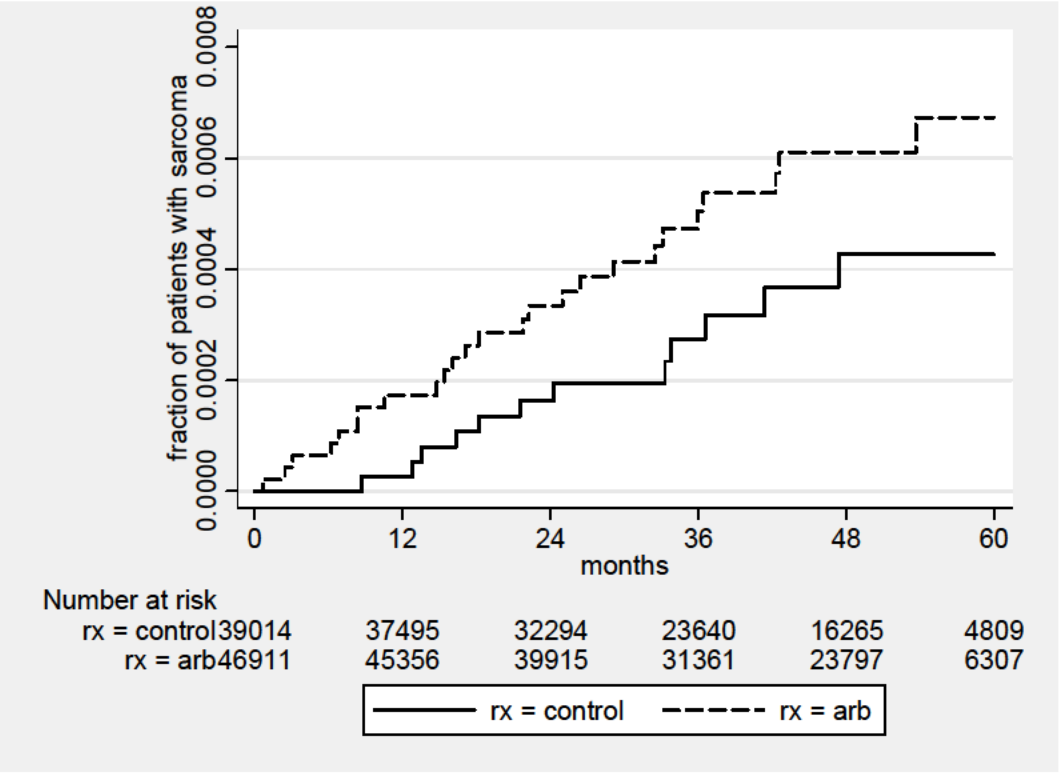
I show the Kaplan-Meier plot of times to first solid cancer events (new or recurrent) in Figure 12. There appears to be slight late divergence of the curves, but the divergence is not statistically significant. The survival curves after a solid cancer event are virtually identical regardless of ARB use (HR 0.99, $p > 0.8$).



p = 0.12 by log rank stratified by study

Figure 12: Times to First Solid Cancer Events

I examined cross-tabulations of the sites of the first solid cancer events by ARB use as exploratory analyses of whether any other specific solid cancer events are imbalanced by ARB use. In addition to lung and prostate cancers sarcomas were imbalanced, with a pooled RR of about 1.8 and p value of 0.081 for eight of the 11 trials having sarcomas and 0.043 for 10 trials having sarcomas. I show the Kaplan-Meier plot of times to first sarcoma events in Figure 12. The incidence curves diverge immediately.



p = 0.037 by log rank stratified by study

Figure 13: Times to First Sarcoma Events

Discussion

ARB use appears to be associated with an increased incidence of lung cancer. The p value for the primary meta-analysis of RR is low ($p = 0.003$) and consistent with a time-to-first-event analysis by a log rank test stratified by study ($p = 0.0033$). The identical meta-analysis except excluding the index LIFE study produces the same estimate for the RR and a similar, highly statistically significant p value ($p = 0.005$). The increased risk of lung cancer with ARBs is robust to sensitivity analyses including a meta-analysis of all 15 large ARB outcome trials that collected cancer sites. The shapes of the incidence curves are consistent with a cancer promoter effect, i.e., delayed initial divergence of the rates in ARB and control arms followed by continuing divergence throughout the duration of follow-up.

The estimate of overall effect size is modest, about a 24% increase in lung cancer incidence. However, some analyses suggest an increasing effect size with increasing duration of therapy. Because ARBs are indicated for life-long treatment (e.g., hypertension, diabetic nephropathy) any consistent or increasing effect upon cancer rates is concerning. The absolute risk difference during the first five years of treatment in the trial populations as a whole is small, i.e., about 0.8 excess lung cancer cases per year per 1,000 patients treated. However, in subgroups at risk for lung cancer, i.e., smokers, the absolute risk increase exceeds 1% at five years. Furthermore, survival following a lung cancer event is dismal, about 34% at one year, and significantly more ARB patients died with lung cancer.

While these absolute risks may not outweigh the cardiovascular benefits of blood pressure reduction in hypertensive patients, there are many other alternative antihypertensives. I believe that these effects of ARBs upon lung cancer should not be ignored and that patients and providers should be fully informed about the risk.

The results regarding prostate cancer are inconclusive. None of the analyses are statistically significant or close to statistically significant. However, because the number of prostate cancer events in the trials excluding most ACEI use and submitted to the FDA is not large and hence the power of these analyses is low and because the results in the non-index trials are supportive, we can not reject definitively an effect of ARBs upon prostate cancer. Additional investigation of this hypothesis is justified. For prostate cancers there is some reassurance: The analyses suggest that, regardless of whether there is some effect of ARBs upon prostate cancer incidence, the effect is not greatly concerning because the data do not suggest a statistically or clinically significant effect upon mortality. Lung cancer, not prostate cancer, appears to be the significant concern for ARBs.

The results regarding hematologic malignancies are also inconclusive. The pre-specified meta-analysis is not statistically significant ($p = 0.07$) but the Kaplan-Meier plot in Figure 10 of times to first hematologic malignancy events is somewhat consistent with a tumor suppressor effect.

For both prostate cancers and hematologic malignancies the inconsistent trial is one of the diabetic nephropathy trials, IDNT or RENAAL. The hematologic malignancy hypothesis, like the one for prostate cancer, needs additional investigation.

The results regarding all solid cancers (excluding non-melanoma skin and brain tumors) are inconclusive but not inconsistent with the lung cancer results. There is a trend towards more solid cancers with ARB use but this may reflect the increased incidence of lung cancers (and possibly prostate cancers.) The sarcoma differences may be chance variations because the incidence curves diverge immediately before we would expect to detect a cancer promotion effect. However, following-up on this possible association is also appropriate.

I did not hypothesize regarding possible effects of dosage because most trials tested the maximum approved dosages and the dosage ranges tested in a few trials were limited to two-fold. In fact, all eleven of the trials included in the primary meta-analyses tested the maximum approved dosages. Of the other trials IRMA 2 tested both maximum and half maximum dosages (b) (4) IRMA 2 is too small, and confounded by poor follow-up, to provide any insight into effects of dosage. (b) (4)

For the prostate cancer and hematologic malignancy hypotheses I postulated that the effects, if real, would be shared with ACEIs. The data appear to support this belief because the analyses including the trials with substantial ACEI use produce RRs very close to 1.0 for both prostate and hematologic malignancies. The picture is less clear for lung cancers. The RR is higher and more significant in the five trials excluding most ACEI use than in the six trials having substantial ACEI use. Whether this is a real difference or a chance effect or related to the differing trial designs and conduct is unclear. For lung cancer we might also speculate that there could be a detection bias with ACEIs resulting from ACEI-induced cough. Other studies have usually not associated ACEI use with a higher risk of cancer. (Grossman, Messerli et al. 2002; Sipahi, Chou et al. 2011) However, we can make a similar statement for ARB use and cancer.

The strengths of this study are that I pre-specified well-defined hypotheses to test and an analytical plan providing details on cancer ascertainment and censoring, I had access to and utilized fully the raw trial data to resolve ambiguities in cancer ascertainment, and I performed patient-level meta-analyses and time-to-event and survival analyses with baseline cofactor explorations. The use of raw trial data is also a limitation because I analyzed only trials submitted to the FDA with such data. While there could be a "submission bias" analogous to a "publication bias", my expectation is that a submission bias would decrease the likelihood of finding an association between ARB use and cancer: If a drug company observed that a clinical trial of an ARB had a suspicious association between an ARB and cancer, the company should

be less likely rather than more likely to submit such a study for FDA review. In fact I believe that the drug companies did not consider cancer events in determining whether or not to submit a trial to the FDA but based their decisions to submit on the targeted efficacy indications and their business goals.

One internal FDA criticism of all of the ARB and cancer meta-analyses is that they are "fishing expeditions" (see email reproduced in Appendix 2) with severe multiplicity issues. However, as I described in the Introduction, I had identified lung cancer as a potential problem for losartan based on my review in 2002 of the LIFE trial. I formulated the lung cancer hypothesis based on the LIFE trial results; I provide documentation of the lung cancer hypothesis in Appendix 2. The one valid criticism is that the most appropriate meta-analysis may be the one excluding the LIFE trial. Because the results for that analysis are highly supportive of a lung cancer risk with ARB use, I argue that multiplicity is not an issue for the principal finding of an increased risk of lung cancer with ARB use.

Another potentially controversial aspect of the analytical plan is the decision to exclude trials because of data quality issues. I believe that the justifications of the exclusion of the five trials are valid and I provide documentation of them as Appendix 1 to this review. However, regardless of whether one considers the exclusions to be appropriate or not, they do not affect the conclusion that some ARBs appear to be associated with a higher incidence of lung cancer; they only affect the conclusion that ARBs as a class have this association. Adding to the meta-analyses the one small irbesartan trial excluded (IRMA 2) changes the results minimally. Hence for the four ARBs contributing the bulk of the data to the primary meta-analyses (candesartan, irbesartan, losartan, and telmisartan) we should have confidence that their use is associated with an increased incidence of lung cancer. Furthermore, the meta-analysis of all 15 trials that collected cancer sites for malignancies (i.e., all trials with data submitted to the FDA except VALIANT) produces a pooled RR of 1.16 and a p value of 0.027. The cancer site data submitted to the FDA are consistent with a class effect on lung cancers.

That missing trials should not negate the association between ARB use and lung cancer is illustrated strikingly by the missing losartan trials. In response to an FDA request Merck initially submitted trial-level data from five losartan clinical outcome studies conducted by Merck: LIFE and RENAAL (with raw data from prior submissions and included in these meta-analyses) (b) (4) I commented in the Introduction that the ARB Trialists Collaboration analyzed only LIFE and, while Bangalore *et al.* analyzed LIFE and RENAAL, they mis-referenced and mis-counted incident cancer cases in RENAAL: Bangalore *et al.* counted only seven cancer cases (actually drug withdrawals for cancer) while I verified from the raw data 55 solid cancers excluding brain and non-melanoma skin cancers. The lung cancer RRs for all five of the trials in the Merck initial submission exceed 1, (b) (4) to 3.0 for RENAAL (b) (4)

(b) (4) The pattern of lung cancer trial RRs, i.e., 10 of 11 trials with RRs exceeding 1 in the primary meta-analysis and two more larger losartan trials with RRs exceeding 1 in the Merck submission (for four out of four larger losartan trials with RRs exceeding 1), supports that ARB use, in particular losartan, is associated with an increased risk of lung cancer.

While we lack good data definitively confirming or refuting an association with lung cancer for four FDA-approved ARBs (azilsartan, eprosartan, olmesartan, and valsartan), the one study with valid data for valsartan (Val-Heft) has a RR estimate for lung cancer nearly identical to the primary meta-analysis. (b) (4) The association of ARBs with lung cancer remains significant in a meta-analysis of all 15 trials collecting cancer sites and having complete data submitted to the FDA. I conclude that the increased incidence of lung cancers with ARB use is likely a class effect of ARBs and that it would be inappropriate to classify azilsartan, eprosartan, olmesartan, and valsartan as safe because of their lack of adequate studies.

References

(b) (4)

ARB_Trialists_Collaboration (2011). "Effects of telmisartan, irbesartan, valsartan, candesartan, and losartan on cancers in 15 trials enrolling 138,769 individuals." J Hypertens 29(4): 623-35.

Bangalore, S., S. Kumar, et al. (2011). "Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials." Lancet Oncol 12(1): 65-82.

Bomback, A. S. and P. J. Klemmer (2007). "The incidence and implications of aldosterone breakthrough." Nat Clin Pract Nephrol 3(9): 486-92.

Brenner, B. M., M. E. Cooper, et al. (2001). "Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy." N Engl J Med 345(12): 861-9.

Cohn, J. N. and G. Tognoni (2001). "A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure." N Engl J Med 345(23): 1667-75.

Coleman, C. I., W. L. Baker, et al. (2008). "Antihypertensive medication and their impact on cancer incidence: a mixed treatment comparison meta-analysis of randomized controlled trials." J Hypertens 26(4): 622-9.

Dahlof, B., R. B. Devereux, et al. (2002). "Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol." Lancet 359(9311): 995-1003.

Dickstein, K. and J. Kjekshus (2002). "Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan." Lancet 360(9335): 752-60.

FDA. (2007). "FDA Backgrounder for the December 11-12, 2007 meeting of the Cardio-Renal Drugs Advisory Committee" Retrieved March 4, 2013, from http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4327b1-02-fda-backgrounder.pdf.

FDA. (2011, June 2, 2011). "FDA Drug Safety Communication: No increase in risk of cancer with certain blood pressure drugs--Angiotensin Receptor Blockers (ARBs)." Retrieved June 6, 2011, from http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm.

Granger, C. B., J. J. McMurray, et al. (2003). "Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial." Lancet 362(9386): 772-6.

Grossman, E., F. H. Messerli, et al. (2002). "Carcinogenicity of antihypertensive therapy." Curr Hypertens Rep 4(3): 195-201.

Haller, H., S. Ito, et al. (2011). "Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes." N Engl J Med 364(10): 907-17.

Harris, R. J., M. J. Bradburn, et al. (2008). "metan: fixed- and random-effects meta-analysis." Stata Journal 8(1): 3-28.

Husten, L. (2012, September 26, 2012). "Merck Returns To Cardiome All Rights To Atrial Fibrillation Drug Vernakalant." Retrieved March 4, 2013, from http://www.forbes.com/sites/larryhusten/2012/09/26/merck-returns-to-cardiome-all-rights-to-atrial-fibrillation-drug-vernakalant/.

Imai, E., J. C. Chan, et al. (2011). "Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study." Diabetologia 54(12): 2978-86.

Leshem-Rubinow, E., A. Steinvil, et al. (2012). "Association of Angiotensin-Converting Enzyme Inhibitor Therapy Initiation With a Reduction in Hemoglobin Levels in Patients Without Renal Failure." Mayo Clin Proc.

Lewis, E. J., L. G. Hunsicker, et al. (2001). "Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes." N Engl J Med 345(12): 851-60.

Marciniak, T. A. (2003, January 15, 2003). "Amended Clinical Review, Supplemental NDA Submission, NDA 20-386." Retrieved November 23, 2012, from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/20-386S032_Cozaar_medr_P1.pdf.

McMurray, J. J., R. R. Holman, et al. (2010). "Effect of valsartan on the incidence of diabetes and cardiovascular events." N Engl J Med 362(16): 1477-90.

McMurray, J. J., J. Ostergren, et al. (2003). "Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial." Lancet 362(9386): 767-71.

Nissen, S. E. (2010). "Angiotensin-receptor blockers and cancer: urgent regulatory review needed." The Lancet Oncology 11(7): 605-606.

Parving, H.-H., H. Lehnert, et al. (2001). "The Effect of Irbesartan on the Development of Diabetic Nephropathy in Patients with Type 2 Diabetes." New England Journal of Medicine 345(12): 870-878.

Pfeffer, M. A., J. J. McMurray, et al. (2003). "Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both." N Engl J Med 349(20): 1893-906.

Remuzzi, G., P. Ruggenenti, et al. (2004). "Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy: a post hoc analysis of the RENAAL trial results." J Am Soc Nephrol 15(12): 3117-25.

Sipahi, I., J. Chou, et al. (2011). "Meta-analysis of randomized controlled trials on effect of angiotensin-converting enzyme inhibitors on cancer risk." Am J Cardiol 108(2): 294-301.

Sipahi, I., S. M. Debanne, et al. (2010). "Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials." Lancet Oncol 11(7): 627-36.

Wood, S. (2010, October 25, 2010). "ACT 5 vernakalant trial suspended." Retrieved March 4, 2013, from http://www.theheart.org/article/1140055.do.

Wood, S. (2011, June 2, 2011). "FDA review concludes: No cancer risk with ARBs." Retrieved November 19, 2012, 2012, from www.theheart.org/article/1234673/print.do.

Yusuf, S., H. C. Diener, et al. (2008). "Telmisartan to prevent recurrent stroke and cardiovascular events." N Engl J Med 359(12): 1225-37.

Yusuf, S., M. A. Pfeffer, et al. (2003). "Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial." Lancet 362(9386): 777-81.

Yusuf, S., K. K. Teo, et al. (2008). "Telmisartan, ramipril, or both in patients at high risk for vascular events." N Engl J Med 358(15): 1547-59.

Appendix 1: Justifications for the Exclusions of Five Studies from the Angiotensin Receptor Blockers and Cancer Meta-analysis

IRMA-2 (The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes.)

The NEJM publication reports the completeness of follow-up ambiguously: "A total of 30 patients in the placebo group, 27 in the group assigned to receive 150 mg of irbesartan per day, and 20 in the group assigned to receive 300 mg of irbesartan per day withdrew from the study for various reasons (Fig. 1)." In Figure 1 an additional 18 patients had no measurement of albuminuria and 3 received no drug treatment. The numbers "Completed study" are 171, 168, and 174 in Figure 1. By these numbers (171+168+174)/611 = 84% completed the study. However, four of the incomplete follow-ups were deaths, so 85% represents better the percentage with complete follow-up.

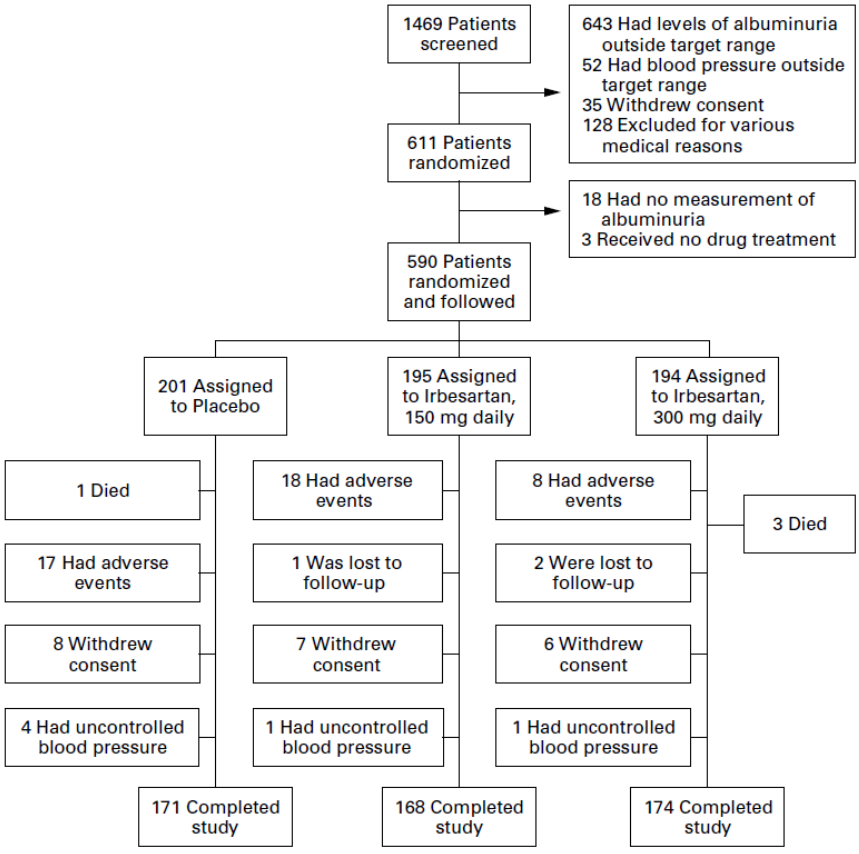


Figure 1. Profile of the Trial.
All 590 patients who underwent randomization and follow-up were included in the intention-to-treat analyses.

The ambiguity is that neither the study report nor the publication defines explicitly what "withdrew from the study" or not "completed study" represents. It is obvious that these patients didn't complete treatment, but did they have follow-up adequate for determining cancer events? The study report states the following:

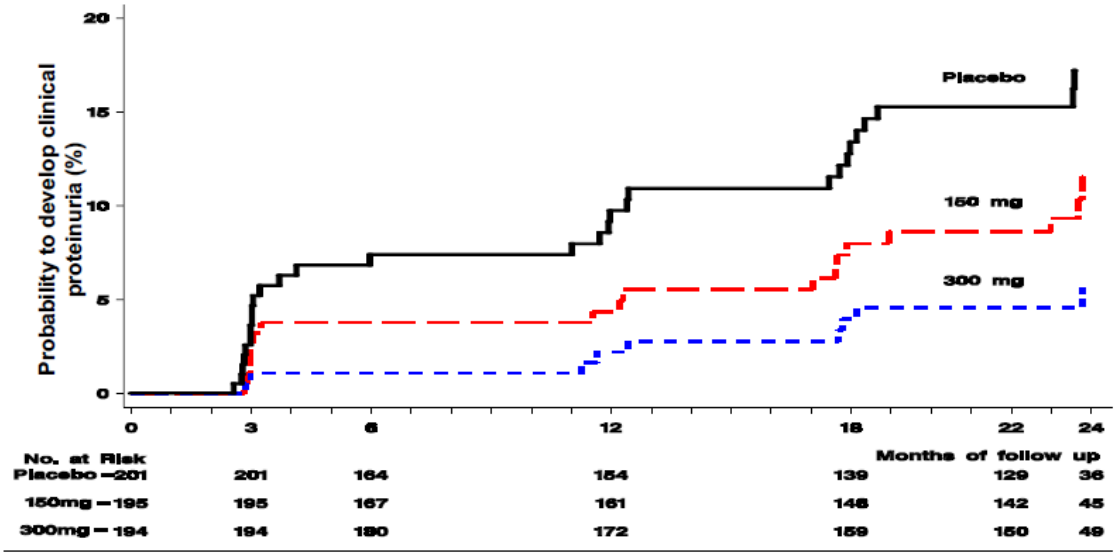
> "In the main study and GFR sub-study, AEs occurring within 10 days after study drug discontinuation were reported to the Sponsor. In the GFR extension study, AEs occurring within 4 weeks of study drug discontinuation were reported to the Sponsor."

It also states:

> "Additionally, all subjects prematurely withdrawn from the study were assessed for survival and nephrology status 2 years after the date of randomization with the exception of those who were lost-to-follow-up or deceased (added by Amendment No. 9)."

The study report has the following figure:

Figure 10.1.1.2 Estimates of Probability to Develop Clinical Proteinuria: Intent-to-Treat Subjects

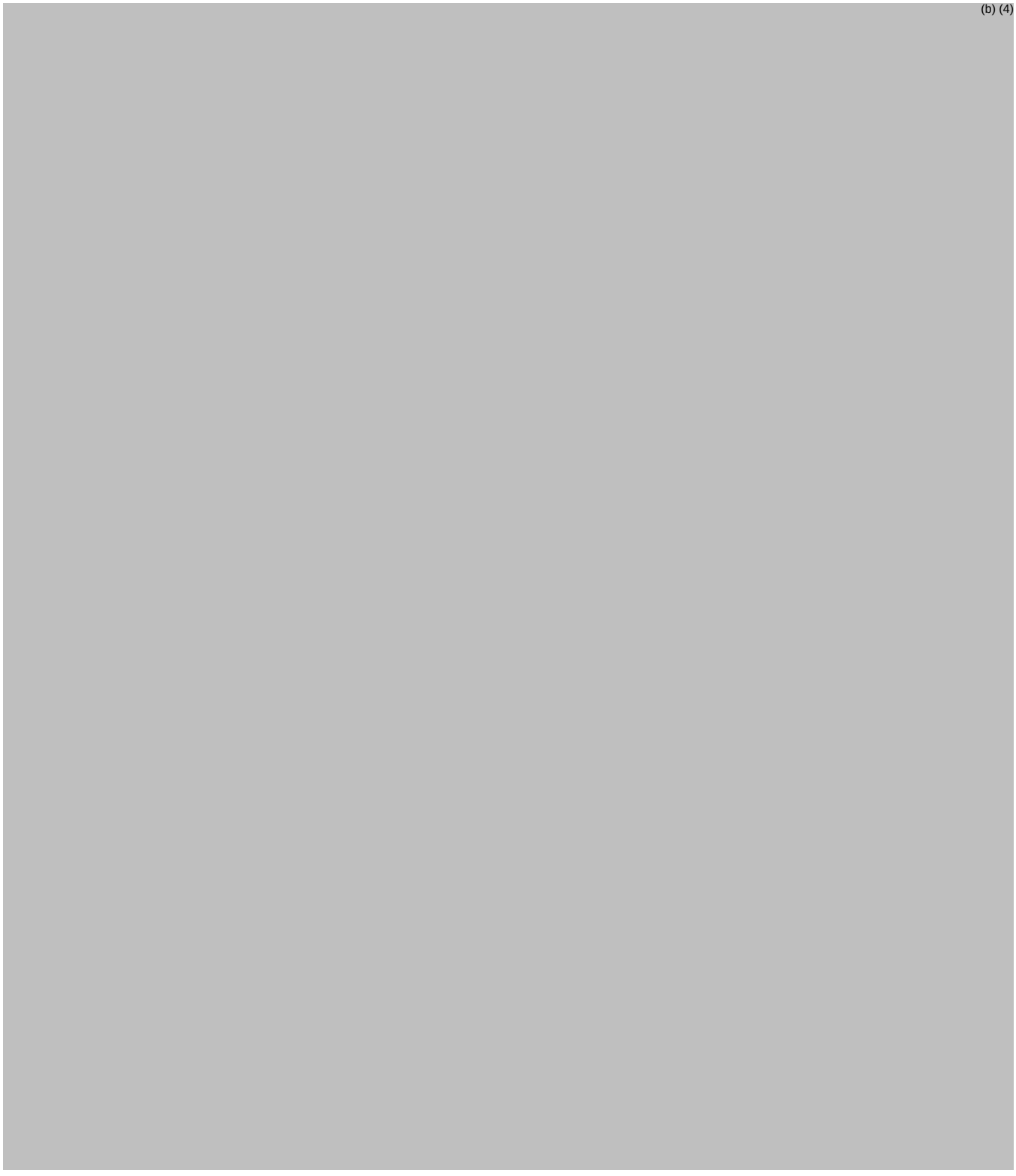


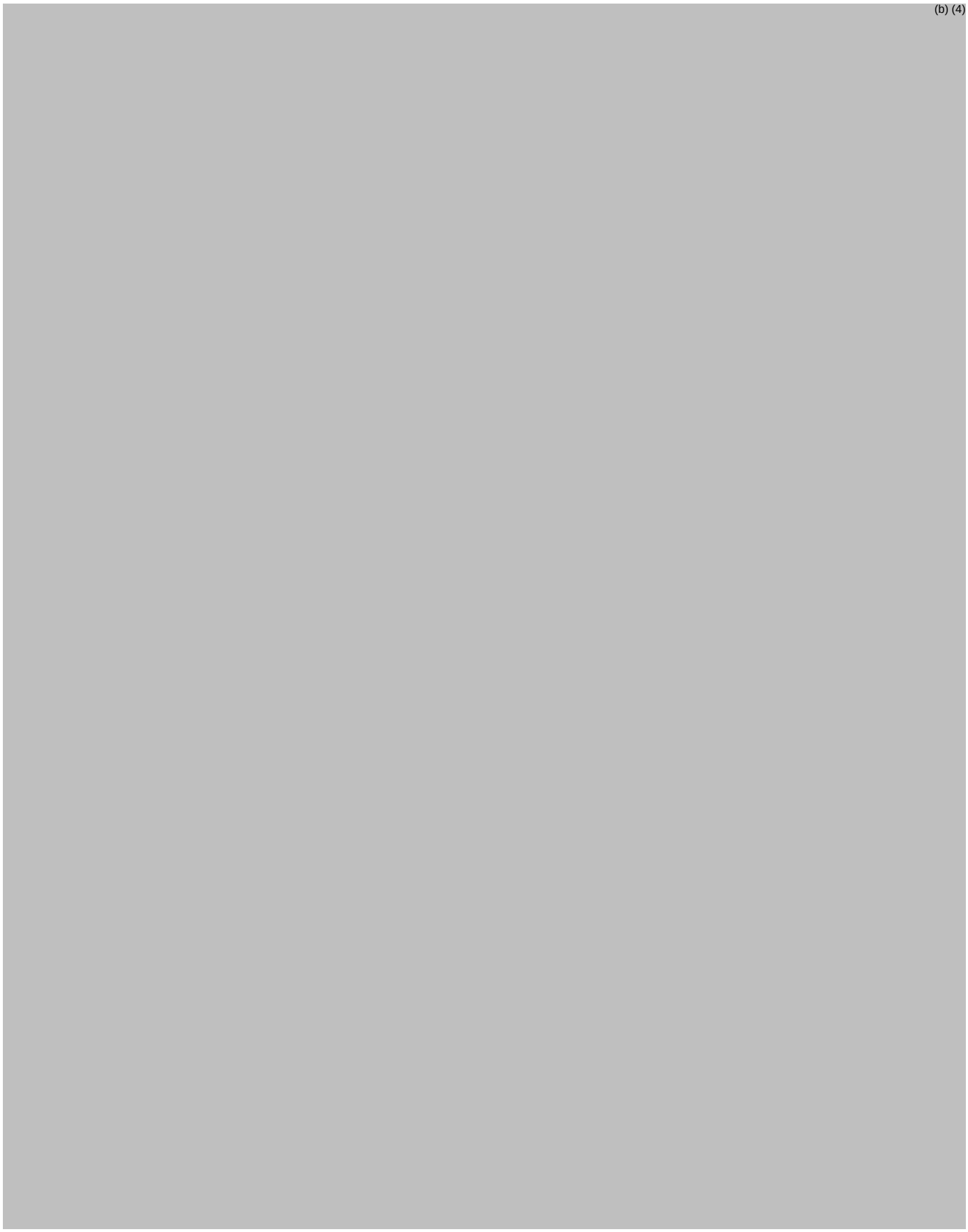
EFC2481
Dataset: Intent-to-Treat Subjects
Source: Appendix 10.1.11.3
Note: The sample size at Month 24 declines because most subjects completed Visit 9 at Month 22. Thus, this decline in sample does not indicate premature discontinuation of these subjects from the study.

Note the low numbers at risk at month 24 (IRMA 2 was reported as a 2-year study) and the explanation in the footnote in the figure.

I interpret the above as that IRMA 2 did not collect AE information 10 days to 4 weeks after treatment discontinuation. Follow-up was early even in those counted as completing the two year study. The 85% complete (about 15% incomplete) likely represents an optimistic estimate of the completeness of follow-up. IRMA 2 fails the pre-specified criterion that incompleteness of follow-up not exceeds 10%.

(b) (4)




(b) (4)

VALIANT (Multinational, multicenter, double-blind, randomized, active controlled, parallel group study comparing the efficacy and safety of long-term treatment with valsartan, captopril and their combination in high-risk patients after myocardial infarction.)

VALIANT has incomplete cancer ascertainment. The reasons for the incomplete cancer ascertainment are complicated and dependent upon the trial design, particularly how adverse event data were collected—or not collected. The most relevant section from the sponsor's "Response to FDA information request: cancer data for valsartan" dated 06-Oct-2010 is the following:

4 Ascertainment scheme for cancer

FDA request

"Comment on the ascertainment scheme for cancer."

Novartis response

Val-HeFT, VALIANT (b) (4)

For the above-mentioned studies, all coding of investigator reported terms was re-mapped to the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0, which is the latest version of MedDRA available at Novartis. Adverse events consistent with solid organ tumors were identified by the use of the Maintenance and Support Services Organization (MSSO) Standardized MedDRA Query (SMQ) "Malignant or unspecified tumors" (Narrow Search MedDRA version 13.0). Per FDA's request, all MedDRA Preferred Terms, considered to be related to hematologic/ liquid tumors, were deleted from the SMQ. Preferred terms consistent with hematologic tumors (e.g. leukemia, lymphomas and myelomas) were identified as hematological malignancies using the most recent International Classification of Diseases for Oncology and are presented in Appendix 1. As a result, 365 of the 1814 preferred terms for malignant or unspecified tumors, in the Narrow Standardized MedDRA version 13, were excluded.

Information on the most frequent MedDRA preferred terms is included for each study to provide additional data on cancer type. In addition, we have included information, using the Narrow Search MedDRA version 13 SMQ, on the incidence of breast neoplasms, malignant and unspecified SMQ, prostate neoplasms, malignant and unspecified SMQ, and lung cancer for these specific cancer types. This information was previously provided in the June 24, 2010 letter sent to FDA. As there is no specific SMQ for lung cancer in MedDRA 13, preferred terms selected by Novartis medical reviewers are used (Appendix 2).

Protocols [redacted] (b) (4) were not mapped to the narrow MedDRA terms as noted above. The cancer adverse events were taken directly from the post-text adverse event tables, as an electronic MedDRA coded dataset was unavailable.

The sponsor's response completely neglects how the cancer events were captured in the valsartan trials. For VALIANT event capture was complicated and ambiguously specified. The protocol specified the following regarding collection of adverse events:

Adverse events

Adverse events will be recorded in the CRF or the Serious Adverse Event (SAE) form if they meet the following criteria:

- Primary and secondary efficacy parameters (as described in Section 3.5.2)
- Pre-specified safety and tolerability parameters (known side effects of either captopril and/or valsartan) as described in the previous section
- Serious adverse events (as described in the following section).

Other non-serious adverse events will not be collected in the CRF. However, information

The criteria for SAEs were the usual regulatory ones with the criteria most applicable to malignancies being fatal or requiring or prolonging hospitalization. However, note that the first method for recording AEs above is "Primary and secondary efficacy parameters". The relevant ones from Section 3.5.2 are the following:

Primary efficacy parameters

The primary efficacy parameter is all-cause mortality (time to death).

Secondary efficacy parameters

Secondary efficacy parameters are as follows:

- All-cause (unplanned and elective) hospitalization

Death and all-cause hospitalizations were the first primary and first secondary efficacy parameters. However, where investigators should have recorded malignancies (on the efficacy and death CRFs or some other CRF) is ambiguous per the following directions reiterated for each visit:

- For adverse events occurring since the last visit:
  - ◊ Complete the Serious Adverse Event CRF for any serious adverse events that are **suspected to be related** to the administration of study medication. (See Section 3.5.3: Safety assessments, for the definitions to be used in evaluating the seriousness of an adverse event and for determining the relationship of an adverse event to study medication.)
  - ◊ Record serious events **not suspected to be related** to study medication in the CRF and/or endpoint documentation.

Potentially an investigator should never have recorded a malignancy event as an AE or SAE but only as a death event or hospitalization event. However, the hospitalization CRF captured only the primary admission diagnosis (e.g., which could be "hemoptysis" or "chest pain" for an eventual lung cancer diagnosis, with the latter never captured on the CRFs):

(b) (4)

And the death form did not capture a text cause for a malignancy death but only a checkbox:

Hence for patients with new malignancies who didn't die during the study we might not know that they had a new malignancy; for those who died we might only know that they died from a malignancy but not know the cancer site (including not knowing hematologic vs. solid cancer.) Similarly, history of cancer at baseline was recorded as a checkbox for "History of Cancer within 5 years." Determining whether cancers are incident (new) or recurrent in VALIANT is impossible for many cases.

The unfortunate ambiguities in the protocol and CRFs are reflected in the data. I analyzed all relevant VALIANT AE, hospitalization, and death datasets for cancer diagnoses. The numbers of neoplasms used for the FDA M-A were 143 valsartan, 83 control. (RR 0.86.) (VALIANT had three arms with 1:1:1 randomization: valsartan alone, valsartan+captopril, and captopril alone. For the FDA M-A and these analyses "ARB" or "valsartan" references the combined valsartan alone and valsartan+captopril arms and "control" references the captopril alone arm.) The counts of patients with neoplasms in the AE datasets are virtually identical (143 valsartan, 82 control, RR 0.87) to the FDA M-A counts. The hospitalization data set identifies another 103

patients with neoplasms not included in these numbers and the death dataset identifies another 79 (55 valsartan, 24 control, RR 1.15) who died of a malignancy excluding patients with reported hematologic malignancies. Combining the AE and death neoplasms yields 198 valsartan and 106 control neoplasms, RR 0.94. Combining the AE, hospitalization, and death neoplasms (all sources) yields 248 valsartan and 134 control neoplasms, RR 0.93. Note that, while the VALIANT FDA M-A results are favorable for valsartan, the unreported cases are unfavorable.

The NDA documents neoplasms for an additional 156 patients, 70% more than those counted in the FDA M-A. All of these numbers are likely still underreporting because, as documented above, the event reporting in VALIANT did not guarantee that all malignancies were reported. The death rate was high in patients with reported neoplasms, i.e., about 44% during the study in neoplasms reported other than death only. There were 46 cases reported only as malignancy deaths. If we assume that the death rate in unreported cases is the same as the death rate in reported neoplasms, then we would expect 46/0.44 = 105 cases either reported as a malignancy death only or not reported at all such that we do not have cancer site data.

The cancer data collected in VALIANT, both regarding completeness of ascertainment and the reporting of cancer sites, are too incomplete to be valid for any cancer M-As.

Appendix 2: Documentation of the ARB and Lung Cancer Hypothesis

One internal FDA criticism of all of the ARB and cancer meta-analyses is that they are "fishing expeditions" with severe multiplicity issues as expressed in the following email message:

From: Unger, Ellis
Sent: Wednesday, September 05, 2012 2:25 PM
To: Soukup, Mat; Jagadeesh, Gowra G; Gordon, Maryann; Stockbridge, Norman L; Nguyen, Quynh M; McCloskey, Carolyn A; Andraca-Carrera, Eugenio; Zornberg, Gwen; Ton, Phuong Nina; Marciniak, Thomas; Wachter, Lori; Southworth, Mary Ross
Cc: Temple, Robert
Subject: RE: Finalized - SAFETY-935 General Review (REV-CLINICAL-03)

I attempted to attach the following comments to Norman's memo without success. (DARRTS would not accept them, presumably because there were too many characters.) I plan to place this into DARRTS in the next day or two:

I agree with Dr. Stockbridge. I also note that no analysis, or group of analyses, no matter how carefully conducted, can circumvent the multiplicity problem here.

When considering adverse events, one can always perform a meta-analysis on a group of randomized controlled studies (RCTs) with a total sample size in the tens of thousands and find statistically significant differences, so-called "signals," especially at p-values that are only barely statistically significant (i.e., p-values just less than 0.05). One has no way of knowing how many other drugs or drug groups were assessed, or how many potential safety issues were considered (e.g., cancer [and many types of cancer], myocardial infarction, stroke, diabetes, dementia, etc.). Moreover, one has no way of knowing how criteria were established to make decisions about which studies to include or exclude in the meta-analysis.

Thus, such analyses amount to post hoc "fishing expeditions;" useful for hypothesis generation, but by no means conclusive. One must be cognizant of the inherent multiplicity and inflation of Type-I error, with the potential, or even the likelihood, of finding false positives. For example, if Sipahi et al had reported ALL safety signals of interest in the 61,590 subjects, it would not have been surprising if they had found some with RR <= 0.93, the reciprocal of 1.08, i.e., suggesting that ARBs prevent some adverse event.

Finally and importantly, it is critical to recognize that performance of additional, related, analyses on the same group of RCTs, no matter how comprehensive and refined those analyses might be, does not circumvent the original multiplicity issue. They amount to "fishing" in the same "waters." Similar findings are expected; they do not "confirm" the original finding

By Dr. Unger's arguments, we could rarely have safety concerns because most safety concerns arise from *post hoc* findings, e.g., *torsades de pointes* with terfenadine, cardiac events with rofecoxib. Dr. Unger in particular should be a supporter of *post hoc* analyses rather than an opponent because, (b) (4)

(b) (4)

However, while Dr. Unger's "fishing expedition" analogy does not even apply to most safety analyses, it is completely inapplicable to the Sipahi *et al.* meta-analysis and to this review. While Sipahi *et al.* initiated their meta-analysis based on *post hoc* findings in the candesartan CHARM trials, they tested their hypothesis prospectively in the other ARB studies. My concerns with losartan and lung cancer predated Sipahi *et al.*'s observations: I noted an imbalance in lung cancers in the LIFE trial in 2002. Because it was not statistically significant and an isolated finding I did not specifically comment upon it in my review. I did include the following table in my review for future reference—and Sipahi *et al.* used the data in the table for their meta-analysis:

Table 82: Sponsor's Serious Adverse Events with Frequencies ≥ 0.5% of Patients

	Losartan (N=4605)		Atenolol (N=4588)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	1715	(37.2)	1660	(36.2)
Patients with no adverse experience	2890	(62.8)	2928	(63.8)
Body as a Whole/Site Unspecified	**414**	**(9.0)**	**398**	**(8.7)**
Abdominal pain	24	(0.5)	31	(0.7)
Chest pain	21	(0.5)	26	(0.6)
Drug overdose	88	(1.9)	65	(1.4)
Inguinal hernia	29	(0.6)	28	(0.6)
Syncope	59	(1.3)	49	(1.1)
Cardiovascular System	**357**	**(7.8)**	**396**	**(8.6)**
Atrial fibrillation	96	(2.1)	93	(2.0)
Bradycardia	9	(0.2)	43	(0.9)
Deep venous thrombosis	30	(0.7)	21	(0.5)
Pulmonary embolism	18	(0.4)	25	(0.5)
Transient ischemic attack	35	(0.8)	49	(1.1)
Digestive System	**287**	**(6.2)**	**261**	**(5.7)**
Colonic malignant neoplasm	26	(0.6)	21	(0.5)
Endocrine System	**39**	**(0.8)**	**39**	**(0.9)**
Eyes, Ears, Nose, and Throat	**92**	**(2.0)**	**93**	**(2.0)**
Cataract	27	(0.6)	22	(0.5)
Hemic and Lymphatic System	**53**	**(1.2)**	**50**	**(1.1)**
Anemia	31	(0.7)	16	(0.3)
Hepatobiliary System	**107**	**(2.3)**	**79**	**(1.7)**
Cholecystitis	29	(0.6)	24	(0.5)
Cholelithiasis	51	(1.1)	46	(1.0)
Metabolism and Nutrition	**26**	**(0.6)**	**28**	**(0.6)**
Musculoskeletal System	**385**	**(8.4)**	**367**	**(8.0)**
Hip osteoarthritis	35	(0.8)	33	(0.7)
Knee osteoarthritis	33	(0.7)	16	(0.3)
Musculoskeletal chest pain	26	(0.6)	24	(0.5)
Nervous System	**122**	**(2.6)**	**124**	**(2.7)**
Vertigo	41	(0.9)	39	(0.9)
Psychiatric Disorder	**57**	**(1.2)**	**37**	**(0.8)**
Respiratory System	**189**	**(4.1)**	**193**	**(4.2)**
Lung malignant neoplasm	29	(0.6)	12	(0.3)
Pneumonia	75	(1.6)	96	(2.1)
Skin and Skin Appendages	**127**	**(2.8)**	**129**	**(2.8)**
Basal cell carcinoma	66	(1.4)	58	(1.3)
Urogenital System	**318**	**(6.9)**	**274**	**(6.0)**
Breast malignant neoplasm	37	(0.8)	36	(0.8)
Prostatic disorder	28	(0.6)	22	(0.5)
Prostatic malignant neoplasm	58	(1.3)	42	(0.9)
Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				

Note that lung malignant neoplasm SAEs as reported by the sponsor are 29:12 losartan:control , a significant imbalance. Both the Sipahi *et al.* and FDA meta-analyses used these numbers. However, not all lung cancers are reported as "lung malignant neoplasm" or as SAEs. The counts of lung cancers in LIFE in the datasets are 45:36, not statistically significant for the LIFE study alone. (Note that the differing LIFE lung cancer counts illustrate well the problems of depending upon published statistics—even from FDA reviews—for meta-analyses. One has to understand completely how the numbers were generated and their limitations in order to perform a definitive meta-analysis. Sipahi *et al.* were correct when they concluded that their findings warranted further investigation—but the FDA meta-analysis did not recognize its limitations. The differing LIFE lung cancer counts also illustrate that the counts used in this review are not always less favorable for ARBs than those used in other meta-analyses.)

When the publication of the Sipahi *et al.* meta-analysis stimulated interest in this topic and a formal response from the FDA, I communicated my observations from the LIFE study to the FDA staff responsible for the formal response in the following email messages:

From: Marciniak, Thomas
Sent: Friday, June 11, 2010 12:43 PM
To: Southworth, Mary Ross
Cc: Stockbridge, Norman L
Subject: RE: ARBs and risk of cancer

Attachments: LIFE cancers.doc

You're right, I didn't include it in my review because the signal is weak so I did not want to create a stir. I've attached what analysis logs regarding cancer stats in LIFE I have.

Tom

_____

From: Southworth, Mary Ross
Sent: Friday, June 11, 2010 12:29 PM
To: Marciniak, Thomas
Subject: RE: ARBs and risk of cancer

Was there a review of the cancer finding in the LIFE study? I have looked through the NDA and IND and am having trouble locating anything pertinent.

_____

From: Marciniak, Thomas
Sent: Friday, June 11, 2010 10:48 AM
To: Southworth, Mary Ross; U, Khin M; Karkowsky, Abraham M
Cc: Pease-Fye, Meg; Stockbridge, Norman L; U, Khin M
Subject: RE: ARBs and risk of cancer

Losartan in the LIFE study (lung cancer if I remember correctly), although weak and there is also a weak signal for HCTZ and renal cell carcinoma. Khin knows about telmisartan.

Tom

_____

From: Southworth, Mary Ross
Sent: Friday, June 11, 2010 10:03 AM
To: Marciniak, Thomas; U, Khin M; Karkowsky, Abraham M
Cc: Pease-Fye, Meg; Stockbridge, Norman L
Subject: ARBs and risk of cancer

We were recently informed about the impending publication of a meta-analysis about the association b/w ARBs and cancer (see below).

In investigating the background of this issue, I see that there was a cancer signal (fatal cancers) in the CHARM program and it looks like some of the more recent large ARB trials (TRANSCEND, ONTARGET) did target collection of cancer events. I imagine this was in an attempt to further investigate this signal. Do any of you have info on this--or point me to a review in which you discussed it? Thanks!

<< OLE Object: Picture (Metafile) >>
THE LANCET ONCOLOGY: PRESS RELEASE
EMBARGO: 1830H (New York time) Sunday 13 June 2010
WIDELY USED CLASS OF BLOOD PRESSURE MEDICATIONS LINKED TO INCREASED CANCER RISK

Note that I reaffirmed at the start of the FDA formal response that the signal in LIFE for losartan was an increased rate of lung cancer.

Analysis Plan for ARBs and Cancer
Version 1.2, August 18, 2012

Background

A recent published meta-analysis (M-A) re-raised the issue of whether angiotensin receptor blockers (ARBs) increase the risk of cancer. (Sipahi, Debanne et al. 2010) In response to publication of the M-A the FDA issued a drug safety communication on July 15, 2010, stating that the Agency's review was on-going. The Division entered a tracked safety issue (TSI) and assembled a team led by the Deputy Director for Safety (DDS) to perform the review. The DDS issued in August 2010 information requests to the developers of innovator ARBs marketed in the US to provide "study-level incidence by treatment arm of cancer (solid tumor only including skin cancer, not hematologic malignancy)" for trials with more than 100 patients and average follow-up of > 1 year. The drug companies submitted responses, among them Merck responses dated November 17, 2010, and February 2, 2011. The TSI team reviewed the responses and performed another M-A. Based on the TSI M-A the Agency issued another drug safety communication on June 2, 2011, stating that the relative risk of incident cancer in patients taking ARBs was 0.99 and the FDA also found no evidence of association between ARBs and cancer-related death, breast cancer, lung cancer, or prostate cancer.

However, the TSI M-A has many problems such that we cannot view it as a definitive answer to the questions of whether ARBs, or some ARBs, are associated with higher rates of cancer. Some of the problems with the TSI M-A are the following:

- The terms used for specific sites were not all inclusive of all malignancies, e.g., for lung cancers, lung cancers coded as malignant lung neoplasms were included but not ones coded as lung carcinomas. Yet the preliminary analyses of the LIFE study, one of the largest studies that prompted the latest round of meta-analyses, suggest that lung cancer is one of the tumors most affected and that ARBs could affect specific sites in different ways (see below.)

- The different sponsor submissions varied widely in how sponsors coded cancers, determined malignancy and new incidence determined, andcenosred cancer events. Several sponsors also had their staff assign a malignancy status to ambiguous cases. The variations in ascertaining cancer events and follow-up are great enough such that we should exclude some studies because of incomplete ascertainment of cancers or incomplete follow-up.

- The TSI M-A lumps studies with different controls together and lumps studies with and without concomitant use of ACE inhibitors (ACEIs). ARBs and ACEIs may affect some cancers similarly (see below).

- The TSI M-A included studies with patients on other drugs that affect cancer rates, e.g., immunosuppressives.

See the review "Losartan and Cancer" filed May 28, 2012, under the NDA 20-386 for more details regarding the problems with the TSI M-A.

An important issue is whether ARBs affect the incidence of all cancers or only specific ones. Most drugs affecting cancer rates have affected only specific sites (or a group of related sites) but the TSI M-A addresses primarily all solid cancers including skin cancers and secondarily breast, lung, and prostate (but inadequately for the latter as described above.) The losartan LIFE trial suggests that, rather than primarily affecting all solid cancers including skin cancers, ARBs may influence cancer rates in three different ways:

1. The strongest signal in LIFE regarding a specific cancer site is for lung cancer by Merck's SAE statistics (29:12 losartan:atenolol). The signal for all cancers is weaker and, in the absence of signals for most sites, appears to be related to the higher rates of lung (and prostate) cancers in the losartan arms. We need to analyze lung cancers separately as one primary hypothesis.

2. Prostate cancer SAE rates were also higher in the losartan arm in LIFE (58:42). In LIFE there is also a suggestion that gynecologic cancers were lower in the losartan arm, possibly implicating a hormonal mechanism. There is a plausible hormonal mechanism whereby ARBs (and ACEIs) could affect prostate cancers: ARBs and ACEIs initially decrease aldosterone levels but later there is "aldosterone breakthrough." If the aldosterone breakthrough is the result of a less specific adrenal stimulation that also increases adrenal androgen production, then an increase in prostate cancers would be expected. Hence, because the mechanism may be different, we should analyze prostate cancers separately taking into account that ACEIs may share the hormonal mechanism. As a secondary analysis we should combine lung and prostate cancer events.

3. Hematologic malignancy rates were lower in the losartan arm in LIFE. There is also a plausible mechanisms whereby ARBs (and ACEIs) could affect hematologic malignancies: Both ARBs and ACEIs suppress hematopoiesis slightly as evidenced by slightly decreased hemoglobin levels with chronic administration. This myelosuppression could also result in lower hematologic malignancy rates. We should analyze hematologic malignancy rates as a third primary hypothesis.

We have no evidence to assume that whatever is responsible for the increased lung cancer rates (if they are really increased) is an effect shared with ACEIs. However, we would expect that mechanisms 2 and 3 above, if real, are shared with ACEIs. Hence the studies included in MAs to address the different mechanisms should be different: For lung cancers (1 above) we may ignore the use of ACEIs as a control or as concomitant therapy for the primary analysis; for a secondary analysis excluding ACEI controls and concomitant ACEI use would be informative. For 2 and 3 above we must exclude ACEI use either as a control or as concomitant therapy (>10%--As a secondary analysis we can analyze trials have ACEI use of >10% by excluding the cases with ACEI use in both

arms.) Crossovers are also of concern and hence we should exclude trials with crossovers to open label ARB use of >10%.

The considerations for the different potential mechanisms are not limited to ACEI use: We must consider explicitly whether there is evidence for an ARB class effect or whether some ARBs could behave differently than others. We presume that mechanisms 2 and 3 are class effects of ARBs, i.e., all ARBs studied have shown aldosterone breakthrough and all ARBs have shown myelosuppression. For mechanisms 2 and 3 we have justification for analyzing all ARBs together (but dosage may be a consideration.) For 1 above we have no *a priori* reason justifying a class effect; conversely, because we do not understand the mechanism, we have no absolute *a priori* reasons to select out one or more of the ARBs. While ARBs do have different properties (e.g., lipophilicity, PPAR agonism) that we can use to group ARBs, we do not know which, if any, of these differing properties are important for cancer promotion. Hence, lacking a clearly justified *a priori* grouping, we default to grouping all ARBs together. However, we must be cognizant that grouping all ARBs may obscure a real signal for an appropriate subgroup and that a strong signal in two or more ARBs is greatly concerning.

In summary, the most important considerations for evaluating the risks of cancers with ARB administration are the following:

1. Assuring that the cancer ascertainments in the studies analyzed are as accurate and complete as possible and rejecting studies with incomplete ascertainment.

2. Selecting the appropriate studies, e.g., ones having appropriate controls and concomitant therapies, and the appropriate cancer sites for the suspected mechanisms.

3. Performing statistically valid meta-analyses.

Considerations 1 and 2 above are the ones that the TSI M-A does not handle appropriately, so I address them in detail below.

Plan

The general criteria used to screen trials initially for inclusion in the TSI M-A, similar to those used for the Sipaphi M-A, are reasonable. They are the following:

- Randomized, placebo-and active comparator-controlled studies for the ARBs
- Enrolled more than 100 patients
- Had a mean or median follow-up of > 1 year
- Collected cancer data (occurrence of cancer or cancer death) either as a prespecified endpoint or adverse event

However, while reasonable initial screening criteria, they are not adequate alone for selecting trials for inclusion in the M-As for two reasons: (1) As discussed above, the M-As for two of the cancer hypotheses should not include trials with ACEI control arms or

concomitant ACEI use. (2) If the cancer collection or follow-up for a trial is incomplete, then the trial may contribute more noise than useful information and we should not use it for the primary analyses. I recommend using these screening criteria with the two amplifications and I specify criteria for the latter below.

The time-consuming part of evaluating the risks of cancers with ARB administration is the work of assuring that the cancer ascertainments in the studies are accurate and complete. However, the time requirements are not excessive per study: I estimate that an experienced reviewer can complete the evaluation of one study in two to three days. Hence the total effort required for the 31 studies analyzed in the TSI M-A is about 62 to 93 man-days. Such an expenditure of effort would appear to be justified given the suggestive evidence from the losartan studies and the seriousness of increased cancer rates. While this level of effort is justified, it may be limited more by another requirement: To assure that cancer ascertainments are accurate and complete we need complete data for the trials, e.g., protocols, case report forms (CRFs), SAE reports, and datasets. I am able to identify submissions including these data for 16 of the 31 trials. (See Table 3 in Appendix 1.) Hence the appropriate next step may be to evaluate these trials completely.

We should consider requesting complete data for all 31 trials analyzed in the TSI M-A [redacted (b) (4)] There are also other ARB studies listed in ClinicalTrials.gov that may also be relevant.) There is a risk of requesting the complete data for trials missing them now: Sponsors could claim not having complete data for trials with unfavorable results while submitting complete data for trials with neutral or favorable results. Hence I would consider an M-A on the trials for which we currently have complete data to be the most reliable. I would also request the data for the losartan trials (i.e., other than LIFE and RENAAL, for which we have NDA submissions) to determine whether the signal for losartan remains strong or diminishes [redacted (b) (4)]

Individual Trial Evaluation

The following is the step-by-step procedure I recommend for evaluating each trial:

1. Collect the following metadata documents for the trial:
    a. Protocol
    b. Statistical analysis plan
    c. Blank annotated CRF
    d. DEFINE.PDF (or equivalent) file for data sets
    e. Study report
    f. Study design publication (if one)
    g. Major study results publication

2. Using the protocol, blank annotated CRF, DEFINE.PDF, and datasets determine which CRFs and datasets have baseline characteristics, randomization, cancer event information, history of cancer, smoking information, end of treatment date, and follow-up. Large outcome trials vary in where cancer event information is recorded. Besides the adverse event (AE) CRFs possible sources of cancer event information include death CRFs, end-of-study CRFs, hospitalization CRFs, endpoint CRFs, and cancer CRFs. An individual experienced in reviewing outcome trial data, including the datasets, should check all of these sources. For trials not specifying collection of all AEs the individual should make an initial assessment of whether the collection of cancer data is likely to be incomplete, including whether cancer site reporting is incomplete.

3. Using the protocol, study report, study publication, and datasets determine the end-of-study date to use as the censoring date for ITT analyses; also get the reported completeness of follow-up. If the reported completeness of follow-up exceeds 10 percent we will not use the trial for the primary analyses. Ten percent, of course, is a somewhat arbitrary number, although trials approaching this level of incompleteness have shown controversial results.

4. Collect the relevant datasets identified in 2 above and delete all treatment information from all datasets except a master dataset created from the baseline characteristics and randomization (treatment assignment) information. For cancer determinations use only datasets lacking the treatment assignments. CRFs typically do not have treatment assignments, with the exception of some PROBE design, open-label studies—not an issue for the 16 trials for which we currently have data. SAE reports occasionally have treatment assignments in the header or as an additional note at the end. Merge the cancer assignments into the master file after finalizing the cancer determinations.

5. Classify malignancies into sites based on the MedDRA "Neoplasms benign, malignant, and unspecified (incl cysts and polyps)" SOC with the following variations:
    a. Our concern is malignancies. Hence exclude benign neoplasms and attempt to determine the malignancy status of unspecified ones. Because unspecified neoplasms at different sites have different likelihoods of being malignant, use the guidance in Table 1 if the CRFs and SAE reports do not provide an unambiguous confirmation of malignancy. For the sites of interest for ARBs, i.e., lung, prostate, and hematologic, the most problematic cases are the lung tumors or lung masses that the records do not confirm as benign or malignant. Check all available records, e.g., CRFs, SAE reports, regarding these cases. Treatment can confirm malignancy, i.e., if the mass was treated with radiation therapy, it was likely malignant. If no other data are available, classify a lung mass as malignant if serious or severe and assume benign otherwise.
    b. While the sites of greatest interest for ARBs are lung, prostate, and hematologic, trying to classify all malignancies is worthwhile: We need to

resolve whether a neoplasm reported at one site is actually a metastasis from another site.

c. The MedDRA neoplasm SOC is predominantly anatomically oriented, although it does classify hematopoietic neoplasms and mesotheliomas separately. Classify hematopoietic neoplasms and mesotheliomas separately and also classify carcinoids and sarcomas separately, including fibrous malignant histiocytoma as a sarcoma. Cystosarcoma phyllodes is usually a benign breast tumor; classify it as a sarcoma if it is malignant.
d. Classify melanomas, including ocular melanomas, separately from all other skin cancers.
e. Brain tumors are not infrequently inadequately reported as benign vs. malignant. Benign brain tumors are also of substantial concern. Hence classify brain tumors into all brain tumors and malignant brain tumors.
f. Combine uncommon sites by anatomy using the site classification in Table 2. The sites in Table 2 link to MedDRA preferred terms that are used in analyzing the trial datasets (see below and Table 4 in Appendix 2.) Table 2 also includes "supersites" that group some sites for analysis purposes, e.g., the "gi" supersite is useful for analyzing gastrointestinal cancers that antiplatelet drugs may be expected to cause to bleed. The most relevant supersite for this effort is the "heme" supersite (hematologic malignancy). The "gyn" supersite (gynecologic malignancy or MedDRA reproductive neoplasms female malignant HLGT) is also relevant.
g. For this effort we are most concerned with lung, prostate, and hematologic malignancies so resolve suspected cases for these sites as completely and accurately as the available documentation permits.

Table 1: Guidance for Classifying Sites and Ambiguous Malignancy

term	guidance
adrenal mass/nodule	assume benign if not serious malignant if serious
bladder mass/lesion/tumor	classify as malignant
bowel/intestine (no small or large)	classify as colon
carcinoid	classify as carcinoid not by site
colon rectum cecum appendix	classify as colon
gall bladder	classify as bile duct
glioblastoma	classify as malignant brain
glioma	assume benign
hepatic nodule/mass/neoplasm/tumor	assume benign if not serious malignant if serious
lung neoplasm/mass/tumor/density etc.	base on characteristics eg seriousness check maximally
lung nodule	assume benign unless stated malignant
lymphoma	classify as lymphoma not by site
mesothelioma	classify as mesothelioma not by site
ovary mass/tumor	assume benign unless stated

term	guidance
	malignant
parotid/salivary gland	assume benign unless stated malignant and classify as head & neck
prostate nodule/enlargement	assume benign
refractory anemia	assume benign unless also stated as myelodysplasia
renal neoplasm/mass/tumor	assume malignant unless cyst
sarcoma	classify as sarcoma not by site
skin naevus/nodule/mole etc.	assume benign unless stated malignant
small intestine/GI	classify as gi
squamous cell carcinoma/scc	when site is not specified but the same patient has other skin cancers classify as skin cancer; check maximally for possible lung ca; classify as squamous if no other info
thrombocytosis/thrombocythemia	assume benign unless also stated as myelodysplasia
thyroid nodule/enlargement/tumor	assume benign unless stated malignant

Table 2: Sites for Grouping Malignancies for Analysis

site	supersite	comment
adrenal		
anus	gi	
bile duct	hepatobiliary	including gall bladder
bladder		including ureter & urethra
brain	brain	all & malignant separately
breast		
carcinoid	(gi)	include gi carcinoids in gi supersite
cervix	gyn	
colon	gi	
esophagus	gi	
eye		
germ cell		rare; resolve by gender
gi other	gi	small bowel & unspecified gi site
head & neck		
kidney		including renal pelvis
leukemia	heme	
liver	hepatobiliary	
lung		
lymphoma	heme	
melanoma		
mesothelioma		regardless of site

site	supersite	comment
myelodys	heme	
myeloma	heme	
other		
ovary	gyn	
pancreas		
penis		
pituitary	brain	benign or (rarely) malignant
prostate		
sarcoma		regardless of site
skin		
squamous		only if no other information
stomach	gi	
testes		
thyroid		
unknown		
uterus	gyn	
vagina	gyn	
vulva	gyn	

6. I have produced some automated tools for assisting with the classifying of cancer cases described in 5 above:
    a. A PTERMCA dataset links the MedDRA preferred terms to the sites in Table 2 as specified in Table 4 in Appendix 2. PTERMCA not only links MedDRA terms for malignancies in the neoplasm SOC but also unspecified malignancy terms in that SOC and procedures suggestive of a malignancy, e.g., colectomy, radiation therapy, etc. The latter are flagged with a binary variable CAUNCERTAIN. The PTERM variable also includes terms from older versions of MedDRA and other coding schemes. To use rename the preferred term variable to PTERM, convert to lowercase, and merge with PTERMCA.
    b. Not all datasets with cancer data have MedDRA coding and not all raw terms are correctly coded. Hence as a check I developed a Stata procedure GENCAMAYBE.DO to search the raw reported event terms for text strings suggestive of cancer. (The Stata procedure can easily be converted to a SAS program.) GENCAMAYBE sets a binary variable CAMAYBE if the raw term contains a string suggestive of cancer. To use rename the raw term variable to AETERM, convert to lowercase, and run GENCAMAYBE. GENCAMAYBE creates a binary flag variable CAMAYBE if the term suggests cancer.

7. I recommend classifying cancer cases operationally as follow:
    a. For each dataset having cancer information apply PTERMCA (if a preferred term is available) and GENCAMAYBE (if a raw term is available).

b. Create a new string variable CASITE. If PTERMCA was used, copy PTCASITE (preferred term cancer site) to CASITE if CAUNCERTAIN is not set.
c. Review all records for which PTCASITE is not null or CAUNCERTAIN or CAMAYBE are set. In my experience one can resolve most of the records without resorting to other documentation. Resolve with other documentation (CRFs, SAE reports, etc.) all possible potential lung, prostate, and heme malignancies. Populate CASITE for all confirmed or highly likely malignancies.
d. UNKNOWN is an appropriate value for CASITE if the reported term is "primary site unknown" or similar. However, if the only information available is that the case is a "cancer" or "malignancy" based on a checkbox on a hospitalization or death form, then enter CASITE as "malignancy". If one can not resolve most, i.e., 95 percent, of these unspecified malignancy cases from other records or documentation, then exclude the trial from the primary analyses.
e. Create binary flag variables for solid cancers excluding brain and non-melanoma skin, lung, prostate, and heme malignancies, assuring that the dates of diagnosis are within the censoring period (see below). Differentiate the flag variables by dataset source, e.g., CAALUNG for lung cancer from the AE dataset, CADLUNG for lung cancer from a DEATH dataset, etc. Merge the flag variables into a master dataset.
f. Generate global binary flag variables for solid cancer, lung, prostate, and heme malignancies using the binary flag variables from the individual dataset sources. Generate the global flags sequentially in the order of data sources AE, event or endpoint, hospitalization, treatment end, study end, and death. If more than a few cases, i.e., 5 percent of all cases, are detected only at study end or death, then exclude the trial from the primary analyses.
g. I believe one individual can perform all of the above evaluations in an unbiased fashion working from datasets without treatment identifiers. However, it is always worthwhile to have one individual's work checked by at least one additional individual. Ideally the second reviewer should have the same skills and experience as the primary reviewer, i.e., skills with dataset manipulations and experience with outcome trial data, preferably with cancer classifications. The time required for the second reviewer should be substantially less, e.g., one day per trial, than that for the first if the second reviewer works from the source documents collected by the first reviewer. If the two reviewers cannot reconcile their classifications of some cases, then we can consider two approaches to resolve: (1) Analyze each reviewer's assignments separately. I believe the results and conclusions will be similar. (2) Enlist a third reviewer to resolve the disputed cases.

8. In addition to the cancer site adjudicating the date of cancer diagnosis is important. I assert that, for the way cancers are reported in CV outcome trials, the

most appropriate definition is the date of first clinical diagnosis of cancer. Tumor registries typically use the date of first histologic diagnosis but CV trial data does not usually include the date of histologic diagnosis. Most cancer events occur during the course of the trial, i.e., "in the middle", so date of diagnosis is not usually problematic. For almost all cases we can use the start date of the AE or the date of hospital admission for a cancer hospitalization. One does have to check, if this date precedes the randomization, whether the start date represents the date of the first sign or symptom of the cancer, e.g., a cough for a lung cancer, or the date of diagnosis. If the AE start date is the first sign or symptom date, we need to determine the date of diagnosis from other sources.

One could exclude cancers at the start of a trial because they are unlikely to have any relationship to ARB use but for how long to exclude them is arbitrary; including them likely does not present a substantial amount of noise and avoids the arbitrary decision on exclusion period. For cancers reported at the end of the trial we could employ an absolute cutoff of the global study end date (see below.) However, a cancer reported one day after this date obviously could be treatment-related and dates have a reasonable amount of uncertainty—see my review of the LIFE study filed January 15, 2003, to NDA 20-386 for a detailed discussion of AE dates. Ideally we should examine cancer diagnoses (for entire studies, not by arm) at and shortly after study end dates. If cancer diagnoses are significantly more frequent around study end (as atrial fibrillation AEs were in LIFE), we should use a cutoff of study end plus the stabilization period—in LIFE for AEs the stabilization period was about 90 days. Until someone performs such analyses the global study end date is the appropriate cutoff to use for ITT analyses.

9. The final cancer case item to be considered is a flag whether the cancer is new (i.e., diagnosed after the randomization date) or recurrent (i.e., diagnosed on or before the randomization date.) While I agree new cancer rates may be informative, I believe that new and recurrent cancer rates are more informative and reliable for the following reasons: (1) Cancer patients typically die from recurrent disease, not their initial primary. Recurrent cancer is equally or more important clinically than new cancer. (2) CV outcome trials frequently record history of cancer as yes/no rather than for specific sites. Analyzing only new cancers will exclude trials with this limited history of cancer recording. (3) New and recurrent cancer rates correspond to our usual AE reporting of treatment-emergent events, e.g., we don't ignore an MI event because the patient also suffered an MI prior to randomization. I advise using treatment-emergent malignancy events for the primary analyses. I would use analyses of new malignancies as secondary analyses.

   Exclude trials without a recording of history of cancer from the new cancer M-As. For trials recording history of cancers by site classify the cancer new if there is no history of cancer for the same site. For ones recording only a yes/no response for history of cancer classify the cancer new if there is no history of cancer; if there is a history of cancer, check all records (particularly SAE reports) for mention of the

prior cancer site and classify the cancer new if the prior cancer site differs, not new otherwise.

10. The last data items that are useful for some analyses are censoring dates for each patient, i.e., the date of last follow-up and last treatment (the latter for on-treatment analyses.) Ideally we need to document two different dates of last follow-up for each patient: (1) the last date for which the records document reasonable ascertainment of events including cancer; and (2) the last date for which the records document vital status. Determining the date of last event follow-up can be difficult and time-consuming. Sponsors usually include a date of last treatment in study datasets and, because the dates of last treatment are usually reasonably well documented, I would use them unless we identify a systematic problem with the recordings for a trial, e.g., use of last dispensing date rather than a reported last administration date. The dates of last follow-up are more problematic and variably described. Because events alone are used for odds ratios, relative risks, and events without using censoring dates and because events largely determine the significance of hazard ratios and other time-to-event analyses, I favor determining initially only one last follow-up date, the vital status follow-up date.

Meta-Analyses

Before specifying the primary analyses there are some general statistical issues worth discussing:

1. This effort is a safety evaluation. For efficacy evaluations we have well-defined, pre-specified, specifically-collected primary endpoints in trials powered to detect reasonable differences between drugs and controls. For efficacy evaluations we insist upon strict statistical significance to guide the critical binary decision of allowing marketing or not. For safety evaluations we frequently start with *post hoc* observations, as is the case for this effort. We do not have data specifically collected to address the question and we do not have studies adequately powered to detect reasonable differences. Hence, while we may still use confidence intervals and p values to guide our safety decisions, we do not typically require strict statistical significance for safety data and we should consider patterns of problems, not just p values. Finally, while the critical efficacy decision is a binary one, we have different levels of action to address different levels of safety concerns. There are at least four levels of action to consider:
    a. Removing a drug from market. For this effort one might still insist upon having strict statistical significance of any result to justify removal.
    b. Including the findings in labeling and requiring an adequate post-marketing study to address the concerns. We typically take this action when the findings are concerning but not strictly statistically significant in any one study or available analysis.
    c. Including the findings in labeling without requiring a post-marketing study. We typically do not require any statistical significance for safety

findings, merely a difference between drug and control. Most of the safety results in existing labels fall into this category.

d. Doing nothing if no M-A confirms any concern.

We should consider all four of these levels of action for any results of these meta-analyses.

2. The index study for the hypotheses regarding lung, prostate, and hematologic malignancies is the LIFE study. Hence, for strict statistical significance one might exclude the LIFE study from the primary meta-analyses. However, for the identical situation with the Sipahi and TSI M-As, for which the CHARM study is considered the index study, neither M-A excluded the CHARM study in the primary analysis. Because LIFE contributes a minority of the patients to the all ARB M-As, I believe that including it in the overall M-As and excluding it for sensitivity analyses is reasonable.

3. For safety studies some prefer an on-treatment evaluation. I prefer an ITT evaluation because, just as for efficacy analyses, it preserves the randomization and minimizes the problems of informative censoring. However, just as for efficacy, if treatment discontinuations are common and follow-up thereafter is poor, either on-treatment or ITT safety evaluations will likely be biased; there is no statistical cure for poor study conduct. Hence for these M-As I am proposing excluding trials with poor cancer ascertainment and poor follow-up. I am proposing ITT for the primary M-As, i.e., randomization to the earlier of death or the global study end date. Because cancers may not manifest themselves or be diagnosed immediately, for secondary "on-treatment" M-As I propose treatment discontinuation plus 90 days (based on my LIFE trial analyses, see above. For ITT I do not recommend continuing beyond the global study end date unless a blinded analysis documents an appropriate stabilization period. However, follow-up is typically variable after the global study end date and I do have concerns that, if there was the potential for end-of-study unblinding, the extended follow-up may be biased.)

4. There are multiplicity issues for these M-As:
   a. I have proposed three different hypotheses. One, that ARBs may reduce hematologic malignancies, is clearly different from the other two in that it hypothesizes a benefit rather than a detriment. The other two are not as distinguishable. While I hypothesize different mechanisms for them, the increases in lung and prostate cancers could be the result of a common mechanism. I favor pursuing the two hypothesizes separately for this safety evaluation particularly because the prostate hypothesis may also be true for ACEIs, suggesting different trial inclusion criteria for the two hypotheses. Because I judge the signal to be stronger in LIFE for these two sites, weak or nonexistent for other sites, and weaker for all cancers, I would not base the primary M-A on all solid cancers.
   b. One approach for proceeding is to perform the proposed patient-level M-As, with the cancer ascertainment as described above, for the 16 trials for

which we have complete data. One might view such an M-A as an interim analysis, i.e., for suggestive or statistically significant results we should proceed to an M-A of all ARB trials for which we can obtain complete data. Because this is a safety evaluation I would not impose any strict statistical penalty for this interim analysis.

c. The more difficult multiplicity issue to address concerns how to resolve whether any positive results are an ARB class effect or an effect of some ARBs but not others. I think most people would be concerned if three ARBs showed a strong, statistically significant signal in an M-A of them alone but the other ARBs were neutral such that an all-ARBs M-A was not statistically significant. Because we have no strong *a priori* reason to hypothesize one or more ARBs as having greater cancer risk than the others, I would leave this issue to *post hoc* exploration.
d. Similarly, currently I cannot justify one of the secondary analyses discussed above (e.g., new malignancies only, on treatment rather than ITT, combined lung and prostate, etc.) as being more important than the others. I am not proposing secondary analysis plans preserving an overall alphas.
e. There are some cofactors that are of great interest. For lung cancers smoking history is critical and whether there is an interaction between treatment and smoking crucial to know. There is a suggestion of a gender effect, e.g., the one common male cancer, prostate, appears to be increased while common female cancers, breast and uterus, are not. Age and race are not specifically implicated for this effort but always of interest. I do not propose to include these cofactors in a analysis plan preserving an overall alpha but propose examining as descriptive factors if any primary analysis is significant.

5. Performing these patient-level evaluations would also open up the possibility of doing additional analyses not possible with the study-level M-As, in particular time-to-event and survival analyses. For the vast majority of clinical trial event analyses I have not encountered significant differences between the event incidence analyses, e.g., logistic regressions, and the time-to-event analyses, e.g., Cox regressions. I have found the subjective evaluation of the time-to-event and survival curves to be very informative. Because patient follow-up is variably defined and reported, I am not sure that there is any advantage to using a relative risk based on patient-years to one based on patients randomized. For the primary M-As I propose M-As of relative risks using fixed effects Mantel-Haenszel models analyzed using the metan package in Stata 12. The fixed effects Mantel-Haenszel model of relative risks is the default model of the metan package for binary outcome data such as cancer event occurrences.

6. Because I am hypothesizing a fixed effect, dosage becomes an issue for some trials. ARBs vary in potency so targeting or comparing mg dosages is not appropriate. Most trials performed a run-in or titrated to the maximum U.S. labeled dosage for hypertension but a few target half of this dosage. While

ideally we would like to know exposures and exposure-response relationships for the proposed mechanism (and for metabolites, etc.), U.S. maximum labeled dosage produce similar reductions in BP for all ARBs; percentage of maximum U.S. labeled dosage is a reasonable approach for standardizing potency. While, because we don't know the dose-response relationship for cancer activity (if one exists), I propose including the trials targeting half maximal dosage in the primary fixed effects M-A if they otherwise qualify, I also propose excluding them from secondary M-As to estimate the maximal treatment effect.

To summarize, my proposal for three primary M-As is the following:

- One primary M-A for each of the three hypotheses (lung, prostate, and hematologic)
- All M-As to use data from all 16 trials for which we currently have complete datasets and CRFs and which have reasonably complete cancer ascertainment and follow-up as defined above (If any FDA staff can identify other trials for which we currently have complete datasets and CRFs and which have reasonably complete cancer ascertainment and follow-up as defined above, I propose adding them to the analyses.)
- Cancer ascertainment as detailed above
- The M-As for prostate and hematologic malignancies excluding ACEI controls and trials with concomitant ACEI use
- Primary analyses of ITT relative risks using fixed effects Mantel-Haenszel models analyzed using the metan package of Stata 12

I argue that the proposed M-As, or variations on them proposed by other staff, will provide a more definitive answer to the question of whether ARBs affect cancer risk than any of the existing M-As, TSI or published. I believe the most critical factor is assuring that cancer ascertainment in the trials is as complete and accurate as possible. I will welcome discussion and proposals for variations on the statistical analyses and for secondary analysis plans preserving overall alpha.

Reference

Sipahi, I., S. M. Debanne, et al. (2010). "Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials." Lancet Oncol **11**(7): 627-36.

Revision History

Version	Date	Modifications
1.0	08/03/12	Original
1.1	08/09/12	1. Added LIFE lung and prostate ca statistics 2. Updated count of ARB trials with data in-house from 14 to 15 3. Added explicit ACEI exclusion criterion 4. Clarified use of dates of last treatment 5. Added discussion of ITT vs. on-treatment analyses 6. Added discussion of dosage issues
1.2	08/18/12	1. Added Revision History 2. Updated count of ARB trials with data in-house from 15 to 16 and added an appendix table identifying the 16 trials 3. Clarified that, if FDA staff identify other eligible trials, they will be added to the analyses 4. Added an appendix table of MedDRA preferred terms with site classifications 5. Specified relative risks, rather than odds ratios, for the primary M-As and the use of the metan package of Stata 12. NOTE: Clinicians and patients understand relative risks better than odds ratios. Switching from odds ratios to relative risks should have minimal to no impact upon the statistical significance of any M-A for these data; we will perform M-As using both measures and report both if there are more than minimal differences, e.g., p value difference ≥0.005. Relative risks are the default for binary outcomes for the metan package. 6. Corrected typos and awkward wording

Appendix 1

Table 3: Major ARB Trials with IND or NDA Data Submissions

ARB	Trial	IND or NDA
candesartan	CharmAdd	N20838S022
	CharmAlt	N20838S022
	CharmPres	N20838S022
irbesartan	(b) (4)	(b) (4)
	IDNT	N20757S021
	IRMA 2	N20757S021
losartan	LIFE	N20386S032
	RENAAL	N20386S028
olmesartan	(b) (4)	(b) (4)
telmisartan	ONTARGET	N20850S025
	PRoFESS	N20850S025
	TRANSCEND	N20850S025
valsartan	(b) (4)	(b) (4)
	Val-Heft	N20665S016
	VALIANT	N21283S011

Appendix 2

NOTE: Some of the MedDRA referred terms below are unspecified regarding malignancy status. Events coded to such unspecified terms need additional documentation to determine malignancy status. See Table 1 for guidance on classifying unspecified terms.

Table 4: MedDRA Preferred Terms and Sites

HLGT	Preferred Term	Site
breast neoplasms malignant and unspecified (incl nipple)	breast cancer	breast
	breast cancer female	breast
	breast cancer in situ	breast
	breast cancer male	breast
	breast cancer metastatic	breast
	breast cancer recurrent	breast
	breast cancer stage i	breast
	breast cancer stage ii	breast
	breast cancer stage iii	breast
	breast cancer stage iv	breast
	breast neoplasm	breast
	breast sarcoma	breast
	breast sarcoma metastatic	breast
	breast sarcoma recurrent	breast
	contralateral breast cancer	breast
	cystosarcoma phyllodes	breast
	inflammatory carcinoma of breast recurrent	breast
	inflammatory carcinoma of breast stage iii	breast
	inflammatory carcinoma of breast stage iv	breast
	inflammatory carcinoma of the breast	breast
	malignant nipple neoplasm	breast
	malignant nipple neoplasm female	breast
	malignant nipple neoplasm male	breast
	nipple neoplasm	breast
	paget's disease of the breast	breast
cancer-related morbidities	acanthosis nigricans	unknown
	acrokeratosis paraneoplastica	unknown
	bence jones proteinuria	myeloma
	cancer pain	unknown
	clonal evolution	unknown
	haemorrhagic tumour necrosis	unknown
	hypercalcaemia of malignancy	unknown
	infected neoplasm	unknown
	intracranial tumour haemorrhage	unknown
	leukostasis	unknown
	malignant ascites	unknown
	malignant dysphagia	unknown
	malignant pleural effusion	unknown
	meigs' syndrome	ovary

HLGT	Preferred Term	Site
	metastatic pain	unknown
	myasthenic syndrome	unknown
	necrolytic migratory erythema	unknown
	neoplasm swelling	unknown
	oncologic complication	unknown
	pancoast's syndrome	lung
	paraneoplastic cerebellar degeneration	unknown
	paraneoplastic dermatomyositis	unknown
	paraneoplastic pemphigus	unknown
	paraneoplastic retinopathy	unknown
	paraneoplastic syndrome	unknown
	pericardial effusion malignant	unknown
	pericarditis malignant	unknown
	polyneuropathy in malignant disease	unknown
	pseudomyxoma peritonei	unknown
	superior vena caval occlusion	unknown
	treatment related secondary malignancy	unknown
	trousseau's syndrome	unknown
	tumour associated fever	unknown
	tumour compression	unknown
	tumour embolism	unknown
	tumour flare	unknown
	tumour haemorrhage	unknown
	tumour local invasion	unknown
	tumour lysis syndrome	unknown
	tumour necrosis	unknown
	tumour pain	unknown
	tumour thrombosis	unknown
	tumour ulceration	unknown
endocrine neoplasms benign	pituitary tumour benign	pituitary
endocrine neoplasms malignant and unspecified	acth-producing pituitary tumour	pituitary
	adrenal carcinoma	adrenal
	adrenal cyst	adrenal
	adrenal gland cancer metastatic	adrenal
	adrenal neoplasm	adrenal
	adrenocortical carcinoma	adrenal
	apudoma	unknown
	carcinoid syndrome	carcinoid
	carcinoid tumour	carcinoid
	carcinoid tumour of the appendix	carcinoid
	carcinoid tumour of the caecum	carcinoid
	carcinoid tumour of the duodenum	carcinoid
	carcinoid tumour of the gastrointestinal tract	carcinoid
	carcinoid tumour of the pancreas	carcinoid
	carcinoid tumour of the prostate	carcinoid
	carcinoid tumour of the small bowel	carcinoid
	carcinoid tumour of the stomach	carcinoid

HLGT	Preferred Term	Site
	carcinoid tumour pulmonary	carcinoid
	craniopharyngioma	brain
	ectopic acth syndrome	unknown
	ectopic aldosterone secretion	unknown
	ectopic antidiuretic hormone secretion	unknown
	ectopic calcitonin production	unknown
	ectopic chorionic gonadotrophin secretion	unknown
	ectopic growth hormone secretion	unknown
	ectopic hormone secretion	unknown
	ectopic parathormone production	unknown
	ectopic prolactin secretion	unknown
	ectopic renin secretion	unknown
	endocrine neoplasm	other
	endocrine neoplasm malignant	other
	gastrinoma	gi other
	gastrinoma malignant	gi other
	glucagonoma	pancreas
	growth hormone-producing pituitary tumour	pituitary
	hormone-secreting ovarian tumour	ovary
	insulinoma	pancreas
	malignant neoplasm of islets of langerhans	pancreas
	malignant pituitary tumour	pituitary
	metastatic carcinoid tumour	carcinoid
	neuroendocrine carcinoma	other
	neuroendocrine tumour	other
	neurotensinoma	gi other
	pancreatic neuroendocrine tumour	pancreas
	paraganglion neoplasm	other
	paraganglion neoplasm malignant	other
	parathyroid tumour	other
	parathyroid tumour malignant	other
	phaeochromocytoma	other
	phaeochromocytoma malignant	other
	pituitary cancer metastatic	pituitary
	pituitary neoplasm malignant recurrent	pituitary
	pituitary tumour	pituitary
	pituitary tumour recurrent	pituitary
	prolactin-producing pituitary tumour	pituitary
	somatostatinoma	gi other
	thyroid cancer	thyroid
	thyroid cancer metastatic	thyroid
	thyroid neoplasm	thyroid
	thyroid stimulating hormone-producing pituitary tumour	pituitary
	vipoma	pancreas
gastrointestinal neoplasms malignant and	abdominal wall neoplasm	skin
	adenocarcinoma pancreas	pancreas
	anal cancer	anus

HLGT	Preferred Term	Site
unspecified	anal cancer metastatic	anus
	anal cancer recurrent	anus
	anal cancer stage 0	anus
	anal cancer stage i	anus
	anal cancer stage ii	anus
	anal cancer stage iii	anus
	anal cancer stage iv	anus
	anal neoplasm	anus
	colon cancer	colon
	colon cancer metastatic	colon
	colon cancer recurrent	colon
	colon cancer stage 0	colon
	colon cancer stage i	colon
	colon cancer stage ii	colon
	colon cancer stage iii	colon
	colon cancer stage iv	colon
	colon neoplasm	colon
	colorectal cancer	colon
	colorectal cancer metastatic	colon
	colorectal cancer recurrent	colon
	colorectal cancer stage i	colon
	colorectal cancer stage ii	colon
	colorectal cancer stage iii	colon
	colorectal cancer stage iv	colon
	colorectal carcinoma stage 0	colon
	desmoplastic small round cell tumour	sarcoma
	duodenal neoplasm	gi other
	erythroplasia of lip	skin
	gastric cancer	stomach
	gastric cancer recurrent	stomach
	gastric cancer stage 0	stomach
	gastric cancer stage i	stomach
	gastric cancer stage ii	stomach
	gastric cancer stage iii	stomach
	gastric cancer stage iv	stomach
	gastric neoplasm	stomach
	gastric sarcoma	stomach
	gastrointestinal cancer metastatic	gi other
	gastrointestinal carcinoma	gi other
	gastrointestinal carcinoma in situ	gi other
	gastrointestinal neoplasm	gi other
	gastrointestinal stromal tumour	gi other
	gastrooesophageal cancer	esophagus
	gingival cancer	head & neck
	hereditary non-polyposis colorectal cancer syndrome	colon
	intestinal adenocarcinoma	gi other
	large intestine carcinoma	colon

HLGT	Preferred Term	Site
	linitis plastica	stomach
	lip and/or oral cavity cancer	head & neck
	lip and/or oral cavity cancer recurrent	head & neck
	lip and/or oral cavity cancer stage 0	head & neck
	lip and/or oral cavity cancer stage i	head & neck
	lip and/or oral cavity cancer stage ii	head & neck
	lip and/or oral cavity cancer stage iii	head & neck
	lip and/or oral cavity cancer stage iv	head & neck
	lip neoplasm	head & neck
	lip neoplasm malignant stage unspecified	head & neck
	malignant anorectal neoplasm	anus
	malignant mesenteric neoplasm	other
	malignant palate neoplasm	head & neck
	malignant peritoneal neoplasm	unknown
	metastatic gastric cancer	stomach
	metastatic salivary gland cancer	head & neck
	mixed salivary tumour	head & neck
	muir-torre syndrome	colon
	neoplasm of appendix	colon
	oesophageal adenocarcinoma	esophagus
	oesophageal adenocarcinoma metastatic	esophagus
	oesophageal adenocarcinoma recurrent	esophagus
	oesophageal adenocarcinoma stage 0	esophagus
	oesophageal adenocarcinoma stage i	esophagus
	oesophageal adenocarcinoma stage ii	esophagus
	oesophageal adenocarcinoma stage iii	esophagus
	oesophageal adenocarcinoma stage iv	esophagus
	oesophageal cancer metastatic	esophagus
	oesophageal carcinoma	esophagus
	oesophageal carcinoma recurrent	esophagus
	oesophageal carcinoma stage 0	esophagus
	oesophageal neoplasm	esophagus
	oesophageal squamous cell carcinoma	esophagus
	oesophageal squamous cell carcinoma metastatic	esophagus
	oesophageal squamous cell carcinoma recurrent	esophagus
	oesophageal squamous cell carcinoma stage 0	esophagus
	oesophageal squamous cell carcinoma stage i	esophagus
	oesophageal squamous cell carcinoma stage ii	esophagus
	oesophageal squamous cell carcinoma stage iii	esophagus
	oesophageal squamous cell carcinoma stage iv	esophagus
	omentum neoplasm	other
	oral cavity cancer metastatic	head & neck
	oral neoplasm	head & neck
	oropharyngeal neoplasm	head & neck
	pancreatic carcinoma	pancreas
	pancreatic carcinoma metastatic	pancreas
	pancreatic carcinoma non-resectable	pancreas

HLGT	Preferred Term	Site
	pancreatic carcinoma recurrent	pancreas
	pancreatic carcinoma resectable	pancreas
	pancreatic carcinoma stage 0	pancreas
	pancreatic carcinoma stage i	pancreas
	pancreatic carcinoma stage ii	pancreas
	pancreatic carcinoma stage iii	pancreas
	pancreatic carcinoma stage iv	pancreas
	pancreatic neoplasm	pancreas
	pancreatic sarcoma	sarcoma
	peritoneal carcinoma	unknown
	peritoneal neoplasm	other
	peritoneal sarcoma	sarcoma
	rectal cancer	colon
	rectal cancer metastatic	unknown
	rectal cancer recurrent	colon
	rectal cancer stage 0	colon
	rectal cancer stage i	colon
	rectal cancer stage ii	colon
	rectal cancer stage iii	colon
	rectal cancer stage iv	colon
	rectal neoplasm	colon
	rectosigmoid cancer	colon
	rectosigmoid cancer recurrent	colon
	rectosigmoid cancer stage 0	colon
	rectosigmoid cancer stage i	colon
	rectosigmoid cancer stage ii	colon
	rectosigmoid cancer stage iii	colon
	rectosigmoid cancer stage iv	colon
	retroperitoneal cancer	other
	retroperitoneal neoplasm	unknown
	retroperitoneal neoplasm metastatic	other
	salivary gland cancer	head & neck
	salivary gland cancer recurrent	head & neck
	salivary gland cancer stage 0	head & neck
	salivary gland cancer stage i	head & neck
	salivary gland cancer stage ii	head & neck
	salivary gland cancer stage iii	head & neck
	salivary gland cancer stage iv	head & neck
	salivary gland neoplasm	head & neck
	small intestine carcinoma	gi other
	small intestine carcinoma metastatic	gi other
	small intestine carcinoma non-resectable	gi other
	small intestine carcinoma recurrent	gi other
	small intestine carcinoma resectable	gi other
	small intestine carcinoma stage 0	gi other
	small intestine carcinoma stage i	gi other
	small intestine carcinoma stage ii	gi other

HLGT	Preferred Term	Site
	small intestine carcinoma stage iii	gi other
	small intestine carcinoma stage iv	gi other
	tongue cancer metastatic	head & neck
	tongue carcinoma stage 0	head & neck
	tongue carcinoma stage i	head & neck
	tongue carcinoma stage ii	head & neck
	tongue carcinoma stage iii	head & neck
	tongue carcinoma stage iv	head & neck
	tongue neoplasm	head & neck
	tongue neoplasm malignant stage unspecified	head & neck
haematopoietic neoplasms (excl leukaemias and lymphomas)	blast cell proliferation	leukemia
	bone marrow leukaemic cell infiltration	leukemia
	bone marrow tumour cell infiltration	unknown
	epstein-barr virus associated lymphoproliferative disorder	lymphoma
	essential thrombocythaemia	myelodys
	haematological malignancy	unknown
	haematopoietic neoplasm	unknown
	leukoerythroblastosis	leukemia
	lymphatic system neoplasm	lymphoma
	lymphohistiocytosis	lymphoma
	lymphoproliferative disorder	lymphoma
	lymphoproliferative disorder in remission	lymphoma
	malignant histiocytosis	other
	malignant mast cell neoplasm	myeloma
	malignant splenic neoplasm	lymphoma
	myeloblastoma	other
	myelofibrosis	myelodys
	myeloid metaplasia	myelodys
	myeloproliferative disorder	myelodys
	polycythaemia vera	myelodys
	rosai-dorfman syndrome	lymphoma
	splenic neoplasm malignancy unspecified	lymphoma
	x-linked lymphoproliferative syndrome	lymphoma
hepatobiliary neoplasms malignant and unspecified	bile duct cancer	bile duct
	bile duct cancer non-resectable	bile duct
	bile duct cancer recurrent	bile duct
	bile duct cancer resectable	bile duct
	bile duct cancer stage 0	bile duct
	bile duct cancer stage i	bile duct
	bile duct cancer stage ii	bile duct
	bile duct cancer stage iii	bile duct
	bile duct cancer stage iv	bile duct
	biliary cancer metastatic	bile duct
	biliary neoplasm	bile duct
	gallbladder cancer	bile duct
	gallbladder cancer metastatic	bile duct
	gallbladder cancer non-resectable	bile duct

HLGT	Preferred Term	Site
	gallbladder cancer recurrent	bile duct
	gallbladder cancer stage 0	bile duct
	gallbladder cancer stage i	bile duct
	gallbladder cancer stage ii	bile duct
	gallbladder cancer stage iii	bile duct
	gallbladder cancer stage iv	bile duct
	hepatic angiosarcoma	sarcoma
	hepatic cancer metastatic	unknown
	hepatic cancer stage i	liver
	hepatic cancer stage ii	liver
	hepatic cancer stage iii	liver
	hepatic cancer stage iv	liver
	hepatic neoplasm	liver
	hepatic neoplasm malignant	liver
	hepatic neoplasm malignant non-resectable	liver
	hepatic neoplasm malignant recurrent	liver
	hepatic neoplasm malignant resectable	liver
	hepatobiliary carcinoma in situ	liver
	hepatobiliary neoplasm	liver
	hepatoblastoma	liver
	hepatoblastoma recurrent	liver
	liver carcinoma ruptured	liver
	malignant hepatobiliary neoplasm	liver
	malignant neoplasm of ampulla of vater	bile duct
	mixed hepatocellular cholangiocarcinoma	liver
leukaemias	5q minus syndrome	myelodys
	acute biphenotypic leukaemia	leukemia
	acute leukaemia	leukemia
	acute leukaemia in remission	leukemia
	acute lymphocytic leukaemia	leukemia
	acute lymphocytic leukaemia (in remission)	leukemia
	acute lymphocytic leukaemia recurrent	leukemia
	acute megakaryocytic leukaemia	leukemia
	acute megakaryocytic leukaemia (in remission)	leukemia
	acute monocytic leukaemia	leukemia
	acute monocytic leukaemia (in remission)	leukemia
	acute myeloid leukaemia	leukemia
	acute myeloid leukaemia (in remission)	leukemia
	acute myeloid leukaemia recurrent	leukemia
	acute myelomonocytic leukaemia	leukemia
	acute promyelocytic leukaemia	leukemia
	aleukaemic leukaemia	leukemia
	b precursor type acute leukaemia	leukemia
	b-cell type acute leukaemia	leukemia
	blast cell crisis	leukemia
	blast crisis in myelogenous leukaemia	leukemia
	burkitt's leukaemia	leukemia

HLGT	Preferred Term	Site
	chloroma	leukemia
	chloroma (in remission)	leukemia
	chronic eosinophilic leukaemia	leukemia
	chronic leukaemia	leukemia
	chronic leukaemia in remission	leukemia
	chronic lymphocytic leukaemia	leukemia
	chronic lymphocytic leukaemia (in remission)	leukemia
	chronic lymphocytic leukaemia recurrent	leukemia
	chronic lymphocytic leukaemia refractory	leukemia
	chronic lymphocytic leukaemia stage 0	leukemia
	chronic lymphocytic leukaemia stage 1	leukemia
	chronic lymphocytic leukaemia stage 2	leukemia
	chronic lymphocytic leukaemia stage 3	leukemia
	chronic lymphocytic leukaemia stage 4	leukemia
	chronic lymphocytic leukaemia transformation	leukemia
	chronic myeloid leukaemia	leukemia
	chronic myeloid leukaemia (in remission)	leukemia
	chronic myeloid leukaemia transformation	leukemia
	chronic myelomonocytic leukaemia	leukemia
	chronic myelomonocytic leukaemia (in remission)	leukemia
	eosinophilic leukaemia	leukemia
	erythraemic myelosis (in remission)	leukemia
	erythroleukaemia	leukemia
	hairy cell leukaemia	leukemia
	juvenile chronic myelomonocytic leukaemia	leukemia
	large granular lymphocytosis	leukemia
	leukaemia	leukemia
	leukaemia basophilic	leukemia
	leukaemia cutis	leukemia
	leukaemia granulocytic	leukemia
	leukaemia in remission	leukemia
	leukaemia monocytic	leukemia
	leukaemia recurrent	leukemia
	leukaemic infiltration brain	leukemia
	leukaemic infiltration extramedullary	leukemia
	leukaemic infiltration gingiva	leukemia
	leukaemic infiltration hepatic	leukemia
	leukaemic infiltration pulmonary	leukemia
	leukaemic retinopathy	leukemia
	lymphocytic leukaemia	leukemia
	lymphoid leukaemia (in remission)	leukemia
	mastocytic leukaemia	leukemia
	mature b-cell type acute leukaemia	leukemia
	monocytic leukaemia in remission	leukemia
	myelodysplastic syndrome	myelodys
	myelodysplastic syndrome transformation	other
	myelodysplastic syndrome unclassifiable	other

HLGT	Preferred Term	Site
	myeloid leukaemia	leukemia
	myeloid leukaemia in remission	leukemia
	natural killer-cell leukaemia	leukemia
	neonatal leukaemia	leukemia
	prolymphocytic leukaemia	leukemia
	refractory anaemia	myelodys
	refractory anaemia with an excess of blasts	myelodys
	refractory anaemia with ringed sideroblasts	myelodys
	refractory cytopenia with multilineage dysplasia	myelodys
	refractory cytopenia with multilineage dysplasia and ringed sideroblasts	myelodys
	t-cell chronic lymphocytic leukaemia	leukemia
	t-cell prolymphocytic leukaemia	leukemia
	t-cell type acute leukaemia	leukemia
	trisomy 12	lymphoma
lymphomas hodgkin's disease	hodgkin's disease	lymphoma
	hodgkin's disease lymphocyte depletion stage i site unspecified	lymphoma
	hodgkin's disease lymphocyte depletion stage i subdiaphragm	lymphoma
	hodgkin's disease lymphocyte depletion stage i supradiaphragm	lymphoma
	hodgkin's disease lymphocyte depletion stage ii site unspecified	lymphoma
	hodgkin's disease lymphocyte depletion stage ii subdiaphragm	lymphoma
	hodgkin's disease lymphocyte depletion stage ii supradiaphragm	lymphoma
	hodgkin's disease lymphocyte depletion type recurrent	lymphoma
	hodgkin's disease lymphocyte depletion type refractory	lymphoma
	hodgkin's disease lymphocyte depletion type stage iii	lymphoma
	hodgkin's disease lymphocyte depletion type stage iv	lymphoma
	hodgkin's disease lymphocyte depletion type stage unspecified	lymphoma
	hodgkin's disease lymphocyte predominance stage i site unspec	lymphoma
	hodgkin's disease lymphocyte predominance stage i subdiaphragm	lymphoma
	hodgkin's disease lymphocyte predominance stage i supradiaphragm	lymphoma
	hodgkin's disease lymphocyte predominance stage ii site unspec	lymphoma
	hodgkin's disease lymphocyte predominance stage ii subdiaphragm	lymphoma
	hodgkin's disease lymphocyte predominance stage ii supradiaphragm	lymphoma
	hodgkin's disease lymphocyte predominance type recurrent	lymphoma
	hodgkin's disease lymphocyte predominance type refractory	lymphoma
	hodgkin's disease lymphocyte predominance type stage	lymphoma

HLGT	Preferred Term	Site
	iii	
	hodgkin's disease lymphocyte predominance type stage iv	lymphoma
	hodgkin's disease lymphocyte predominance type stage unspecified	lymphoma
	hodgkin's disease mixed cellularity recurrent	lymphoma
	hodgkin's disease mixed cellularity refractory	lymphoma
	hodgkin's disease mixed cellularity stage i site unspecified	lymphoma
	hodgkin's disease mixed cellularity stage i subdiaphragmatic	lymphoma
	hodgkin's disease mixed cellularity stage i supradiaphragmatic	lymphoma
	hodgkin's disease mixed cellularity stage ii subdiaphragmatic	lymphoma
	hodgkin's disease mixed cellularity stage ii supradiaphragmatic	lymphoma
	hodgkin's disease mixed cellularity stage iii	lymphoma
	hodgkin's disease mixed cellularity stage iv	lymphoma
	hodgkin's disease mixed cellularity stage unspecified	lymphoma
	hodgkin's disease nodular sclerosis recurrent	lymphoma
	hodgkin's disease nodular sclerosis refractory	lymphoma
	hodgkin's disease nodular sclerosis stage i site unspecified	lymphoma
	hodgkin's disease nodular sclerosis stage i subdiaphragmatic	lymphoma
	hodgkin's disease nodular sclerosis stage i supradiaphragmatic	lymphoma
	hodgkin's disease nodular sclerosis stage ii subdiaphragmatic	lymphoma
	hodgkin's disease nodular sclerosis stage ii supradiaphragmatic	lymphoma
	hodgkin's disease nodular sclerosis stage iii	lymphoma
	hodgkin's disease nodular sclerosis stage iv	lymphoma
	hodgkin's disease nodular sclerosis stage unspecified	lymphoma
	hodgkin's disease recurrent	lymphoma
	hodgkin's disease refractory	lymphoma
	hodgkin's disease stage i	lymphoma
	hodgkin's disease stage ii	lymphoma
	hodgkin's disease stage iii	lymphoma
	hodgkin's disease stage iv	lymphoma
	hodgkin's disease unclassifiable	lymphoma
lymphomas nec	central nervous system lymphoma	lymphoma
	disseminated large cell lymphoma	lymphoma
	lymph node cancer metastatic	breast
	lymphocytic lymphoma	lymphoma
	lymphoma	lymphoma
	lymphoma aids related	lymphoma
	lymphoma transformation	lymphoma
	malignant lymphoid neoplasm	lymphoma

HLGT	Preferred Term	Site
	malignant lymphoma unclassifiable high grade	lymphoma
	malignant lymphoma unclassifiable low grade	lymphoma
lymphomas non-hodgkin's b-cell	b-cell lymphoma	lymphoma
	b-cell lymphoma recurrent	lymphoma
	b-cell lymphoma refractory	lymphoma
	b-cell lymphoma stage i	lymphoma
	b-cell lymphoma stage ii	lymphoma
	b-cell lymphoma stage iii	lymphoma
	b-cell lymphoma stage iv	lymphoma
	b-cell small lymphocytic lymphoma	lymphoma
	b-cell small lymphocytic lymphoma recurrent	lymphoma
	b-cell small lymphocytic lymphoma refractory	lymphoma
	b-cell small lymphocytic lymphoma stage i	lymphoma
	b-cell small lymphocytic lymphoma stage ii	lymphoma
	b-cell small lymphocytic lymphoma stage iii	lymphoma
	b-cell small lymphocytic lymphoma stage iv	lymphoma
	b-cell unclassifiable lymphoma high grade	lymphoma
	b-cell unclassifiable lymphoma low grade	lymphoma
	burkitt's lymphoma	lymphoma
	burkitt's lymphoma recurrent	lymphoma
	burkitt's lymphoma refractory	lymphoma
	burkitt's lymphoma stage i	lymphoma
	burkitt's lymphoma stage ii	lymphoma
	burkitt's lymphoma stage iii	lymphoma
	burkitt's lymphoma stage iv	lymphoma
	diffuse large b-cell lymphoma	lymphoma
	diffuse large b-cell lymphoma recurrent	lymphoma
	diffuse large b-cell lymphoma refractory	lymphoma
	diffuse large b-cell lymphoma stage i	lymphoma
	diffuse large b-cell lymphoma stage ii	lymphoma
	diffuse large b-cell lymphoma stage iii	lymphoma
	diffuse large b-cell lymphoma stage iv	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type)	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) recurrent	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) refractory	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) stage i	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) stage ii	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) stage iii	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) stage iv	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma recurrent	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma	lymphoma

HLGT	Preferred Term	Site
	refractory	
	follicle centre lymphoma diffuse small cell lymphoma stage i	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma stage ii	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma stage iii	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma stage iv	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii recurrent	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii refractory	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii stage i	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii stage ii	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii stage iii	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii stage iv	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma recurrent	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma refractory	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma stage i	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma stage ii	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma stage iii	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma stage iv	lymphoma
	lymphoma cutis	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma recurrent	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma refractory	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma stage i	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma stage ii	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma stage iii	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma stage iv	lymphoma
	mantle cell lymphoma	lymphoma
	mantle cell lymphoma recurrent	lymphoma
	mantle cell lymphoma refractory	lymphoma
	mantle cell lymphoma stage i	lymphoma
	mantle cell lymphoma stage ii	lymphoma
	mantle cell lymphoma stage iii	lymphoma
	mantle cell lymphoma stage iv	lymphoma
	nodal marginal zone b-cell lymphoma	lymphoma
	nodal marginal zone b-cell lymphoma recurrent	lymphoma
	nodal marginal zone b-cell lymphoma refractory	lymphoma

HLGT	Preferred Term	Site
	nodal marginal zone b-cell lymphoma stage i	lymphoma
	nodal marginal zone b-cell lymphoma stage ii	lymphoma
	nodal marginal zone b-cell lymphoma stage iii	lymphoma
	nodal marginal zone b-cell lymphoma stage iv	lymphoma
	precursor b-lymphoblastic lymphoma	lymphoma
	precursor b-lymphoblastic lymphoma recurrent	lymphoma
	precursor b-lymphoblastic lymphoma refractory	lymphoma
	precursor b-lymphoblastic lymphoma stage i	lymphoma
	precursor b-lymphoblastic lymphoma stage ii	lymphoma
	precursor b-lymphoblastic lymphoma stage iii	lymphoma
	precursor b-lymphoblastic lymphoma stage iv	lymphoma
	primary effusion lymphoma	lymphoma
	primary mediastinal large b-cell lymphoma	lymphoma
	primary mediastinal large b-cell lymphoma recurrent	lymphoma
	primary mediastinal large b-cell lymphoma refractory	lymphoma
	primary mediastinal large b-cell lymphoma stage i	lymphoma
	primary mediastinal large b-cell lymphoma stage ii	lymphoma
	primary mediastinal large b-cell lymphoma stage iii	lymphoma
	primary mediastinal large b-cell lymphoma stage iv	lymphoma
	splenic marginal zone lymphoma	lymphoma
	splenic marginal zone lymphoma recurrent	lymphoma
	splenic marginal zone lymphoma refractory	lymphoma
	splenic marginal zone lymphoma stage i	lymphoma
	splenic marginal zone lymphoma stage ii	lymphoma
	splenic marginal zone lymphoma stage iii	lymphoma
	splenic marginal zone lymphoma stage iv	lymphoma
	waldenstrom's macroglobulinaemia	myeloma
	waldenstrom's macroglobulinaemia recurrent	myeloma
	waldenstrom's macroglobulinaemia refractory	myeloma
	waldenstrom's macroglobulinaemia stage i	myeloma
	waldenstrom's macroglobulinaemia stage ii	myeloma
	waldenstrom's macroglobulinaemia stage iii	myeloma
	waldenstrom's macroglobulinaemia stage iv	myeloma
lymphomas non-hodgkin's t-cell	adult t-cell lymphoma/leukaemia	leukemia
	adult t-cell lymphoma/leukaemia recurrent	leukemia
	adult t-cell lymphoma/leukaemia refractory	leukemia
	adult t-cell lymphoma/leukaemia stage i	leukemia
	adult t-cell lymphoma/leukaemia stage ii	leukemia
	adult t-cell lymphoma/leukaemia stage iii	leukemia
	adult t-cell lymphoma/leukaemia stage iv	leukemia
	anaplastic large cell lymphoma t- and null-cell types	lymphoma
	anaplastic large cell lymphoma t- and null-cell types recurrent	lymphoma
	anaplastic large cell lymphoma t- and null-cell types refractory	lymphoma
	anaplastic large cell lymphoma t- and null-cell types stage i	lymphoma
	anaplastic large cell lymphoma t- and null-cell types	lymphoma

HLGT	Preferred Term	Site
	stage ii	
	anaplastic large cell lymphoma t- and null-cell types stage iii	lymphoma
	anaplastic large cell lymphoma t- and null-cell types stage iv	lymphoma
	angiocentric lymphoma	lymphoma
	angiocentric lymphoma recurrent	lymphoma
	angiocentric lymphoma refractory	lymphoma
	angiocentric lymphoma stage i	lymphoma
	angiocentric lymphoma stage ii	lymphoma
	angiocentric lymphoma stage iii	lymphoma
	angiocentric lymphoma stage iv	lymphoma
	angioimmunoblastic t-cell lymphoma	lymphoma
	angioimmunoblastic t-cell lymphoma recurrent	lymphoma
	angioimmunoblastic t-cell lymphoma refractory	lymphoma
	angioimmunoblastic t-cell lymphoma stage i	lymphoma
	angioimmunoblastic t-cell lymphoma stage ii	lymphoma
	angioimmunoblastic t-cell lymphoma stage iii	lymphoma
	angioimmunoblastic t-cell lymphoma stage iv	lymphoma
	extranodal nk/t-cell lymphoma, nasal type	lymphoma
	hepatosplenic t-cell lymphoma	lymphoma
	intestinal t-cell lymphoma	lymphoma
	intestinal t-cell lymphoma recurrent	lymphoma
	intestinal t-cell lymphoma refractory	lymphoma
	intestinal t-cell lymphoma stage i	lymphoma
	intestinal t-cell lymphoma stage ii	lymphoma
	intestinal t-cell lymphoma stage iii	lymphoma
	intestinal t-cell lymphoma stage iv	lymphoma
	mycosis fungoides	lymphoma
	mycosis fungoides recurrent	lymphoma
	mycosis fungoides refractory	lymphoma
	mycosis fungoides stage i	lymphoma
	mycosis fungoides stage ii	lymphoma
	mycosis fungoides stage iii	lymphoma
	mycosis fungoides stage iv	lymphoma
	natural killer-cell lymphoblastic lymphoma	lymphoma
	peripheral t-cell lymphoma unspecified	lymphoma
	peripheral t-cell lymphoma unspecified recurrent	lymphoma
	peripheral t-cell lymphoma unspecified refractory	lymphoma
	peripheral t-cell lymphoma unspecified stage i	lymphoma
	peripheral t-cell lymphoma unspecified stage ii	lymphoma
	peripheral t-cell lymphoma unspecified stage iii	lymphoma
	peripheral t-cell lymphoma unspecified stage iv	lymphoma
	precursor t-lymphoblastic lymphoma/leukaemia	leukemia
	precursor t-lymphoblastic lymphoma/leukaemia recurrent	leukemia
	precursor t-lymphoblastic lymphoma/leukaemia refractory	leukemia

HLGT	Preferred Term	Site
	precursor t-lymphoblastic lymphoma/leukaemia stage i	leukemia
	precursor t-lymphoblastic lymphoma/leukaemia stage ii	leukemia
	precursor t-lymphoblastic lymphoma/leukaemia stage iii	leukemia
	precursor t-lymphoblastic lymphoma/leukaemia stage iv	leukemia
	t-cell lymphoma	lymphoma
	t-cell lymphoma recurrent	lymphoma
	t-cell lymphoma refractory	lymphoma
	t-cell lymphoma stage i	lymphoma
	t-cell lymphoma stage ii	lymphoma
	t-cell lymphoma stage iii	lymphoma
	t-cell lymphoma stage iv	lymphoma
	t-cell unclassifiable lymphoma high grade	lymphoma
	t-cell unclassifiable lymphoma low grade	lymphoma
lymphomas non-hodgkin's unspecified histology	immunoblastic lymphoma	lymphoma
	leukaemic lymphoma	leukemia
	non-hodgkin's lymphoma	lymphoma
	non-hodgkin's lymphoma recurrent	lymphoma
	non-hodgkin's lymphoma refractory	lymphoma
	non-hodgkin's lymphoma stage i	lymphoma
	non-hodgkin's lymphoma stage ii	lymphoma
	non-hodgkin's lymphoma stage iii	lymphoma
	non-hodgkin's lymphoma stage iv	lymphoma
	non-hodgkin's lymphoma transformed recurrent	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive recurrent	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive refractory	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive stage i	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive stage ii	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive stage iii	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive stage iv	lymphoma
	non-hodgkin's lymphoma unspecified histology indolent	lymphoma
	non-hodgkin's lymphoma unspecified histology indolent stage i	lymphoma
	non-hodgkin's lymphoma unspecified histology indolent stage ii	lymphoma
	non-hodgkin's lymphoma unspecified histology indolent stage iii	lymphoma
	non-hodgkin's lymphoma unspecified histology indolent stage iv	lymphoma
	plasmablastic lymphoma	lymphoma
mesotheliomas	mesothelioma	mesothelioma
	mesothelioma malignancy unspecified	mesothelioma
	mesothelioma malignant	mesothelioma

HLGT	Preferred Term	Site
	mesothelioma malignant advanced	mesothelioma
	mesothelioma malignant recurrent	mesothelioma
	pericardial mesothelioma malignant advanced	other
	pericardial mesothelioma malignant localised	other
	pericardial mesothelioma malignant recurrent	other
	peritoneal mesothelioma malignant	other
	peritoneal mesothelioma malignant advanced	other
	peritoneal mesothelioma malignant recurrent	other
	pleural mesothelioma	mesothelioma
	pleural mesothelioma malignant	mesothelioma
	pleural mesothelioma malignant advanced	mesothelioma
	pleural mesothelioma malignant recurrent	mesothelioma
metastases	lymphangiosis carcinomatosa	unknown
	metastases to abdominal cavity	unknown
	metastases to abdominal wall	unknown
	metastases to adrenals	unknown
	metastases to biliary tract	unknown
	metastases to bladder	unknown
	metastases to bone	unknown
	metastases to bone marrow	unknown
	metastases to breast	unknown
	metastases to central nervous system	unknown
	metastases to chest wall	unknown
	metastases to diaphragm	unknown
	metastases to eustachian tube	unknown
	metastases to eye	unknown
	metastases to fallopian tube	unknown
	metastases to gallbladder	unknown
	metastases to gastrointestinal tract	unknown
	metastases to heart	unknown
	metastases to kidney	unknown
	metastases to large intestine	unknown
	metastases to larynx	unknown
	metastases to liver	unknown
	metastases to lung	unknown
	metastases to lymph nodes	unknown
	metastases to meninges	unknown
	metastases to mouth	unknown
	metastases to muscle	unknown
	metastases to nasal sinuses	unknown
	metastases to neck	unknown
	metastases to nervous system	unknown
	metastases to oesophagus	unknown
	metastases to ovary	unknown
	metastases to pancreas	unknown
	metastases to penis	unknown
	metastases to perineum	unknown

HLGT	Preferred Term	Site
	metastases to peripheral nervous system	unknown
	metastases to peripheral vascular system	unknown
	metastases to peritoneum	unknown
	metastases to pharynx	unknown
	metastases to pituitary gland	pituitary
	metastases to placenta	unknown
	metastases to pleura	unknown
	metastases to prostate	unknown
	metastases to rectum	unknown
	metastases to reproductive organ	unknown
	metastases to retroperitoneum	unknown
	metastases to salivary gland	unknown
	metastases to skin	unknown
	metastases to small intestine	unknown
	metastases to soft tissue	unknown
	metastases to spine	unknown
	metastases to spleen	unknown
	metastases to stomach	unknown
	metastases to testicle	unknown
	metastases to the mediastinum	unknown
	metastases to the respiratory system	unknown
	metastases to thorax	unknown
	metastases to thyroid	unknown
	metastases to trachea	unknown
	metastases to urinary tract	unknown
	metastases to uterus	unknown
	metastasis	unknown
miscellaneous and site unspecified neoplasms malignant and unspecified	abdominal neoplasm	unknown
	adenocarcinoma	unknown
	adenoid cystic carcinoma	other
	angiosarcoma	sarcoma
	angiosarcoma metastatic	sarcoma
	angiosarcoma non-metastatic	sarcoma
	angiosarcoma recurrent	sarcoma
	basosquamous carcinoma	skin
	cancer in remission	unknown
	carcinoma in situ	unknown
	cardiac neoplasm malignant	other
	cardiac neoplasm unspecified	other
	cardiac teratoma	other
	cartilage neoplasm	sarcoma
	choriocarcinoma	other
	congenital teratoma	other
	ear neoplasm	skin
	ear neoplasm malignant	skin
	erythroplasia	skin
	extragonadal primary embryonal carcinoma	other

HLGT	Preferred Term	Site
	extragonadal primary germ cell cancer	germ cell
	extragonadal primary germ cell tumour mixed stage i	germ cell
	extragonadal primary germ cell tumour mixed stage ii	germ cell
	extragonadal primary germ cell tumour mixed stage iii	germ cell
	extragonadal primary malignant teratoma	other
	extragonadal primary non-seminoma	other
	extragonadal primary non-seminoma stage i	other
	extragonadal primary non-seminoma stage ii	other
	extragonadal primary non-seminoma stage iii	other
	extragonadal primary non-seminoma stage iv	other
	extragonadal primary seminoma (pure) stage i	testes
	extragonadal primary seminoma (pure) stage ii	testes
	extragonadal primary seminoma (pure) stage iii	testes
	extragonadal primary seminoma (pure) stage iv	testes
	germ cell cancer	germ cell
	gestational trophoblastic tumour	uterus
	granular cell tumour	unknown
	haemangiopericytoma	sarcoma
	head and neck cancer	head & neck
	malignant haemangiopericytoma	sarcoma
	malignant haemangiopericytoma metastatic	sarcoma
	malignant haemangiopericytoma non-metastatic	sarcoma
	malignant haemangiopericytoma recurrent	sarcoma
	malignant hydatidiform mole	uterus
	malignant melanoma of sites other than skin	melanoma
	malignant middle ear neoplasm	other
	malignant neoplasm of auricular cartilage	sarcoma
	malignant neoplasm progression	unknown
	malignant pericardial neoplasm	other
	malignant transformation	unknown
	metastatic neoplasm	unknown
	metastatic squamous cell carcinoma	squamous
	mucoepidermoid carcinoma	head & neck
	neoplasm	unknown
	neoplasm malignant	unknown
	neoplasm progression	unknown
	neoplasm recurrence	unknown
	otic cancer metastatic	other
	pelvic neoplasm	unknown
	pericardial neoplasm	other
	pseudosarcoma	esophagus
	queyrat erythroplasia	penis
	recurrent cancer	unknown
	signet-ring cell carcinoma	colon
	small cell carcinoma	unknown
	smooth muscle cell neoplasm	sarcoma
	squamous cell carcinoma	squamous

HLGT	Preferred Term	Site
	stewart-treves syndrome	sarcoma
	teratoma	unknown
	tumour invasion	unknown
	vascular neoplasm	other
	yolk sac tumour site unspecified	other
nervous system neoplasms benign	astrocytoma, low grade	brain
	brain neoplasm benign	brain
	brain stem glioma benign	brain
	craniopharyngioma benign	brain
	haemangioblastoma	brain
	meningioma benign	brain
	oligodendroglioma benign	brain
	spinal meningioma benign	brain
nervous system neoplasms malignant and unspecified nec	aesthesioneuroblastoma	head & neck
	anaplastic astrocytoma	brain
	astrocytoma	brain
	astrocytoma malignant	brain
	brain cancer metastatic	unknown
	brain neoplasm	brain
	brain neoplasm malignant	brain
	brain stem glioma	brain
	brain teratoma	brain
	carotid body tumour	other
	central nervous system dermoid tumour	brain
	central nervous system leukaemia	leukemia
	central nervous system neoplasm	brain
	cerebellar tumour	brain
	cerebral neuroblastoma	brain
	choroid plexus carcinoma	other
	cns germinoma	brain
	ependymoma	brain
	ependymoma malignant	brain
	ganglioneuroblastoma	other
	glioblastoma	brain
	glioblastoma multiforme	brain
	glioma	brain
	gliomatosis cerebri	brain
	glioneuronal tumour	other
	gliosarcoma	sarcoma
	haemangiopericytoma of meninges	sarcoma
	intracranial meningioma malignant	melanoma
	malignant cranial nerve neoplasm	brain
	malignant glioma	brain
	malignant neoplasm of spinal cord	brain
	malignant nervous system neoplasm	other
	malignant oligodendroglioma	brain
	medulloblastoma	brain

HLGT	Preferred Term	Site
	medulloblastoma recurrent	brain
	melanomatous meningitis	melanoma
	meningeal neoplasm	brain
	meningioma	brain
	meningioma malignant	brain
	metastatic glioma	brain
	mixed astrocytoma-ependymoma	brain
	mixed oligo-astrocytoma	brain
	neonatal neuroblastoma	other
	nervous system neoplasm	other
	neurilemmoma	other
	neurilemmoma malignant	lung
	neuroblastoma	other
	neuroblastoma recurrent	other
	neuroectodermal neoplasm	other
	nongerminomatous germ cell tumour of the cns	brain
	non-secretory adenoma of pituitary	pituitary
	oligodendroglioma	brain
	optic nerve glioma	eye
	peripheral nervous system neoplasm	other
	pineal germinoma	brain
	pineal neoplasm	brain
	pineal parenchymal neoplasm malignant	brain
	pinealoblastoma	brain
	pinealoma	brain
	pineocytoma	brain
	primitive neuroectodermal tumour	other
	secretory adenoma of pituitary	pituitary
	spinal cord neoplasm	unknown
	spinal meningioma malignant	brain
ocular neoplasms	carcinoma in situ of eye	eye
	choroid melanoma	melanoma
	choroid neoplasm	other
	conjunctival melanoma	melanoma
	conjunctival neoplasm	eye
	conjunctival primary acquired melanosis	eye
	extraocular retinoblastoma	eye
	eyelid tumour	skin
	intraocular melanoma	melanoma
	intraocular retinoblastoma	eye
	iris neoplasm	eye
	iritic melanoma	melanoma
	lacrimal duct neoplasm	eye
	malignant melanoma of eyelid	melanoma
	malignant neoplasm of choroid	eye
	malignant neoplasm of conjunctiva	eye
	malignant neoplasm of cornea	eye

HLGT	Preferred Term	Site
	malignant neoplasm of eye	eye
	malignant neoplasm of eyelid	skin
	malignant neoplasm of lacrimal duct	eye
	malignant neoplasm of lacrimal gland	eye
	malignant neoplasm of orbit	eye
	malignant neoplasm of retina	eye
	metastatic ocular melanoma	melanoma
	neoplasm of cornea unspecified malignancy	eye
	neoplasm of orbit	eye
	ocular cancer metastatic	eye
	ocular haemangiopericytoma	eye
	ocular neoplasm	eye
	optic nerve neoplasm	eye
	optic tract glioma	eye
	retinal melanoma	melanoma
	retinal neoplasm	eye
	retinoblastoma	eye
	retinoblastoma bilateral	eye
	retinoblastoma unilateral	eye
	retro-orbital neoplasm	eye
plasma cell neoplasms	gammopathy	myeloma
	heavy chain disease	myeloma
	leukaemia plasmacytic	leukemia
	leukaemia plasmacytic (in remission)	leukemia
	light chain disease	myeloma
	multiple myeloma	myeloma
	myeloma recurrence	myeloma
	paraproteinaemia	myeloma
	plasmacytoma	myeloma
renal and urinary tract neoplasms malignant and unspecified	bladder adenocarcinoma recurrent	bladder
	bladder adenocarcinoma stage 0	bladder
	bladder adenocarcinoma stage i	bladder
	bladder adenocarcinoma stage ii	bladder
	bladder adenocarcinoma stage iii	bladder
	bladder adenocarcinoma stage iv	bladder
	bladder adenocarcinoma stage unspecified	bladder
	bladder cancer	bladder
	bladder cancer recurrent	bladder
	bladder cancer stage 0, with cancer in situ	bladder
	bladder cancer stage 0, without cancer in situ	bladder
	bladder cancer stage i, with cancer in situ	bladder
	bladder cancer stage i, without cancer in situ	bladder
	bladder cancer stage ii	bladder
	bladder cancer stage iii	bladder
	bladder cancer stage iv	bladder
	bladder neoplasm	bladder
	bladder squamous cell carcinoma recurrent	bladder

HLGT	Preferred Term	Site
	bladder squamous cell carcinoma stage 0	bladder
	bladder squamous cell carcinoma stage i	bladder
	bladder squamous cell carcinoma stage ii	bladder
	bladder squamous cell carcinoma stage iii	bladder
	bladder squamous cell carcinoma stage iv	bladder
	bladder squamous cell carcinoma stage unspecified	bladder
	bladder transitional cell carcinoma	bladder
	bladder transitional cell carcinoma recurrent	bladder
	bladder transitional cell carcinoma stage 0	bladder
	bladder transitional cell carcinoma stage i	bladder
	bladder transitional cell carcinoma stage ii	bladder
	bladder transitional cell carcinoma stage iii	bladder
	bladder transitional cell carcinoma stage iv	bladder
	carcinoma in situ of bladder	bladder
	clear cell sarcoma of the kidney	sarcoma
	hereditary leiomyomatosis renal cell carcinoma	kidney
	hereditary papillary renal carcinoma	kidney
	malignant neoplasm of paraurethral glands	bladder
	malignant neoplasm of renal pelvis	kidney
	malignant urinary tract neoplasm	bladder
	metastatic carcinoma of the bladder	bladder
	metastatic renal cell carcinoma	kidney
	nephroblastoma	kidney
	non-renal cell carcinoma of kidney	kidney
	renal cancer	kidney
	renal cancer metastatic	kidney
	renal cancer recurrent	kidney
	renal cancer stage i	kidney
	renal cancer stage ii	kidney
	renal cancer stage iii	kidney
	renal cancer stage iv	kidney
	renal cell carcinoma	kidney
	renal cell carcinoma recurrent	kidney
	renal cell carcinoma stage i	kidney
	renal cell carcinoma stage ii	kidney
	renal cell carcinoma stage iii	kidney
	renal cell carcinoma stage iv	kidney
	renal neoplasm	kidney
	rhabdoid tumour of the kidney	kidney
	transitional cell cancer of renal pelvis and ureter metastatic	bladder
	transitional cell cancer of the renal pelvis and ureter	bladder
	transitional cell cancer of the renal pelvis and ureter localised	bladder
	transitional cell cancer of the renal pelvis and ureter recurrent	bladder
	transitional cell cancer of the renal pelvis and ureter regional	bladder

HLGT	Preferred Term	Site
	transitional cell carcinoma	bladder
	ureteral neoplasm	bladder
	ureteric cancer	bladder
	ureteric cancer local	bladder
	ureteric cancer metastatic	bladder
	ureteric cancer recurrent	bladder
	ureteric cancer regional	bladder
	urethral cancer	bladder
	urethral cancer local	bladder
	urethral cancer metastatic	bladder
	urethral cancer recurrent	bladder
	urethral cancer regional	bladder
	urethral neoplasm	bladder
	urinary tract carcinoma in situ	bladder
	urinary tract neoplasm	bladder
reproductive and genitourinary neoplasms gender unspecified nec	buschke-lowenstein's tumour	other
	genitourinary tract neoplasm	unknown
reproductive neoplasms female malignant and unspecified	adenocarcinoma of the cervix	cervix
	adenosquamous carcinoma of the cervix	cervix
	borderline ovarian tumour	ovary
	cervix cancer metastatic	cervix
	cervix carcinoma	cervix
	cervix carcinoma recurrent	cervix
	cervix carcinoma stage 0	cervix
	cervix carcinoma stage i	cervix
	cervix carcinoma stage ii	cervix
	cervix carcinoma stage iii	cervix
	cervix carcinoma stage iv	cervix
	cervix neoplasm	cervix
	clear cell endometrial carcinoma	uterus
	endometrial cancer	uterus
	endometrial cancer metastatic	uterus
	endometrial cancer recurrent	uterus
	endometrial cancer stage 0	uterus
	endometrial cancer stage i	uterus
	endometrial cancer stage ii	uterus
	endometrial cancer stage iii	uterus
	endometrial cancer stage iv	uterus
	endometrial neoplasm	uterus
	endometrial sarcoma	uterus
	endometrial sarcoma metastatic	uterus
	endometrial sarcoma recurrent	uterus
	erythroplasia of vulva	skin
	fallopian tube cancer	ovary
	fallopian tube cancer metastatic	uterus

HLGT	Preferred Term	Site
	fallopian tube cancer stage i	uterus
	fallopian tube cancer stage ii	uterus
	fallopian tube cancer stage iii	uterus
	fallopian tube cancer stage iv	uterus
	fallopian tube neoplasm	uterus
	female reproductive neoplasm	unknown
	female reproductive tract carcinoma in situ	unknown
	genital neoplasm malignant female	unknown
	malignant neoplasm of placenta	uterus
	malignant neoplasm of uterine adnexa	ovary
	malignant ovarian cyst	ovary
	metastatic uterine cancer	uterus
	mucinous endometrial carcinoma	uterus
	mueller's mixed tumour	uterus
	ovarian cancer	ovary
	ovarian cancer metastatic	ovary
	ovarian cancer recurrent	ovary
	ovarian dysgerminoma stage i	ovary
	ovarian dysgerminoma stage ii	ovary
	ovarian dysgerminoma stage iii	ovary
	ovarian dysgerminoma stage iv	ovary
	ovarian dysgerminoma stage unspecified	ovary
	ovarian embryonal carcinoma	ovary
	ovarian epithelial cancer	ovary
	ovarian epithelial cancer metastatic	ovary
	ovarian epithelial cancer recurrent	ovary
	ovarian epithelial cancer stage i	ovary
	ovarian epithelial cancer stage ii	ovary
	ovarian epithelial cancer stage iii	ovary
	ovarian epithelial cancer stage iv	ovary
	ovarian germ cell cancer	ovary
	ovarian germ cell cancer stage i	ovary
	ovarian germ cell cancer stage ii	ovary
	ovarian germ cell cancer stage iii	ovary
	ovarian germ cell cancer stage iv	ovary
	ovarian germ cell choriocarcinoma stage i	ovary
	ovarian germ cell choriocarcinoma stage ii	ovary
	ovarian germ cell choriocarcinoma stage iii	ovary
	ovarian germ cell choriocarcinoma stage iv	ovary
	ovarian germ cell embryonal carcinoma stage i	ovary
	ovarian germ cell embryonal carcinoma stage ii	ovary
	ovarian germ cell embryonal carcinoma stage iii	ovary
	ovarian germ cell embryonal carcinoma stage iv	ovary
	ovarian germ cell endodermal sinus tumour stage i	ovary
	ovarian germ cell endodermal sinus tumour stage ii	ovary
	ovarian germ cell endodermal sinus tumour stage iii	ovary
	ovarian germ cell endodermal sinus tumour stage iv	ovary

HLGT	Preferred Term	Site
	ovarian germ cell polyembryoma stage i	ovary
	ovarian germ cell polyembryoma stage ii	ovary
	ovarian germ cell polyembryoma stage iii	ovary
	ovarian germ cell polyembryoma stage iv	ovary
	ovarian germ cell teratoma stage i	ovary
	ovarian germ cell teratoma stage ii	ovary
	ovarian germ cell teratoma stage iii	ovary
	ovarian germ cell teratoma stage iv	ovary
	ovarian granulosa-theca cell tumour	ovary
	ovarian low malignant potential tumour	ovary
	ovarian neoplasm	ovary
	ovarian stromal cancer	ovary
	paget's disease of the vulva	skin
	papillary serous endometrial carcinoma	uterus
	placental neoplasm	other
	small cell carcinoma of the cervix	cervix
	squamous cell carcinoma of the cervix	cervix
	squamous endometrial carcinoma	uterus
	uterine cancer	uterus
	uterine carcinoma in situ	uterus
	uterine neoplasm	uterus
	vaginal cancer	vagina
	vaginal cancer metastatic	vagina
	vaginal cancer recurrent	vagina
	vaginal cancer stage 0	vagina
	vaginal cancer stage i	vagina
	vaginal cancer stage ii	vagina
	vaginal cancer stage iii	vagina
	vaginal cancer stage iva	vagina
	vaginal cancer stage ivb	vagina
	vaginal neoplasm	vagina
	vulval cancer	vulva
	vulval cancer metastatic	vulva
	vulval cancer recurrent	vulva
	vulval cancer stage 0	vulva
	vulval cancer stage i	vulva
	vulval cancer stage ii	vulva
	vulval cancer stage iii	vulva
	vulval cancer stage iv	vulva
	vulval neoplasm	vulva
reproductive neoplasms male malignant and unspecified	carcinoma in situ of penis	penis
	erythroplasia of penis	skin
	genital neoplasm malignant male	prostate
	male reproductive tract carcinoma in situ	prostate
	male reproductive tract neoplasm	prostate
	malignant neoplasm of epididymis	testes
	malignant neoplasm of seminal vesicle	testes

HLGT	Preferred Term	Site
	malignant neoplasm of spermatic cord	testes
	neoplasm prostate	prostate
	paget's disease of penis	penis
	penile malignant neoplasm	penis
	penile neoplasm	penis
	penis carcinoma	penis
	penis carcinoma metastatic	penis
	penis carcinoma recurrent	penis
	penis carcinoma stage i	penis
	penis carcinoma stage ii	penis
	penis carcinoma stage iii	penis
	penis carcinoma stage iv	penis
	prostate cancer	prostate
	prostate cancer metastatic	prostate
	prostate cancer recurrent	prostate
	prostate cancer stage 0	prostate
	prostate cancer stage i	prostate
	prostate cancer stage ii	prostate
	prostate cancer stage iii	prostate
	prostate cancer stage iv	prostate
	scrotal cancer	skin
	seminoma	testes
	teratoma of testis	testes
	testicular cancer metastatic	testes
	testicular choriocarcinoma	testes
	testicular choriocarcinoma stage i	testes
	testicular choriocarcinoma stage ii	testes
	testicular choriocarcinoma stage iii	testes
	testicular embryonal carcinoma	testes
	testicular embryonal carcinoma stage i	testes
	testicular embryonal carcinoma stage ii	testes
	testicular embryonal carcinoma stage iii	testes
	testicular germ cell cancer	testes
	testicular germ cell cancer metastatic	testes
	testicular germ cell tumour mixed stage i	testes
	testicular germ cell tumour mixed stage ii	testes
	testicular germ cell tumour mixed stage iii	testes
	testicular malignant teratoma stage i	testes
	testicular malignant teratoma stage ii	testes
	testicular malignant teratoma stage iii	testes
	testicular neoplasm	testes
	testicular seminoma (pure)	testes
	testicular seminoma (pure) stage i	testes
	testicular seminoma (pure) stage ii	testes
	testicular seminoma (pure) stage iii	testes
	testicular yolk sac tumour stage i	testes
	testicular yolk sac tumour stage ii	testes

HLGT	Preferred Term	Site
	testicular yolk sac tumour stage iii	testes
	testis cancer	testes
respiratory and mediastinal neoplasms malignant and unspecified	adenosquamous cell lung cancer	lung
	adenosquamous cell lung cancer recurrent	lung
	adenosquamous cell lung cancer stage 0	lung
	adenosquamous cell lung cancer stage i	lung
	adenosquamous cell lung cancer stage ii	lung
	adenosquamous cell lung cancer stage iii	lung
	adenosquamous cell lung cancer stage iv	lung
	bronchial carcinoma	lung
	bronchial neoplasm	lung
	bronchioloalveolar carcinoma	lung
	carcinoma in situ of trachea	lung
	diaphragm neoplasm	other
	epiglottic carcinoma	head & neck
	glottis carcinoma	head & neck
	hypopharyngeal cancer	head & neck
	hypopharyngeal cancer recurrent	head & neck
	hypopharyngeal cancer stage 0	head & neck
	hypopharyngeal cancer stage i	head & neck
	hypopharyngeal cancer stage ii	head & neck
	hypopharyngeal cancer stage iii	head & neck
	hypopharyngeal cancer stage iv	head & neck
	hypopharyngeal neoplasm	head & neck
	large cell carcinoma of the respiratory tract stage unspecified	lung
	large cell lung cancer recurrent	lung
	large cell lung cancer stage 0	lung
	large cell lung cancer stage i	lung
	large cell lung cancer stage ii	lung
	large cell lung cancer stage iii	lung
	large cell lung cancer stage iv	lung
	laryngeal cancer	head & neck
	laryngeal cancer recurrent	head & neck
	laryngeal cancer stage 0	head & neck
	laryngeal cancer stage i	head & neck
	laryngeal cancer stage ii	head & neck
	laryngeal cancer stage iii	head & neck
	laryngeal cancer stage iv	head & neck
	laryngeal neoplasm	head & neck
	lung adenocarcinoma	lung
	lung adenocarcinoma metastatic	lung
	lung adenocarcinoma recurrent	lung
	lung adenocarcinoma stage 0	lung
	lung adenocarcinoma stage i	lung
	lung adenocarcinoma stage ii	lung
	lung adenocarcinoma stage iii	lung

HLGT	Preferred Term	Site
	lung adenocarcinoma stage iv	lung
	lung cancer metastatic	lung
	lung carcinoma cell type unspecified recurrent	lung
	lung carcinoma cell type unspecified stage 0	lung
	lung carcinoma cell type unspecified stage i	lung
	lung carcinoma cell type unspecified stage ii	lung
	lung carcinoma cell type unspecified stage iii	lung
	lung carcinoma cell type unspecified stage iv	lung
	lung infiltration malignant	unknown
	lung neoplasm	lung
	lung neoplasm malignant	lung
	lung squamous cell carcinoma recurrent	lung
	lung squamous cell carcinoma stage 0	lung
	lung squamous cell carcinoma stage i	lung
	lung squamous cell carcinoma stage ii	lung
	lung squamous cell carcinoma stage iii	lung
	lung squamous cell carcinoma stage iv	lung
	lung squamous cell carcinoma stage unspecified	lung
	malignant mediastinal neoplasm	lung
	malignant neoplasm of pleura	mesothelioma
	malignant neoplasm of thorax	unknown
	malignant respiratory tract neoplasm	lung
	maxillofacial sinus neoplasm	head & neck
	mediastinum neoplasm	lung
	metastatic bronchial carcinoma	lung
	nasal cavity cancer	head & neck
	nasal neoplasm	head & neck
	nasal sinus cancer	head & neck
	nasopharyngeal cancer	head & neck
	nasopharyngeal cancer recurrent	head & neck
	nasopharyngeal cancer stage 0	head & neck
	nasopharyngeal cancer stage i	head & neck
	nasopharyngeal cancer stage ii	head & neck
	nasopharyngeal cancer stage iii	head & neck
	nasopharyngeal cancer stage iv	head & neck
	neoplasm of thymus	other
	non-small cell lung cancer	lung
	non-small cell lung cancer metastatic	lung
	non-small cell lung cancer recurrent	lung
	non-small cell lung cancer stage 0	lung
	non-small cell lung cancer stage i	lung
	non-small cell lung cancer stage ii	lung
	non-small cell lung cancer stage iii	lung
	non-small cell lung cancer stage iiia	lung
	non-small cell lung cancer stage iiib	lung
	non-small cell lung cancer stage iv	lung
	oropharyngeal cancer recurrent	head & neck

HLGT	Preferred Term	Site
	oropharyngeal cancer stage 0	head & neck
	oropharyngeal cancer stage i	head & neck
	oropharyngeal cancer stage ii	head & neck
	oropharyngeal cancer stage iii	head & neck
	oropharyngeal cancer stage iv	head & neck
	oropharyngeal cancer stage unspecified	head & neck
	pancoast's tumour	lung
	paranasal sinus and nasal cavity malignant neoplasm	head & neck
	paranasal sinus and nasal cavity malignant neoplasm recurrent	head & neck
	paranasal sinus and nasal cavity malignant neoplasm stage 0	head & neck
	paranasal sinus and nasal cavity malignant neoplasm stage i	head & neck
	paranasal sinus and nasal cavity malignant neoplasm stage ii	head & neck
	paranasal sinus and nasal cavity malignant neoplasm stage iii	head & neck
	paranasal sinus and nasal cavity malignant neoplasm stage iv	head & neck
	paranasal sinus neoplasm	head & neck
	pharyngeal cancer metastatic	head & neck
	pharyngeal cancer recurrent	head & neck
	pharyngeal cancer stage 0	head & neck
	pharyngeal cancer stage i	head & neck
	pharyngeal cancer stage ii	head & neck
	pharyngeal cancer stage iii	head & neck
	pharyngeal cancer stage iv	head & neck
	pharyngeal cancer stage unspecified	head & neck
	pharyngeal neoplasm	head & neck
	pleura carcinoma	other
	pleural neoplasm	other
	pleural sarcoma	sarcoma
	postcricoid cancer	head & neck
	respiratory tract carcinoma in situ	lung
	respiratory tract neoplasm	lung
	sinus cancer metastatic	head & neck
	small cell lung cancer extensive stage	lung
	small cell lung cancer limited stage	lung
	small cell lung cancer metastatic	lung
	small cell lung cancer recurrent	lung
	small cell lung cancer stage unspecified	lung
	throat cancer	head & neck
	thymic cancer metastatic	other
	thymoma	other
	thymoma malignant	other
	thymoma malignant recurrent	other

HLGT	Preferred Term	Site
	tonsil cancer	head & neck
	tonsillar neoplasm	head & neck
	tracheal cancer	lung
	tracheal neoplasm	lung
	vocal cord neoplasm	head & neck
skeletal neoplasms malignant and unspecified	bone cancer metastatic	unknown
	bone giant cell tumour	sarcoma
	bone neoplasm	sarcoma
	bone neoplasm malignant	unknown
	bone sarcoma	sarcoma
	chondrosarcoma	sarcoma
	chondrosarcoma metastatic	sarcoma
	chondrosarcoma recurrent	sarcoma
	chordoma	brain
	ewing's sarcoma	sarcoma
	ewing's sarcoma metastatic	sarcoma
	ewing's sarcoma recurrent	sarcoma
	giant cell tumour of tendon sheath	sarcoma
	osteosarcoma localised	sarcoma
	osteosarcoma metastatic	sarcoma
	osteosarcoma recurrent	sarcoma
	peripheral neuroepithelioma of bone	other
	peripheral neuroepithelioma of bone metastatic	other
	peripheral neuroepithelioma of bone recurrent	other
skin neoplasms malignant and unspecified	acral lentiginous melanoma stage i	melanoma
	acral lentiginous melanoma stage ii	melanoma
	acral lentiginous melanoma stage iii	melanoma
	acral lentiginous melanoma stage iv	melanoma
	acral lentiginous melanoma stage unspecified	melanoma
	atypical fibroxanthoma	skin
	basal cell carcinoma	skin
	basosquamous carcinoma of skin	skin
	bowen's disease	skin
	carcinoma in situ of skin	skin
	dysplastic naevus syndrome	skin
	extramammary paget's disease	skin
	lentigo maligna recurrent	melanoma
	lentigo maligna stage i	melanoma
	lentigo maligna stage ii	melanoma
	lentigo maligna stage iii	melanoma
	lentigo maligna stage iv	melanoma
	lentigo maligna stage unspecified	melanoma
	malignant melanoma	melanoma
	malignant melanoma in situ	melanoma
	malignant melanoma stage i	melanoma
	malignant melanoma stage ii	melanoma
	malignant melanoma stage iii	melanoma

HLGT	Preferred Term	Site
	malignant melanoma stage iv	melanoma
	mastocytoma	skin
	melanoma recurrent	melanoma
	metastatic malignant melanoma	melanoma
	neoplasm skin	skin
	neuroendocrine carcinoma of the skin	skin
	paget's disease of skin	skin
	porocarcinoma	other
	skin cancer	skin
	skin cancer metastatic	skin
	skin neoplasm bleeding	skin
	squamous cell carcinoma of skin	skin
	superficial spreading melanoma stage i	melanoma
	superficial spreading melanoma stage ii	melanoma
	superficial spreading melanoma stage iii	melanoma
	superficial spreading melanoma stage iv	melanoma
	superficial spreading melanoma stage unspecified	melanoma
soft tissue neoplasms malignant and unspecified (excl sarcomas)	amyloidoma	unknown
	inflammatory myofibroblastic tumour	unknown
	malignant fibrous histiocytoma	sarcoma
	malignant fibrous histiocytoma metastatic	sarcoma
	malignant fibrous histiocytoma non-metastatic	sarcoma
	malignant fibrous histiocytoma recurrent	sarcoma
	malignant soft tissue neoplasm	sarcoma
	peripheral neuroepithelioma	other
	peripheral neuroepithelioma of soft tissue	other
	tendon neoplasm	sarcoma
soft tissue sarcomas	alveolar soft part sarcoma	sarcoma
	alveolar soft part sarcoma metastatic	sarcoma
	alveolar soft part sarcoma non-metastatic	sarcoma
	alveolar soft part sarcoma recurrent	sarcoma
	congenital fibrosarcoma	sarcoma
	dermatofibrosarcoma	sarcoma
	epithelioid sarcoma	sarcoma
	epithelioid sarcoma metastatic	sarcoma
	epithelioid sarcoma non-metastatic	sarcoma
	epithelioid sarcoma recurrent	sarcoma
	extra-osseous ewing's sarcoma	sarcoma
	extra-osseous ewing's sarcoma metastatic	sarcoma
	extra-osseous ewing's sarcoma nonmetastatic	sarcoma
	extra-osseous ewing's sarcoma recurrent	sarcoma
	extraskeletal chondrosarcoma	sarcoma
	extraskeletal chondrosarcoma metastatic	sarcoma
	extraskeletal chondrosarcoma non-metastatic	sarcoma
	extraskeletal chondrosarcoma recurrent	sarcoma
	extraskeletal osteosarcoma	sarcoma
	extraskeletal osteosarcoma metastatic	sarcoma

HLGT	Preferred Term	Site
	extraskeletal osteosarcoma non-metastatic	sarcoma
	extraskeletal osteosarcoma recurrent	sarcoma
	fibrosarcoma	sarcoma
	fibrosarcoma metastatic	sarcoma
	fibrosarcoma non-metastatic	sarcoma
	kaposi's sarcoma	sarcoma
	kaposi's sarcoma aids related	sarcoma
	kaposi's sarcoma classical type	sarcoma
	leiomyosarcoma	sarcoma
	leiomyosarcoma metastatic	sarcoma
	leiomyosarcoma non-metastatic	sarcoma
	leiomyosarcoma recurrent	sarcoma
	liposarcoma	sarcoma
	liposarcoma metastatic	sarcoma
	liposarcoma non-metastatic	sarcoma
	liposarcoma recurrent	sarcoma
	lymphangiosarcoma	sarcoma
	malignant mesenchymoma	other
	malignant mesenchymoma metastatic	other
	malignant mesenchymoma non-metastatic	other
	malignant mesenchymoma recurrent	other
	malignant muscle neoplasm	sarcoma
	neurofibrosarcoma	sarcoma
	neurofibrosarcoma metastatic	sarcoma
	neurofibrosarcoma non-metastatic	sarcoma
	neurofibrosarcoma recurrent	sarcoma
	rhabdomyosarcoma	sarcoma
	rhabdomyosarcoma recurrent	sarcoma
	sarcoma	sarcoma
	sarcoma metastatic	sarcoma
	sarcoma of skin	sarcoma
	sarcoma uterus	uterus
	sarcomatosis	sarcoma
	small intestine leiomyosarcoma	sarcoma
	spindle cell sarcoma	sarcoma
	synovial sarcoma	sarcoma
	synovial sarcoma metastatic	sarcoma
	synovial sarcoma non-metastatic	sarcoma
	synovial sarcoma recurrent	sarcoma
	testicular leiomyosarcoma	sarcoma
	undifferentiated sarcoma	sarcoma
	urinary bladder sarcoma	sarcoma
	uterine leiomyosarcoma	uterus

Attachment: Comments on Plan

From: Stockbridge, Norman L
Sent: Monday, August 20, 2012 6:04 AM
To: Marciniak, Thomas
Cc: Southworth, Mary Ross; Temple, Robert; Unger, Ellis
Subject: FW: Emailing: ARB ca review plan v1p2.doc

Attachments: ARB ca review plan v1p2.doc

I am replying by forwarding, so some other interested parties have a chance to comment on your proposed patient-level meta-analysis plan if they choose.

For my part, I think you did well in anticipating my major concerns--blinding, multiplicity, what studies to include, what to lump or split, and how the results might influence regulatory decision-making. We aren't likely to agree about how exactly those issues are handled, but I think you did well by addressing each.

As I noted in an email on Aug 4, I do not consider this 90-person-day effort to be worthwhile given the results of the subject-level meta-analysis, so, despite your assertions to the contrary (email of Aug 10), this project is not part of your assigned work. If nonetheless, it obtains findings you think would be of interest, I am sure all of us will be open to reviewing its results.

I assume that, pending completion of your meta-analysis project, there is nothing further you wish to include in reviews of ARB-cancer TSI. We will proceed with steps to close it.
Regards,
Norman

-----Original Message-----
From: Marciniak, Thomas
Sent: Sunday, August 19, 2012 2:31 PM
To: Stockbridge, Norman L
Subject: Emailing: ARB ca review plan v1p2.doc

I've attached an updated plan. Note that it now includes a revision history (at the end of the text following the Reference.) I'll file it after you return from leave pending your final comments.

Tom

-----Original Message-----
From: Marciniak, Thomas
Sent: Friday, August 03, 2012 4:13 PM
To: Stockbridge, Norman L
Subject: Emailing: ARB ca review plan v1p0.doc

Attachments: ARB ca review plan v1p0.doc

There is still much work to do on the stats side of the analysis plan, but I believe the cancer ascertainment plans are most critical and there is plenty to comment uon.

Tom

From: Marciniak, Thomas
Sent: Friday, August 31, 2012 3:08 PM
To: Unger, Ellis
Cc: Southworth, Mary Ross; Temple, Robert; Stockbridge, Norman L
Subject: RE: Emailing: ARB ca review plan v1p2.doc

To address Ellis' comments:

o First, this would represent a lot of man-hours, so I have to assume that there is a paucity of work in the Division at this point, or that you will be doing this mostly after hours.

You are faced with a serious, unanswered question of whether drugs taken by millions of Americans increase cancer rates and you're concerned about 62 to 93 man-days for my entire plan and half of that for trials for which we currently have data? You have already wasted more effort than that on your ill-conceived and poorly executed TSI meta-analysis. Whether or not there is a paucity of work in the Division at this point may be one of your concerns; mine is protecting the public health particularly regarding those drugs for which I have primary responsibility.

O Second, when we get into writing analytic plans, and specifically plans for adjudicating clinical endpoints, the plan/protocol might need to be reviewed at a high level – i.e., the OND IO or higher. There is a MAPP on this, I believe. You should consult that MAPP before you start any work to see if it applies here. If it applies, the protocol will need to go up to for review and comment before you begin.

Your second email indicates that the MAPP is not applicable. I have submitted my plan for comments, but please note the limitations regarding higher level review that I describe in my response to your last comment.

O Third, if you were to go ahead with this and find a RR of, say 1.3, I doubt there would be much enthusiasm for basing a regulatory decision (labeling or otherwise) on that. People would have various opinions on where the meaningful threshold is, but it might be worth asking for some input before you start.

How do you know what the RR is until you do an adequate study? And astonishingly, you would ignore a 30% increase in cancer rates for any drug, much less drugs for which there are many alternatives? I believe that we must inform patients and providers if there is any risk and that they, not you, should make the decisions. Furthermore, even if the population RR is 1.3 we should expect that risks in subgroups will vary and that some have substantially higher risks than 30% or special concerns. For lung cancer interaction with smoking is always a concern. Prostate cancer is only a problem for males.

O Finally, given you familiarity with some of the trial data, any decision YOU make regarding inclusion and exclusion of trials can be called into question after the fact. It

doesn't matter that your criteria are reasonable and defensible, because you can know the effect that your criteria will have on the trials to be included/excluded before you begin.

Anyone can always call analyses in question after the fact, but that is precisely why I submitted my plan prospectively. You also appear to be making your usual prejudicial assumptions: First, all of us have a familiarity with some of the trial data but I am the only one who appears to believe that the "trial data" we have is questionable—why else would I be insisting upon analyses from the raw data? So, I don't know the trial results and I don't know the inclusion and exclusion criteria for the trials. Second, you are implying that I have manipulated the inclusion and exclusion criteria to achieve some prejudicial result or goal. My only goal is to answer as best possible the question of whether ARBs affect cancer rates. I have no commitment to a positive or negative answer to that question as you do (see my final comments below.) It is always dismaying that, when you wish to disagree with a reviewer, you accuse them of biases while you readily accept sponsor assertions—despite sponsors literally having billions of dollars of incentives to bias the results.

Finally, you have issued a final FDA Drug Safety Communication declaring unequivocally that "treatment with an ARB medication does not increase the risk of cancer." You have based this unequivocal statement on the substantially flawed TSI meta-analysis. So the "YOU" that has a problem with credibility currently is a plural you: You and everybody else in the management chain from Dr. Southworth through Dr. Hamburg. Your emails and meeting discussions have the appearance of discouraging me from pursuing a legitimate safety concern while my efforts reveal facts that reflect poorly upon your performance. I suggest that it is more appropriate for you to encourage my efforts in the interest of public health.

Tom

-----Original Message-----
From: Unger, Ellis
Sent: Tuesday, August 21, 2012 2:41 PM
To: Marciniak, Thomas
Cc: Southworth, Mary Ross; Temple, Robert; Stockbridge, Norman L
Subject: RE: Emailing: ARB ca review plan v1p2.doc

Here's a link to the MAPP.

http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM229716.pdf

It turns out that the MAPP covers new NDAs and BLAs, and so is not really applicable here. It's a good thing to keep in mind, however.

Ellis

-----Original Message-----
From: Unger, Ellis
Sent: Monday, August 20, 2012 11:04 PM
To: Marciniak, Thomas
Cc: Southworth, Mary Ross; Temple, Robert; Stockbridge, Norman L
Subject: RE: Emailing: ARB ca review plan v1p2.doc

Tom, et al,

I've gone through the protocol only fairly quickly, but I have a few comments.

First, this would represent a lot of man-hours, so I have to assume that there is a paucity of work in the Division at this point, or that you will be doing this mostly after hours.

Second, when we get into writing analytic plans, and specifically plans for adjudicating clinical endpoints, the plan/protocol might need to be reviewed at a high level – i.e., the OND IO or higher. There is a MAPP on this, I believe. You should consult that MAPP before you start any work to see if it applies here. If it applies, the protocol will need to go up to for review and comment before you begin.

Third, if you were to go ahead with this and find a RR of, say 1.3, I doubt there would be much enthusiasm for basing a regulatory decision (labeling or otherwise) on that. People would have various opinions on where the meaningful threshold is, but it might be worth asking for some input before you start.

Finally, given you familiarity with some of the trial data, any decision YOU make regarding inclusion and exclusion of trials can be called into question after the fact. It doesn't matter that your criteria are reasonable and defensible, because you can know the effect that your criteria will have on the trials to be included/excluded before you begin.

Ellis

-----Original Message-----
From: Stockbridge, Norman L
Sent: Monday, August 20, 2012 6:04 AM
To: Marciniak, Thomas
Cc: Southworth, Mary Ross; Temple, Robert; Unger, Ellis
Subject: FW: Emailing: ARB ca review plan v1p2.doc

I am replying by forwarding, so some other interested parties have a chance to comment on your proposed patient-level meta-analysis plan if they choose.

For my part, I think you did well in anticipating my major concerns--blinding, multiplicity, what studies to include, what to lump or split, and how the results might

influence regulatory decision-making. We aren't likely to agree about how exactly those issues are handled, but I think you did well by addressing each.

As I noted in an email on Aug 4, I do not consider this 90-person-day effort to be worthwhile given the results of the subject-level meta-analysis, so, despite your assertions to the contrary (email of Aug 10), this project is not part of your assigned work. If nonetheless, it obtains findings you think would be of interest, I am sure all of us will be open to reviewing its results.

I assume that, pending completion of your meta-analysis project, there is nothing further you wish to include in reviews of ARB-cancer TSI. We will proceed with steps to close it.
Regards,
Norman

-----Original Message-----
From: Marciniak, Thomas
Sent: Sunday, August 19, 2012 2:31 PM
To: Stockbridge, Norman L
Subject: Emailing: ARB ca review plan v1p2.doc

I've attached an updated plan. Note that it now includes a revision history (at the end of the text following the Reference.) I'll file it after you return from leave pending your final comments.

Tom

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

/s/

THOMAS A MARCINIAK
08/31/2012
Original version 1.0 submitted to Dr. Stockbridge on August 3, 2012.

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

/s/

THOMAS A MARCINIAK
07/24/2014

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

/s/

THOMAS A MARCINIAK
12/12/2014

CLINICAL REVIEW

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

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

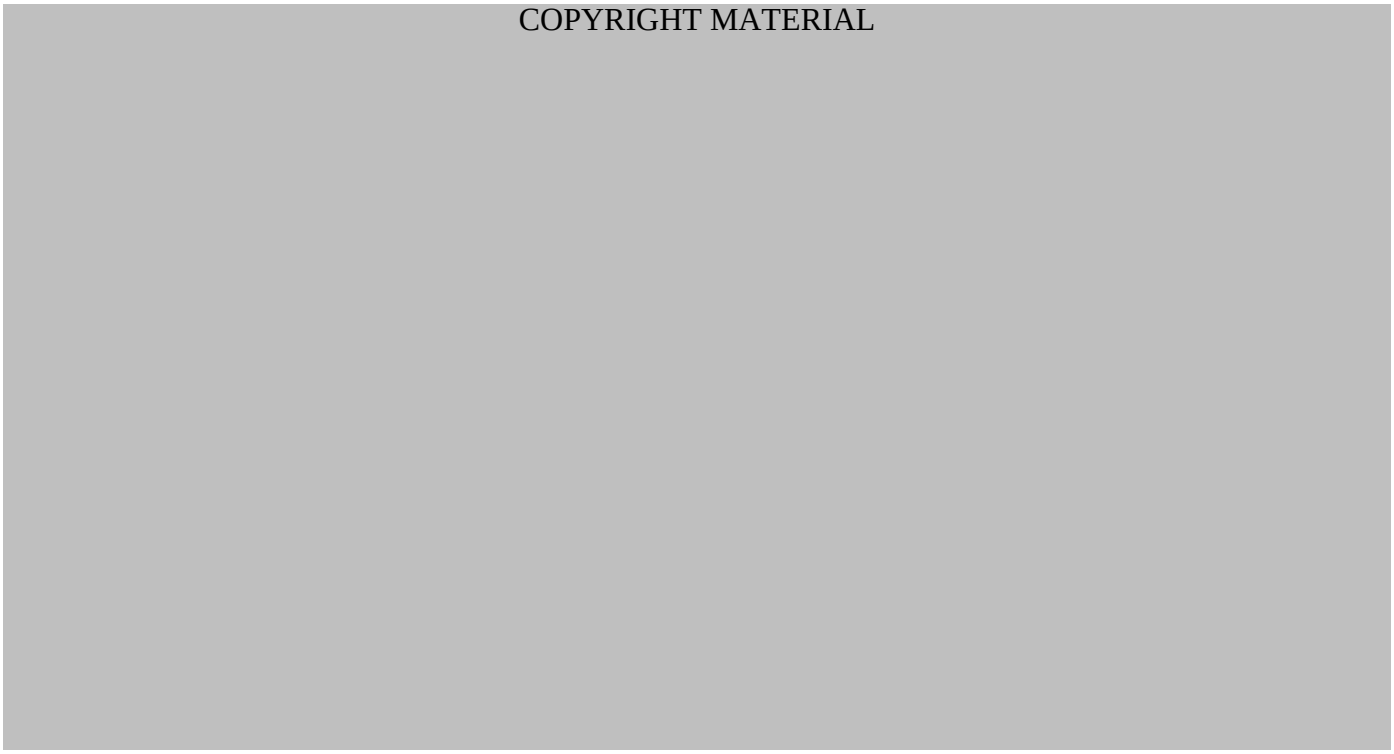
After considering the overall trial data, subgroup analyses and exposure-outcomes relationships in the context of 3 other approved novel oral anticoagulants (NOACs) the primary clinical reviewers are currently recommending approval of edoxaban 60 mg QD in patients with NVAF, with a limitation of use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

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

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

[1] "Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) study group". Lancet 1993;342:1255-62.
[2] "2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC2006 Guidelines for the Management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines". Circulation 2011; 123:e269-e367.

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



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

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

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

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

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

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

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

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

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

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

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

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

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

The results of the primary safety analysis showed that both edoxaban groups were superior to warfarin for modified International Society on Thrombosis and Hemostasis (ISTH) major bleeding[3] [HR: 0.47 (0.41-0.55), 0.80 (0.71-0.91) for edoxaban 30 mg (15 mg DA) and 60 mg (30 mg DA), respectively]. The superiority of bleeding results in the edoxaban groups was robust across other major bleeding categories including intracranial hemorrhage (ICH), life threatening bleeds and fatal bleeds. However, edoxaban 60 mg (30 mg DA) increased the risk of major GI bleeding compared with warfarin (HR: 1.24, 95% CI: 1.02-1.50).

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

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

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

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

[3] Modified ISTH major bleeding used in ENGAGE AF: fatal bleeding, bleeding in a critical organ or any bleed leading to transfusion-adjusted drops in hemoglobin level of ≥ 2.0 g/dl (1 unit of packed RBC = 1 g/dl drop in hemoglobin). See Appendix 7 for overview of all bleeding category definitions in ENGAGE AF.
[4] "Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices," 60 Federal Register 147 (1 August 1995) pp.39180-39181.

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

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

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

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

E30/15 DA= Edoxaban 30 mg/ 15 mg Dose Adjustment
E60/ 30 DA= Edoxaban 60 mg/ 30 mg Dose Adjustment
Disabling Stroke is ModifiedRankin Score 3-5 (moderate to severely disabling and not fatal)
Dataset: ADJEFFCA.xpt, BASEGP.xpt; HRs calculated using modeling with Dose Adjustment, yes or no, CHADS2≤3=0, or >3=1. (More details of this analysis are shown in Table 40, Table 42, Table 43, Table 45, and Table 46).
Reviewer's Table

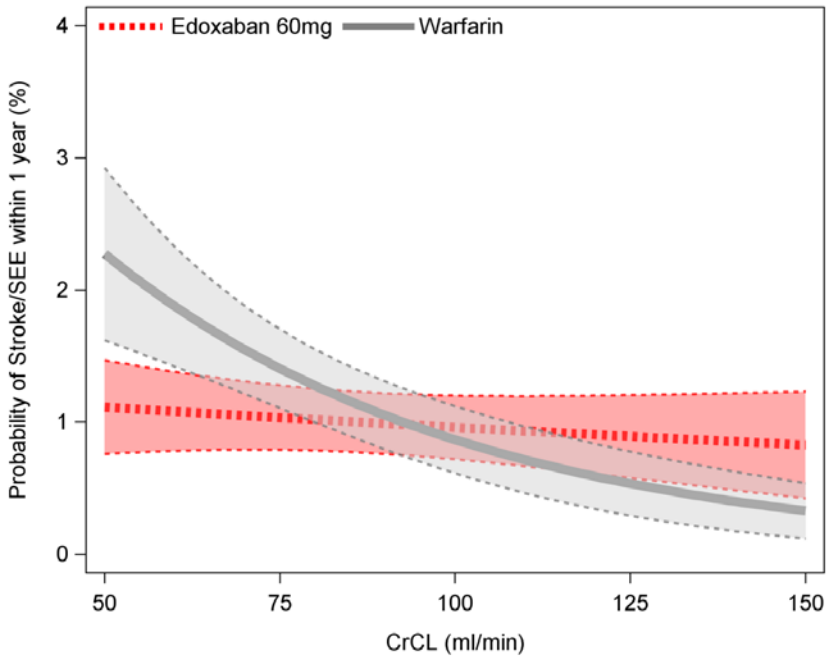
Table 2: Primary Efficacy Endpoint: Stroke/SEE by quintile of CrCL (mITT population, on treatment)

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

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

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

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



CrCL in mL/min	Model prediction (95% CI)
50	0.48 (0.33-0.70)
65	0.62 (0.47-0.82)
80	0.80 (0.62-1.01)
95	1.02 (0.76-1.38)
110	1.31 (0.87-1.97)
125	1.69 (0.98-2.89)

The risk of first Stroke/SEE was modeled as a function of history of stroke, $CHADS_2$ score, CrCL, treatment, and CrCL*treatment using a Cox proportional hazard model among subjects with no dose adjustment. Reviewer's Analysis, Datasets: ADJEFFCA, BASEGP and DM.

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

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

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

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

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

1) Issue a complete response (CR). A CR is reasonable because edoxaban failed to show consistency of efficacy across renal function subgroups with efficacy in the normal renal function subgroup, a substantial segment of the affected population, appearing to be inferior to warfarin. In the CR we would ask the applicant to perform another trial as a condition for approval in the normal renal function subgroup, preferably with a higher dose. This option is problematic because another trial would be resource intensive and hence, there is some probability that the trial would never be conducted. Edoxaban seems to have promise as an alternative to other anticoagulant therapies in most patients and it would be unfortunate to risk losing it as a therapeutic option.

2) Approve edoxaban only in the subpopulation of patients with abnormal renal function. The problem with this option is that the only way to be reasonably confident that this limitation of use would work as intended would be to implement a Risk Evaluation and Mitigation Strategy (REMS) with an ETASU (element to assure safe use, such as a restricted distribution system that incorporates a mandatory pre-use determination of creatinine clearance). Such a REMS would have a negative impact on use of the drug by making it difficult to prescribe. Also, it would be difficult to fashion an ETASU REMS for the atrial fibrillation indication if edoxaban is approved for treatment of deep vein thrombosis at a 60 mg dose without a REMS. A REMS with only a Medication Guide and communication plan for the NVAF

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

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

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

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

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

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

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

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

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

1.2 Risk Benefit Assessment

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

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

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

Table 3 Benefit-Risk Assessment by CrCL

			Benefit				Risk				
			Efficacy (Ischemic Stroke/SEE)				Safety (Life Threatening Bleed†)				
		N	Edoxaban 60 mg (%/pt-yr)	Warfarin (%/pt-yr)	Delta†† (%/pt-yr)	HR	Edoxaban 60 mg (%/pt-yr)	Warfarin (%/pt-yr)	Delta†† (%/pt-yr)	HR	ΔΔ†† (%/pt-yr)
All		14024	0.9	1.0	-0.1	0.92	0.6	1.1	-0.5	0.53	-0.6
CrCL	30 to <50.6	2704	1.3	1.3	-0.1	0.95*	0.7	1.6	-0.9	0.45	-1.0
(ml/min)	>50.6 - ≤ 63.6	2737	0.9	1.6	-0.7	0.57	0.5	1.4	-0.9	0.37	-1.5
	>63.6 - ≤ 77.9	2823	0.7	1.0	-0.3	0.68	0.7	1.1	-0.4	0.63	-0.7
	>77.9 - ≤ 98.1	2751	0.9	0.8	0.1	1.14	0.6	0.9	-0.3	0.67	-0.2
	>98.1	2791	0.9	0.5	0.5	2.00	0.3	0.5	-0.2	0.68	0.3

†Definition of life threatening bleeds (=GUSTO Severe bleeds): ICH or bleeds causing hemodynamic compromise requiring treatment, including fatal bleeds
†† A negative value indicates an absolute risk reduction (%/patient-years) of endpoint in the edoxaban group compared to warfarin.
ΔΔ (the net clinical benefit) was assessed based on equal weight of the efficacy and safety endpoint.
%/patient year = # events per 100 patient years.
*Note that the HR relative to warfarin is higher in subjects with CrCL of 30-50.6 mL/min than in subjects with CrCL 50.6 -77.9 mL/min. Most of the subjects in the first quintile (CrCL of 30-50.6 mL/min) were dose adjusted (reduced) and that dose reduction is now thought to have been excessive and probably accounted for the relatively higher HR. Further discussion in Section 6.1.8.3. Reviewer's table.

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

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

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

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

1. The reviewers are concerned that extrapolating bleeding outcomes solely on the basis of systemic edoxaban exposures may underestimate GI bleeding risk. Some have speculated that the increased risk of GI bleeds seen with the NOACs may be in part due to high concentrations of active drug in the GI tract. Whereas there was less bleeding with edoxaban than warfarin, there was more GI bleeding. All the models performed by the clinical pharmacology reviewers were assessed based on systemic edoxaban exposure. If local exposure indeed plays a significant role in the probability of developing GI bleeds, the impact of edoxaban 90 mg on the risk of major GI bleeds cannot be assessed adequately and could be underestimated.

2. Another problem with incurring more major bleeds is that cessation of drug is required which inevitably increases risk of consequent stroke. Additionally, patients and physicians may become less willing to reinitiate indicated anticoagulant therapy.

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

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

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

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

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

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

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

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

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

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

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

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

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

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1.4 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.5 Recommendations for Postmarket Requirements and Commitments

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

2 Introduction and Regulatory Background

2.1 Product Information

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

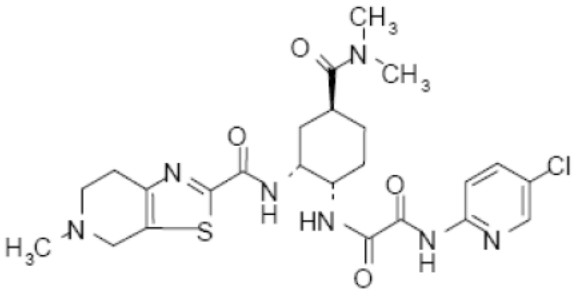
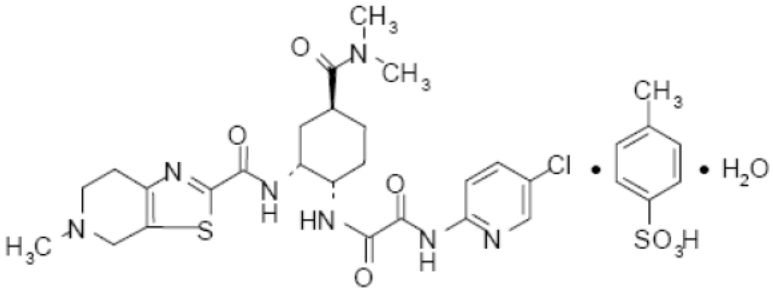
Edoxaban is the pharmacologically active moiety of this anticoagulant. It is the anhydrous free base with a molecular mass of 548.06. The drug substance is the monohydrate tosylate salt of edoxaban, which has a molecular mass of 738.27. The tosylate monohydrate salt was selected for formulation because of its favorable physicochemical properties, solubility, non-hygroscopicity and stability. Edoxaban is formulated as an immediate release tablet for oral administration. The solubility of edoxaban tosylate is pH-dependent, with high solubility in acidic conditions (4.4 mg/mL at pH 3.0) and very low solubility above pH 6.0 (0.14 mg/mL at pH 7.0).

The phase 3 clinical trial formulations of edoxaban were 15 mg and 30 mg immediate release, round-shaped, film-coated, unscored, debossed tablets. The proposed 15 mg and 30 mg commercial formulations are identical to the respective clinical trial formulations with the exception of colors. Tablet strength is expressed as the amount of edoxaban, the free base of the drug substance, edoxaban tosylate. Also, the proposed commercial formulations of edoxaban 15mg, 30mg and 60mg tablets are manufactured (b) (4)

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

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

Table 6: Edoxaban Product Information

Attribute	Description
Non-proprietary Name	Edoxaban
USAN	Edoxaban (as anhydrous salt free form) Edoxaban Tosylate (as anhydrous form)
Chemical Name	*N*-(5-chloropyridin-2-yl)-*N'*-[(1*S*,2*R*,4*S*)-4-(*N*,*N*dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-*c*]pyridine-2-carboxamido)cyclohexyl]oxamide
Structural Formula of Edoxaban	
Structural Formula of Edoxaban Tosylate Monohydrate (ETM)	
Molecular Formula of ETM	$C_{24}H_{30}ClN_7O_4S.C_7H_8O_3S.H_2O$
Molecular Weight	548.06 Daltons as edoxaban anhydrous free form (738.27 for edoxaban tosylate)
Stereochemistry	(b) (4)
Excipients	No novel excipients: Carnauba wax, mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, mannitol, magnesium stearate, talk, (b) (4) and commonly used coating agents (titanium dioxide, yellow ferric oxide, and red ferric oxide)
Solubility of ETM	pH dependent; slightly soluble in water, pH 3, 4 and 5 buffer; very slightly soluble in pH 6 and 7 and practically insoluble in pH 8 and 9.
Dosage Forms	15, 30 and 60 mg film-coated, immediate release, round shape, de-bossed oral tablets. Each 60 mg tablet contains 80.8 mg edoxaban tosylate equivalent to 60 mg of edoxaban. Each 30 mg tablet contains 40.4 mg edoxaban tosylate equivalent to 30 mg of edoxaban. Each 15 tablet contains 20.2 mg edoxaban tosylate equivalent to 15 mg of edoxaban. Each strength is differentiated by color and debossing.

ETM: Edoxaban Tosylate Monohydrate. Reviewer's Table.

2.2 Tables of Currently Available Treatments for Proposed Indications

2.2.1 Overview of Atrial Fibrillation (AF) and Stroke

AF is a common supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. An estimated 2.5 million Americans have the condition. Incidence of AF increases with age and approximately 8% of the population over 80 years of age have AF. Subjects with AF are at increased risk for stroke (~5% per year) and SEE, especially those with medium to high risk as determined by the risk assessment scheme, the $CHADS_2$ score[7]. The $CHADS_2$ score considers and weighs the following risk factors: congestive heart failure, hypertension, age > 75 years, diabetes mellitus (1 point each) and previous stroke or transient ischemic attack (2 points). Current American Heart Association (AHA) guidelines for subjects with documented AF recommend that life-long anticoagulant therapy for preventing stroke and systemic embolic events may be initiated when the $CHADS_2$ score is 1 (1 moderate risk factor which include age ≥ 75 years, hypertension , heart failure, LV EF ≤35% or diabetes mellitus) but aspirin 81 to 325 mg daily is also acceptable. However, when there are 2 moderate risk factors or 1 high-risk factor (previous stroke, TIA or embolism, mitral stenosis or prosthetic heart valve), vitamin K antagonists (warfarin almost exclusively in the U.S.) or a novel oral anticoagulant (NOAC) is recommended. [8,9]

2.2.2 Current Available Treatments

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

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7 $CHADS_2$ is an acronym for **C**ongestive heart failure, **H**ypertension, **A**ge > 75 years, **D**iabetes mellitus, and prior history of **S**troke or TIA.

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

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

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

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

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

trial focused on secondary prevention among patients who had survived nondisabling stroke or cerebral TIA.[14] Meta-analysis according to the principle of intention to treat showed that adjusted-dose oral anticoagulation is highly efficacious for prevention of all stroke (both ischemic and hemorrhagic), with a risk reduction of 61% (95% CI 47% to 71%) versus placebo[15] (Figure 3). A separate meta-analysis done at the FDA which combined the same 6 studies using a random effects model gave similar results [risk reduction of 64% (95% CI 47% to 75%)][16]. The limitation of these analyses to assess benefit/ risk is that the duration of follow-up in the clinical trials was generally between 1 and 2 years; whereas in clinical practice, the need for antithrombotic therapy in patients with AF typically extends over much longer periods. The recent warfarin-controlled trials of novel anticoagulants in patients with NVAF have shown no notable increase in thrombosis after approximately two and a half years of treatment in either the warfarin or experimental treatment arms. Efficacy after 2 ½ years of treatment is not known.

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

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

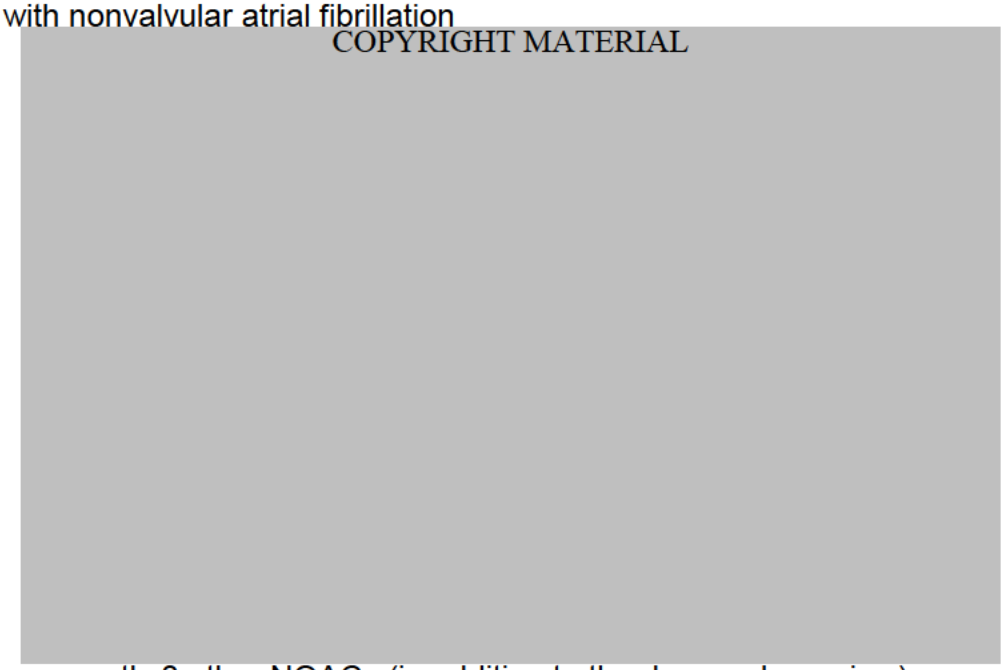
14 Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet. 1993; 342: 1255–62.

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

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

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

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



There are currently 3 other NOACs (in addition to the drug under review) now available in the U.S. for prevention of stroke and systemic embolism; dabigatran (a direct thrombin inhibitor), rivaroxaban and apixaban (also Factor Xa inhibitors). Table 7 summaries the trial design and main efficacy/safety results for each NOAC. Both dabigatran150 mg and apixaban were shown in their pivotal trials to be superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (SEE) [HR was 0.66 (95% CI: 0.53-0.82, $p < 0.003$) and 0.79 (95% CI: 0.66-0.95, $p = 0.01$), respectively]. Rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint but superiority to warfarin was not demonstrated. Dabigatran 150 mg is the only NOAC demonstrated to decrease risk of ischemic stroke compared to warfarin.

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

Table 7: Other Novel Anticoagulants approved for atrial fibrillation

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

(%/ y)= number of events per 100 patient years
SP=safety population (randomized patients who took at least one dose of study drug)
ITP=Intended treatment period
Dabi=dabigatran, Riva=rivaroxaban, Apix = apixaban, tx=treatment
A= Major Bleed definition: (ISTH definition) Satisfying at least one: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood or packed cells; symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding) or fatal bleeding

[1] p <.0001 for non-inferiority and p <.003 for superiority
[2] p <.0001 for non-inferiority and p = 0.3 for superiority
[3] p < 0.001 for non-inferiority and p = 0.12 for superiority
[4] p < 0.001 for non-inferiority and p = 0.01 for superiority
[5]Ischemic stroke without hemorrhage
Reviewer's Table

2.3 Availability of Proposed Active Ingredient in the United States

Edoxaban is not marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

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

Ximelagatran, an oral thrombin inhibitor, was associated with serious drug induced liver injury (DILD) and was not approved in the US. Liver abnormalities are discussed in the safety review in Section 7.3.5.1.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Date	Regulatory Activity
May 14, 2007	Submission of IND 77,254
August 13, 2008	EOP2 meeting: • FDA agreed that the target indication (to reduce the risk of stroke and SEE in patients with atrial fibrillation) "is potentially supportable with the proposed study, because the historical trials used to estimate the treatment effect of warfarin had a composite of stroke and SEE as their primary endpoints." • The sponsor agreed that there would be a 60% cap on warfarin-experienced patients. • FDA stated, "A single study may be sufficient if the results are compelling".
October 15, 2008	SPA agreement with responses guiding the sponsor on various aspects of the protocol: 1. Advised that use of the $CHADS_2$ score for eligibility could result in a different study population than historical trials and in so doing, make the constancy assumption with the comparator invalid 2. Advised that the superiority testing should be at a total type I error rate of 0.01 or less 3. There were originally three expected dose groups but one was expected to be terminated possibly prior to study completion. FDA suggested that if one is terminated, the remaining regimens should be tested at the alpha/3 significance level. 4. Agreed to count events in the mITT that occurred during treatment and during the 3 days after any dose interruption for the primary analysis. 5. A randomization encryption code was requested at time of NDA study submission. 6. We asked for a detailed justification of the proposed doses and dosing regimen which the sponsor stated was based on the phase 2 trial (PRT-018).
May 8, 2009	Submission of analysis of phase 2 study PRT-018 for dose justification.

Date	Regulatory Activity
December 11, 2009	Revised SAP: • Instead of 3 edoxaban groups (low exposure, high exposure and 30 mg allocated), the statistical testing was changed to the high (60 mg with 30 mg dose adjustment for prespecified criteria[18]) and low (30 mg with 15 mg dose adjustment for the same prespecified criteria) exposure groups with the 30 mg allocated group to be analyzed in a prespecified exploratory analysis. • Changed superiority testing (as FDA recommended) so that only the high exposure group (ITT/ overall treatment period) would be tested and would be successful with a p value of ≤ 0.01 [for primary and the ordered secondary endpoints; (1) stroke/SEE/All-cause mortality and (2) MACE]. The FDA statistics team agreed with the changes. • The sponsor was advised that crossover rate (percentage of discontinued edoxaban patients switching to warfarin) needs to be reported and if not small may have serious implications on interpretability of NI results.
January 31, 2011	A statistical analysis plan (SAP) was submitted to the Division with subsequent concurrence returned to the Sponsor on 3/16/2011. The following major agreements were established: • Comparison of each edoxaban treatment group (High Dose, Low Dose) versus warfarin will be performed at α = 0.05/2 for non-inferiority. • Information on how many randomized subjects (ITT set) did not receive at least one dose of the study drug (mITT set) will be reported in the clinical study report. • Superiority testing will be performed only for the High Exposure group with α=0.01 (using the ITT population and the overall treatment period). • The non-inferiority (NI) margin will be performed at 1.38. • A modified Intent-To-Treat (mITT) population will be used for non-inferiority analyses for the primary efficacy endpoints and an Intent-To-Treat (ITT) population will be used for the subsequent superiority analyses.

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

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

Reviewer's Table

2.6 Other Relevant Background Information

2.6.1 Foreign Approval

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

2.6.2 Other U.S. Activity

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

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

Table 8: Adjudication data discrepancies between databases and documentations

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

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

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

3.2 Compliance with Good Clinical Practices

3.2.1 Ethical Conduct of the Study

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

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

3.2.2 Subject Information and Consent

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

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

3.2.3 Medical/Scientific/ Clinical Trial Oversight

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

Table 9: Organizational Structure of ENGAGE AF

Organization	Responsibilities
TIMI Study Group	Responsible for medical/scientific oversight, medical monitoring, services, and medical support for the study sites and contract research organization (CRO) monitors. The Clinical Events Committee (CEC), which was a subgroup of the TIMI Study Group, reviewed and adjudicated key efficacy and safety endpoint events (all deaths, suspected strokes/transient ischemic attacks, suspected systemic embolic events, suspected myocardial infarctions, overt bleeding events that required medical attention, and cases of pre-defined hepatic dysfunction/liver enzyme elevation) in a blinded manner. The CEC coordinator received packages from Clinical Event Validation and Adjudication (CEVA) department (see Quintiles, below) and facilitated transfer of packages to the CEC.[1]
TIMI HOTLINE	24/7 medical support for sites
Quintiles, the contract research organization (CRO)	Responsible for the conduct of the study including site management and monitoring, data management, statistical analysis of the data, and pharmacovigilance. The internal committee called the Clinical Event Validation and Adjudication (CEVA) department was responsible for compiling and sending completed efficacy/ safety endpoint packages to the TIMI CEC coordinator. Responsibilities included collecting all relevant documentation, preparing an English document and masking any identifying information that might lead to unblinding of the CEC members.[1]
Quintiles Central Laboratory (Q-Lab)	Provided the laboratory test supplies
(b) (4)	Supplied encrypted POC devices for INR testing and trained the sites on how to use the POC device.
(b) (4)	Developed and maintained the Interactive Web/Voice Response System (IXRS) that served as the central randomization center for this study. Sites obtained their INR results through the IXRS to maintain warfarin blinding. (b) (4) was also responsible for the labeling, packaging, storage, and distribution of clinical supplies to sites.

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

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

3.2.4 Major Protocol Deviations

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

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

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

Table 10: Major Protocol Deviations

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

DA=Dose Adjusted; h/o IC bleed= history of intracranial bleed; AF/flut=atrial fibrillation/ flutter
[a]: Subjects in the ITT Analysis Set with critical protocol violations directly affecting the evaluation of the primary endpoint are excluded from the Per Protocol Analysis Set.
[b]: Subjects violated critical entry criteria include those who did not have documentation of atrial f brillation or atrial flutter at baseline or during study participation, or who had history of intracranial bleeding.
[c]: Subjects received wrong study drug include those who received incorrect study drug other than the randomized treatment for more than 104 consecutive days at any time during the study, or for the entire duration of the study participation if duration was 104 days or less.
[d]: Subjects received disallowed concomitant medications include those who received an oral or parenteral anticoagulant at a therapeutic dose, concomitantly with study drug for more than 30 consecutive days.
Note: Subjects could be counted in multiple categories.
Source: ENGAGE AF CSR, p. 105

3.2.5 Site-specific issues

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

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

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

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

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

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

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

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

3.3 Financial Disclosures

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

Table 12: Financial Disclosures

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

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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

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

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

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

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

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

4.2 Clinical Microbiology

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

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

4.3 Preclinical Pharmacology/Toxicology

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

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

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

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

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

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

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

4.4 Clinical Pharmacology

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

4.4.1 Mechanism of Action

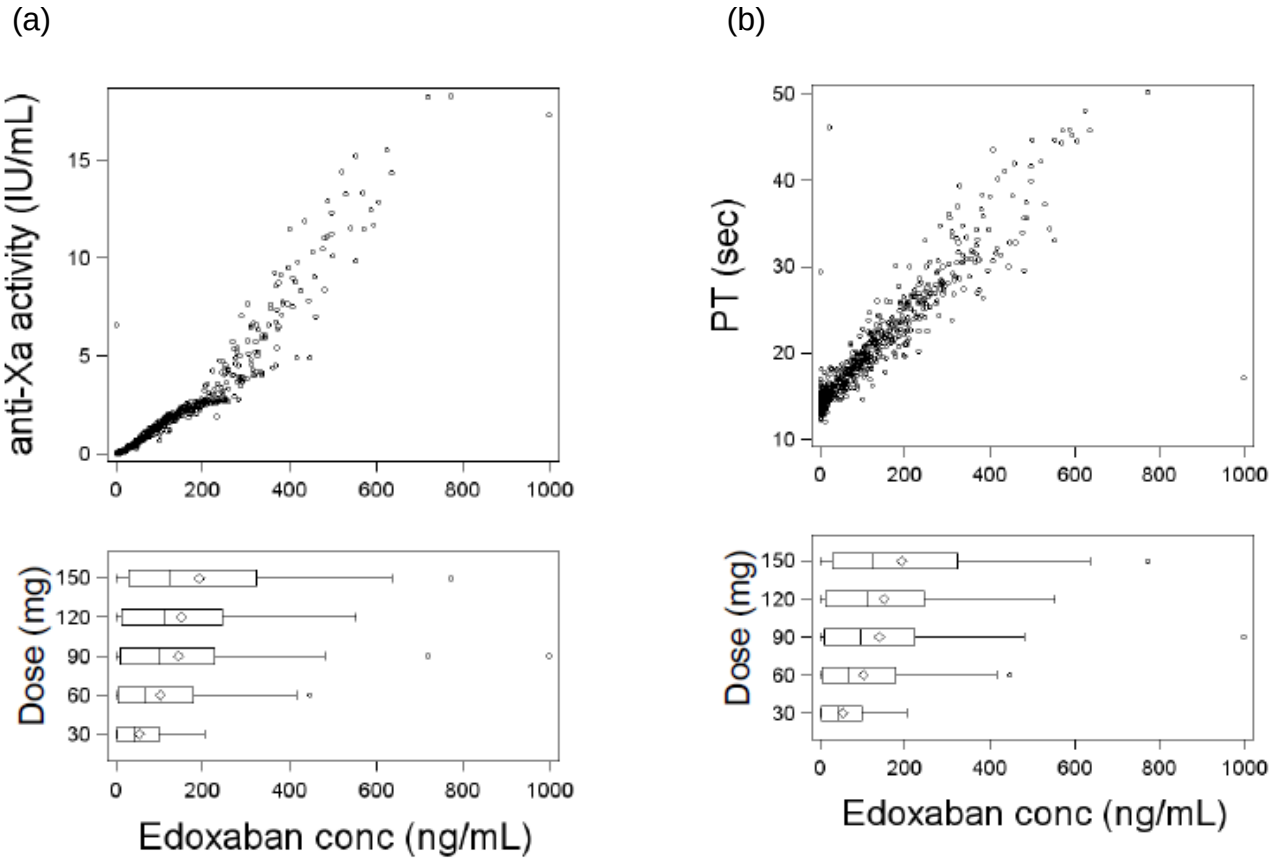
Edoxaban is a highly selective, direct and reversible inhibitor of factor Xa (FXa), the serine protease located in the final common pathway of the coagulation cascade. Edoxaban inhibits free FXa, and prothrombinase activity. Inhibition of FXa in the coagulation cascade reduces thrombin generation and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

4.4.2 Pharmacodynamics

Single oral doses of edoxaban from 10 mg to 150 mg result in rapid (within 1-2 hours) increase in anti-FXa activity and rapid prolongation of PT and aPTT. For all dose levels, the maximum activity is observed between 1 to 3 hours post-dose which corresponds with peak edoxaban concentrations (Cmax). Recovery to pre-dose values is dose-dependent with return to baseline by 24 to 36 hours post-dose in all subjects.
For once daily dosing, multiple-dose administration of edoxaban results in similar peak activity for PT, aPTT and anti-FXa activity on Day 10 as on Day 1. A direct linear correlation was observed between plasma concentrations and aPTT, PT, and anti-FXa activity, suggesting that single doses up to 150 mg (maximum dose administered) do not achieve maximum response. In summary, a concentration dependent effect of edoxaban was observed on all pharmacodynamic markers measured in the edoxaban development program. Figure 4 shows the relationship between plasma edoxaban concentration and anti-FXa/PT.

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

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



Source: Clinical Pharmacology Review

4.4.3 Pharmacokinetics

4.4.3.1 PK parameters

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

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

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

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

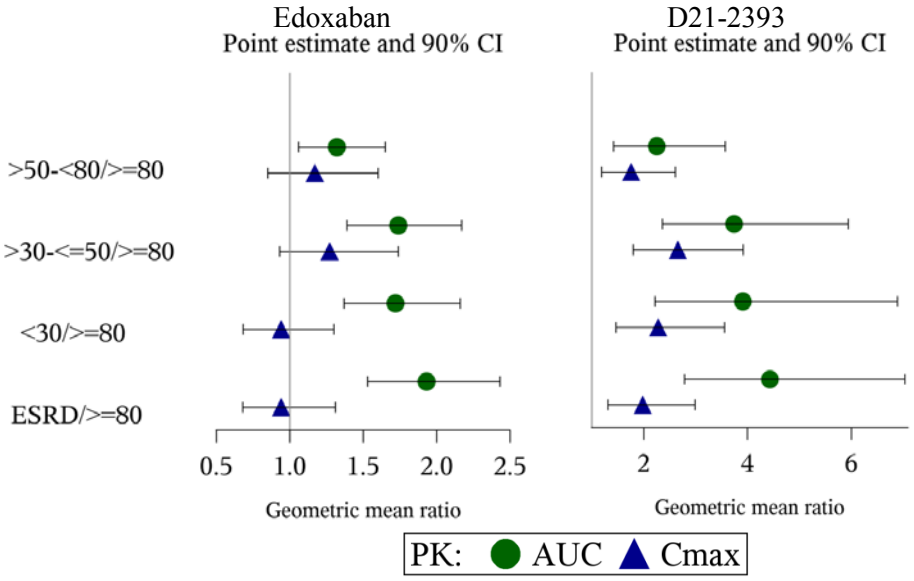
4.4.3.2 Intrinsic factors

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

Renal function

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

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



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

Hepatic function

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

Weight

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

Genetics

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

4.4.3.3 Extrinsic factors

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

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

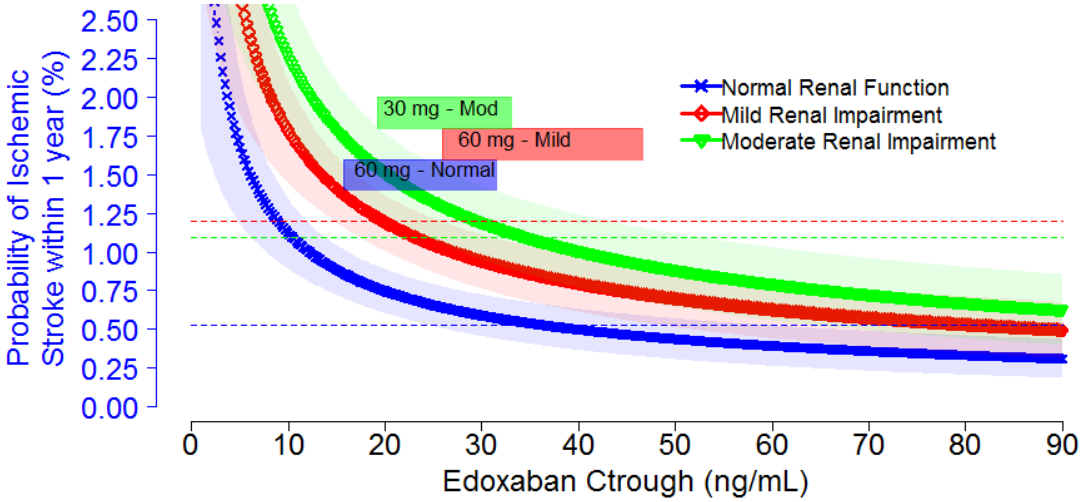
4.4.3.4 Exposure-Response Modeling

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

Exposure-Response Relationships for Efficacy

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

Figure 6 Exposure-Response for Ischemic Stroke by Renal Function



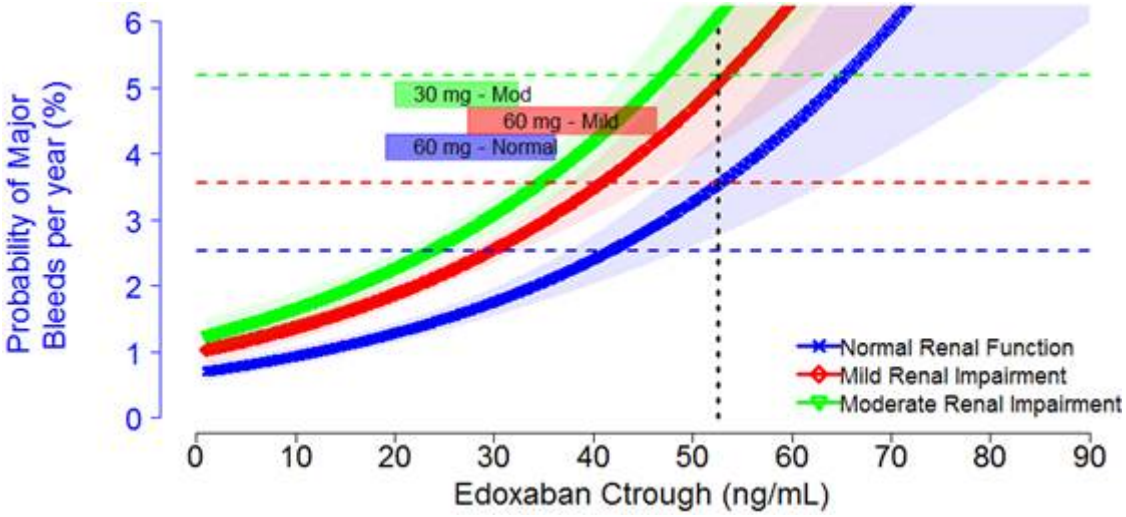
Source: Clinical Pharmacology Review
Predicted 1 year probability of ischemic stroke and 95% CI for a typical patient are shown for normal renal function (blue line), mild renal impairment (red line) and moderate renal impairment (green line). Horizontal bands indicate the exposure range (5th to 95th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

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

Exposure-Response Relationships for Safety

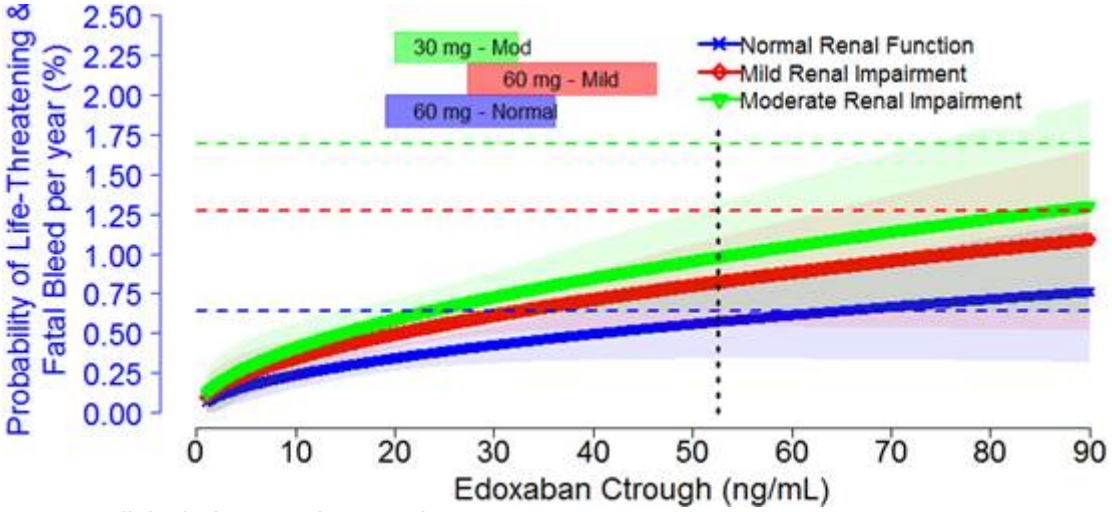
The exposure-response relationship for bleeding events clearly illustrates that the risk of bleeding increases with edoxaban exposure (Figure 7 and Figure 8). The edoxaban exposures at the studied doses produce rates of bleeding that are similar or less than those for warfarin in each respective renal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

Figure 7 Exposure-Response for Major Bleeds by Renal Function



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

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

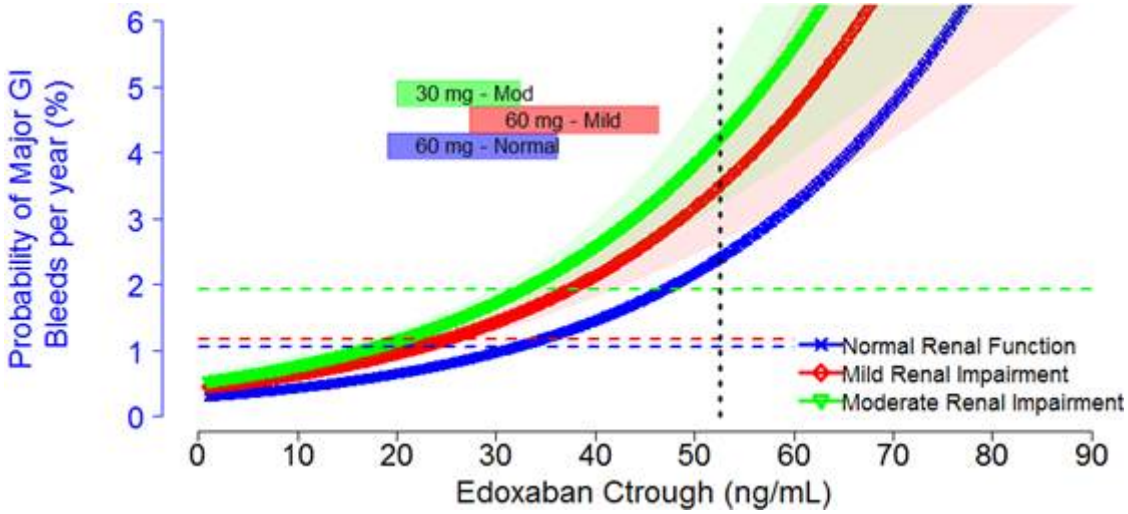


Source: Clinical Pharmacology Review
Predicted 1 year probability of life threatening & fatal bleeds and 95% CI for a typical patient are shown for normal renal function (blue line), mild renal impairment (red line) and moderate renal impairment (green line). Horizontal bands indicate the exposure range (5^{th} to 95^{th} percentile) for edoxaban in each renal function group. Horizontal dashed reference lines indicate the observed rate of life threatening &fatal bleeds for the warfarin group for the corresponding color coded renal function groups
Definition of life-threatening/fatal bleeds: ICH and bleeds causing hemodynamic compromise requiring treatment (=GUSTO severe bleeding which includes fatal bleeds)

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

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

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



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

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5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

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

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

Table 13: Phase 2 Studies in Subjects with NVAF

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

Source: Summary of Clinical Safety, p. 21

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

5.2 Review Strategy

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

5.3 Discussion of Individual Studies/Clinical Trials

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

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

5.3.2 Study objectives:

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

The protocol specified four secondary objectives:

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

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

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

There were three randomized treatment groups:

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

Edoxaban (15 and 30 mg and matching placebo) were supplied in (b) (4) foil blister packs. Blinded warfarin (1 and 2.5 mg tablets) and matching placebo were supplied in blister packs by the Sponsor. In addition, for China, Japan, Korea and Taiwan, 0.5 mg blinded warfarin and matching placebo were also supplied.

5.3.4 Study Scope and Population:

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

5.3.5 Main Inclusion Criteria

1. Male or female subjects with age ≥ 21 years
2. History of AF documented by any electrical tracing within the prior 12 months and for which anticoagulation therapy is indicated and planned for the duration of the study (Subjects with AF includes subjects with paroxysmal, persistent, or permanent AF and subjects with or without previous VKA (including warfarin) experience
3. $CHADS_2$ index score ≥ 2. The $CHADS_2$ scoring is performed by assigning 1 point each for a history of Congestive heart failure, Hypertension, Age ≥ 75 years, or Diabetes mellitus; and by assigning 2 points for history of Stroke or TIA (APPENDIX 2)

5.3.6 Main Exclusion Criteria

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

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

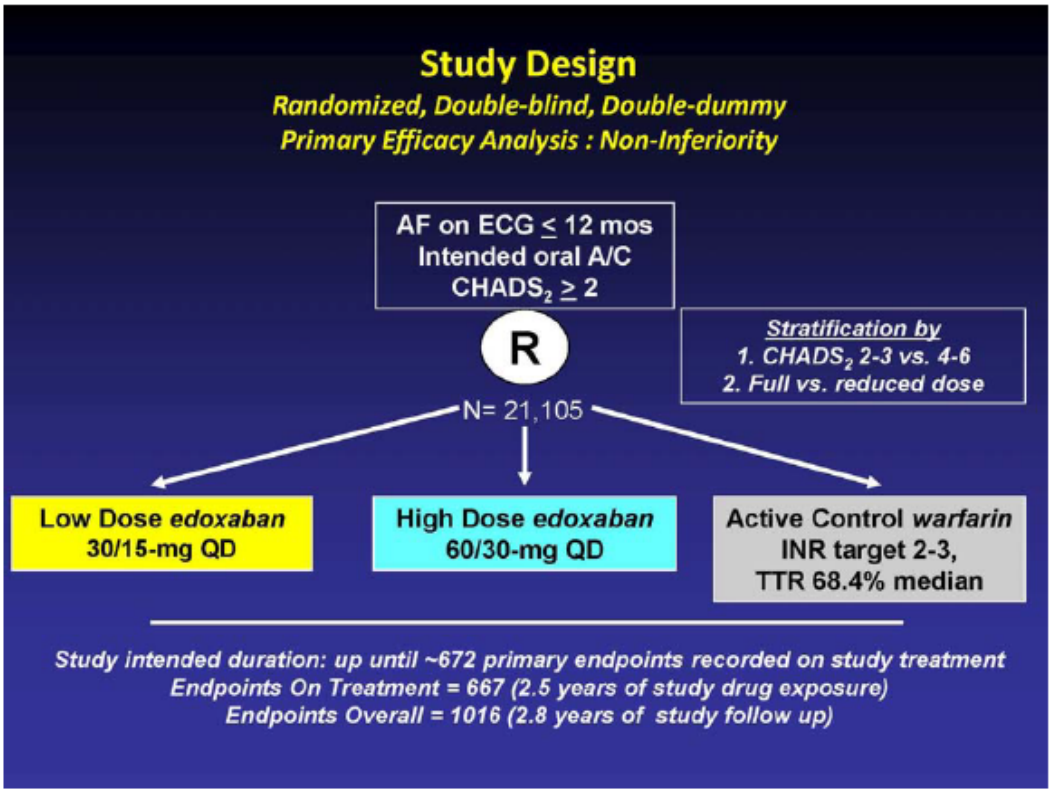
5.3.7 Stratification and Randomization

Eligible subjects were stratified by $CHADS_2$ risk score at randomization.
Stratum 1: $CHADS_2$ risk score 2 and 3
Stratum 2: $CHADS_2$ risk score 4, 5, and 6

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

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

Figure 10: Study Design in ENGAGE AF



Source: CSR, ENGAGE-AF, Figure 9.1

5.3.8 Edoxaban Dosage Modifications during Trial

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

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

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

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

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

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

5.3.9 Study Procedures

5.3.9.1 Study Qualification:

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

5.3.9.2 Randomization (Day 1):

All baseline procedures were performed on this day. These included completing a worksheet that documented subject's age, body weight, eGFR, $CHADS_2$ score, vital signs, 12-lead ECG, laboratory tests, INR assessments and concomitant medications. Study drug was dispensed.

5.3.9.3 Monitoring:

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

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

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

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

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

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

5.3.9.4 Special Considerations Regarding Aspirin Use

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

5.3.9.5 Treatment Interruptions or Discontinuations

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

1. AE (eg. major life-threatening bleeding or SAE, CrCL decreased to < 30 mL/min, confirmed by repeat testing at least one week later, or need for kidney dialysis); or liver abnormalities.

2. Marked liver enzyme elevation. Additional evaluations (i.e. hepatitis A, B, C, and E screening, abnormal ultrasound) were to be performed if the temporarily interruption of study drug was due to confirmed liver enzyme abnormalities or jaundice.

3. Other causes for study treatment interruption or discontinuation:

    a. Withdrawal of Informed Consent
    b. Initiation of fibrinolytic or additional anticoagulant therapy for MI or PE
    c. Initiation of dual antiplatelet therapy
    d. Initiation of strong P-gp inhibitors ritonavir, nelfinavir, indinavir, saquinavir and cyclosporine

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

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

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

Table 14: Study Drug Discontinuation Rules

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

Reviewer's Table

Special Cases of Transitioning:

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

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

Bridging anticoagulation therapies that could be considered included:

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

5.3.9.6 Subjects Undergoing Special Procedures

5.3.9.6.1 Subjects Undergoing Cardioversion

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

5.3.9.6.2 Subjects Undergoing Surgical/Invasive Procedures

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

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

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

5.3.9.7 Study Drug Discontinuation Visit procedures

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

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

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

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

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

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

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

5.3.9.8 Other Subject-Related Considerations

5.3.9.8.1 Re-qualification procedures

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

5.3.10 Committees

There were three independent committees by design:

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

5.3.11 Efficacy Endpoint Considerations

5.3.11.1 Primary Efficacy Endpoint

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

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

5.3.11.2 Secondary Efficacy Endpoints

• Composite of stroke, SEE, and CV mortality

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

5.3.12. Safety Endpoint and Safety Events of Special Interest

5.3.12.1 Primary Safety Endpoint.

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

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

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

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

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

5.3.12.2 Secondary Safety Endpoint

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

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

5.3.12. 3 Evaluation of Liver abnormalities

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

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

5.3.13 Adjudications

5.3.13.1 Investigator-Prompted Adjudications

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

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

5.3.13.2 eCRF Event-Prompted Adjudications

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

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

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

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

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

5.3.14 Role of Quintiles CRO

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

5.3.15 Adjudication Process

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

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

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

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

5.3.16 Statistical Analysis

5.3.16.1 Sample Size

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

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

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

5.3.16.2 Efficacy analyses:

5.3.16.2.1 Primary statistical analyses

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

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

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

The primary analysis was designed to compare treatment efficacy for the first occurrence of a primary efficacy endpoint event (stroke or SEE) that occurred during the "on-treatment" period for all subjects in the mITT Analysis Set. For those subjects who had an efficacy endpoint event the "On-Treatment" period was defined as starting when the subject took study drug and ended at the date of the first event. If the patient had an event, however, after the CSED visit at which time the patient would have been off treatment, this would not be considered "on treatment" and would not count in the primary efficacy analysis. For subjects who did not have an endpoint event, the censoring period for the "On-Treatment" period began at the first dose and continued until the earlier of the last dose +3 days or the Common Study End Date (CSED) announcement +90 days, the CSED visit, death date, withdrawal of consent date, or last assessment date. The rationale for the 3 days following the last dose was based on 3 days being approximately 5 times the t1/2 of edoxaban. The Cox proportional hazards model included treatments and the following two stratification factors as covariates:

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

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

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

Additional non-inferiority analyses were to be performed using the following datasets:
1. mITT population including events occurring during on-treatment study period only
2. mITT population including events occurring throughout the overall study period from the first dose to CSED Visit
3. Per Protocol (PP)[21] Population including events occurring during on-treatment study period only
4. PP Population including events occurring throughout the overall study period from the first dose to CSED Visit

5.3.16.2.2 Secondary efficacy analyses:

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

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

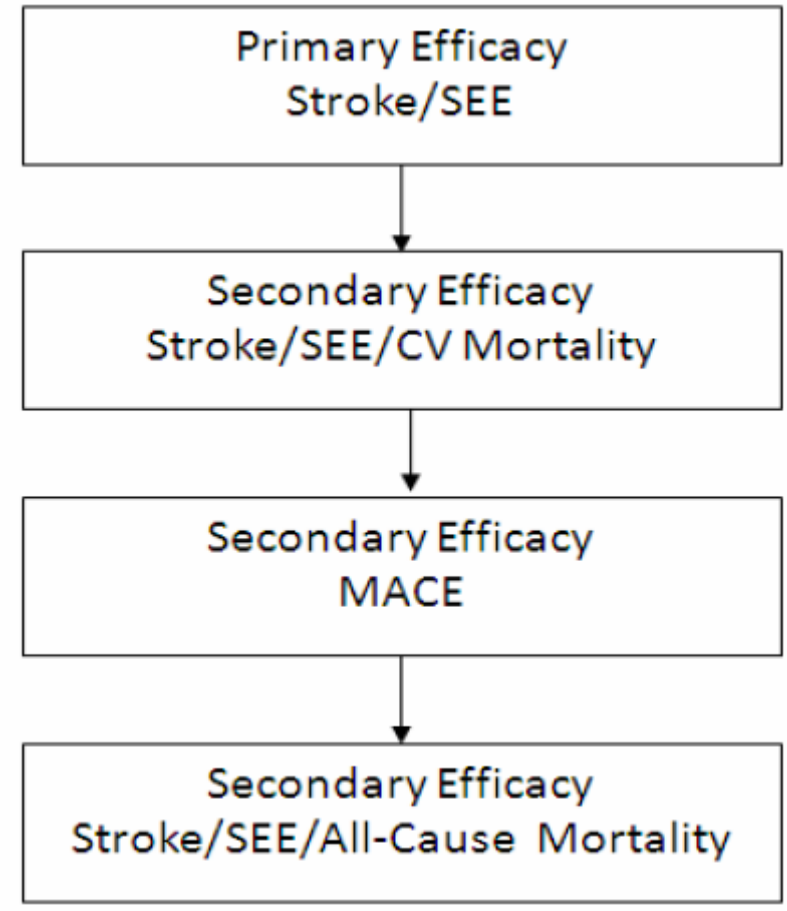
The secondary endpoints were as follows:

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

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

3. Composite of stroke, SEE, and all-cause mortality. The time to first event was defined as the time (years) from the day of randomization to the first event experienced by a subject.

Figure 11: Planned Hierarchical Sequence for Superiority Testing



Source: CSR, ENGAGE-AF

5.3.16.3 Safety Analyses

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

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

5.3.17 Protocol Amendments

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

Original Protocol: September 15, 2008

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

- 2nd amendment, Version 3, April 12, 2010. Number of overall first stroke/SEEs in mITT population: (38 edoxaban 30mg (15 mg DA), 29 edoxaban 60 mg (30 mg DA), 26 warfarin, 93 total (~ 9% of overall events in mITT population).

Description of Change:

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

- 3rd amendment, Version 4, July 29, 2010. Number of overall first strokes/SEEs in mITT population: 67 edoxaban 30 mg (15 mg DA), 45 edoxaban 60 mg (30 mg DA), 56 warfarin, 168 total (~ 17% of overall events in mITT population).
  Description of Changes:
  1. Protocol clarifications
  2. Added telephone calls at Week 6 and Week 10 to review study medication dosing with subject and confirm subject's understanding.

- 4th amendment, Version 5, August 26, 2010. Number of overall first strokes/SEEs in mITT population: 72 edoxaban 30mg (15 mg DA), 51 edoxaban 60 mg (30 mg DA), 70 warfarin, 193 total (~ 20% of overall events in mITT population).
  Description of Change:
  Removal of all mention of the 5-mg warfarin and placebo-to-match tablets because the 5 mg dose of warfarin was no longer to be used in the study because there were warfarin overdoses.

- 5th amendment, Version 6, December 22, 2010. Number of overall first strokes/SEEs in mITT population: 115 edoxaban 30 mg (15 mg DA), 83 edoxaban 60 mg (30 mg DA), 114 warfarin, 312 total (~ 30% of overall events in mITT population).
  Description of Change:
  The purpose of this amendment was to include dronedarone as a concomitant medication that needed edoxaban dose adjustment. Results of a completed Phase 1 dronedarone drug-drug interaction study showed that the plasma levels (PK exposure) of edoxaban (Cmax, AUC, and C24h) increased significantly.

- 6th amendment, Version 7, January 12, 2011, Number of overall first strokes/SEEs in mITT population: 124 edoxaban 30 mg (15 mg DA), 93 edoxaban 60 mg (30 mg DA), 118 warfarin, 335 total (~33% of overall events in mITT population).
  Description of Change:
  Administrative change that deleted the following text: "Future knowledge of additional concomitant drugs requiring dosage adjustments for edoxaban will not result in a protocol amendment. These changes will be communicated to the sites via a memo."

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

Update of the statistical section and secondary objectives and endpoints to make them consistent with the revised Statistical Analysis Plan (SAP).
The main change in the SAP was the change from 3 to 2 treatment regimens to be compared to warfarin for primary non-inferiority testing:

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

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

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

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

6 Review of Efficacy

Efficacy Summary

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1. The HRs (compared to warfarin) were worse (higher) in both edoxaban groups for sub-components of the primary efficacy endpoint and CV death in the normal renal function subgroup (CrCL ≥80 mL/min) compared to the mild renal impairment subgroup (CrCL > 50 - < 80 mL/min) (Table 15). Analyses of efficacy by CrCL quintiles (Table 16) and continuous CrCL level (Figure 17) also supported this finding.

2. There is a mechanistic basis for the observed findings. Edoxaban is 50% renally excreted so it is expected that renal function would be a major determinant of edoxaban pharmacokinetics (PK) and pharmacodynamics (PD). In fact, median trough edoxaban concentrations were ~1/3 lower (see Table 47) and median changes from trough to peak anti-Factor Xa activity were ~1/4 lower in subjects with CrCL ≥ 80 mL/min than in subjects with mild renal impairment (CrCL >50-<80 mL/min, see Table 48) .

3. While not an efficacy endpoint, the major bleeding results are useful to discuss here because the major bleeding event rates in the normal renal function subgroup (relative to warfarin) are consistent with what would be expected in the setting of lower exposures. The HRs of major bleeding relative to warfarin were lower in subjects with CrCL≥ 80 mL/min (HR: 0.70, 95%CI: 0.55-0.89) compared to subjects with mild renal impairment (CrCL> 50 - < 80 mL/min) (HR: 0.90, 95% CI: 0.74-1.08). See Table 15.

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

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

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

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

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

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

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

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

Reviewer's Table.

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

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

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

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

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

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

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

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

E 60 NOT DA = Edoxaban 60 mg NOT Dose Adjusted
E 60, DA = Edoxaban 60 mg, Dose Adjusted (i.e., administered 30 mg edoxaban QD)
Dataset: ADJEFFCA.xpt, BASEGP.xpt; HRs calculated using modeling with Dose Adjustment, yes or no, CHADS2≤3=0, or >3=1.
(More details of this analysis are shown in Table 58 and Table 59).
Reviewer's Table.

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

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

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

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

E 60 NOT DA = Edoxaban 60 mg NOT Dose Adjusted

E 60, DA = Edoxaban 60 mg, Dose Adjusted (i.e., administered 30 mg edoxaban QD)
Datasets: XB.xpt, PCANAL.xpt, BASEGP.xpt
(More details of this analysis are shown in Table 47 and Table 48).
Reviewer's Table.

6.1 Indication

6.1.1 Methods

6.1.1.1 Important Study Dates:

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

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

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

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

6.1.2 Demographics

Table 19, Table 20, and Table 21 are tabular summaries of the demographic data. The treatment groups were well matched demographically. The population was predominantly elderly (median age of 72), Caucasian (~80%) and male (~60%). ~25% of subjects in the edoxaban arms had their doses adjusted at baseline because of reduced renal function (~ 18% of all edoxaban subjects), weight ≤ 60 kg (~10% of the edoxaban subjects) or concomitant P-gp inhibitors that required dose adjustment (~3.5% of edoxaban subjects). Approximately half of the subjects were $CHADS_2$ score 2 and most of the other half had $CHADS_2$ scores between 3 and 5. There were a few subjects with $CHADS_2$ scores of 1 and 6. Most subjects had hypertension and > 50% had a history of congestive heart failure. Approximately 30% had prior strokes or TIAs. Approximately 40% were VKA naïve. Approximately 30% were on aspirin at baseline.

Refer to APPENDIX 10 for a comparison between demographics in ENGAGE AF and studies of other NOACs.

Table 19: Demographics and Other Baseline Characteristics

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

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

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

Source: ENGAGE-AF CSR, p.108

Table 20: Baseline Cardiovascular Status

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

DA= Dose Adjustment

Source: ENGAGE-AF CSR,p.130

Table 21: Medication at Baseline

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

Source: ENGAGE-AF CSR, p.108

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

Table 22: Dose Adjustment at randomization

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

Reviewer's Table.

6.1.3 Subject Disposition

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

See Table 23 for a tabular listing of subject disposition categories by treatment. Importantly, most subjects were followed to the end of the trial and median study follow-up was 2.8 years, longer than the other studies that have supported NOAC approvals.

Table 23: Subject Disposition

	Edoxaban 30mg (15 mg DA)	Edoxaban 60mg (30mg DA)	Warfarin	Total
Total Screened				25,497
ITT/ Randomized and Assigned Treatments	7034	7035	7036	21, 105
mITT/ Safety set (received at least one dose of treatment)	7002	7012	7012	21,026
PP analysis set	6982	6995	6993	20,970
Median Study Drug Exposure	916 days (2.5 yr)	904 days (2.5 yr)	904 days (2.5 yr)	
Subject-year Exposure	15,840	15,471	15,569	
Median Study Follow-up	1023 days (2.8 yr)	1023 days (2.8 yr)	1021 days (2.8 yr)	
Mean Percentage of Exposed Days (SD)	82.2 (30.6)	80.3 (32.5)	81.4 (31.3)	
Completed Study	6956 (98.9%)	6956 (98.9%)	6946 (98.7%)	
Completed CSED Visit (Did not die before CSED visit, withdraw consent or get lost to follow-up)	6250 (88.9%)	6228 (88.5%)	6157 (87.5%)	
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

6.1.4 Treatment Interruptions and Discontinuations

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

Table 24: Treatment Interruptions

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

Source: ENGAGE-AF CSR, p.165

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

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

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

Source: ENGAGE-AF CSR, p. 166

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

Table 26: Study Drug Discontinuation

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

Source: ENGAGE-AF CSR, p. 168

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

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

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

DA=dose adjustment
noDA=no dose adjustment
Source: ENGAGE-AF CSR, p. 170

Study Drug Compliance

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

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

6.1.5 Analysis of Primary Endpoint(s)

6.1.5.1 Prespecified Primary Endpoint Results:

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

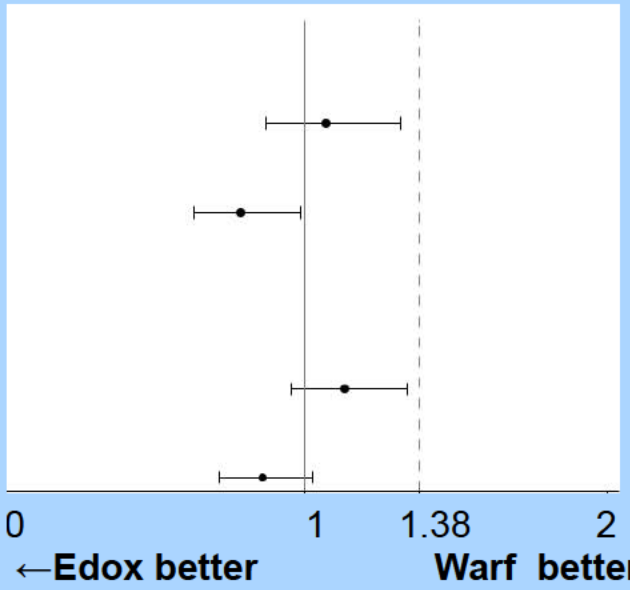
Table 28: Adjudicated Primary Endpoint (Stroke or SEE), mITT Analysis Set - On-Treatment and Overall Study Period (Non-Inferiority)

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

Abbreviations: DA = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, mITT = Modified Intent-to-Treat, SEE = Systemic Embolic Event, yr = year.
[a]: The event rate (%/yr) is calculated as # of events/subject-year exposure (%/yr = events/100 patient-years).
[b]: The two-sided p-value is based on the non-inferiority margin of 1.38
Source data: Tables 14.2.1.1 and 14.2.1.2
ENGAGE-AF CSR p. 121

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

Study Period / Edoxaban Group	Edoxaban n/N (%/yr)	Warfarin n/N (%/yr)	p-value for NI
Treatment period			
30 mg (15 mg DA)	253/7002 (1.61)	232/7012 (1.50)	<0.01
60 mg (30 mg DA)	182/7012 (1.18)	232/7012 (1.50)	<0.0001
Overall Study Period			
30 mg (15 mg DA)	382/7002 (2.04)	336/7012 (1.8 0)	<0.01
60 mg (30 mg DA)	292/7012 (1.55)	336 /7012 (1.80)	<0.001



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

6.1.5.2 Superiority Testing (ITT Overall Study Period)

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

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

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

Abbreviations: DA = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, ITT = Intent-to-Treat, SEE = Systemic Embolic Event, yr =year.
(%/yr) is # of events/ 100 subject-year exposure.
Source data: Table 14.2.1.7, ENGAGE AF CSR p.125

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

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

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

HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, SEE = Systemic Embolic Event, DA= Dose Adjusted
(%/yr) is # of events/ 100 subject-year exposure.
Source: Table 14.2.1.10, ENGAGE AF CSR p.127
* p value for analyses with 95% confidence interval

6.1.5.3 Analysis of Components and Select Subcomponents of the Primary Endpoint

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

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

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

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

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

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

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, MITT = Modified Intent-to-Treat, SEE = Systemic Embolic Event, yr = year, n = number of events.
(%/yr) is calculated as # of events/subject-year exposure and = events/100 patient-years.
[a]: Disabling is based on the Rankin score (3 to 5) supplied by the Investigator as well as taking into account if the stroke event was adjudicated as fatal. Rankin score 3 = Moderate disability requiring some help, but able to walk without assistance; 4 = Moderately severe disability, unable to

walk without assistance and unable to attend to own bodily needs without assistance; 5 = Severe disability, bedridden, incontinent, and requiring constant nursing care and attention.
Source data: Tables 14.2.1.14 and 14.2.1.19
Source: ENGAGE AF CSR p. 132

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

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

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, MITT = Modified Intent-to-Treat, SEE = Systemic Embolic Event, yr = year, n = number of events.
[a]:The event rate (%/yr) is calculated as # of events/subject-year exposure.
[b]: Disabling is based on the Rankin score (3 to 5) supplied by the Investigator as well as taking into account if the stroke event was adjudicated as fatal. Rankin score 3 = Moderate disability requiring some help, but able to walk without assistance; 4 = Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = Severe disability, bedridden, incontinent, and requiring constant nursing care and attention.
Source data: Tables 14.2.1.10 and 14.2.1.15
ENGAGE-AF CSR. P. 133

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

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

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

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

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

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

Abbreviations: DA = Dose Adjusted, NoDA = Not Dose Adjusted, Plb Edo = Placebo Edoxaban, CI = Confidence Interval, HR = Hazard Ratio versus Warfarin, mITT = Modified Intent-to-Treat, SEE = Systemic Embolic Event, yr = year.
The dose adjustment for the warfarin group represents edoxaban-placebo dose adjustment
(%/yr) is # of events/ 100 subject-year exposure
[a]: The pairwise comparisons include Column (1) versus (5), (2) versus (6), (3) versus (5),and (4) versus (6).
Source Data: Tables 14.2.4.1 and 14.2.4.2
Source: ENGAGE AF CSR, p. 139

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

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

Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.
Source: ENGAGE AF CSR, p. 142

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

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

Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.
Reviewer's Table: Datasets: DM, CENTTTR, BASEGRP, ADJEFFCA

6.1.5.4 Analysis of Warfarin Active Control Arm

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

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

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

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

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

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

Abbreviations: INR = International Normalized Ratio, SD = Standard Deviation, TTR = Time in Therapeutic Range.
[a]: Percent Time in INR range is defined by the percentage of days the subjects have been within the specified range. Percent Time in Therapeutic Range (TTR) is calculated as the mean percentage in the range 2-3.
Note: N = Number of subjects with at least 1 INR recorded beyond Day 7.
Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.
Note: Analyses of INR use a linear interpolation method to impute INR for study days that do not have an actual INR value.
Source data: Table 14.3.4.1
ENGAGE AF CSR p. 117

6.1.6 Analysis of Secondary Endpoints(s)

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

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

Breaking down the secondary endpoints further, edoxaban-treated subjects had a lower CV and all-cause mortality than those treated with warfarin. Fewer subjects in the edoxaban 60 mg and edoxaban 30 mg groups experienced CV mortality than the warfarin group, with a hazard ratio of 0.86 and 0.85, respectively (Table 38). Fewer subjects in the edoxaban 60 mg and edoxaban 30 mg groups experienced all-cause mortality than the warfarin group, with a hazard ratio of 0.92 and 0.87, respectively. As expected for the study population (median age 72 years, average $CHADS_2$ score 2.8), approximately 70% of deaths were due to CV causes. Fatal bleeds were included in the category of CV deaths, and edoxaban-treated subjects experienced fewer deaths due to bleed events. MI also trended favorably for edoxaban 60 mg except for fatal MI in the ITT population, overall study period (Table 38). Table 39 shows the CV mortality, all-cause mortality and MI results in the mITT population, on-treatment period.

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

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

Abbreviations: DA = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, ITT = Intent-to-Treat, yr = year, SEE = Systemic Embolic Event, CV = cardiovascular, MACE = MI, Stroke, SEE, and Death due to Cardiovascular Cause or Bleeding.
The event rate (%/yr) is # of events/ 100 subject-year exposure.
Source data: Table 14.2.2.1
Source: ENGAGE AF CRF, p. 129

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

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

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, ITT = Intent-to-Treat, yr = year, CV = cardiovascular, MI = Myocardial Infarction. %/yr = n events/ 100 years patient exposure
Note: A subject can appear in multiple rows of this table (eg, MI and death).
Source data: Table 11.10, p. 136 of ENGAGE AF CSR, and Table 14.2.2.6

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

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

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, MITT = Modified Intent-to-Treat, yr = year, CV = cardiovascular, MI = Myocardial Infarction.%/yr = n events/ 100 years patient exposure
Note: A subject can appear in multiple rows of this table (eg, MI and death).
Source data: Table 11.11, p.137 of ENGAGE AF CSR, and Table 14.2.2.8

6.1.7 Other Endpoints

Not applicable.

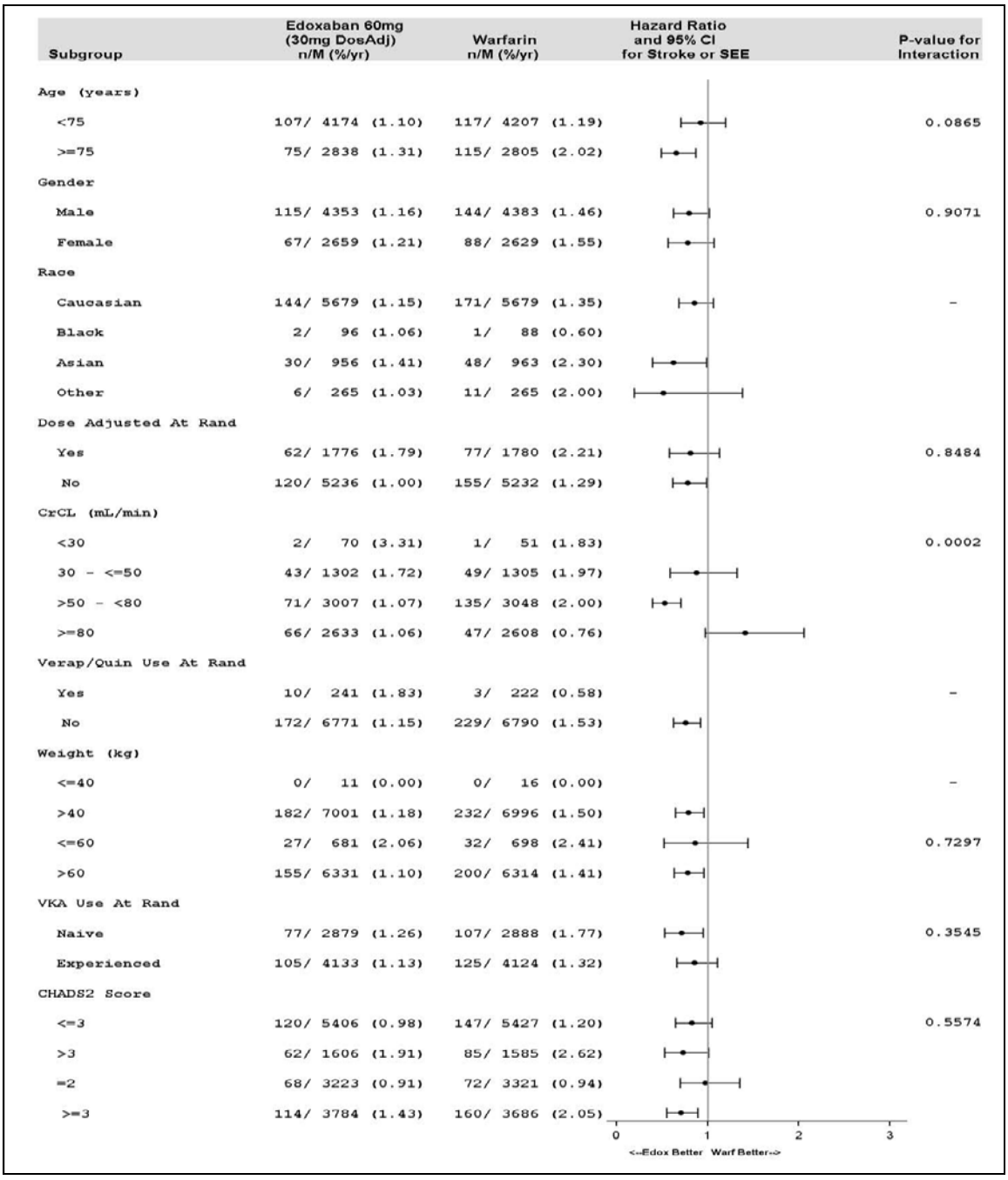
6.1.8 Subpopulations

6.1.8.1 Efficacy by Subgroup

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

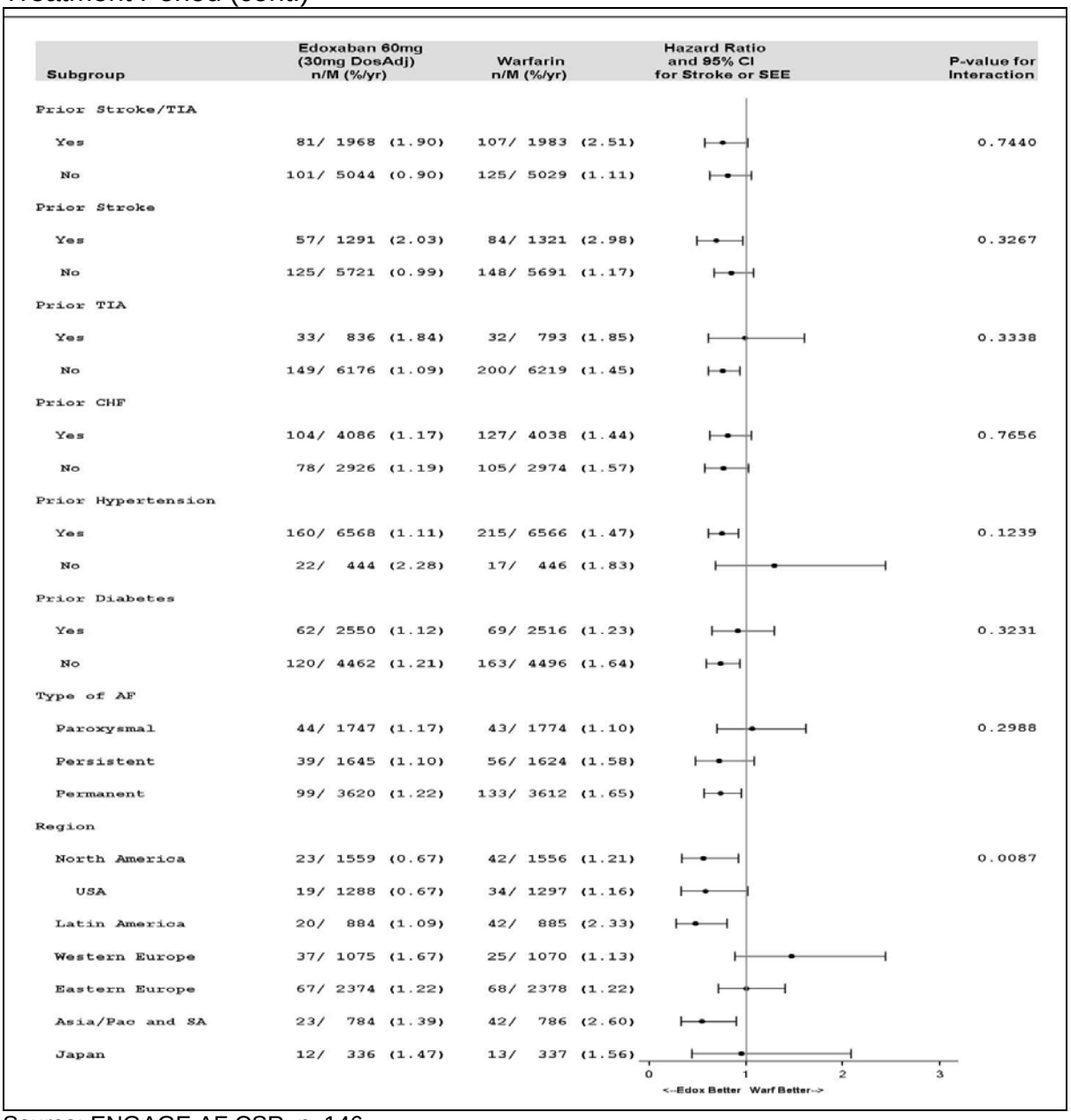
There were too few enrolled Blacks (1.3%) to assess performance in this subpopulation.

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



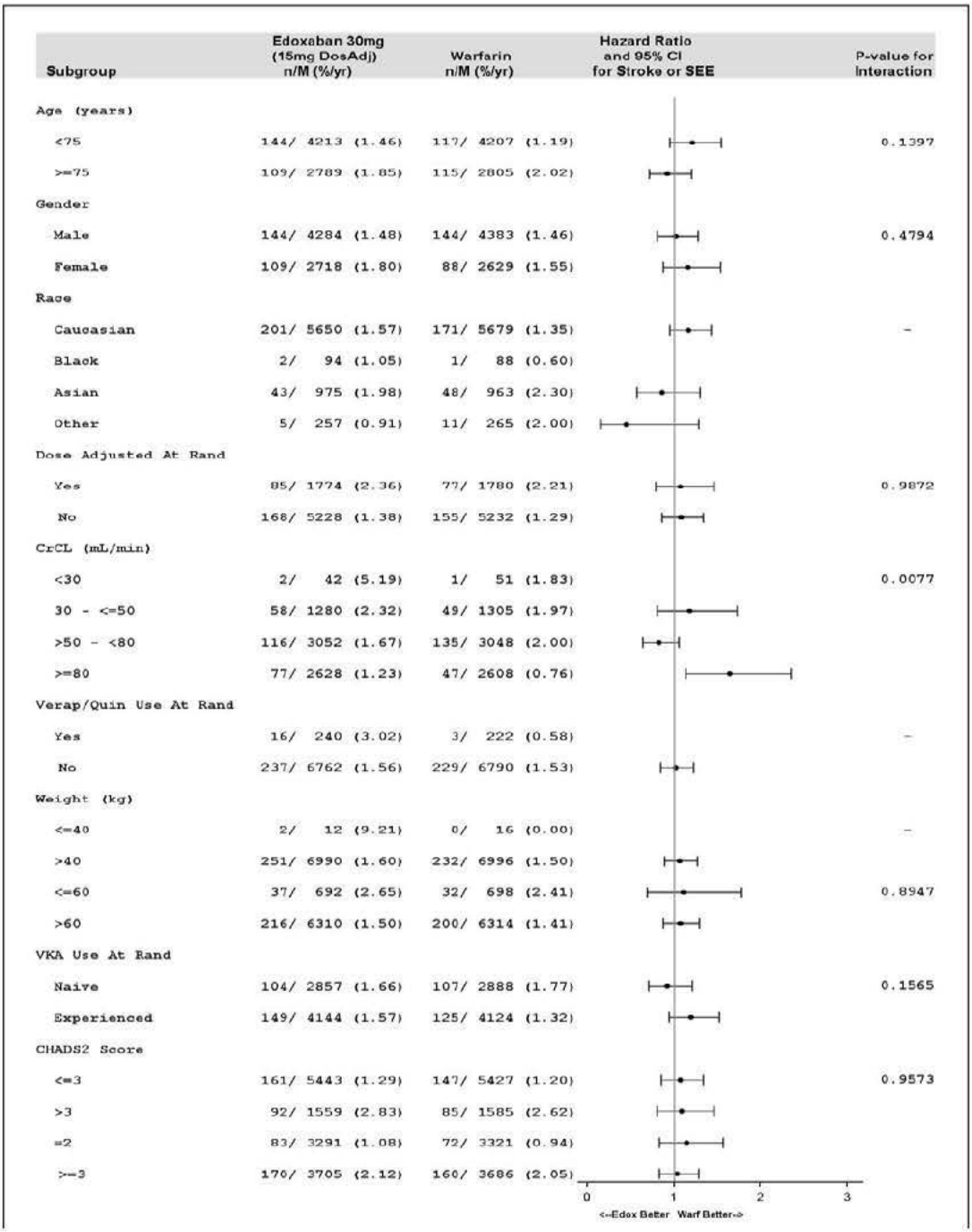
Source: ENGAGE AF CSR, p. 145

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



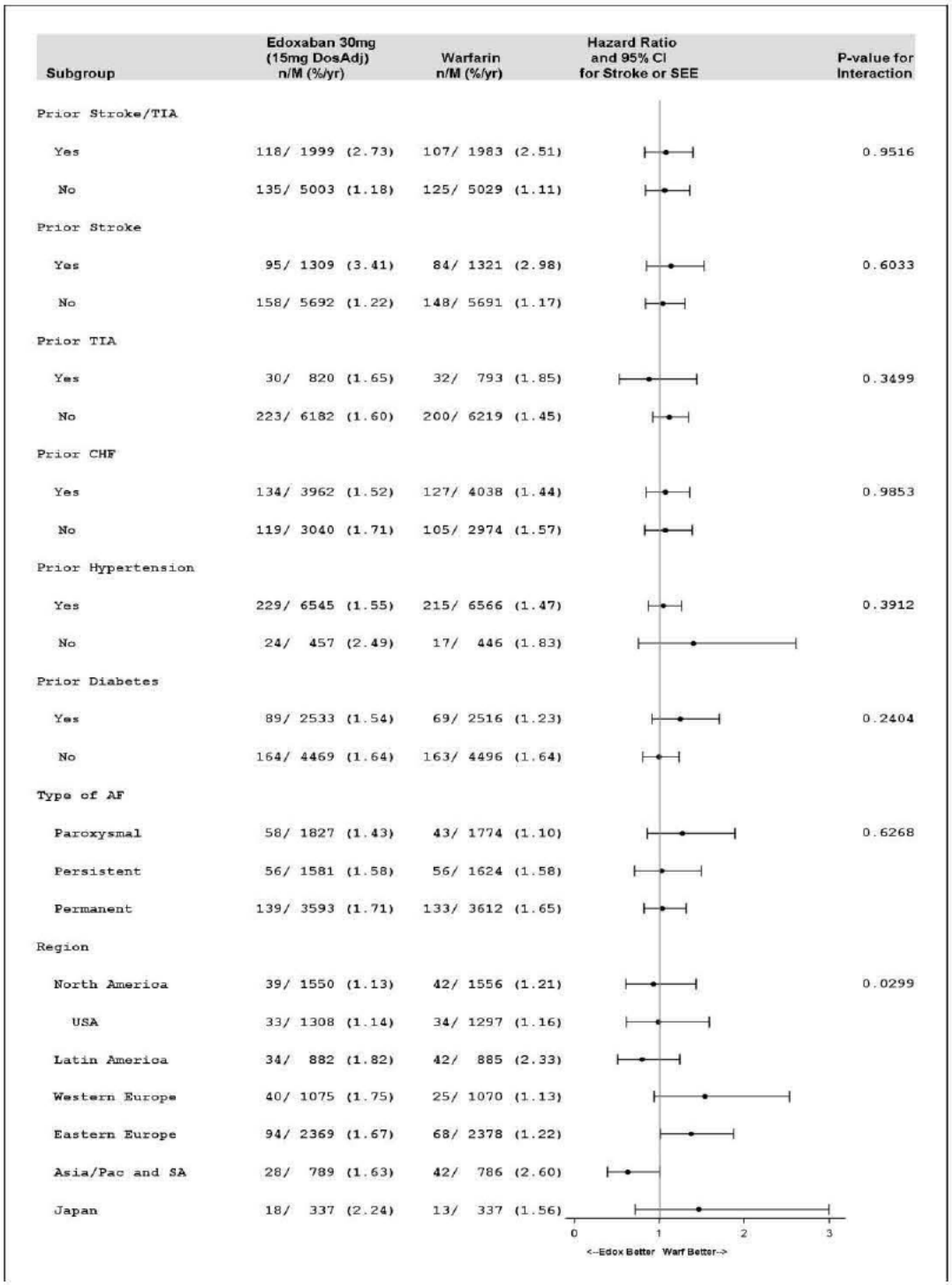
Source: ENGAGE AF CSR, p. 146

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



Source: ENGAGE AF CSR p. 147

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



Source: p. 148, CSR

6.1.8.2 Efficacy by Renal Function

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Reviewer's Table

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

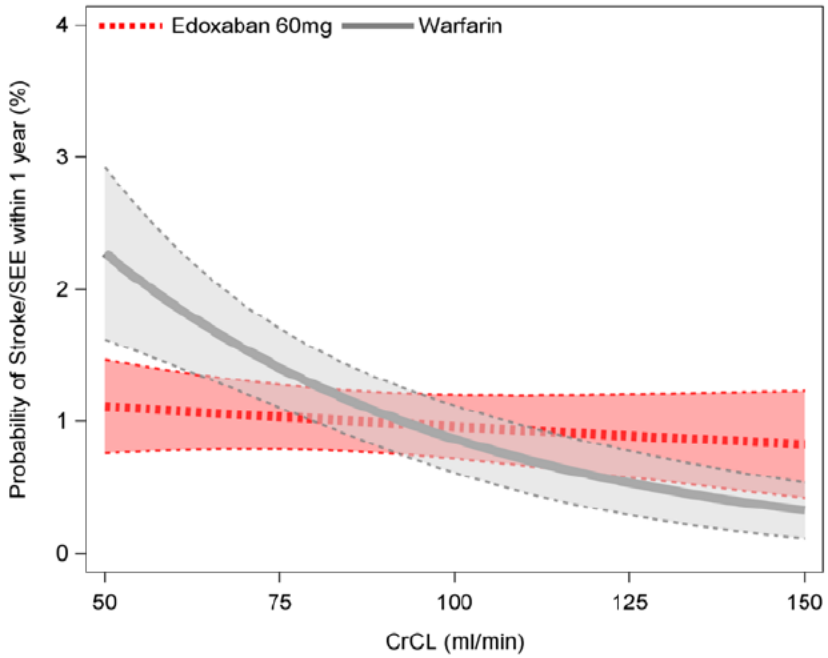
Table 57: CV Death, mITT population, Overall Study Period by CrCL quintile

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

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

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

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



CrCL (mL/min)	HR (95% CI)
50	0.48 (0.33-0.70)
65	0.62 (0.47-0.82)
80	0.80 (0.62-1.01)
95	1.02 (0.76-1.38)
110	1.31 (0.87-1.97)
125	1.69 (0.98-2.89)

The risk of first Stroke/SEE was modeled as a function of history of stroke, $CHADS_2$ score, CrCL, treatment, and CrCL*treatment using a Cox proportional hazard model among subjects with no dose adjustment
Dr. McDowell's analysis and figure, Dataset: ADJEFFCA, BASEGP and DM

6.1.8.3 Efficacy by Dose Adjustment

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

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

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

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

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

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

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

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

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

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

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

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

6.1.8.4 Efficacy by Multiple Stokes/SEEs

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

Table 60: Multiple Stroke/SEE Events in ENGAGE AF

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

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

6.1.8.5 Efficacy by $CHADS_2$ score

For the edoxaban 60 mg dose cohort there was little difference in HR compared to warfarin for Stroke/SEE among the subgroups of subjects with different $CHADS_2$ scores (Table 61). In the three $CHADS_2$ score groups (2, 3 and > 3), edoxaban 60 mg always had a HR < 1 compared to warfarin. The edoxaban 30 mg dose HR compared to warfarin became slightly worse with increasing $CHADS_2$ score.

Table 61: Stroke/SEE by CHADS2 score

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

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

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

6.1.7.6 Efficacy by Proton Pump Inhibitor (PPI) at baseline

[redacted] (b) (4) we were concerned that absorption might be decreased at increased pH. For this reason we were concerned that PPIs could impair absorption and decrease efficacy. We did an analysis of the event rate of stroke/SEE (the primary endpoint) in the mITT population on treatment and ischemic stroke (mITT, on treatment) by PPI use during the trial (≥ 3 month consecutive PPI use, Yes/No) (Table 62 and Table 63). The event rate was stable irrespective of whether the subject was on a PPI for at least 3 months in the edoxaban 60 mg (30 mg DA) group, but the warfarin subjects on a PPI for at least 3 months had an increase in event rate by ~50%. This resulted in a decreased HR for edoxaban 60 mg (30 mg DA) for first stroke/SEE and first ischemic stroke (mITT, on treatment). The subjects on PPIs for at least 3 months who were randomized to the edoxaban 30 mg (15 mg DA) dose had a higher event rate than edoxaban 30 mg (15 mg DA) subjects who were not on PPIs for at least 3 months [also ~50% increase which resulted in stable HR for first stroke/SEE and first ischemic stroke relative to warfarin (mITT, on treatment)]. PPI use does not appear to reduce efficacy of drug in the edoxaban 60 mg group and therefore, [redacted] (b) (4) does not appear to be clinically relevant.

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

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

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

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

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

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

6.1.8.6 Investigator Reported Efficacy Events

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

Table 64: Investigator Reported Efficacy Events

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

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

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Study PRT018 was the three month phase 2 dose ranging study that helped guide the applicant's dose choice for the pivotal trial. It was a multinational, randomized, parallel group, double blind study (DB to dose of edoxaban) but open label to whether subjects were on warfarin or edoxaban conducted mostly in Eastern Europe. Subjects had NVAF with a $CHADS_2$ index score of at least 2 and were equally randomized to 4 dose regimens of edoxaban (30 mg QD, 60 mg QD, 30 mg BID, 60 mg BID) or warfarin. The study was designed to evaluate safety and was underpowered for an efficacy assessment. D-dimer levels and prothrombin fragment 1 and 2 (F12) levels were used to evaluate efficacy. The safety assessments were focused on hepatic enzymes and bleeding. Analysis of bleeding events was based on blinded adjudication provided by the CEC.

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

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

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

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

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

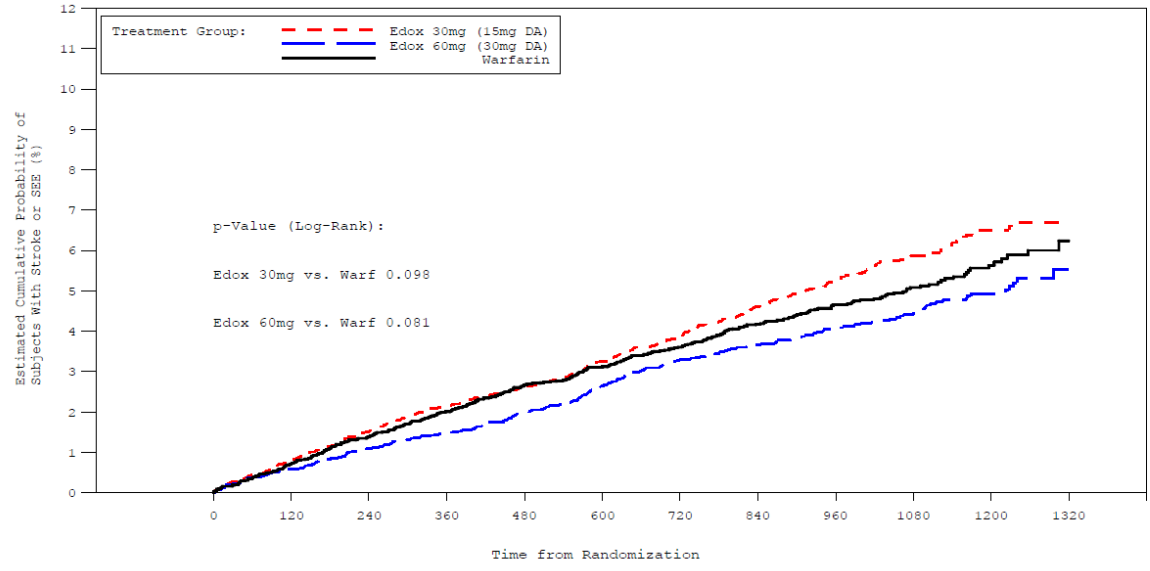
One might wonder what the bleeding rates would have been for a somewhat higher daily dose. Unfortunately, this was not tested.

Refer to Appendix 9 for a detailed summary of the protocol and clinical results.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

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

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



Number at Risk:

Edox 30mg (15mg DA)	7034	6876	6754	6639	6533	6411	6293	5551	4219	2652	1222	336
Edox 60mg (30mg DA)	7035	6895	6767	6656	6556	6426	6302	5615	4258	2683	1258	359
Warfarin	7036	6879	6748	6618	6485	6363	6244	5523	4167	2632	1243	353

Source: p. 126, CSR ENGAGE AF

6.1.11 Additional Efficacy Issues/Analyses

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

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

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

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

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

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

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

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

6.1.11.2 Efficacy during the Transition Period

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

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

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

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

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

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

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

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

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

Source: ENGAGE AF CSR, p. 233,235

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

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

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

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

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

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

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

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

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

Source: Table 14.2.4.10, ENGAGE AF CSR
Event Rate (%/yr): events per 100 patient years

7 Review of Safety

Safety Summary

Clinical safety of edoxaban in AF population was primarily evaluated based on the safety data from ENGAGE AF. This pivotal trial was the largest randomized trial with the longest follow-up time (median: 2.8 years) to study the risk of stroke/SEE in AF population to date. As described in Section 5, a total of 21,105 AF patients were randomized to three treatment groups: edoxaban 30 mg, edoxaban 60 mg and warfarin with 1:1:1 ratio. Edoxaban was administered once daily with required dose adjustment (50% dose reduction: 15 mg or 30 mg) for subjects with moderate renal impairment (CrCL 30-50 ml/min), low body weight (≤60 kg) and concomitant use of P-gp inhibitors. The safety dataset contains a total of 21,026 subjects who received at least one dose of study drug [n = 7002, 7012 and 7012 for edoxaban 30 mg[24], edoxaban 60 mg[25] and warfarin, respectively]. The size of the dataset should provide sufficient information to evaluate the safety of edoxaban in AF population. The three treatment groups in general had comparable duration of drug exposure and similar patterns in terms of dropouts and discontinuation.

The primary adjudicated safety endpoint was modified ISTH major bleeding[26]. Although ISTH major bleeding could include some clinically insignificant and readily reversible bleeds, it was the primary safety endpoint in the AF trials for the other three NOACs and has been historically used in studies of long-term anticoagulation. The Applicant also categorized major bleeding events using TIMI Major[27] and GUSTO Severe[28] definitions which allow an evaluation of more serious major bleeding events. The primary safety analysis was to compare on-treatment ISTH major bleeding events (last dose + 3 days) between each group of edoxaban and warfarin using a Cox-proportional Hazard Model controlled for dose adjustment and $CHADS_2$ covariates.
Both edoxaban groups were superior to warfarin for ISTH major bleeding [HR: 0.47 (0.41-0.55), 0.80 (0.71-0.91) for edoxaban 30 mg and 60 mg, respectively]. The superiority of bleeding results in the edoxaban groups were consistent across other major bleeding categories including ISTH major bleeding without hemorrhagic stroke,

[24] Edoxaban 30 mg refers to subjects receiving edoxaban 30 mg /15 mg dose adjusted.
[25] Edoxaban 60 mg refers to subjects receiving edoxaban 60 mg /30 mg dose adjusted
[26] Definition of modified ISTH major bleeding used in ENGAGE AF: fatal bleeding, bleeding in a critical organ or any bleed leading to transfusion-adjusted drops in hemoglobin level of ≥ 2.0 g/dl (1 unit of packed RBC = 1 g/dl drop in hemoglobin). See APPENDIX 7 for details.
[27] Definition of TIMI Major bleeding: : ICH, or clinical overt bleeding with a ≥ 5 mg/dL fall in hemoglobin or a 15% fall in hematocrit
[28] Definition of GUSTO Severe bleeding: ICH or bleeding resulting in hemodynamic compromise requiring treatment

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

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

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

*ISTH major bleeding without hemorrhagic stroke (HS)

Reviewer's Table. Source: Table 70 and Table 79 See APPENDIX 7 for overview of all bleeding category definitions.

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

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

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

Reviewer's Table. Source: Table 76

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

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

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

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

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

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

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

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

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

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

7.1 Methods

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

Table 72. Studies for Summary of Clinical Safety for Edoxaban

Type of Study	Planned Duration of Treatment	Number of Subjects Treated		
		Edoxaban	Control Group	Total
AF: Phase 3, C-U301 (ENGAGE AF-TIMI 48)	2.5 years	14,014	7012 (warfarin)	21,026
VTE Treatment and Secondary Prevention: Phase 3, D-U305 (Hokusai VTE)	3 to12 months	4118	4122 (warfarin)	8240
AF: Phase 2 studies	6 to 12 weeks	1502	450 (warfarin)	1952
VTE-Prophylaxis: Subjects undergoing orthopedic surgeries (Phase 2/3)	7 to 14 days (post-operative; in-hospital)	2638	1040 (enoxaparin, dalteparin or placebo)	3678
Phase 1PK/PD/DDI Studies (Integrated): Healthy volunteers or special populations	Single or multiple dose	1250[a]	159[b]	1409
Phase 1 PK/PD Studies (Non-Integrated): Healthy volunteers or subjects with end-stage renal disease undergoing hemodialysis	Single or multiple dose	218	0	218
Phase 3 Severe Renal Impairment studies in Japanese Subjects	2 or 12 weeks	152	20 (fondaparinux)	172
Other Ongoing Studies: (eTRIS, ePAD)	12 weeks	34 (160 planned)	21 (130 planned) (LMWH/warfarin or clopidogrel)	55 (290 planned)
Post-Marketing Experience (Japan)	NA	134,875	NA	134,875

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

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

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

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

In ENGAGE AF, the Applicant's primary analysis for bleeding events evaluated on-treatment events in the safety population set (subjects who received at least one dose of study treatment). The definition of "on treatment" was the period between first dose and 3 days after study drug discontinuation (temporary or permanent) unless the subject completed the CSED visit. For subjects who completed the CSED visit the "on treatment" period was the period between first dose and the CSED visit. Time to the first major bleeding event was examined using a Cox-proportional hazard model to estimate HR and 95% CI while adjusting two covariates: dichotomized $CHADS_2$ (1 if $CHADS_2 \geq 4$, 0 otherwise) and dichotomized dose-adjustment factor (1 if dose adjustment, 0 otherwise). The Applicant also conducted safety analysis during the overall study period, which is defined as the time from the initial dose of study drug date to the CSED visit[29].

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

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

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

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

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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

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

7.1.2 Categorization of Adverse Events

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

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

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

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

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

7.2 Adequacy of Safety Assessments

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

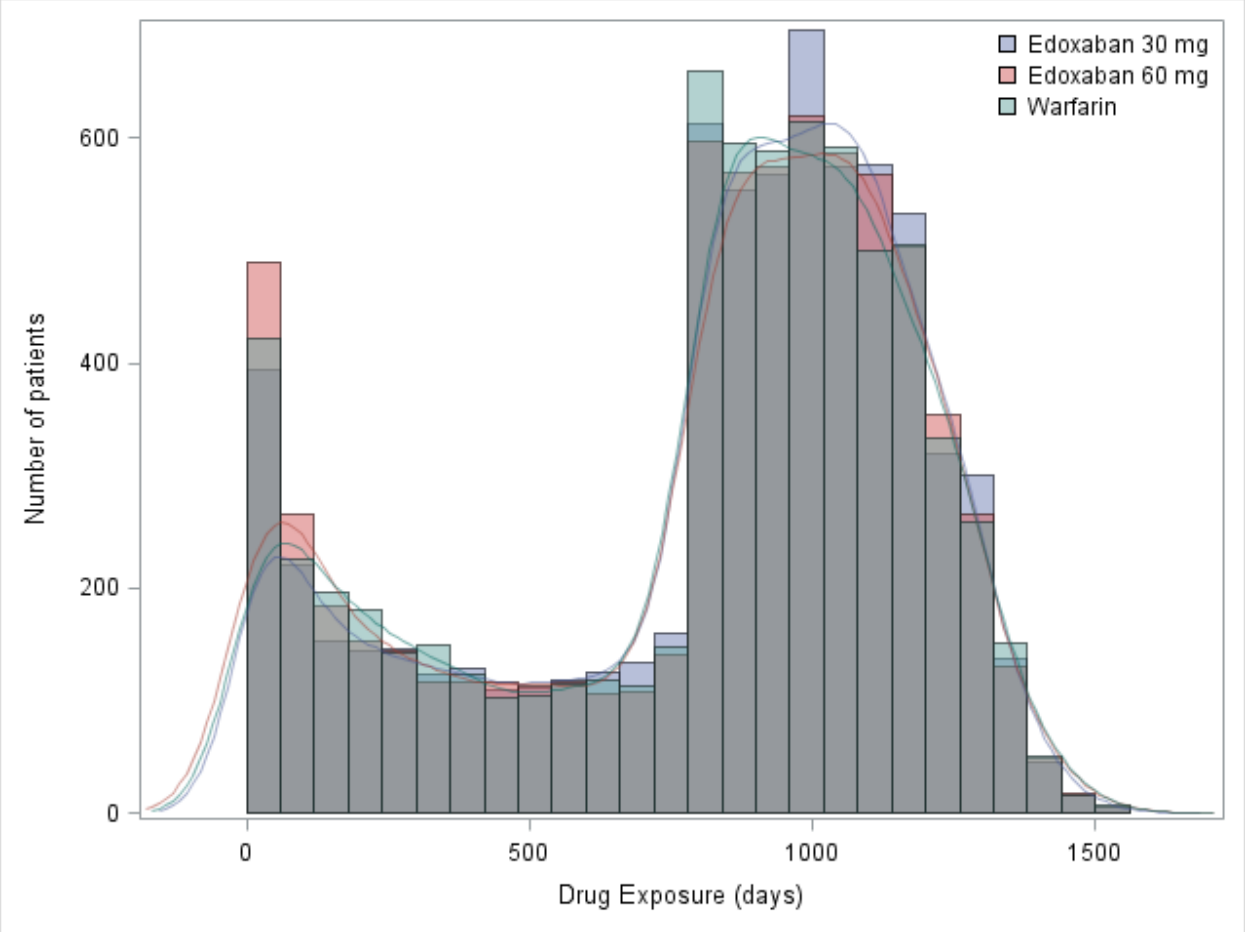
The median duration of study drug exposure, accounting for drug interruptions, in ENGAGE AF was ~ 2.5 years in all three groups. Figure 19 shows the distribution of study drug exposure by treatment arm. Table 73 summarizes study drug exposure by treatment arm and by different subsets (e.g. VKA naïve).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

Table 73 Study Drug Exposure in ENGAGE AF

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

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

Figure 19 Drug Exposure by Treatment group



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

7.2.2 Explorations for Dose Response

See Section 6.1.9

7.2.3 Special Animal and/or In Vitro Testing

Non-clinical testing was adequate to investigate potential adverse reactions. See brief summary in Section 4.3.

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4 Clinical Pharmacology

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

The major safety concern of anticoagulant drugs is pathological bleeding. Ximelagatran, an oral thrombin inhibitor, was not approved in the US because of an associated risk of serious drug induced liver injury (DILI). Both bleeding event and liver-related AEs/liver chemistries abnormalities were adjudicated in ENGAGE AF.

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

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

7.3 Major Safety Results

7.3.1 Deaths

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

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

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

Table 74 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

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

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

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

Reviewer's analysis, Source: the Applicant's dataset: AEEV1, DM. Analyses were based on MedDRA broad SMQ.
*Hypersensitivity reactions include three SMQs: anaphylactic reaction, angioedema and severe cutaneous adverse reaction

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

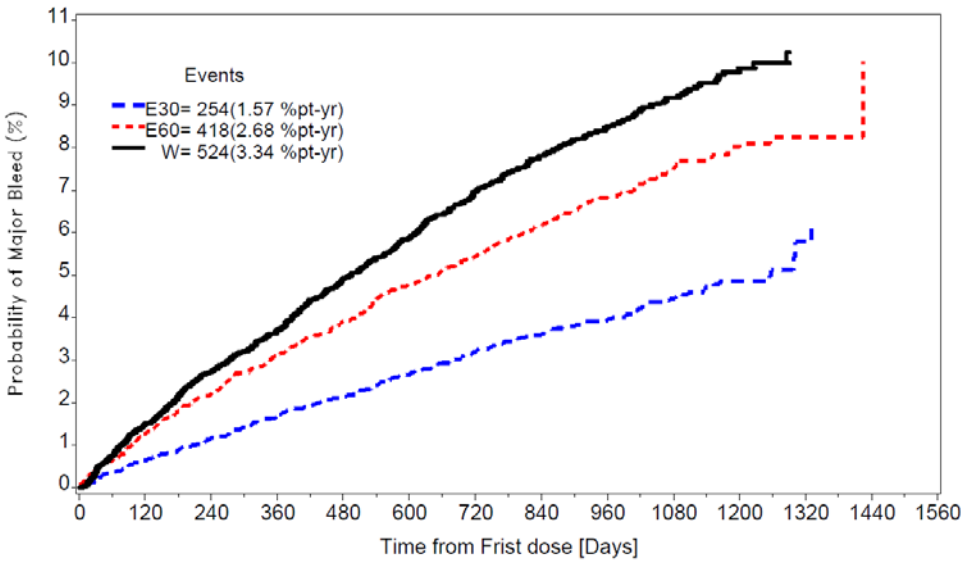
Reviewer's Comment: The imbalanced finding between edoxaban and warfarin in ILD-related death was still present after further evaluation of each individual fatal case. Higher frequency of ILD SAEs was also reported in the edoxaban groups compared with warfarin (See Section 7.3.2.2). There was no imbalance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

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Major Bleeding Events

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

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



No. at risk

E30	7002	6393	6082	5829	5582	5376	5172	4517	3360	2269	979	251	44	0
E60	7012	6254	5905	5634	5384	5155	4960	4343	3192	2162	915	222	41	0
W	7012	6335	5960	5666	5416	5215	4999	4339	3136	2124	934	246	51	0

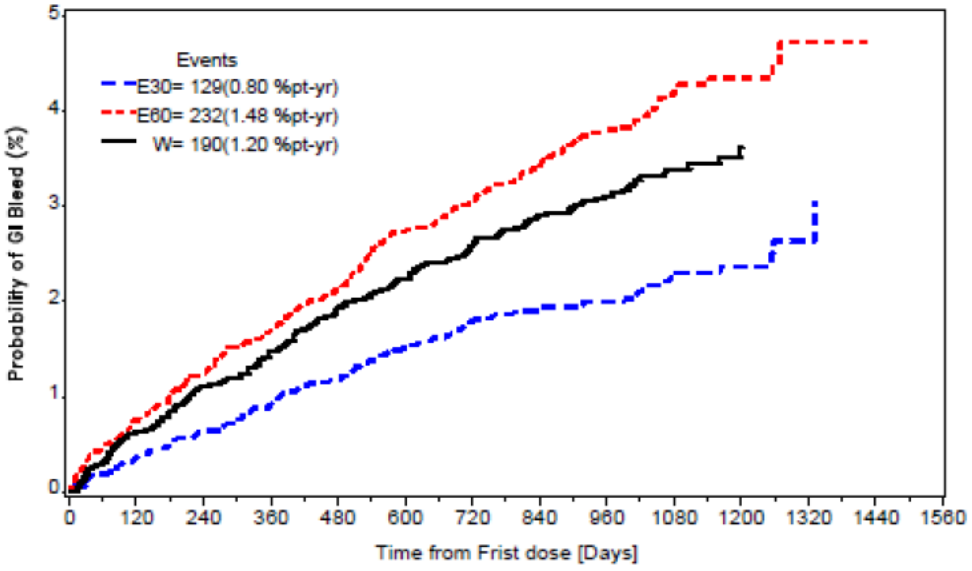
Reviewer's Analysis, Source: the Applicant's dataset: BLDDATA, DM,

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

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

[†]See APPENDIX 7 for overview of all bleeding category definitions in ENGAGE AF
Reviewer's analysis, Source: Applicant's dataset: BLDDATA, BASEGRP and DM. First major bleeding event for each category was used. Subjects without a major bleeding event were censored at the earliest day of death, last dose +3 days, withdrawal of consent, or last known information about the event of interest.
Definition of GUSTO Severe Bleeds: ICH or bleeding resulting in hemodynamic compromise requiring treatment. Definition of TIMI Major Bleeds: ICH, or clinical overt bleeding with a ≥ 5 mg/dL fall in hemoglobin or a 15% fall in hematocrit.

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



No. at risk

E30	7002	6398	6097	5850	5608	5404	5201	4548	3383	2284	986	254	45	0
E60	7012	6272	5938	5675	5431	5209	5021	4408	3241	2193	936	230	43	0
W	7012	6355	6001	5723	5492	5297	5099	4442	3219	2182	958	255	54	0

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

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

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

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

For total bleed, if multiple major bleeds occurred in a day, only one bleed event was counted.
*(+n) = the difference between total bleeds compared to the first bleed
Reviewer's Analysis, Source: the Applicant's dataset: BLDDATA, DM

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

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

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

†See APPENDIX 7 for overview of all bleeding category definitions in ENGAGE AF
Reviewer's analysis, Source: Applicant's dataset: BLDDATA and BASEGRP. First bleeding event was used. Subjects without a bleeding event were censored at the earliest day of death, last dose +3 days, withdrawal of consent, or last known information about the event of interest.

7.3.2.1.1 Major Bleeding without Hemorrhagic Stroke

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

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

Name	*Edoxaban 30 mg N = 7002* *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.

7.3.2.1.2 Major bleeding by level of INR control

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

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

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

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

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

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

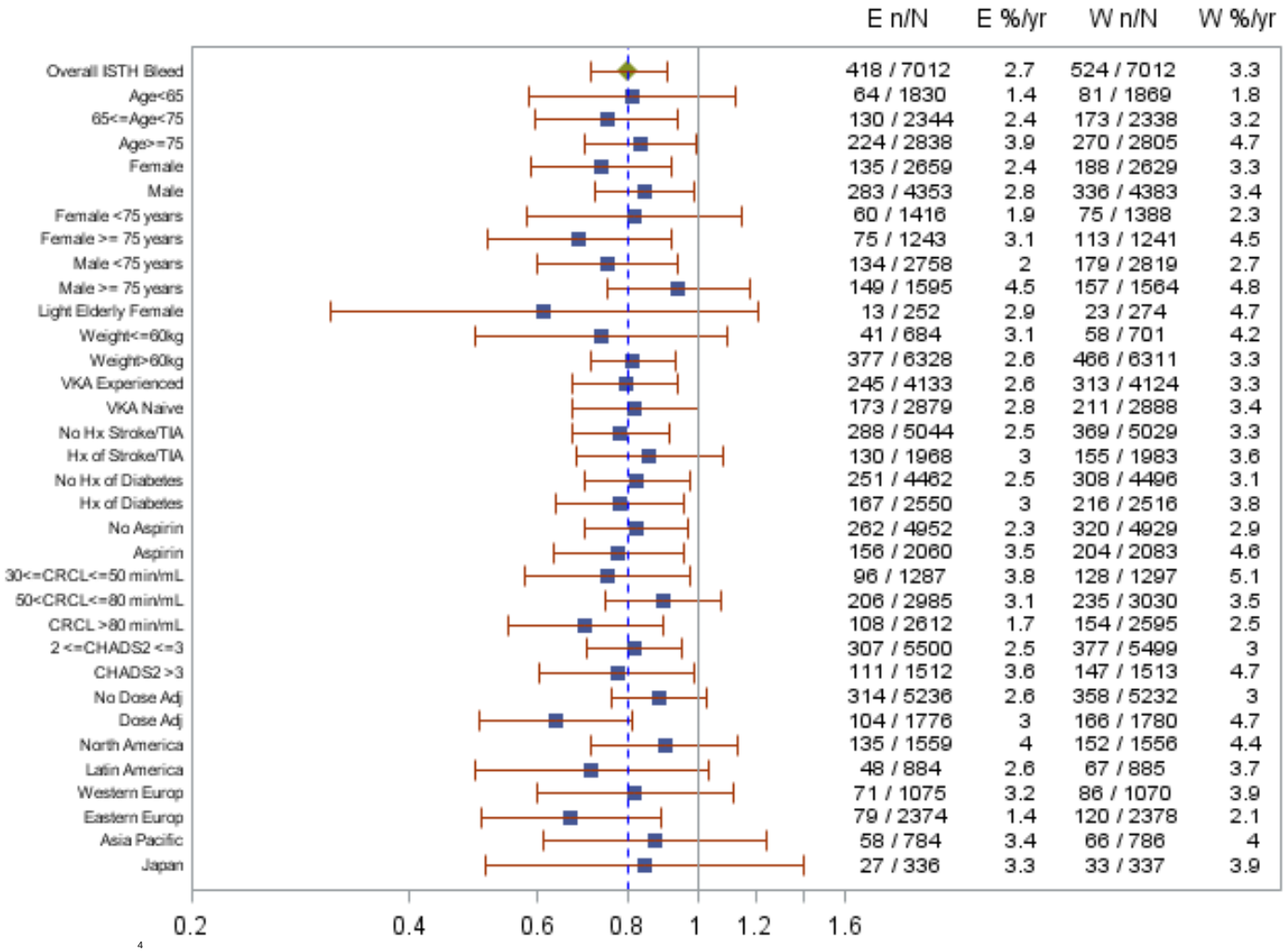
Center TATR	*Edoxaban 30 mg N = 7002* *n (per 100 pt-year)*		*Edoxaban 60 mg N = 7012* *n (per 100 pt-year)*		*Warfarin N = 7012* *n (per 100 pt-year)*		*Edoxaban 30mg vs. W* *HR (95% CI)*		Edoxaban 60 mg vs. W HR (95% CI)	
Q1: <=8.9%	62 / 1614	1.66	115 / 1734	2.98	128 / 1720	3.35	0.49	(0.36, 0.66)	0.89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

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

7.3.2.1.3 Subgroup analysis –Demographics/Medical Conditions at Baseline

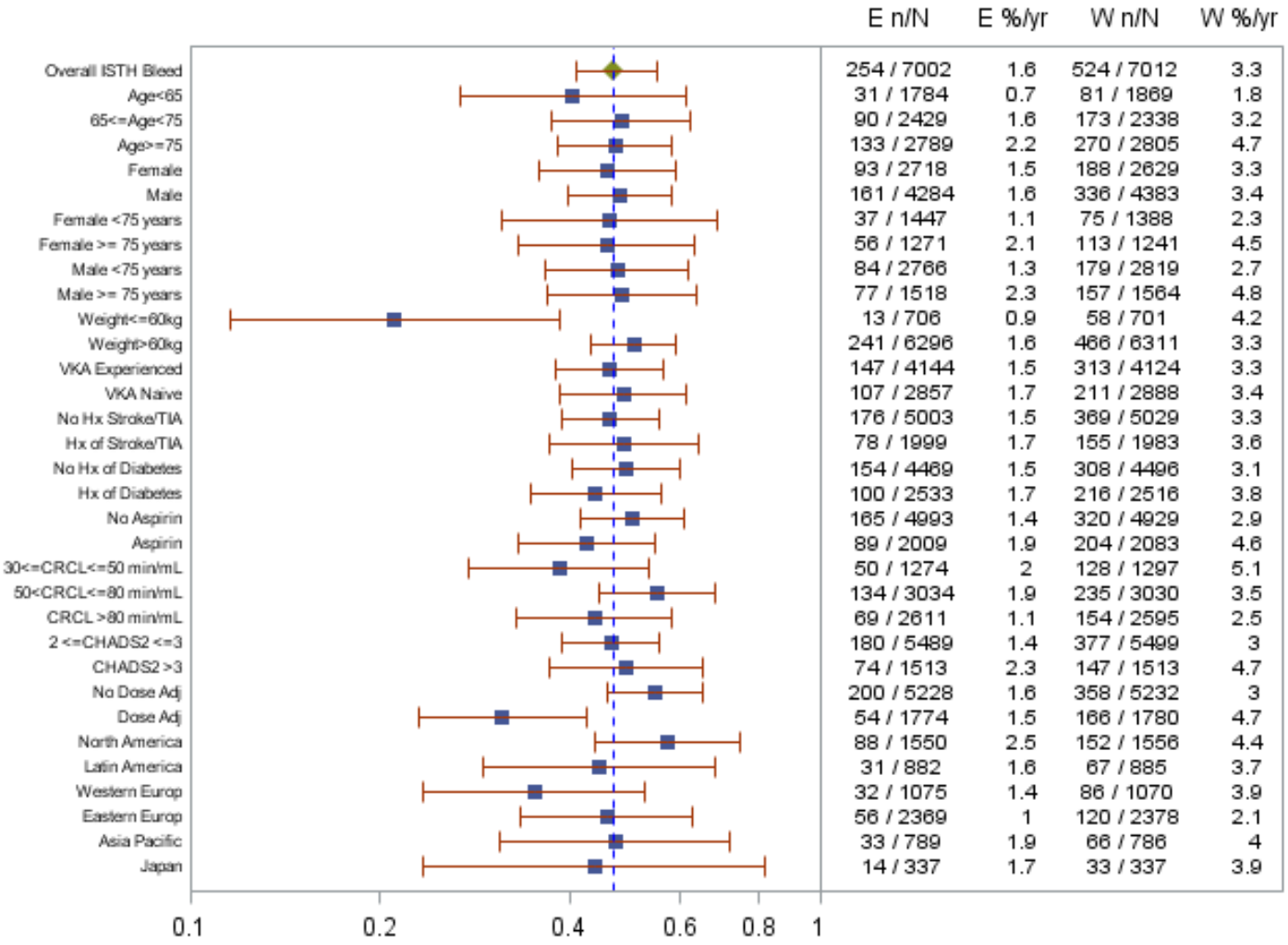
The major bleeding results were in general consistent across subgroups and regions with the point estimates favoring both edoxaban groups (Figure 22 and Figure 23). A few subgroups in the edoxaban arms had considerably less bleeding compared with warfarin including dose adjustment subgroups in both high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

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



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

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



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

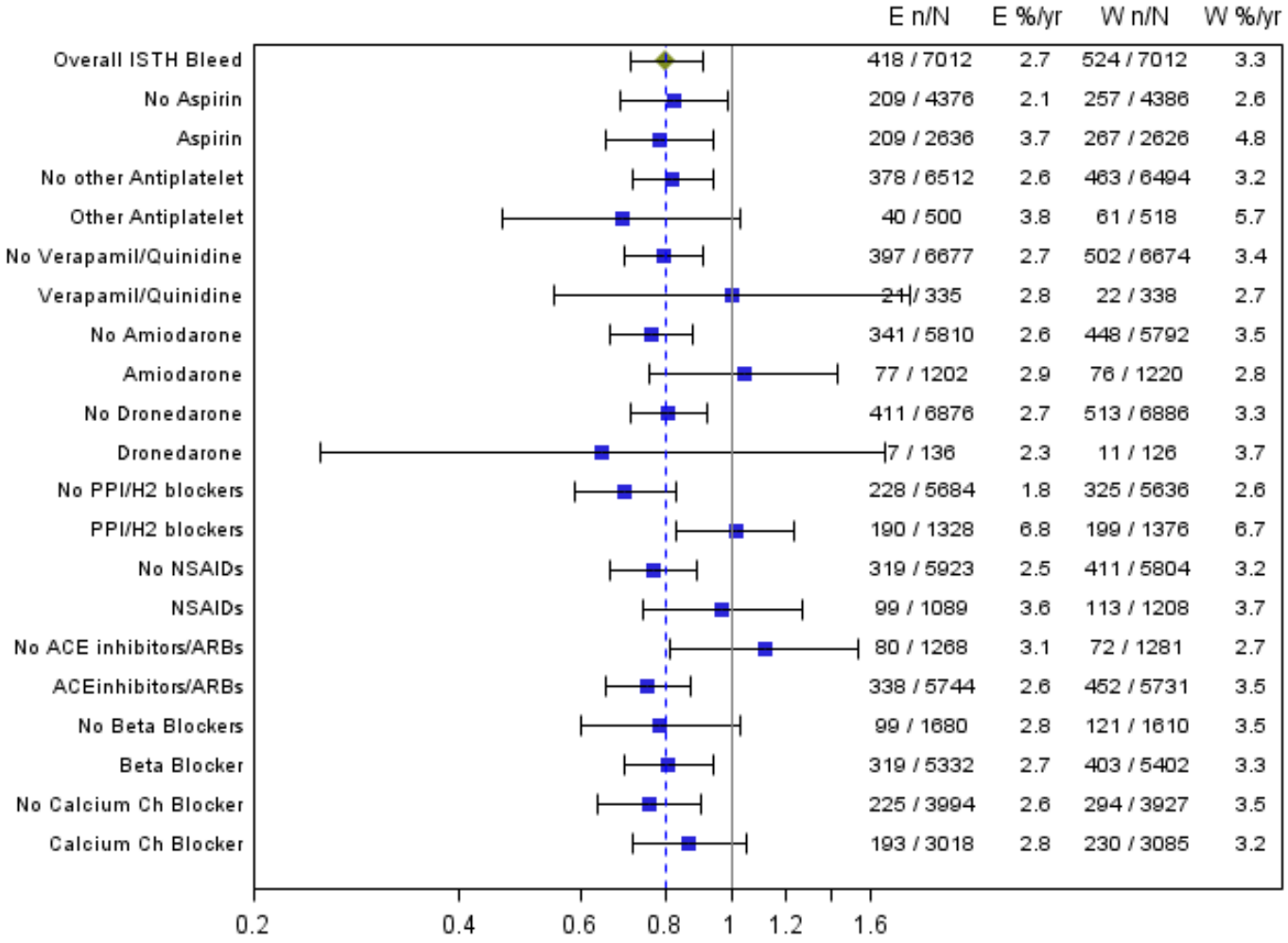
7.3.2.1.4 Subgroup analysis –Concomitant Medication

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

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

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

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



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

7.3.2.1.5 Sensitivity analysis - Overdose/Dosing Error

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

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

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

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

Source: CSR Table 12.31

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

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

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)
Before 12/01/2010*					
Major Bleeding	*74(1.70)*	*146 (3.42)*	*179 (4.17)*	*0.41 (0.31-0.54)*	0.82 (0.66-1.02)
GI	41 (0.94)	82 (1.91)	65 (1.51)	0.62 (0.42-0.92)	1.27 (0.92-1.76)
Intracranial (ICH)	9 (0.21)	20 (0.46)	43 (0.99)	0.21 (0.10-0.43)	0.47 (0.28-0.80)
Fatal Bleeding	5 (0.11)	14 (0.32)	20 (0.46)	0.25(0.09-0.66)	0.71 (0.36-1.40)
On or After 12 /01/2010*					
Major Bleeding	*180 (1.14)*	*272 (1.79)*	*345 (2.25)*	*0.50 (0.42-0.60)*	0.79 (0.68-0.93)
GI	*88 (0.55)*	*150 (0.98)*	*125 (0.80)*	*0.69 (0.52-0.90)*	1.22 (0.96-1.54)
Intracranial (ICH)	32 (0.20)	41 (0.26)	89 (0.57)	0.35 (0.23-0.53)	0.47 (0.32-0.67)
Fatal Bleeding	15 (0.09)	18 (0.12)	39 (0.25)	0.38 (0.21-0.68)	0.47 (0.27-0.81)

Reviewer's analysis, Source: the Applicant's datasets: Blddata, DM and Basegrp.
*Subjects with the first dose after 12/01/2010 were excluded in the analysis
** Subjects with the event or was censored before 12/01/2010 were excluded in the analysis

7.3.2.2 Other Non-major bleeding SAEs

The percentages of subjects in the edoxaban 30 mg, edoxaban 60 mg and the warfarin groups with non-bleeding SAEs were similar during the on-treatment (34.5% 33.0% and 35.9%) and overall study period (43.3%, 42.5% and 44.5%). The most common non-bleeding SAEs were CV diseases in all three treatment groups (~13%).
The reviewer evaluated incidence of SAEs during the on-treatment and overall study period by the MedDRA SOC and PT terms. For the most part, the frequency of SAEs and type of SAEs were similar between the edoxaban and warfarin groups with few exceptions. Table 84 lists the on-treatment SAEs by SOC and related PT terms with a notable difference among the treatment groups (≥ 0.5% more frequently in either edoxaban group compared to the warfarin group). The notable differences during the overall study period are listed in the Appendix 11.

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

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

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

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

Reviewer's analysis. Applicant's dataset: AEEV1 and DM.
*Anemia-related PT include hematocrit abnormal, hematocrit decreased, hemoglobin decreased, red blood cell count decreased, and any PT term containing anemia

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

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

Reviewer's analysis. Applicant's dataset: AEEV1 and DM
*Anemia-related PT include hematocrit abnormal, hematocrit decreased, hemoglobin decreased, red blood cell count decreased, and any PT term containing anemia

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

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

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

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

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

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

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

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

After reviewing the individual cases, 12 vs. 0 ILD SAEs were observed in the edoxaban groups compared with the warfarin group. Additionally, the incidence of ILD SAEs in the edoxaban groups was much higher among subjects with prior history of ILD. Considering the findings in ENGAGE AF in light of the similar post-marketing findings seen in Japanese patients who received rivaroxaban, the potential that edoxaban could cause or exacerbate ILD among those with an existing condition cannot be ruled out. As discussed in Section 7.3.1, the reviewer recommends adding these imbalanced findings to the label.

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

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

Reviewer's Table. Applicant's dataset: AEEV1 & DM.
† SMQ broad terms were used for the analysis
[a]. Hypersensitivity reactions include three SMQs: anaphylactic reaction, angioedema and severe cutaneous adverse reaction
[b]. PTs include alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, blood bilirubin unconjugated increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, liver function test abnormal and transaminases increased.

Table 88 MedDRA Prefer Terms associated with Hypersensitivity Reaction SAEs

MedDRAM 14.1 SMQ	Prefer Term	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Hypersensitivity Reaction SAEs		**104 (1.5%)**	**119 (1.7%)**	**107 (1.5%)**
Anaphylactic reaction (SMQ)	Acute Respiratory Failure	9	11	10
	Anaphylactic Reaction	0	1	1
	Angioedema	0	2	0
	Asthma	15	11	17
	Blood Pressure Decreased	0	0	1
	Bronchospasm	2	1	1
	Cardiac Arrest	8	16	12
	Cardio-Respiratory Arrest	7	9	10
	Cardiovascular Insufficiency	2	1	3
	Chest Discomfort	4	2	4
	Choking	0	0	1
	Circulatory Collapse	1	1	1
	Cough	0	1	0
	Dyspnea	12 (0.17%)	16 (0.23%)	9 (0.13%)
	Hypotension	23	17	15
	Edema	0	1	0
	Rash	0	1	0
	Respiratory Arrest	0	1	0
	Respiratory Distress	3	3	2
	Respiratory Failure	8 (0.11%)	15 (0.21%)	8 (0.11%)
	Swelling Face	1	0	0
	Urticaria	0	0	2
Angioedema (SMQ)	Angioedema	0	2	0
	Choking	0	0	1
	Drug Hypersensitivity	1	3	2
	Generalized Edema	1	0	0
	Hypersensitivity	2	1	1
	Obstructive Airways Disorder	1	0	0
	Edema	0	1	0
	Edema Peripheral	2	3	5
	Scrotal Edema	1	0	0
	Swelling Face	1	0	0
	Urticaria	0	0	2
Severe cutaneous adverse reactions (SMQ)	Conjunctivitis	1	0	0
	Drug Eruption	2	1	3
	Drug Rash With Eosinophilia And Systemic	0	1	0
	Erythema Multiforme	0	1	0
	Skin Necrosis	0	1	1
	Stevens-Johnson Syndrome	2	1	0

Table 89 MedDRA Prefer Terms for Acute central respiratory depress (SMQ) and Interstitial lung disease (SMQ) SAEs

MedDRAM 14.1 SMQ	Prefer Term	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Acute central respiratory depression (SMQ)	Acute Respiratory Distress Syndrome	1	1	1
	Acute Respiratory Failure	9	11	10
	Asphyxia	0	0	1
	Cardiac Arrest	8	16	12
	Cardiopulmonary Failure	5	2	1
	Cardio-Respiratory Arrest	7	9	10
	Dyspnea	12	16	9
	Hypercapnia	0	0	1
	Hypoxia	1	1	0
	Respiratory Arrest	0	1	0
	Respiratory Disorder	0	1	0
	Respiratory Distress	3	3	2
	Respiratory Failure	8	15	8
	Sleep Apnea Syndrome	6	5	2
Interstitial lung disease (SMQ)	Acute Respiratory Distress Syndrome	1	1	1
	Allergic Granulomatous Angiitis	0	0	1
	Alveolitis Allergic	1	0	0
	Bronchiolitis	0	1	1
	Interstitial Lung Disease	7	6	3
	Organizing Pneumonia	2	1	0
	Pneumonitis	2	2	1
	Pulmonary Fibrosis	3	4	1
	Pulmonary Granuloma	0	0	1
	Pulmonary Toxicity	0	2	0
	Radiation Pneumonitis	0	1	0

Reviewer's table, the Applicant's dataset: AEEV1 and

Table 90 Reported ILD status at Baseline*

	Edoxaban 30 mg N = 7002	Edoxaban 60 mg N = 7012	Warfarin N=7012
ILD-related Conditions	76 (1.1%)	66 (0.9%)	66 (0.9%)
Idiopathic Pulmonary Fibrosis	0	0	1 (0.0%)
Interstitial Lung Disease	13 (0.2%)	8 (0.1%)	10 (0.1%)
Pulmonary Fibrosis	65 (0.9%)	59 (0.8%)	56 (0.8%)

Reviewer's Table. Applicant's dataset: MH & DM.
*Pulmonary status was not systematically examined at baseline (i.e. no chest x-ray at baseline). The analyses were based on the reported medical history at baseline.

7.3.3 Dropouts and/or Discontinuations

In ENGAGE AF, subjects were allowed to have multiple interruptions and resumptions of study drug. A study drug interruption was defined as > 3 consecutive days during which the subject did not take study drug. Discontinuation of study drug was evaluated at the end of study based on those subjects who never resumed study drug after the last interruption. Subjects were identified as discontinuation of study drug if they were not on study drug within 30 days of the CSED visit (subjects with a CSED visit) or within 30 days of CSED announcements (subjects without a CSED visit). Data on study drug interruptions/discontinuation and the reasons for interruptions/disconsolation by treatment regimen are shown in Table 91 and Table 92.

Overall, a higher percentage of subjects discontinued study drug temporarily or permanently in dose-adjusted subset compared to no dose-adjusted subset in each of the three treatment groups. The proportion was similar among the three treatments.

There was no imbalance among treatment groups regarding the number of and reason for study drug interruptions. However, the duration of study drug interruptions was longer in both edoxaban groups compared with the warfarin group (Table 91).

The most common reason for discontinuation of study drug was AE or suspected endpoint event in all treatment groups. A slightly higher percent of subjects discontinued study drug due to cardiac ischemic events in the edoxaban 30 mg group (both dose-adjusted and no dose adjusted subsets) and edoxaban 60 mg dose adjusted subset compared with the warfarin group. Also, a higher percent of subjects discontinued study drug due to investigator's decision in the dose adjusted subset of the edoxaban groups compared to the dose adjusted subset of the warfarin group (Table 92). Time to study drug discontinuation was similar among the treatment groups (Figure 25).

Table 91 Study Drug Interruption by Dose Regimen

	Edoxaban 30mg N = 7002		Edoxaban 60mg N = 7012		Warfarin N = 7012	
	Dose Adj (N =1774)	No Dose Adj (N = 5228)	Dose Adj (N = 1776)	No Dose Adi (N=5236)	Dose Adj (N=1780)	No Dose Adj (N = 5232)
Subjects with at least one study drug interruption, n(%)	1228 (69.2)	3098 (59.3)	1257 (70.8)	3129 (59.8)	1325(74.4)	3265(62.4)
Number of Occurrences, n(%)						
≥ 2	482 (27.2)	1219 (23.3)	453 (25.5)	1248 (23.8)	544 (30.6)	1352 (25.8)
≥ 4	95 (5 4)	238 (4 6)	75 (4 2)	238 (4 5)	103 (5 8)	244 (4 7)
≥ 6	13 (<1)	59 (1.1)	14 (<1)	43 (<1)	29 (1.6)	47 (<1)
Median maximum days of interruptions (Days)	99	48	131	50	82	38
Median total days of interruptions (Days)	118	61.5	159	62	103	49
Reason for interruption, n(%)						
AE or Suspected Endpoint Event	689 (38.8)	1567 (30.0)	699 (39.4)	1628 (31.1)	823 (46.2)	1692 (32.3)
Death	75 (4.2)	127 (2.4)	62 (3.5)	142 (2.7)	67 (3.8)	156 (3.0)
Investigator Decision	472 (26.6)	1404 (26.9)	474 (26.7)	1351 (25.8)	485 (27.2)	1456 (27.8)
Subject Decision*	241 (13.6)	677 (12.9)	227 (12.8)	644 (12.3)	248 (13.9)	704 (13.5)
Subject Refused Routine Follow-up	50 (2.8)	106 (2.0)	62 (3.5)	137 (2.6)	58 (3.3)	138 (2.6)
Unknown	2 (<1)	3 (<1)	1 (<1)	3 (<1)	2 (<1)	2 (<1)

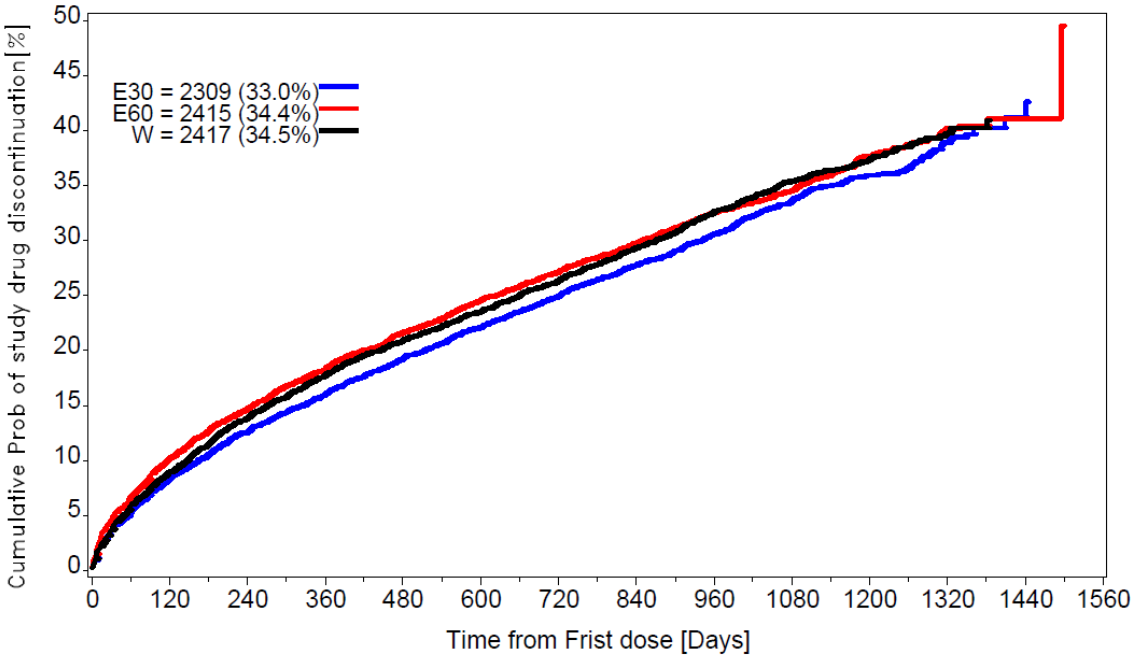
This table includes all the interruptions whether or not study drug was reassumed after the interruption.
Reviewer's Table. Applicant's datasets: DM and EX.
Table 12.3 in CSR did not include some patients who discontinued the study drug due to death, withdrawal of consent or unknown reason (The Applicant's response [seq0037] to IR dated on April 11, 2014)
*withdrawal of consent is included in subject decision

Table 92 Study Drug Discontinuation by Dose Regimen

	Edoxaban 30mg N = 7002		Edoxaban 60mg N = 7012		Warfarin N = 7012	
	Dose Adj (N =1774)	No Dose Adj (N = 5228)	Dose Adj (N = 1776)	No Dose Adi (N=5236)	Dose Adj (N=1780)	No Dose Adj (N = 5232)
Subjects who discontinued study drug	774 (43.6)	1535 (29.4)	817 (46.0)	1598 (30.5)	837(47.0)	1580 (30.2)
Reason for discontinuation, n(%)						
AE or Suspected Endpoint Event	396 (22.3)	697 (13.3)	426 (24.0)	778 (14.9)	476 (26.7)	692 (13.2)
1. Cerebrovascular Event	57 (3.2)	107 (2.0)	52 (2.9)	75 (1.4)	51 (2.9)	98 (1.9)
2. Systemic Embolic Event	3 (0.2)	10 (0.2)	1 (0.1)	5 (0.1)	3 (0.2)	2 (0.0)
3. Bleeding/Surgery	35 (2.0)	111 (2.1)	56 (3.2)	181 (3.5)	77 (4.3)	126 (2.4)
4. Cardiac Ischemic Event	9 (0.5)	44 (0.8)	11 (0.6)	29 (0.6)	6 (0.3)	33 (0.6)
5. Hepatic Event	11 (0.6)	23 (0.4)	12 (0.7)	26 (0.5)	12 (0.7)	25 (0.5)
6. Bone Fracture	15 (0.8)	17 (0.3)	9 (0.5)	12 (0.2)	20 (1.1)	18 (0.3)
7. Malignancy Event	20 (1.1)	54 (1.0)	15 (0.8)	62 (1.2)	21 (1.2)	55 (1.1)
8. Other AE or SAE	246 (13.9)	331 (6.3)	270 (15.2)	388 (7.4)	285 (16.0)	334 (6.4)
Death	72 (4.1)	122 (2.3)	60 (3.4)	137(2.6)	65 (3.7)	149 (2.8)
Investigator Decision	120 (6.8)	229 (4.4)	127 (7.2)	190 (3.6)	96 (5.4)	222 (4.2)
Subject Decision	139 (7.8)	401 (7.7)	148 (8.3)	375 (7.2)	144 (8.1)	408 (7.8)
Subject Refused Routine Follow-up	45 (2.5)	83 (1.6)	55 (3.1)	114 (2.2)	54 (3.0)	107 (2.0)
Unknown	2 (<1)	3 (<1)	1 (<1)	3 (<1)	2 (<1)	2 (<1)

Reviewer's Table. Applicant's datasets: DM, EX.

Figure 25 Kaplan-Meier Estimate of time to study drug discontinuation



No. at risk														
E30	7002	6403	6110	5872	5644	5446	5251	4528	3400	2099	940	256	32	0
E60	7012	6293	5974	5721	5491	5285	5101	4427	3294	2018	909	236	39	0
W	7012	6380	6030	5758	5540	5358	5160	4443	3250	2017	921	256	42	0

Reviewer's analysis, Source: Applicant dataset: DM

Reviewer's Comment(s): In general, the three treatments groups (both dose and non-dose adjustment subsets) had very similar patterns in terms of dropouts and discontinuation. The observed differences are small and should not significantly impact the study findings.

7.3.4 Significant Adverse Events

The Applicant discussed hepatic abnormalities, malignancy, bone fracture and anemia as adverse events of interest in the CSR. Hepatic abnormalities and malignancies are reviewed in Section 7.3.5.1 and Section 7.3.5.2. Anemia is reviewed in Section 7.4.1. There is no imbalance observed for the frequency and type of bone fracture among the treatment groups. The percentage of new bone fractures was similar in the edoxaban 30 mg, edoxaban 60 mg and warfarin groups (6.3%, 5.7% and 6.4%, respectively)

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Hepatic abnormalities

7.3.5.1.1 Hepatic Laboratory Data

Pre-defined liver laboratory abnormalities and hepatic cases of special interest (SAEs, or AEs leading to study drug interruption/discontinuation) were independently reviewed by two CEC hepatic specialists for adjudication. Table 93 summarizes liver enzyme and bilirubin abnormalities during the study period (on treatment + 30 days). The percentage of subjects in the edoxaban 30 mg, edoxaban 60 mg and warfarin groups with ALT or AST ≥ 3 x ULN was similar (2.5%, 2.6% and 2.5 %, respectively). However, it is noted that the edoxaban 60 mg had more cases with extremely high liver enzyme values compared to the warfarin group. The number of subjects with ALT or AST ≥ 3 x ULN and beyond was consistently higher in the edoxaban 60 mg group compared with the warfarin group. The number of subjects with combination abnormality seems similar among the treatment groups.

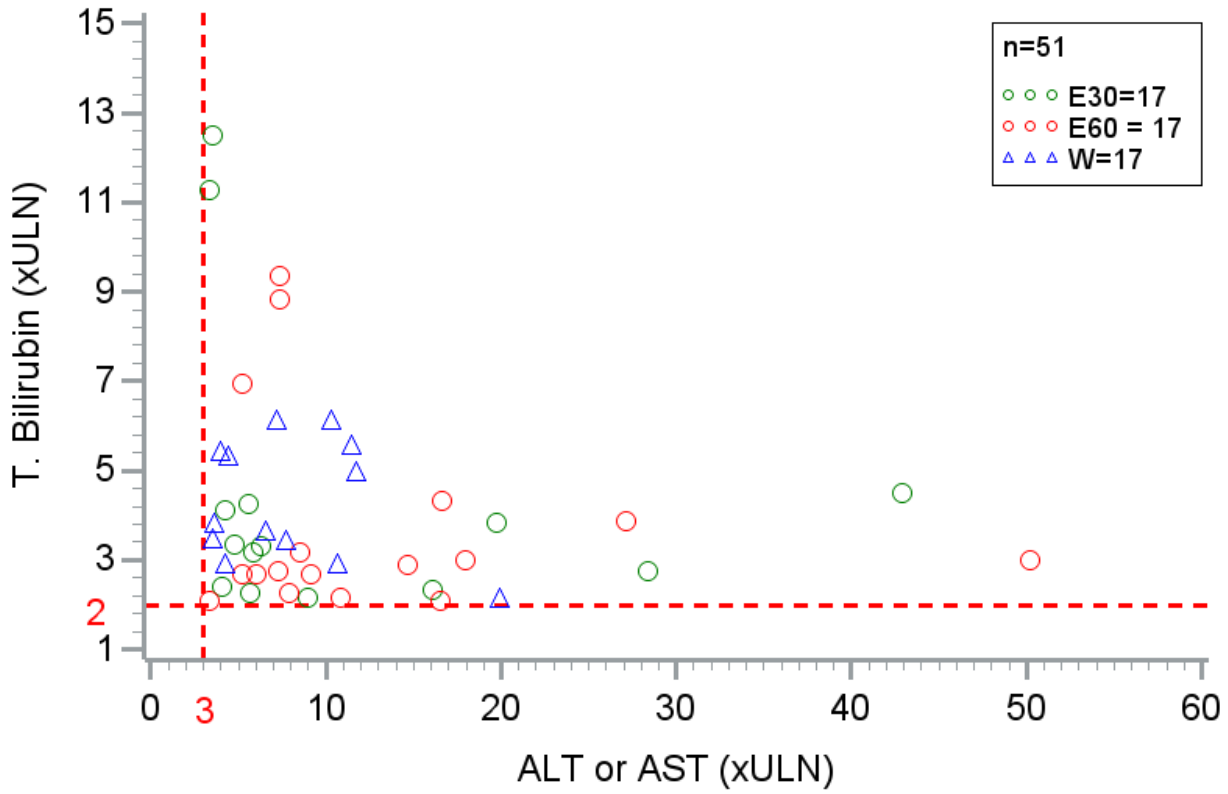
Figure 26 shows the potential Hy's law cases using the combination abnormality for liver enzyme and total bilirubin (TBL). All these 51 potential Hy's law cases were adjudicated by the hepatic specialists in the study. The reviewers reviewed the patient profile for each case, including reported AE/SAE, laboratory data, and concomitant medicines. The majority of cases had clear alternative reasons for elevated transaminases or bilirubin. There were a few cases in the edoxaban groups who presented with complex clinical manifestations and the reviewers were not certain about the adjudication results. In combination with the findings from the adjudication results (3 adjudicated Hy's law cases in the edoxaban groups, see Section 7.3.5.1.2), the reviewers were not totally comfortable about the observed liver data and decided to request an OSE liver consultation. Please see a brief summary of the consultation result in Section 7.3.5.1.3

Table 93 Liver Enzyme and Bilirubin Abnormalities – On Treatment Period + 30 days†

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Subject with ALT	**M = 6917**	**M = 6915**	**M = 6938**
≥ 2 x ULN	343 (5.0%)	342 (4.9%)	324 (4.7%)
≥ 3 x ULN	145 (2.1%)	137 (2.0%)	132 9 (1.9%)
≥ 5 x ULN	49 (0.7%)	62 (0.9%)	47 (0.7%)
≥ 8 x ULN	21 (0.3%)	30 (0.4%)	18 (0.3%)
≥ 10 x ULN	14 (0.2%)	23 (0.3%)	13 (0.2%)
≥ 20 x ULN	5 (0.1%)	9 (0.1%)	2 (<0.1%)
Subject with ALT or AST	**M = 6917**	**M = 6915**	**M = 6938**
≥ 2 x ULN	419 (6.1%)	436 (6.3%)	411 (5.9%)
≥ 3 x ULN	176 (2.5%)	181 (2.6%)	171 (2.5%)
≥ 5 x ULN	64 (0.9%)	76 (1.1%)	67 (1.0%)
≥ 8 x ULN	29 (0.4%)	38 (0.5%)	28 (0.4%)
≥ 10 x ULN	20 (0.3%)	28 (0.4%)	17 (0.2%)
≥ 20 x ULN	9 (0.1%)	9 (0.1%)	3 (<0.1%)
Subjects with Total Bilirubin	**M = 6927**	**M = 6914**	**M = 6940**
≥ 1.5 x ULN	472 (6.8%)	487 (7.0%)	462 (6.7%)
≥ 2 x ULN	167 (2.4%)	179 (2.6%)	174 (2.5%)
Combination abnormality	**M = 6925**	**M = 6914**	**M = 6938**
ALT or AST > 3 x ULN and concurrent TB > 2 x ULN and ALP < 2 x ULN*	17 (0.2%)	17 (0.2%)	17 (0.2%)

†Percentage was calculated based on number of subject (M) who had at least one liver measurement
*Concurrent defined as TBL and ALP within 30 days after the ALT or AST. All lab measurements during on-treatment + 30 days were included. Reviewer's Table. The Applicant's dataset: LB & DM

Figure 26 Potential Hy's law subjects based on liver chemistries (Max ALT or AST > 3 x ULN concurrent TBL > 2xULN & AP <2xULN)

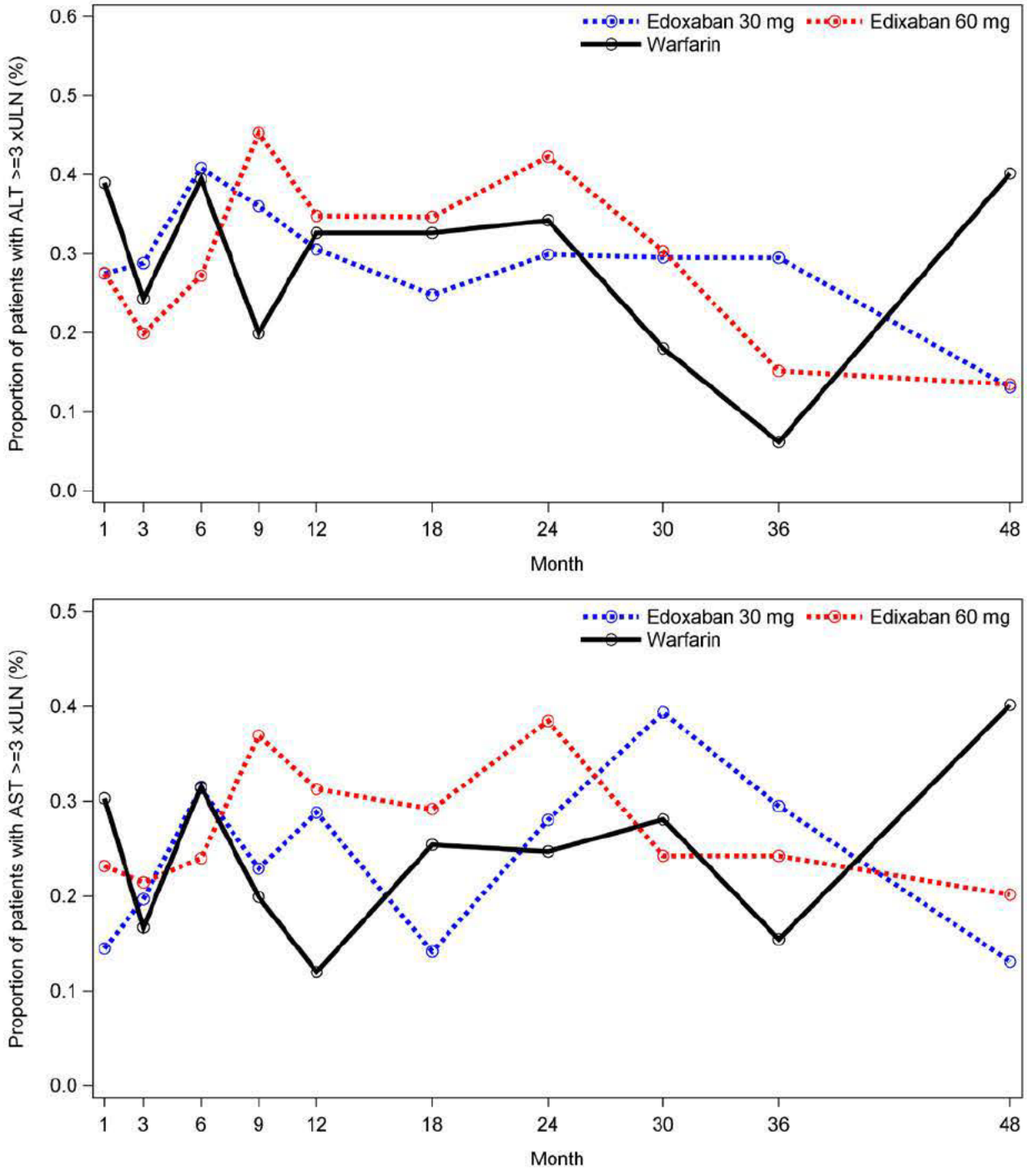


Reviewer's analysis. Source: Applicant's dataset: lbliv."Concurrent" defined as TB and ALP within 30 days after the ALT or AST. When ALT or AST were greater than 3 x ULN with "concurrent" total bilirubin > 2xULN and ALP < 2x ULN, the ALT or AST with associated TB were plotted. All lab values within 30 days after the last study drug were used for the safety analysis set.

Reviewer's Comment(s): There were different criteria for combination liver abnormality. The reviewer used more "specific" criteria (Max ALT or AST > 3 x ULN concurrent TBL > 2xULN & AP <2xULN) and found no imbalance regarding number of potential Hy's law cases based on liver chemistries.

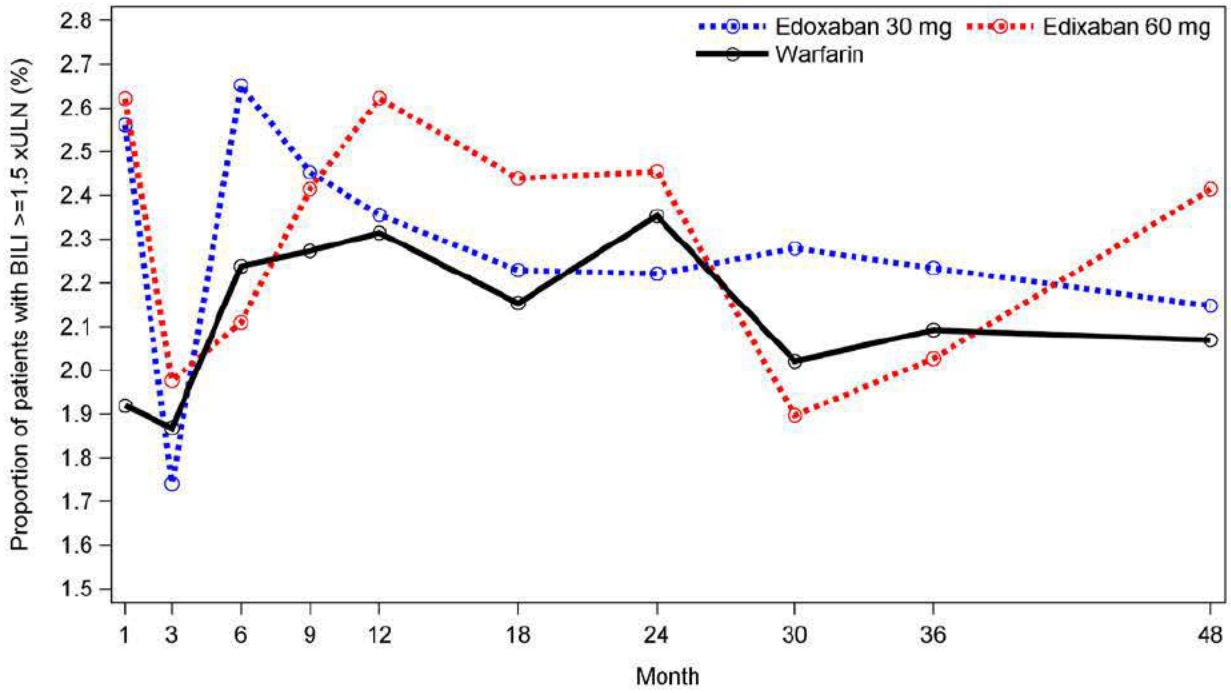
The reviewer also evaluated the time course of liver abnormalities in each treatment group. The rate of cases with abnormal transaminases was low and very similar among the treatment groups (Figure 27). As for TBL, edoxaban groups had a markedly higher percent of subjects with TBL ≥ 1.5 x ULN compared with the warfarin group at month one after study drug exposure, though the difference diminished over time and was less apparent using the criteria of TBL ≥ 2 x ULN (Figure 28). Overall, there were no clinically meaningful differences among the treatment groups with regard to incidence of liver abnormalities.

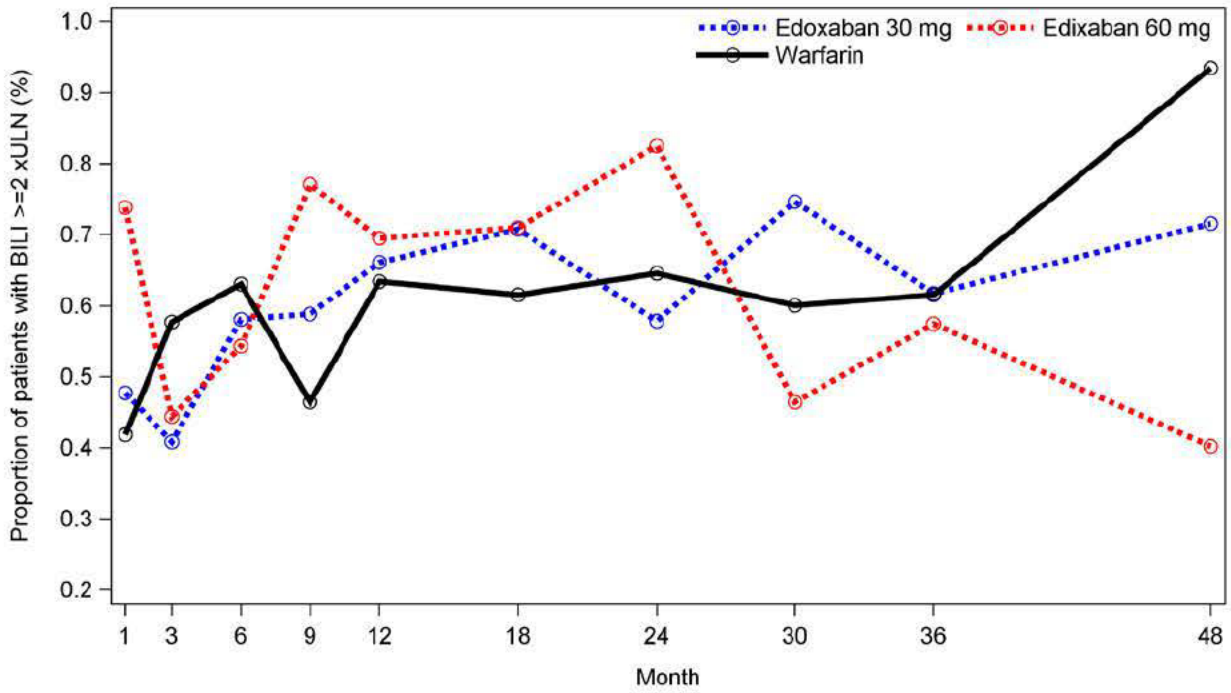
Figure 27 Percentage of patients with liver enzyme abnormalities across the study period



Reviewer's Figure, the Applicant's dataset: LB & DM. All the liver measurements during on treatment + 30 days were included in the analyses.

Figure 28 Percentage of patients with Total Bilirubin abnormalities

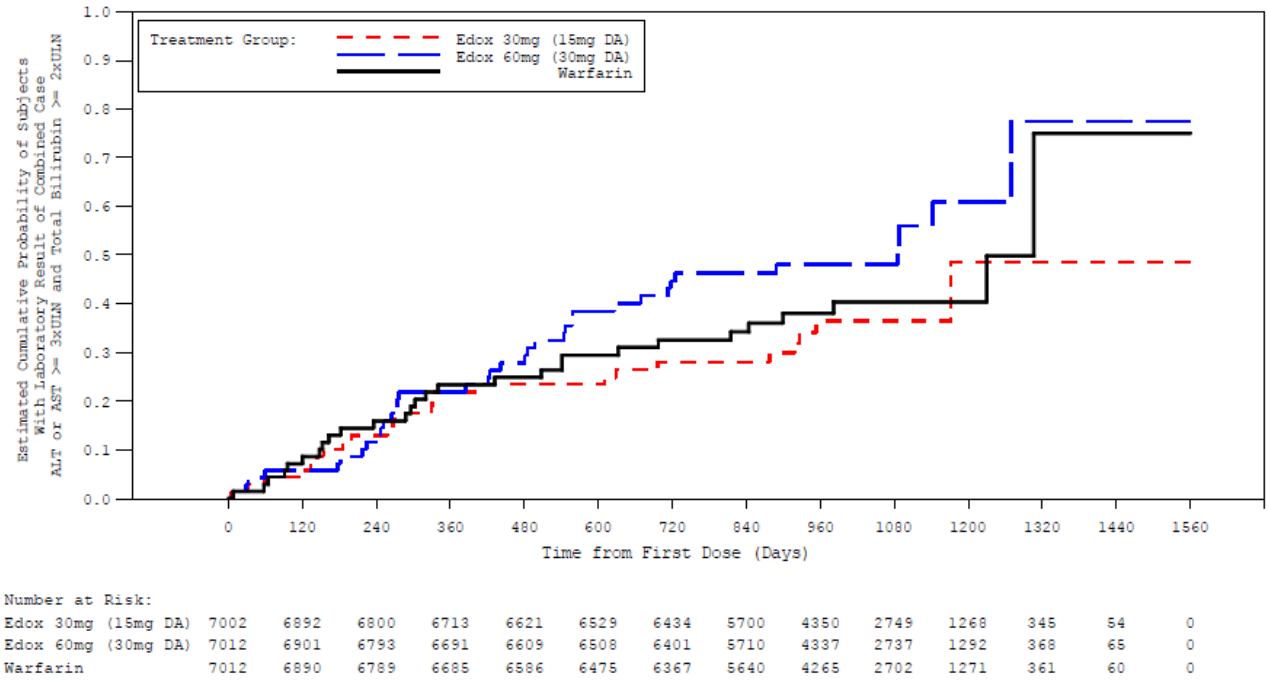




Reviewer's Figure, the Applicant's dataset: LB & DM. All the liver measurements during on treatment + 30 days were included in the analyses.

Figure 29 shows the KM curves of time to the first laboratory result of combined ALT or AST ≥ 3 x ULN and concurrent TBL ≥ 2 x ULN during the overall study period. The KM curves were very similar for the first 14 months and started separating after that with slightly more subjects in the edoxaban 60mg group having combination liver abnormality.

Figure 29 The KM plot for time to first combination abnormality (ALT or AST≥ 3xULN and TB ≥2xULN) during the overall study period



Source: the Applicant's CSR Figure 14.3.1.154

Reviewer's Comment(s): Slightly higher numbers of subjects in the edoxaban 60 mg group compared with warfarin (n = 22 vs. 15) had liver combination abnormality defined using more "sensitive" criteria such as Max ALT or AST ≥ 3x ULN concurrent with TBL ≥ 2x ULN.

It is possible that subjects discontinued the study when their transaminases or TBL started going up but not yet reached the Hy's Law criteria for abnormalities. Therefore, the reviewer evaluated liver enzyme and TBL among subjects who permanently discontinued the study to check if there is any imbalance among the treatment groups (Table 94). In general, the percentage of subjects who discontinued and who had liver abnormalities was similar among the treatment groups. There was a slightly higher percentage of subjects in the edoxaban groups, particularly in the edoxaban 30 mg group, compared with the warfarin group with ALT ≥ 1.5 x ULN before study drug discontinuation.

Table 94 Liver Enzyme and Bilirubin Abnormalities among subjects with permanent discontinuation – On Treatment Period + 30 days[†]

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Subject with ALT	**M=2234**	**M=2318**	**M=2343**
≥ 1.5xULN	224 (10.0%)	222 (9.6%)	213 (9.1%)
≥ 2 x ULN	111 (5.0%)	122 (5.3%)	113 (4.8%)
≥ 3 x ULN	59 (2.6%)	63 (2.7%)	56 (2.4%)
Subject with ALT or AST	**M=2235**	**M=2318**	**M=2343**
≥ 1.5 x ULN	278 (12.4%)	277 (12.0%)	281 (12.0%)
≥ 2 x ULN	142 (6.4%)	159 (6.9%)	151 (6.4%)
≥ 3 x ULN	70 (3.1%)	82 (3.5%)	74 (3.2%)
Subjects with Total Bilirubin	**M=2234**	**M=2317**	**M=2345**
≥ 1.5 x ULN	157 (7%)	169(7.3%)	171(7.3%)
≥ 2 x ULN	56 (2.5%)	65 (2.8%)	73 (3.1%)

[†]Percentage was calculated based on number of subject (M) who had at least one liver measurement of interest . Reviewer's Table, the Applicant's dataset: LB & DM

7.3.5.1.2 Cases Evaluated and Adjudicated by Hepatic Specialists

Table 95 summarizes the results of adjudication performed by the hepatic specialists in ENGAGE AF. The incidence across the types of liver injury was similar among the treatment groups. For the hepatocellular injury events, a slightly higher percent of cases in the edoxaban 60 mg group compared with the warfarin group were adjudicated as possibly related to the study drug and as a severe event. There were 3 adjudicated Hy's law cases, 2 in the edoxaban 60 mg group and 1 in the edoxaban 30 mg group. The adjudication criteria for Hy's law case was liver abnormality of ALT ≥ 3 x ULN and simultaneous TLB ≥ 2 x ULN. Alternative causes (e.g., biliary obstruction) must be excluded to satisfy Hy's law rule.

Table 95 Hepatic events adjudicated by hepatic specialists – on treatment period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Subjects with Events set for adjudication	146 (2.1%)	145(2.1%)	144 (2.1%)
Number of adjudicated events	170 (2.4%)	163 (2.3%)	164 (2.3%)
Nature of Liver Injury for all events			
Hepatocellular Injury	73 (1.0%)	84 (1.2%)	83 (1.2%)
Mixed Hepatocellular/Cholestasis	19 (0.3%)	16 (0.2%)	21 (0.3%)
Cholestasis	10 (0.1%)	4 (<0.1%)	6 (<0.1%)
Other	47 (0.7%)	41 (0.6%)	37 (0.5%)
Unable to assess due to insufficient data	0	0	0
No liver injury	8 (0.1%)	5 (0.1%)	7(0.1%)
Causal Relationship to Study Drugs of All Hepatocellular Injury Events			
Probably/Possible	11 (0.2%)	23 (0.3%)	12(0.2%)
Unlikely/Unrelated	65 (0.9%)	65 (0.9%)	75 (1.1%)
Severity of All Hepatocellular Injury Events			
Severe Liver Injury	9 (0.1%)	16 (0.2%)	10 (0.1%)
Hy's Rule Satisfied	1 (<0.1)	2 (<0.1)	0 (0.0)
Moderate Liver Injury	11 (0.2%)	9 (0.1%)	12 (0.2%)
Mild Liver Injury	50 (0.7%)	59 (0.8%)	58 (0.8%)
Minimal Liver Injury	4 (0.1%)	1 (<0.1%)	3 (<0.1%)
Unable To Assess Due To Insufficient Data	0 (0.0%)	0 (0.0%)	1 (<0.1%)

Reviewer's analysis, the Applicant's dataset: Hadjinv, DM

Reviewer's Comment(s): The liver laboratory data and the adjudication results of hepatic cases in the trial revealed a slightly worse profile for the edoxaban 60 mg group compared with the warfarin group. Although the imbalance was small, the reviewer requested an OSE liver consultation for a comprehensive review on the liver data in both ENGAGE AF and Hokusai VTE (see Section 7.3.5.1.3)

7.3.5.1.3 OSE Liver Consultation

The DCRP requested a liver consultation through OSE dated May 2014 after preliminary review of the liver data in ENGAGE AF. Dr. Senior reviewed data related to liver toxicity in both ENGAGE AF and HOKUSAI VTE trials. He used the eDISH program to review all the cases with both ALT/AST and TBL elevations above 3 x ULN and 2 x ULN (17 cases in HOKUSAI- VTE and 84 cases in ENGAGE AF). The time course of all liver tests (ALT, TBL, AST and ALP) plus a narrative describing all pertinent clinical factors observed and recorded were inspected (see OSE consult review for detail dated September 26, 2014).

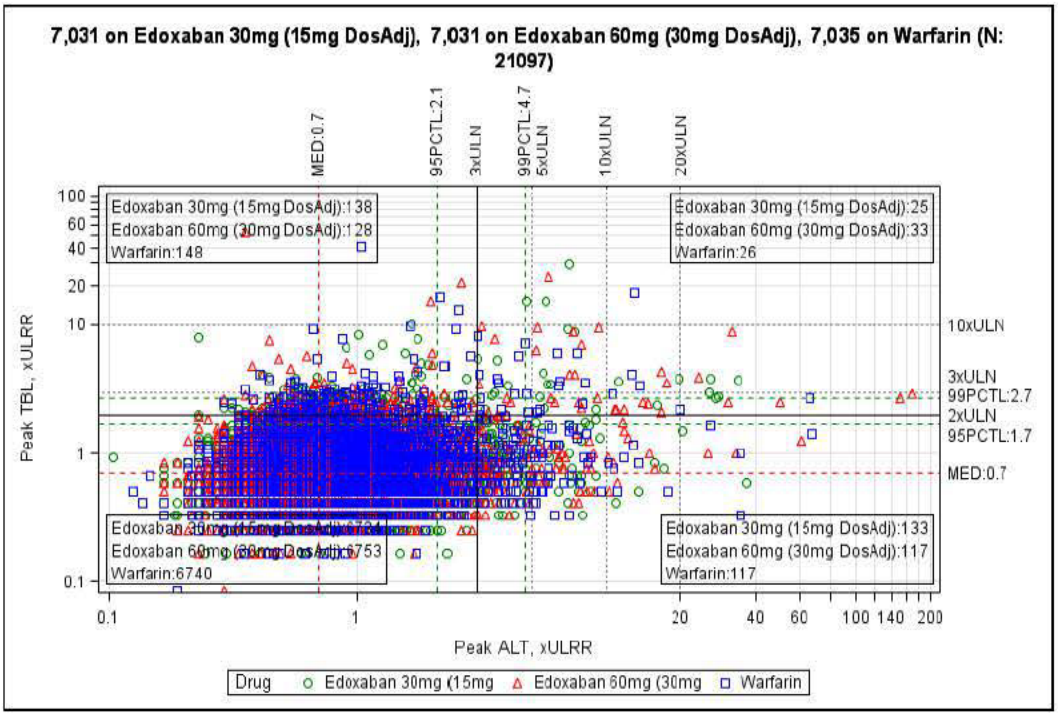
Figure 30 showed the eDISH graphs for ENGAGE AF, illustrating the peak observed ALT on the x-axis and TBL concentration on the y-axis for all the randomized subjects and cases in the upper-right quadrant. After thorough review of individual cases in the upper-right quadrant, Dr. Senior did not identify a clear-cut case of edoxaban-induced serious[30] and probably[31] drug-caused hepatocellular jaundice in ENGAGE AF (see Appendix 12 for review of each individual case), as well as HOKUSAI- VTE. As mentioned in Section 7.3.5.1.2, the hepatic adjudication revealed 3 Hy's law cases. However, Dr. Senior did not think those cases met the criteria for serious/probable Hy's law case. Overall, the liver safety profile for edoxaban is consistent with findings for the previously approved drugs in the class.

Dr. Senior pointed out that there was a fairly high incidence of liver test abnormalities, higher and more than seen with most drugs (e.g. ALT or AST > 20x ULN) in ENGAGE AF as well as in other NOACs trials. He believed that this high proportion of liver dysfunction or elevations of ALT and AST seen in ENGAGE AF was secondary to cardiac disease and the diagnosis of "cardiac hepatopathy"[32] was overlooked in this AF population. Figure 31 shows an example of the effect of acute heart failure and shock on liver tests illustrated by an extremely sharp rise in serum aminotransferases, AST earlier, faster, and higher than ALT, and very rapid decline of AST and ALT more slowly, with little change in TBL and none in ALP. Dr. Senior stated that there were probably many patients who drifted in and out of mild to moderate heart failure in this study of elderly patients with chronic AF. He stressed the importance of distinguishing cases with "cardiac hepatopathy" from liver disease in order to provide correct management of the care because liver dysfunction could rapidly improve with the proper treatment of heart failure in those cases.

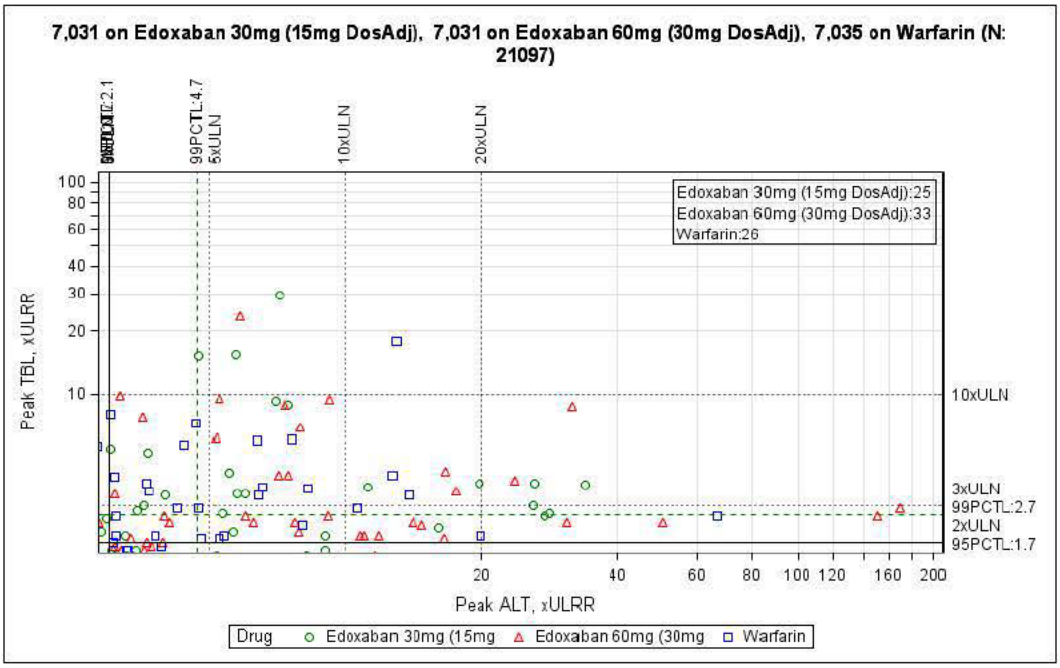
[30] Dr. Senior defined serious as liver functional disorder sufficient to disable the patient so he/she can't work, or require hospital care, liver failure with secondary renal or brain dysfunction, death due to liver failure or need for liver transplantation
[31] Dr. Senior defined probable as more likely than all other possible causes combined, roughly in the range of >50 to 75% likely
[32] Dr. Senior used the term "cardiac hepatopathy" to represent hepatic effects and complications caused by vascular shock including terms such as "nutmeg liver", "ischemic hepatitis", "hypoxic hepatitis" and "hypoxic hepatopathy"

Figure 30 Liver serum chemistries plot: (a) Peak ALT vs. Peak TBL for all randomized subjects (b) Cases in the upper- right quadrant (Max ALT> 3xULN vs. Max TBL> 2xULN)

(a)

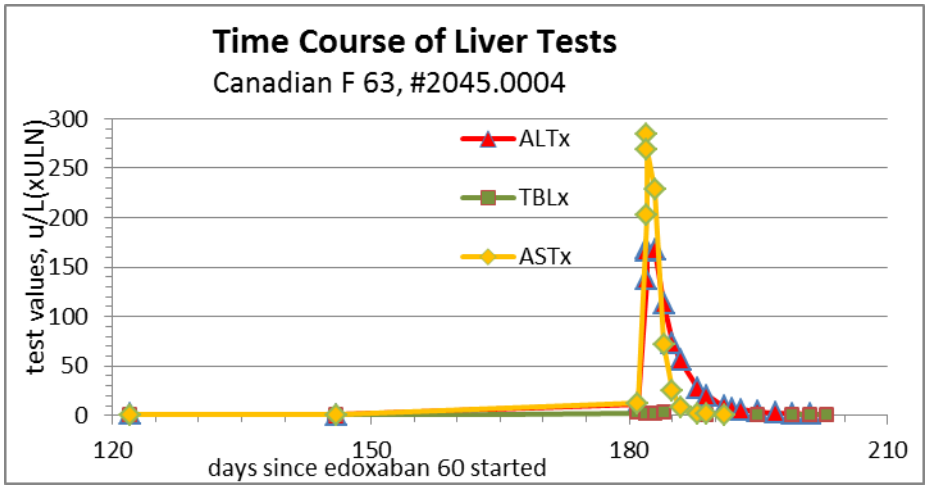


(b)



Source: OSE Hepatology Consultation

Figure 31 A classic picture of cardiac hepatopathy in ENGAGE AF-TIMI48



Source: OSE Hepatology Consultation

Reviewer's Comment(s): The current available data show that edoxaban is unlikely to cause drug-induced liver injury and suggest that edoxaban is not different from warfarin and other approved NOACs with regard to liver toxicity. The fairly frequent elevation of liver transaminases is likely to be associated with an underlying cardiac condition in AF population.

7.3.5.2 Malignancy

The incidence of investigator reported clinically evident post randomization malignancies was similar among the edoxaban 30 mg, edoxaban 60mg and warfarin groups (2.5%, 2.7% and 2.6%) (Table 96).

Table 96 Investigator Reported Clinically Evident Post Randomization Malignancies by Location, overall study period

Malignancies Category/Location	Edoxaban 30mg (15mg DosAdj) (N=7002)		Edoxaban 60mg (30mg DosAdj) (N=7012)		Warfarin (N=7012)	
	n	Event Rate (%/yr)	n	Event Rate (%/yr)	n	Event Rate (%/yr)
Any Location	463	2.50	494	2.68	485	2.64
Skin[a]	150	0.80	178	0.95	163	0.87
Small or Large Bowel	51	0.27	52	0.27	60	0.32
Lung	44	0.23	50	0.26	40	0.21
Prostate	48	0.41	48	0.41	53	0.45
Bladder	29	0.15	32	0.17	29	0.15
Breast	21	0.11	25	0.13	27	0.14
Stomach	15	0.08	19	0.10	20	0.11
Other	23	0.12	17	0.09	17	0.09
Pancreatic	16	0.08	16	0.08	10	0.05
Esophageal	13	0.07	14	0.07	4	0.02
Multiple	3	0.02	13	0.07	11	0.06
Liver, Gall Bladder, or Bile Ducts	18	0.09	10	0.05	17	0.09
Lymphoma	6	0.03	10	0.05	8	0.04
Lip, Oral, Pharynx	15	0.08	9	0.05	9	0.05
Uterine	7	0.09	8	0.11	6	0.08
Leukemia	12	0.06	6	0.03	13	0.07
Renal	8	0.04	6	0.03	12	0.06
Thyroid	1	0.01	6	0.03	2	0.01
Brain	6	0.03	5	0.03	8	0.04
Genital	3	0.02	3	0.02	8	0.04
Other Respiratory (Excluding Lung)	1	0.01	2	0.01	1	0.01
Unspecified	8	0.04	2	0.01	4	0.02

Source: CSR Table 12.25

This reviewer evaluated MedDRA SMQs related to malignancy and did not find any meaningful imbalance among the treatment groups except premalignant disorder SMQ. Most premalignant disorders occurred in the GI tract and the edoxaban 60 mg group had a higher percent of subjects compared with the warfarin group with AEs or SAEs in the GI premalignant disorders SMQ (Table 97).

Pre-clinical carcinogenic studies showed no evidence of increased neoplasia in the animals treated with edoxaban. The observed imbalance in premalignant disorder SMQ might have resulted from the higher rate of GI bleeding events in the edoxaban 60 mg group and a consequent higher rate of diagnostic workup of the GI tract in that treatment arm. The investigator reported GI bleeds were higher in the edoxaban 60 mg group compared with the warfarin group (0.64 vs. 0.47 % per patient-years, respectively).

Table 97 Summary of Premalignant disorder (SMQ) by Treatment group and AE/SAE

	Edoxaban 30mg N = 7002		Edoxaban 60mg N = 7012		Warfarin N = 7012	
SMQ Category	AE	SAE	AE	SAE	AE	SAE
Premalignant disorders (SMQ)	254 (3.6%)	29 (0.4%)	277 (4.0%)	46 (0.7%)	229 (3.3%)	16 (0.2%)
Blood premalignant disorders (SMQ)	7 (0.1%)	3 (<0.1%)	11 (0.2%)	7 (0.1%)	4 (0.1%)	1 (<0.1%)
Gastrointestinal premalignant disorders (SMQ)	169 (2.4%)	26 (0.4%)	212 (3.0%)	37 (0.5%)	170 (2.4%)	13 (0.2%)
Premalignant disorders, general conditions and other site specific disorders (SMQ)	1 (<0.1%)	0	1 (<0.1%)	0	2 (<0.1%)	0
Reproductive premalignant disorders (SMQ)	5 (0.1%)	0	6 (0.1%)	1 (<0.1%)	4 (0.1%)	2 (<0.1%)
Skin premalignant disorders (SMQ)	78 (1.1%)	1 (<0.1%)	54 (0.8%)	1 (<0.1%)	57 (0.8%)	0

Reviewer's Table. The Applicant's datasets: AEEV1 & DM

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The percentage of subjects among the treatment groups that reported non-bleeding AEs was similar during the on-treatment period (Table 98).

Table 98 Overview of AEs in ENGAGE AF

	Edoxaban 30mg (15mg DosAdj) (N=7002) n (%)	Edoxaban 60mg (30mg DosAdj) (N=7012) n (%)	Warfarin (N=7012) n (%)
On-Treatment Period			
Subjects With Non-Bleeding TEAEs[a]			
All	5868 (83.8)	5866 (83.7)	5867 (83.7)
Drug-Related	703 (10.0)	773 (11.0)	856 (12.2)
Severe	1270 (18.1)	1201 (17.1)	1280 (18.3)
With Fatal Outcome	274 (3.9)	284 (4.1)	316 (4.5)
Subjects With Non-Bleeding TESAEs			
All	2418 (34.5)	2315 (33.0)	2516 (35.9)
Drug-Related	66 (0.9)	74 (1.1)	116 (1.7)
Subjects With Non-Bleeding TEAEs that Caused Temporary Study Drug Interruption[b]			
All	2271 (32.4)	2235 (31.9)	2480 (35.4)
Drug-Related	246 (3.5)	281 (4.0)	374 (5.3)
TESAEs	1279 (18.3)	1268 (18.1)	1413 (20.2)
Subjects With Non-Bleeding TEAEs that Caused Study Drug Discontinuation[c]			
All	709 (10.1)	784 (11.2)	768 (11.0)
Drug-Related	132 (1.9)	166 (2.4)	141 (2.0)
TESAEs	377 (5.4)	417 (5.9)	420 (6.0)
Overall Study Period			
Subjects With Non-Bleeding TEAEs[a]			
All	6045 (86.3)	6092 (86.9)	6065 (86.5)
Drug-Related	714 (10.2)	782 (11.2)	869 (12.4)
Severe	1676 (23.9)	1662 (23.7)	1749 (24.9)
With Fatal Outcome	568 (8.1)	632 (9.0)	662 (9.4)
Subjects With Non-Bleeding TESAEs			
All	3031 (43.3)	2979 (42.5)	3118 (44.5)
Drug-Related	72 (1.0)	80 (1.1)	125 (1.8)

Source: The Applicant's CSR Table 12.15

The most frequently reported (at least 5% of subjects from each treatment group) non-bleeding AEs is summarized in Table 99. For the most part, the frequency of AEs was similar among the treatment groups except anemia, which was reported more frequently in the edoxaban 60 mg group than in the warfarin group.

Table 99 The most frequent reported AEs[†] by SOC and PT-on treatment

SOC/Preferred Term	Edoxaban 30mg (15mg DosAdj) (N=7002) n (%)	Edoxaban 60mg (30mg DosAdj) (N=7012) n (%)	Warfarin (N=7012) n (%)
Infections And Infestations	3129 (44.7)	3126 (44.6)	3142 (44.8)
Urinary Tract Infection	698 (10.0)	688 (9.8)	703 (10.0)
Nasopharyngitis	645 (9.2)	620 (8.8)	620 (8.8)
Bronchitis	584 (8.3)	567 (8.1)	572 (8.2)
Upper Respiratory Tract Infection	443 (6.3)	411 (5.9)	445 (6.3)
Blood And Lymphatic System Disorders	486 (6.9)	632 (9.0)	475 (6.8)
Anaemia	261 (3.7)	368 (5.2)	242 (3.5)
Nervous System Disorders	1484 (21.2)	1454 (20.7)	1481 (21.1)
Dizziness	537 (7.7)	514 (7.3)	592 (8.4)
Headache	356 (5.1)	334 (4.8)	336 (4.8)
Cardiac Disorders	1759 (25.1)	1711 (24.4)	1784 (25.4)
Atrial Fibrillation	528 (7.5)	474 (6.8)	491 (7.0)
Cardiac Failure	373 (5.3)	425 (6.1)	448 (6.4)
Vascular Disorders	990 (14.1)	985 (14.0)	992 (14.1)
Hypertension	475 (6.8)	481 (6.9)	438 (6.2)
Respiratory, Thoracic And Mediastinal Disorders	1370 (19.6)	1382 (19.7)	1395 (19.9)
Dyspnoea	434 (6.2)	456 (6.5)	470 (6.7)
Cough	416 (5.9)	383 (5.5)	365 (5.2)
Gastrointestinal Disorders	1934 (27.6)	2005 (28.6)	1947 (27.8)
Diarrhoea	486 (6.9)	482 (6.9)	499 (7.1)
Musculoskeletal And Connective Tissue Disorders	1826 (26.1)	1790 (25.5)	1843 (26.3)
Back Pain	496 (7.1)	476 (6.8)	478 (6.8)
Arthralgia	417 (6.0)	385 (5.5)	386 (5.5)
General Disorders And Administration Site Conditions	1490 (21.3)	1476 (21.0)	1589 (22.7)
Oedema Peripheral	578 (8.3)	577 (8.2)	675 (9.6)
Injury, Poisoning And Procedural Complications	1259 (18.0)	1216 (17.3)	1410 (20.1)
Fall	452 (6.5)	453 (6.5)	565 (8.1)

Source: The Applicant's CSR Table 12.16
[†] AEs other than primary efficacy endpoints and bleeding events.

Table 100 summarizes the incidence and severity of anemia during the overall study period. It is evident that edoxaban 60 mg had more anemia AEs and SAEs compared with the warfarin group. The imbalance increased when the reviewer grouped more relevant PT terms (Table 101).

However, the majority of anemia AEs were mild to moderate and very few lead to discontinuation of study drug (Table 100). Evaluation of laboratory data also indicated more subjects in the edoxaban 60 mg group had > 2 g/dL drop in hemoglobin from baseline (see Section 7.4.2.2). Moreover, a higher percentage of subjects in the edoxaban 60 mg group compared with the warfarin group had ≥ 2 units of transfusion (5.4% vs. 4.9%, respectively). There was also a higher incidence of anemia-related conditions in the edoxaban group compared with the warfarin group among subjects who did not report any bleed in the study (4.9% vs. 3.1%). These imbalanced findings in anemia-related AEs are likely partly due to a higher incidence of GI bleeds or non-apparent bleeds in the edoxaban 60 mg group compared with the warfarin group.

Table 100 Summary of Anemia AE/SAE during the overall study period

	Edoxaban 30mg (15mg DosAdj) (N=7002) n (%)	**Edoxaban 60mg (30mg DosAdj) (N=7012) n (%)**	**Warfarin (N=7012) n (%)**
Anemia TEAEs	339 (4.8)	447 (6.4)	313 (4.5)
by Maximum Severity			
Mild	199 (2.8)	267 (3.8)	165 (2.4)
Moderate	110 (1.6)	141 (2.0)	120 (1.7)
Severe	30 (0.4)	39 (0.6)	28 (0.4)
Anemia TEAEs leading to discontinuation of study drug	14 (0.2)	29 (0.4)	13 (0.2)
Anemia TESAEs	53 (0.8)	70 (1.0)	45 (0.6)
Anemia TEAEs with fatal outcome	0 (0.0)	2 (<0.1)	0 (0.0)

Source: the Applicant's CSR Table 12.26

Table 101 Anemia-related AEs during the on-treatment period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Any Anemia related PTs[a]	403 (5.8%)	578 (8.2%)	396 (5.6%)

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

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

7.4.1.1 Other AEs of interest by SMQ or clinical event groups

Additional safety data searching for SMQs (broad terms) or clinical event groups of interest are summarized in Table 102. Both edoxaban 30 mg and 60 mg groups had slightly higher incidence of AEs indicating for acute renal failure SMQ, liver function test elevation and drug related hepatic disorders-severe events only SMQ. However, all these SMQs as SAEs were very similar among the treatment groups (see Section 7.3.2.2). Further evaluation of the reported PTs for acute renal failure SMQ found that the imbalanced results were largely driven by PTs such as creatinine renal clearance decreased and renal impairment. These AE findings are consistent with our laboratory findings with regard to changes in creatinine clearance and serum creatinine (see Figure 32, Figure 33, Table 103 and Table 104). The edoxaban 60 mg group also had a higher percent of subjects with the hematopoietic erythropenia SMQ compared with the warfarin group (6.0% vs. 4.1%), which is consistent with the findings related to anemia AEs. Unlike the findings in death and SAEs, there was no imbalance among the treatment groups with regard to the AEs related to acute central respiratory depression SMQ and ILD SMQ.

Table 102 AEs by SMQs and clinical event groups- on-treatment period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Hematopoietic erythropenia (SMQ)	291 (4.2%)	419 (6.0%)	289 (4.1%)
Acute central respiratory depression (SMQ)	535 (7.6%)	564 (8.0%)	553 (7.9%)
Interstitial lung disease (SMQ)	34 (0.5%)	40 (0.6%)	41 (0.6%)
Hypersensitivity reactions[a]	1731 (24.7%)	1751 (25.0%)	1862 (26.6%)
Torsade de pointes/QT prolongations (SMQ)	312 (4.5%)	285 (4.1%)	318 (4.5%)
Hepatic Disorder			
Liver function test elevation PTs[b]	426 (6.1%)	407 (5.8%)	398 (5.7%)
Drug related hepatic disorders-comprehensive search (SMQ)	669 (9.6%)	654 (9.3%)	813 (11.6%)
Drug related hepatic disorders-comprehensive search (SMQ)-excluding INR increase PT term	655(9.4%)	639 (9.1%)	642 (9.2%)
Drug related hepatic disorders-severe events only— (SMQ)	114 (1.6%)	121 (1.7%)	103 (1.5%)
Renal Disorder			
Acute Renal Failure (SMQ)[c]	735 (10.5%)	741 (10.6%)	668 (9.5%)
Acute Renal Failure (SMQ) [c] - narrow	346 (4.9%)	355 (5.1%)	305 (4.3%)

a. Hypersensitivity reactions include three SMQs: anaphylactic reaction, angioedema and severe cutaneous adverse reaction
b. PTs include alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, blood bilirubin unconjugated increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, liver function test abnormal and transaminases increased.
c.see APPENDIX 13 for reported PTs
Reviewer's Table. Applicant's dataset: AEEV1 & DM

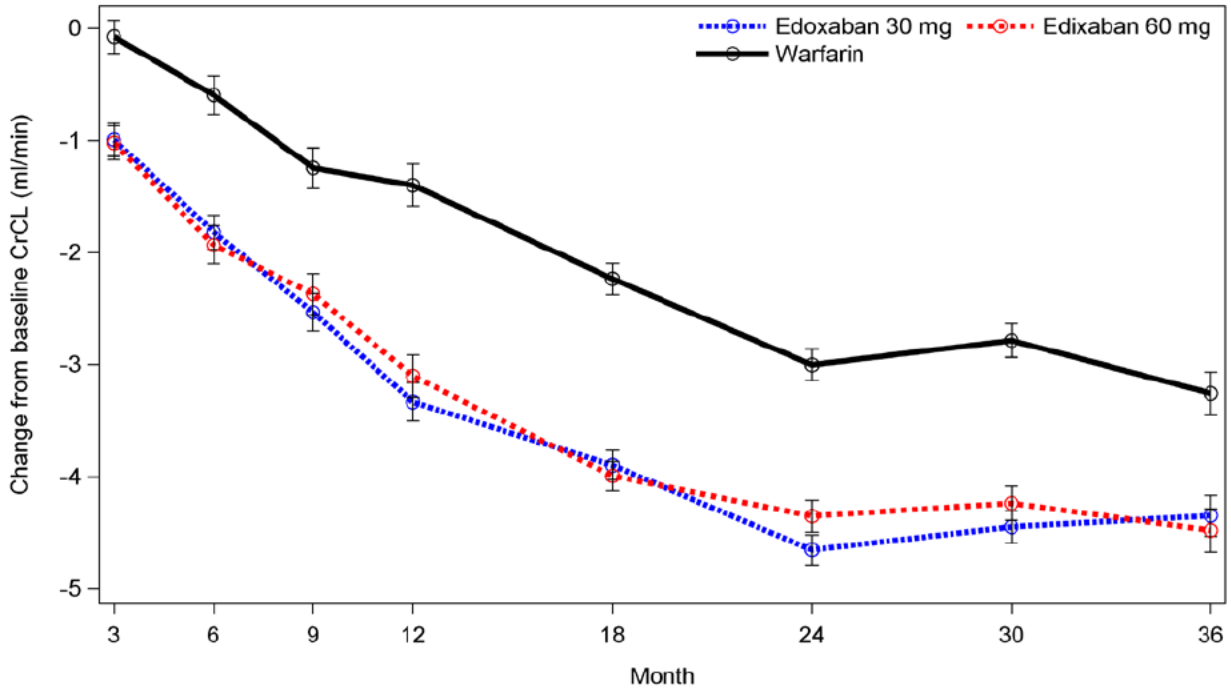
7.4.2 Laboratory Findings

7.4.2.1 Renal parameters

The time course of change of creatinine clearance (CrCL) from baseline shows that the edoxaban groups on average had slightly greater CrCL decreases during the study period compared with the warfarin group (Figure 32). These differences seem constant between the edoxaban arm and warfarin arm throughout the study. The categorical shift table (Table 103) shows that a slightly higher proportion of subjects shifted from > 50 ml/min or 30-50 ml/min to lower CrCL categories at any point of time during the study

(on treatment +30 days) in the edoxaban groups compared with the warfarin group . Similarly, a higher proportion of subjects in the edoxaban groups had a greater than 25% decrease in CrCL from baseline compared with warfarin.

Figure 32 Time course of change of Creatinine Clearance (CrCL, ml/min) from baseline



Reviewer's Figure. The Applicant's dataset: LB & DM. The mean creatinine clearance at baseline was similar among the three groups (~ 76 ml/min). All the lab measurements collected during on treatment + 30 days were used for the analysis. Standard error was plotted for each mean CrCL change from baseline by study group and time point.

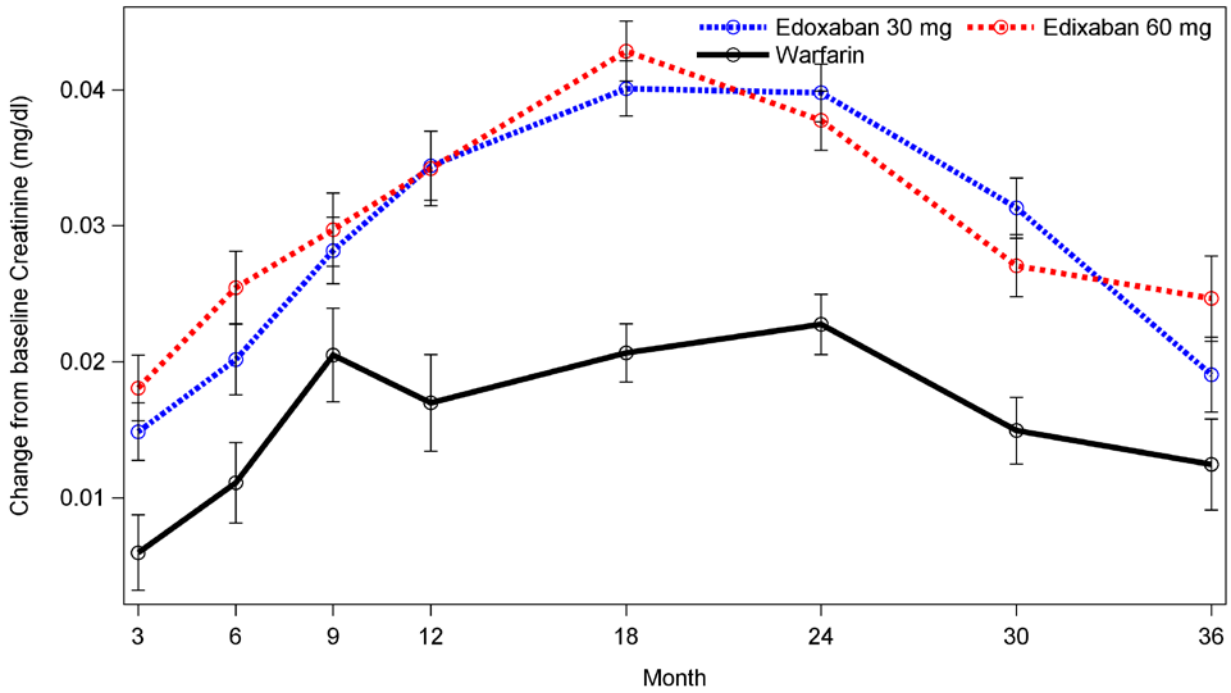
Table 103 Changes in Creatinine Clearance in ENGAGE AF

	Edoxaban 30 mg N* = 6676	Edoxaban 60 mg N=6609	Warfarin N=6664
Creatinine Clearance decrease			
>50 ml/min shift to 30-50 or <30 ml/min OR 30-50 ml/min shit to < 30 ml/min	1532 (22.9%)	1470 (22.2%)	1375 (20.6%)
≥25% decrease from baseline	1801 (27.0%)	1791 (27.1%)	1656 (24.8%)
≥50% decrease from baseline	159 (2.4%)	178 (2.7%)	151 (2.3%)

Reviewer's Table, Applicant's dataset: LB & DM. *N is number of patients who had at least one creatinine clearance measurement during on treatment + 30 days. Percentage was calculated using N.

Subjects in the edoxaban groups also had on average greater serum creatinine increases during the study period compared with the warfarin group (Figure 33). Although the difference was small, a higher percent of subjects in the edoxaban groups compared with the warfarin group had increased serum creatinine greater than the specified criteria (Table 104).

Figure 33 Time Course of Change in Serum Creatinine from Baseline



Reviewer's Figure. The Applicant's dataset: LB & DM. All serum creatinine collected during on treatment + 30 days were used for the analysis. Standard error was plotted for each mean creatinine change from baseline by study group and time point.

Table 104 Changes in Serum Creatinine in ENGAGE AF

	Edoxaban 30 mg N* = 6683	Edoxaban 60 mg N=6627	Warfarin N=6674
Serum Creatinine increase			
≥ 0.3 mg/dL	1637 (24.5%)	1628 (24.6%)	1493 (22.4%)
≥ 0.5 mg/dL	624 (9.3%)	648 (9.8%)	642 (9.6%)
≥25% increase from baseline	2145 (32.1%)	2093 (31.6%)	1945 (29.1%)
≥50% increase from baseline	634 (9.5%)	643 (9.7%)	600 (9.0%)

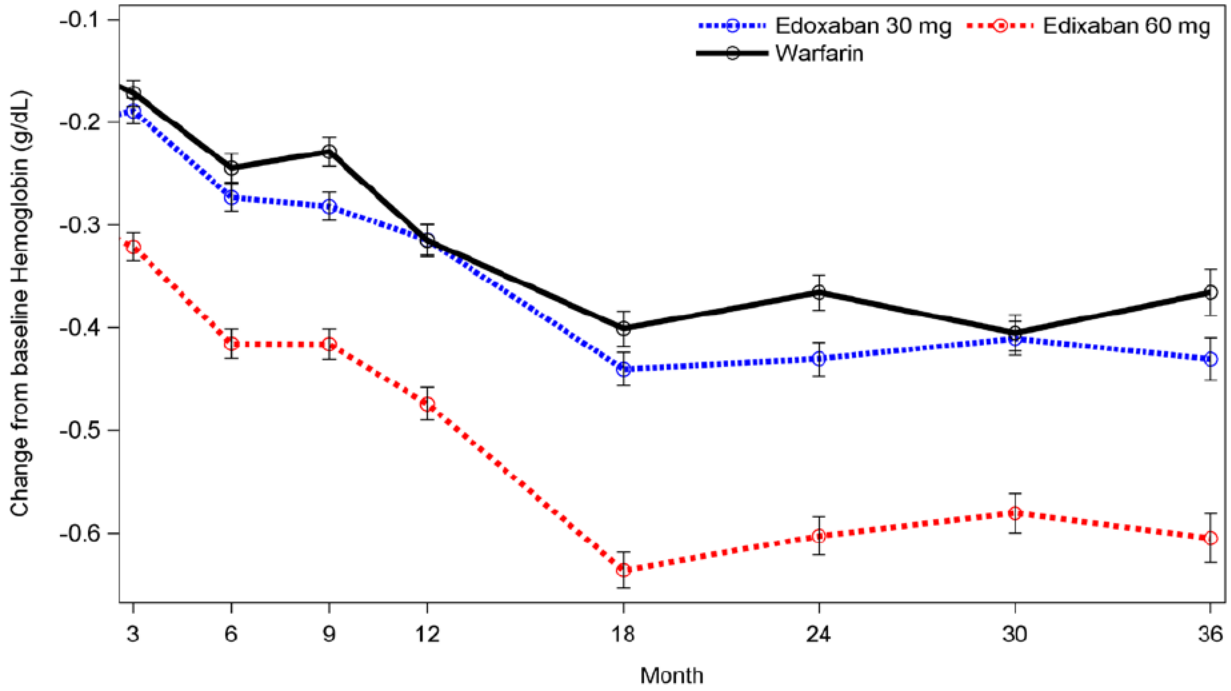
Reviewer's Table. The Applicant's dataset: LB & DM. *N is number of patients who had at least one serum creatinine measurement during on treatment + 30 days. Percentage was calculated using N.

Reviewer's comment(s): Both edoxaban groups had a slightly worse profile with regard to the renal parameters during the study (on-treatment +30 days). The Applicant did not systematically collect renal parameters after study drug discontinuation. Thus, we do not have sufficient data to evaluate if this phenomenon is reversible once off edoxaban treatment. Pre-clinical studies did not suggest that edoxaban poses a risk to the renal system. These laboratory findings are aligned with the AE results showing that slightly higher percentages of subjects in the edoxaban arms compared to warfarin reported AEs such as decreased creatinine renal clearance and renal impairment (see APPENDIX 13). Because there were no imbalanced findings with regard to SAEs for acute renal failure and the changes in renal parameters are small, the reviewer does not think these renal findings represent a significant safety concern and could be due to a PD effect of the drug. The reviewer recommends including the information about changes in creatinine clearance and serum creatinine in the label.

7.4.2.2 Hematology

The time course plot shows minor decreases in hemoglobin across all 3 treatment groups (Figure 34). The edoxaban 60 mg group had greater decreases in hemoglobin compared with the warfarin group during the study period. More subjects had hemoglobin drops ≥ 2 g/dL or ≥ 4 g/dL in the edoxaban 60 mg group compared with warfarin. There were no differences between the edoxaban 30 mg and the warfarin group in hemoglobin change from baseline. These results are consistent with the findings of anemia AE. There were no noteworthy changes in other parameters such as platelets and hematocrit.

Figure 34 Time Course of Change in Hemoglobin from Baseline



Reviewer's Figure. The Applicant's dataset: LB & DM All hemoglobin collected during on treatment + 30 days were used for the analysis. Standard error was plotted for each mean hemoglobin change from baseline by study group and time point.

Table 105 Changes in Hemoglobin in ENGAGE AF

	Edoxaban 30 mg N* = 6824	Edoxaban 60 mg N=6798	Warfarin N=6833
Hemoglobin Drop			
>2 g/dL	1348 (19.8%)	1628 (23.9%)	1330 (19.5%)
>4 g/dL	264(3.9%)	398 (5.9%)	260 (3.8%)
≥25% decrease from baseline	344 (5.0%)	537 (7.9%)	346 (5.1%)

Reviewer's Table. The Applicant's dataset: LB & DM. *N is number of patients who had at least one hemoglobin measurement during on treatment + 30 days. Percentage was calculated using N.

7.4.2.3 Other laboratory parameters

There were no meaningful difference observe among the treatment groups for other chemistry parameters.

7.4.3 Vital Signs

Vital signs were similar between the edoxaban and warfarin groups. There was no safety signal detected from the vital sign data.

7.4.4 Electrocardiograms (ECGs)

We did not observe clinically relevant difference between treatment groups in AEs/SAEs using Torsade de pointes/QT prolongations (SMQ). Negative results were found in the Thorough QT study (See Section 7.4.5).

7.4.5 Special Safety Studies/Clinical Trials

The FDA QT Inter-Disciplinary Review Team reviewed the Thorough QT study (DU176b-PRT021), and found no significant QT prolongation effects with edoxaban (90 mg and 180 mg). Please refer to the QT-IRT review (DARRTS date 11/10/2008).

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Anemia was more frequently reported in the edoxaban 60 mg group compared to the edoxaban 30 mg group. AEs related to elevation of liver function tests in edoxaban groups did not seem to be dose-dependent; however SAEs related to elevation of liver function tests were reported more frequently in the edoxaban 60 mg group.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was explored for the primary safety concerns (major bleeding and hepatic abnormality) and review findings are explained in the respective sections.

7.5.3 Drug-Demographic Interactions

See Section 7.3.2.1.3 for subgroup analysis

7.5.4 Drug-Disease Interactions

Renal elimination accounts for ~50% of edoxaban excretion. Subjects with moderate renal impairment (CrCL: 30-50 ml/min) had about 1.75 times increased exposure compared to those with CrCL ≥ 80 mL/min in the phase 2 study and received dose adjustment in ENGAGE AF. The subgroup analysis by CrCL levels (Figure 22 and Figure 23) show that major bleeding results were consistent across CrCL subgroups and numerically better in both edoxaban groups compared with warfarin.

According to the efficacy findings and exposure-response analyses, there was convincing evidence suggesting that the proposed dose (60 mg) was not optimal (under-dosed) for subjects with normal renal function. While the efficacy may be attainable by increasing the dose in this subgroup, safety concerns with respect to bleeding risk, particularly GI bleeds, has been raised. The reviewer evaluated the location of major bleeds by CrCL levels to assess further the potential safety impact (Table 106). It is noted that the rate of major bleeding event was markedly decreased among subjects with CrCL≥ 80 mL/min in both treatment groups. These results are expected given that the normal renal function subgroup represents younger and healthier subjects. Among subjects with CrCL ≥ 80 mL/min, event rates in all categories of major bleeds, including GI major bleeds, were lower in the edoxaban 60 mg group compared with warfarin. These results are somewhat reassuring. They suggest that there is some wiggle room for bleeding risk, including GI bleeds, if one would increase the dose of edoxaban among subjects with normal renal function. However, an appropriate dose still needs to be identified to balance efficacy and safety in the subgroup.

Table 106 Major Bleeding Results by CrCL and Sub-Categories – on treatment

		Edoxaban 60 mg		*Warfarin*		*E60 mg vs. W*	
CRCL min/ml	*Event*	*n/N*	*ER (%pt-yr)*	*n/N*	*ER (%pt-yr)*	*HR*	*95 CI*
30<=CRCL<=50	Major Bleeding	96 / 1306	3.81	128 / 1352	5.09	0.75	(0.58, 0.98)
	ICH	16	0.62	35	1.36	0.45	(0.25, 0.81)
	Fatal Bleeding	9	0.35	18	0.70	0.52	(0.23, 1.15)
	-ICH	7	0.27	13	0.51	0.55	(0.22, 1.39)
	-Non-ICH	2	0.08	5	0.19	0.42	(0.08, 2.14)
	GI Bleeding	49	1.92	42	1.65	1.15	(0.76, 1.74)
	-Upper GI	35	1.36	21	0.82	1.64	(0.95, 2.82)
	-Lower GI	15	0.58	21	0.82	0.70	(0.36, 1.37)
	GUSTO severe	20	0.77	43	1.68	0.46	(0.27, 0.78)
	-GI	3	0.12	4	0.16	0.75	(0.17, 3.34)
	TIMI Major	34	1.32	59	2.31	0.57	(0.37, 0.87)
	-GI	13	0.50	13	0.51	0.98	(0.45, 2.11)
50<CRCL<80	Major Bleeding	206 / 3062	3.10	235 / 3034	3.45	0.90	(0.74, 1.08)
	ICH	27	0.40	70	1.01	0.39	(0.25, 0.61)
	Fatal Bleeding	13	0.19	27	0.39	0.49	(0.25, 0.95)
	-ICH	9	0.13	19	0.27	0.48	(0.22, 1.07)
	-Non-ICH	4	0.06	8	0.11	0.51	(0.15, 1.69)
	GI Bleeding	124	1.85	79	1.14	1.61	(1.22, 2.14)
	-Upper GI	68	1.01	47	0.68	1.48	(1.02, 2.14)
	-Lower GI	58	0.86	33	0.48	1.81	(1.18, 2.77)
	GUSTO severe	42	0.62	87	1.25	0.49	(0.34, 0.71)
	-GI	9	0.13	10	0.14	0.93	(0.38, 2.28)
	TIMI Major	86	1.27	127	1.84	0.69	(0.53, 0.91)
	-GI	44	0.65	35	0.50	1.29	(0.83, 2.01)
CRCL ≥80	Major Bleeding	108 / 2644	1.73	154 / 2626	2.48	0.70	(0.55, 0.89)
	ICH	16	0.25	25	0.39	0.64	(0.34, 1.21)
	Fatal Bleeding	10	0.16	13	0.20	0.78	(0.34, 1.78)
	-ICH	8	0.13	9	0.14	0.90	(0.35, 2.33)
	-Non-ICH	2	0.03	4	0.06	0.51	(0.09, 2.78)
	GI Bleeding	56	0.89	66	1.05	0.85	(0.59, 1.21)
	-Upper GI	35	0.55	42	0.67	0.84	(0.53, 1.31)
	-Lower GI	22	0.35	25	0.40	0.88	(0.49, 1.55)
	GUSTO severe	28	0.44	41	0.65	0.68	(0.42, 1.10)
	-GI	9	0.14	9	0.14	1.00	(0.40, 2.52)
	TIMI Major	42	0.66	69	1.09	0.61	(0.41, 0.89)
	-GI	22	0.35	34	0.54	0.64	(0.38, 1.10)

Reviewer's Analysis. The Applicant's dataset: BLDDAT, BASEGRP, DM

Pharmacometrics reviewers conducted exposure-response relationships for both efficacy and safety (See Section 4.4.3.4 and clinical pharmacology review for details). In general, these relationships project a decrease in efficacy event rates with increasing edoxaban doses and a subsequent increase in safety event rates with increasing edoxaban doses. One could approach the decreased efficacy in subjects with normal renal function by increasing the dose based on exposure matching. A 90 mg dose is a reasonable choice for patients with normal renal function because it should result in exposures similar to that achieved in the subjects with mild renal dysfunction who received edoxaban 60 mg (the best performing renal function subgroup). The exposure-response models predict an increased dose in the subjects with CrCL ≥ 80 mL/min from 60 mg to 90 mg (to match the exposure to the best performing subgroup: CrCL >50-<80 mL/min) could reduce ~ 1.4 ischemic strokes per 1,000 patient-years but increase ~ 10.7 major bleeds (~8.6 major GI bleeds) and 0.6 hemorrhagic stroke per 1,000 patient-years. Relative to warfarin, edoxaban 90 mg is predicted to have slightly more ischemic strokes (0.8 more events per 1,000 patient-years), more major bleeds (~4.8 more events per 1,000 patient-years, particularly more major GI bleeds (~8.1 more events per 1,000 patient-years) but ~1.4 less life-threatening/fatal bleeds per 1,000 patient-years. Overall, these findings do not suggest an obvious gain in net benefit with edoxaban 90 mg in normal renal function subgroup. It is unclear if the models can accurately predict the net clinical benefit of a higher dose than what was tested in the trial when there is a potential for serious safety consequences. Our concern is that increasing edoxaban dose in subjects with low risk of ischemic stroke would have minimal improvement in efficacy but result in considerably more major bleeding events (See Section 1.2). The choice of an appropriate edoxaban dose based on the exposure-response analyses depends on the benefit/risk that will be considered acceptable, a topic for discussion at the Cardiovascular and Renal Drugs Advisory Committee meeting on Oct 30, 2014.

Another uncertainty is that some have speculated that the increased risk of GI bleeds seen with the NOACs may be in part due to high concentrations of active drug in the GI tract. All the models performed by the clinical pharmacology reviewers were assessed based on systemic edoxaban exposure. If local exposure indeed plays a significant role in the probability of developing GI bleeds, the impact of edoxaban 90 mg on the risk of major GI bleeds cannot be assessed adequately and could be underestimated.
Table 107 shows the major bleeding results among subjects without any dose adjustment in both edoxaban groups. Edoxaban 60 mg increased the risk of major bleeds by about 60% compared with edoxaban 30 mg with an absolute risk difference of ~ 1 additional major bleed per 100 patients per year. The increased risk of major bleeds in the edoxaban 60 mg was primarily driven by a higher incidence of major GI bleeds, particularly lower GI bleed. On the contrary, the event rates of ICH and fatal bleeds increased to a relatively small degree in the edoxaban 60 mg group compared with the edoxaban 30 mg group. Similar results were found using more severe major bleeding definitions: GUSTO severe and TIMI major bleeding, though event rates of GI bleeds were much lower using such definitions. Although these findings do not directly support the role of local exposure in the risk of major GI bleeds, it does raise concerns about the possibility.

Table 107 Major Bleeding events by location among subjects without dose adjustment

	Edoxaban 30 mg No dose adj N = 5228		*Edoxaban 60 mg No dose adj N = 5236*		*Rate difference E60 vs. E30*	*Rate Ratio[†] E60 vs. E30*
event	*n (%)*	*ER (%/pt-yr)*	*n(%)*	*ER (%/pt-yr)*		
Major Bleeding	200 (3.8%)	1.61	314 (6.0%)	2.60	0.99	1.61
GI Bleeding	99 (1.9%)	0.79	182 (3.5%)	1.49	0.70	1.89
-Upper GI	67 (1.3%)	0.54	102 (1.9%)	0.83	0.29	1.54
-Lower GI	34 (0.7%)	0.27	82 (1.6%)	0.67	0.40	2.48
ICH	36 (0.7%)	0.29	41 (0.8%)	0.33	0.04	1.14
Non-ICH	164 (3.1%)	1.32	274 (5.2%)	2.27	0.95	1.72
Fatal	16 (0.3%)	0.13	20 (0.4%)	0.16	0.03	1.23
GUSTO Severe	46 (0.9%)	0.37	67 (1.3%)	0.54	0.17	1.46
-GI	7 (0.1%)	0.06	18 (0.3%)	0.15	0.09	2.50
TIMI Major	87 (1.7%)	0.69	127 (2.4%)	1.04	0.35	1.51
-GI	36 (0.7%)	0.29	68 (1.3%)	0.55	0.26	1.90

Reviewer's Analysis, the Applicant datasets: BLDDAT, BASEGRP, DM
[†]Rate ratio was ratio of the event rate between groups

7.5.5 Drug-Drug Interactions

The results of drug-drug interaction studies were discussed in Section 4 and major bleeding results by concomitant medication of interest can be found in Section 7.3.2.1.4.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Malignancy was a special event of interest in ENGAGE AF. In general, there was no imbalance found in terms of type and incidence of malignancies among treatments. Please see Section 7.3.5.2.

7.6.2 Human Reproduction and Pregnancy Data

Edoxaban has not been studied in pregnant or lactating women. There were no pregnancies in ENGAGE AF-TIMI 48. Non-clinical studies in animals suggest that edoxaban did not affect mating and fertility. Edoxaban-associated embryo-fetal toxicity in animals such as fewer live fetuses and lower fetal weight were considered to be secondary effects of maternal toxicity, rather than a direct edoxaban effect (see Section 4.3).

7.6.3 Pediatrics and Assessment of Effects on Growth

NA

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were only 7 subjects with at least 1 edoxaban overdose/dose error in ENGAGE AF and 11 from postmarking data including data from 120 day safety updates. There was no major bleeding event associated with edoxaban overdose among the 7 subjects in ENGAGE AF. One subject had taken 96 edoxaban tables instead of 69 between 07 Sep 2011 to 29 Sep 2011 and had died during sleep on (b) (6) The cause of death was uncertain and no autopsy was performed. There were no signs and symptoms reported prior to the subject's death.

There was only one AE associated with edoxaban overdose among 11 cases from postmarketing data. The AE was a non-serious subcutaneous hemorrhage, vomiting and rash. Overall, the edoxaban overdose cases represent isolated events with different dose and duration, and were not suggestive of safety concern, abuse or unclear packaging/labeling.

There was no evidence suggesting drug abuse/dependence on edoxaban.

7.7 Additional Submissions / Safety Issues

The Applicant submitted the required 120-Day Safety Update, dated 17 April, 2014, which include safety information (cut-off date 31 Dec 2013) from five phase 2 studies, two ongoing Phase 2 studies, post-marketing data for Edoxaban and AEs reported after 06 Aug 2013-31 in ENGAGE AF (database lock date)

Ongoing Phase 1/2 studies

The safety data in the ongoing phase 1 and 2 studies are generally consistent with the safety profile reported in the edoxaban phase 3 trials.

In an ongoing phase 2 study (56 in the edoxaban group and 28 in the LMWH/warfarin group), there were 2 hepatic abnormality events adjudicated by independent hepatologists, both in the edoxaban group. One was adjudicated as moderate hepatocellular injury, and was considered probably/possibly related to the study drug; the other was adjudicated as severe cholestasis, and was considered unlikely/unrelated to the study drug.

Post marketing data

The Applicant estimates that approximately 20,000 patients were treated with Edoxaban during the reporting period from 01 Oct 2013 through 31 Dec 2013.

A total of 134 AEs were reported in 113 cases (17 SAEs in 12 cases) during this period. Consistent with the safety profile of edoxaban, bleeding was the most frequently reported AEs (haemorrhage subcutaneous was the most frequent reported PT term) and most were non serious.

There were 11 Hepatic related AEs and 3 were serious (1 hepatic enzyme increased, 1 hepatic function abnormal and 1 jaundice). The 3 serious hepatic events were reported in 2 cases. The two cases were both immediate post-operative patients and were not carefully investigated as to the cause of the liver abnormality.

8 Postmarket Experience

Edoxaban was approved in Japan in 2011 for prevention of VTE after orthopedic surgery. It was launched as LIXIANA® on July 19, 2011. The Applicant reported all AEs from the relevant post-marketing safety data sources including spontaneous reports (regulatory authority and literature) as well as Drug Use Survey, which were received between the launch and September 30, 2013.

There were a total of 931 adverse events reported in 724 patients (88 SAEs in 70 cases) among approximately (b) (4) patients exposed to Edoxaban. Table shows top 10 most frequent AEs by PT.

	Drug Use Survey		Spontaneous		
Preferred Term (PT)	Serious	Non-Serious	Serious	Non-Serious	Total
Haemorrhage subcutaneous	1	24	5	79	109
Deep vein thrombosis	2	85	1	2	90
Hepatic function abnormal	0	33	1	38	72
Haemorrhage	1	10	7	43	61
Haemoglobin decreased	1	13	1	37	52
Anaemia	5	28	0	8	41
Wound haemorrhage	1	19	5	16	41
Platelet count increased	0	14	0	10	24
Local swelling	0	3	0	20	23
Alanine aminotransferase increased	0	12	0	7	19

Source: The Applicant's Table 2 in Module 5.3.6. post-marketing experience

During the review, we requested the narratives for 2 serious cases (one for hepatic function abnormal, one for liver disorder) and 2 non-serious cases (one for jaundice and one for hyperbilirubinemia). Two hepatic SAEs were spontaneously received cases reported by a healthcare professional. One case had limited information to assess liver abnormality. The other case was a 90 year old female who had elevated liver function tests after several says on edoxaban treatment. Edoxaban was discontinued and the patient was referred to a liver specialist. The doctor considered that edoxaban was suspected to be the cause of the hepatic function disorder. The patient recovered from the hepatic function disorder.

Overall, the post-marketing data are consistent with the known safety profile of edoxaban and no new safety concern has been identified. There were no noticed regulatory actions taken or labeling changes with respect to safety of edoxaban since launch.

9 Appendices

APPENDIX 1: Benefit-Risk Assessment Tables

			Benefit Efficacy (Ischemic Stroke/SEE)				Risk Safety (Life Threatening Bleed)				
		N	Edoxaban 60 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	Edoxaban 60 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	ΔΔ (% pt yr)
All		14024	0.9	1.0	-0.1	0.92	0.6	1.1	-0.5	0.53	-0.6
Age	<64 yr	3328	0.7	0.7	0.0	1.05	0.3	0.4	-0.1	0.73	-0.1
	64 to <72	3452	0.9	0.8	0.1	1.12	0.6	1.1	-0.5	0.53	-0.4
	72 to <78	3700	1.1	1.2	-0.2	0.86	0.7	1.3	-0.6	0.51	-0.8
	≥78	3544	1.1	1.4	-0.3	0.77	0.8	1.6	-0.8	0.48	-1.2
Sex	Female	5288	1.1	1.1	0.1	1.05	0.2	1.2	-0.9	0.21	-0.8
	Male	8736	0.8	1.0	-0.2	0.83	0.8	1.1	-0.3	0.73	-0.5
Elderly Female	<75 yrs	2804	0.9	0.7	0.2	1.24	0.2	0.9	-0.7	0.24	-0.5
	≥ 75	2484	1.4	1.5	-0.1	0.94	0.3	1.5	-1.2	0.19	-1.3
Elderly Male	<75 yrs	5577	0.9	0.8	0.1	1.05	0.6	0.8	-0.2	0.72	-0.2
	≥ 75	3159	0.7	1.4	-0.6	0.53	1.1	1.5	-0.4	0.73	-1.1
Weight	<70 kg	3378	1.3	1.2	0.1	1.07	0.9	1.5	-0.6	0.61	-0.5
	70 to <81.8	3584	0.8	1.4	-0.5	0.59	0.5	1.2	-0.7	0.43	-1.2
	81.8 to <95	3415	0.8	0.9	-0.2	0.84	0.5	1.0	-0.4	0.55	-0.6
	≥ 95	3647	0.8	0.6	0.3	1.48	0.4	0.8	-0.4	0.54	-0.1
Weight Female	<64 kg	1317	1.4	1.3	0.2	1.15	0.3	1.9	-1.6	0.16	-1.4
	64 to <74	1268	1.2	1.3	-0.1	0.89	0.4	1.2	-0.8	0.36	-0.9
	74 to <86	1396	1.1	1.5	-0.4	0.72	0.2	1.0	-0.8	0.19	-1.2
	≥ 86.2	1307	0.8	0.3	0.6	3.59	0.1	0.7	-0.6	0.10	0.0
Weight Male	<75 kg	2172	1.0	1.4	-0.4	0.73	1.4	1.5	-0.1	0.91	-0.5
	75 to <86	2102	0.6	1.0	-0.4	0.65	0.6	1.1	-0.5	0.59	-0.8
	86 to <99	2278	0.8	0.9	-0.1	0.83	0.6	0.8	-0.2	0.71	-0.4
	≥ 99.2	2184	0.8	0.7	0.2	1.26	0.6	0.8	-0.3	0.67	-0.1
CrCL (ml/min)	30 to ≤50.6	2704	1.3	1.3	-0.1	0.95	0.7	1.6	-0.9	0.45	-1.0
	50.6< to 63.6	2737	0.9	1.6	-0.7	0.57	0.5	1.4	-0.9	0.37	-1.5
	63.6 < to 77.9	2823	0.7	1.0	-0.3	0.68	0.7	1.1	-0.4	0.63	-0.7
	77.9 < to 98.1	2751	0.9	0.8	0.1	1.14	0.6	0.9	-0.3	0.67	-0.2
	≥ 98.1	2791	0.9	0.5	0.5	2.00	0.3	0.5	-0.2	0.68	0.3
VKA naive	No	8257	0.9	0.9	0.1	1.07	0.6	1.1	-0.5	0.54	-0.4
	Yes	5767	0.9	1.2	-0.3	0.75	0.6	1.1	-0.6	0.51	-0.9
CHADS2	2-3	10999	0.8	0.8	0.0	1.01	0.5	0.9	-0.4	0.55	-0.4
	>3	3025	1.6	2.0	-0.5	0.77	0.8	1.7	-0.9	0.49	-1.3
Stroke/TIA	No	10073	0.7	0.7	0.0	1.02	0.5	1.0	-0.5	0.51	-0.5
	Yes	3951	1.6	1.9	-0.3	0.82	0.8	1.4	-0.6	0.56	-0.9
Diabetes	No	8958	1.0	1.1	-0.2	0.85	0.6	1.0	-0.4	0.59	-0.6
	Yes	5066	0.9	0.8	0.1	1.09	0.5	1.2	-0.7	0.43	-0.6
Aspirin *	No	8762	0.7	0.7	0	0.96	0.5	0.8	-0.3	0.66	-0.3
	Yes	5262	1.3	1.5	-0.2	0.88	0.7	1.7	-1.0	0.43	-1.1
PPI/h2 blocker*	No	11320	0.9	0.8	0	1.05	0.5	1.0	-0.5	0.52	-0.4
	Yes	2704	1.2	1.8	-0.6	0.67	0.9	1.6	-0.7	0.57	-1.3
Dose Adj	No	10468	0.8	0.9	-0.1	0.91	0.5	1.0	-0.4	0.57	-0.5
	Yes	3556	1.4	1.5	-0.1	0.93	0.7	1.5	-0.8	0.45	-1.0
Location	Outside US	11439	1.0	1.1	-0.1	0.93	0.6	1.0	-0.4	0.58	-0.5
	US	2585	0.5	0.6	-0.1	0.82	0.5	1.4	-0.9	0.35	-1.0

Reviewer's Table. Source: the Applicant's dataset: DM, BASEGRP, POSTGRP, ADJEFFCA and BLDDATA
† A negative value indicates an absolute risk reduction (%/patient-year) of endpoint in the edoxaban group compared with warfarin.
ΔΔ (the net clinical benefit) was assessed based on equal weight of the efficacy and safety endpoint.
††Definition of life threatening bleeds (=GUSTO Severe bleeds): ICH or bleeds causing hemodynamic compromise requiring treatment, including fatal bleeds *Medication was taken at any time on or after the first dose through the last dose

			Benefit Efficacy (Ischemic Stroke/SEE)				Risk Safety (Major Bleed)				
		N	Edoxaban 60 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	Edoxaban 60 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	ΔΔ (% pt yr)
All		14024	0.9	1.0	-0.1	0.92	2.7	3.3	-0.6	0.80	-0.7
Age	<64 yr	3328	0.7	0.7	0.0	1.05	1.3	1.7	-0.4	0.76	-0.4
	64 to <72	3452	0.9	0.8	0.1	1.12	2.6	3.2	-0.6	0.81	-0.5
	72 to <78	3700	1.1	1.2	-0.2	0.86	3.0	3.5	-0.5	0.85	-0.7
	≥ 78	3544	1.1	1.4	-0.3	0.77	4.0	5.2	-1.2	0.77	-1.6
Sex	Female	5288	1.1	1.1	0.1	1.05	2.4	3.3	-0.9	0.74	-0.8
	Male	8736	0.8	1.0	-0.2	0.83	2.8	3.4	-0.6	0.84	-0.7
Elderly Female	<75 yrs	2804	0.9	0.7	0.2	1.24	1.9	2.3	-0.4	0.82	-0.2
	≥ 75	2484	1.4	1.5	-0.1	0.94	3.1	4.5	-1.4	0.68	-1.5
Elderly Male	<75 yrs	5577	0.9	0.8	0.1	1.08	2.0	2.7	-0.7	0.75	-0.6
	≥ 75	3159	0.7	1.4	-0.6	0.53	4.5	4.8	-0.3	0.94	-1.0
Weight	<70 kg	3378	1.3	1.2	0.1	1.07	3.5	3.6	-0.1	0.98	0.0
	70 to <81.8	3584	0.8	1.4	-0.5	0.59	2.5	3.5	-1.0	0.71	-1.6
	81.8 to <95	3415	0.8	0.9	-0.2	0.84	2.5	3.3	-0.8	0.77	-0.9
	≥ 95	3647	0.8	0.6	0.3	1.48	2.3	2.9	-0.7	0.77	-0.4
Weight Female	<64 kg	1317	1.4	1.3	0.2	1.15	2.9	4.5	-1.5	0.66	-1.4
	64 to <74	1268	1.2	1.3	-0.1	0.89	2.3	3.1	-0.8	0.72	-1.0
	74 to <86	1396	1.1	1.5	-0.4	0.72	2.4	3.2	-0.8	0.75	-1.2
	≥ 86.2	1307	0.8	0.3	0.6	3.59	2.1	2.4	-0.4	0.83	0.2
Weight Male	<75 kg	2172	1.0	1.4	-0.4	0.73	4.2	3.8	0.4	1.10	0.0
	75 to <86	2102	0.6	1.0	-0.4	0.65	2.4	3.5	-1.1	0.71	-1.4
	86 to <99	2278	0.8	0.9	-0.1	0.83	2.6	3.0	-0.4	0.86	-0.5
	≥99.2	2184	0.8	0.7	0.2	1.26	2.2	3.3	-1.1	0.68	-0.9
CrCL (ml/min)	30 to ≤50.6	2704	1.3	1.3	-0.1	0.95	3.7	5.1	-1.3	0.74	-1.4
	50.6< to 63.6	2737	0.9	1.6	-0.7	0.57	3.5	3.8	-0.4	0.90	-1.0
	63.6 < to 77.9	2823	0.7	1.0	-0.3	0.68	2.8	2.9	-0.0	0.98	-0.4
	77.9 < to 98.1	2751	0.9	0.8	0.1	1.14	2.3	2.9	-0.6	0.80	-0.5
	≥ 98.1	2791	0.9	0.5	0.5	2.00	1.3	2.3	-1.0	0.56	-0.6
VKA naive	No	8257	0.9	0.9	0.1	1.07	2.6	3.3	-0.7	0.79	-0.6
	Yes	5767	0.9	1.2	-0.3	0.75	2.8	3.4	-0.6	0.82	-0.9
CHADS2	2-3	10999	0.8	0.8	0.0	1.01	2.5	3.0	-0.6	0.82	-0.5
	>3	3025	1.6	2.0	-0.5	0.77	3.6	4.7	-1.1	0.77	-1.5
Stroke/TIA	No	10073	0.7	0.7	0.0	1.02	2.5	3.3	-0.7	0.78	-0.7
	Yes	3951	1.6	1.9	-0.3	0.82	3.0	3.6	-0.5	0.86	-0.9
Diabetes	No	8958	1.0	1.1	-0.2	0.85	2.5	3.1	-0.5	0.82	-0.7
	Yes	5066	0.9	0.8	0.1	1.09	3.0	3.8	-0.9	0.78	-0.8
Aspirin*	No	8762	0.7	0.7	0	0.96	2.1	2.6	-0.5	0.82	-0.5
	Yes	5262	1.3	1.5	-0.2	0.88	3.7	4.8	-1.0	0.79	-1.2
PPI/h2 blocker*	No	11320	0.9	0.8	0	1.05	1.8	2.6	-0.8	0.70	-0.7
	Yes	2704	1.2	1.8	-0.6	0.67	6.8	6.8	0	1.01	-0.6
Dose Adj	No	10468	0.8	0.9	-0.1	0.91	2.6	3.0	-0.4	0.88	-0.4
	Yes	3556	1.4	1.5	-0.1	0.93	3.0	4.7	-1.7	0.64	-1.8
Location	Outside US	11439	1.0	1.1	-0.1	0.93	2.4	3.1	-0.6	0.79	-0.7
	US	2585	0.5	0.6	-0.1	0.82	3.9	4.5	-0.7	0.85	-0.8

Reviewer's Table. Source: the Applicant's dataset: DM, BASEGRP, POSTGRP, ADJEFFCA and BLDDATA
† A negative value indicates an absolute risk reduction (%/patient-year) of endpoint in the edoxaban group compared with warfarin.
ΔΔ (the net clinical benefit) was assessed based on equal weight of the efficacy and safety endpoint.
***Medication was taken at any time on or after the first dose through the last dose**

			Benefit				Risk				
			Efficacy (Ischemic Stroke/SEE)				Safety (Life Threatening Bleed)				
		N	Edoxaban 30 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	Edoxaban 30 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	ΔΔ (% pt yr)
All		14014	1.5	1.0	0.5	1.47	0.3	1.1	-0.8	0.31	-0.3
Age	<64 yrs	3264	1.2	0.7	0.5	1.76	0.1	0.4	-0.3	0.30	0.2
	64 to <72	3554	1.3	0.8	0.5	1.67	0.3	1.1	-0.8	0.29	-0.3
	72 to <78	3685	1.6	1.2	0.4	1.28	0.4	1.3	-0.9	0.30	-0.5
	≥ 78	3511	1.9	1.4	0.5	1.38	0.5	1.6	-1.1	0.33	-0.6
Sex	Female	5347	1.7	1.1	0.7	1.62	0.3	1.2	-0.8	0.28	-0.2
	Male	8667	1.4	1.0	0.4	1.37	0.4	1.1	-0.7	0.34	-0.3
Elderly Female	<75 yrs	2835	1.5	0.7	0.7	2.01	0.2	0.9	-0.7	0.25	0.1
	≥ 75	2512	2.0	1.5	0.5	1.39	0.4	1.5	-1.1	0.29	-0.5
Elderly Male	<75 yrs	5585	1.3	0.8	0.5	1.59	0.3	0.8	-0.6	0.32	-0.1
	≥ 75	3082	1.5	1.4	0.1	1.10	0.5	1.5	-1.0	0.36	-0.9
Weight	<70 kg	3365	2.3	1.2	1.0	1.85	0.4	1.5	-1.0	0.28	0.0
	70 to <81.8	3634	1.4	1.4	0.1	1.05	0.4	1.2	-0.8	0.33	-0.7
	81.8 to <95	3389	1.3	0.9	0.3	1.39	0.4	1.0	-0.6	0.37	-0.3
	≥ 95	3626	1.1	0.6	0.5	1.95	0.2	0.8	-0.6	0.28	-0.1
Weight Female	<64 kg	1318	2.5	1.3	1.2	2.01	0.3	1.9	-1.5	0.19	-0.3
	64 to <74	1264	1.9	1.3	0.6	1.40	0.4	1.2	-0.8	0.34	-0.2
	74 to <86	1402	1.5	1.5	-0.1	0.95	0.1	1.0	-0.8	0.12	-0.9
	≥ 86.2	1363	1.2	0.3	0.9	5.20	0.4	0.7	-0.3	0.61	0.7
Weight Male	<75 kg	2160	2.2	1.4	0.9	1.62	0.5	1.5	-1.0	0.34	-0.1
	75 to <86	2151	1.1	1.0	0.1	1.08	0.4	1.1	-0.7	0.37	-0.7
	86 to <99	2199	1.3	0.9	0.3	1.34	0.4	0.8	-0.5	0.43	-0.1
	≥ 99.2	2157	0.9	0.7	0.3	1.41	0.2	0.8	-0.7	0.22	-0.4
CrCL (ml/min)	30 to ≤50.6	2700	2.4	1.3	1.0	1.75	0.4	1.6	-1.2	0.24	-0.2
	50.6< to 63.6	2794	1.7	1.6	0.1	1.05	0.4	1.4	-1.0	0.27	-0.9
	63.6 < to 77.9	2794	1.3	1.0	0.3	1.28	0.4	1.1	-0.7	0.34	-0.4
	77.9 < to 98.1	2822	1.2	0.8	0.5	1.59	0.4	0.9	-0.5	0.40	-0.1
	≥ 98.1	2731	1.0	0.5	0.5	2.10	0.2	0.5	-0.3	0.46	0.2
VKA naive	No	8268	1.5	0.9	0.6	1.73	0.3	1.1	-0.8	0.29	-0.1
	Yes	5745	1.5	1.2	0.3	1.19	0.4	1.1	-0.7	0.35	-0.5
CHADS2	2-3	10988	1.2	0.8	0.4	1.55	0.3	0.9	-0.7	0.30	-0.2
	>3	3026	2.8	2.0	0.7	1.36	0.6	1.7	-1.1	0.34	-0.4
Stroke/TIA	No	10032	1.1	0.7	0.4	1.64	0.3	1.0	-0.7	0.29	-0.3
	Yes	3982	2.5	1.9	0.6	1.31	0.5	1.4	-0.9	0.35	-0.3
Diabetes	No	8965	1.5	1.1	0.4	1.38	0.3	1.0	-0.7	0.31	-0.3
	Yes	5049	1.4	0.8	0.6	1.71	0.4	1.2	-0.8	0.33	-0.2
Aspirin*	No	8760	1.1	0.7	0.4	1.56	0.3	0.8	-0.4	0.40	0.0
	Yes	5254	2.1	1.5	0.6	1.37	0.4	1.7	-1.3	0.24	-0.7
PPI/h2 blocker*	No	11301	1.2	0.8	0.4	1.49	0.3	1.0	-0.7	0.28	-0.3
	Yes	2713	2.7	1.8	0.8	1.48	0.7	1.6	-1.0	0.41	-0.1
Dose Adj	No	10460	1.2	0.9	0.4	1.40	0.4	1.0	-0.6	0.38	-0.2
	Yes	3554	2.4	1.5	0.9	1.63	0.3	1.5	-1.3	0.17	-0.4
Location	Outside US	11409	1.6	1.1	0.5	1.45	0.3	1.0	-0.7	0.32	-0.2
	US	2605	1.0	0.6	0.4	1.62	0.4	1.4	-1.0	0.30	-0.6

Reviewer's Table. Source: the Applicant's dataset: DM, BASEGRP, POSTGRP, ADJEFFCA and BLDDATA

† A negative value indicates an absolute risk reduction (%/patient-year) of endpoint in the edoxaban group compared with warfarin. ΔΔ (the net clinical benefit) was assessed based on equal weight of the efficacy and safety endpoint.

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

***Medication was taken at any time on or after the first dose through the last dose**

			Benefit				Risk				
			Efficacy (Ischemic Stroke/SEE)				Safety (Major Bleed)				
		N	Edoxaban 30 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	Edoxaban 30 mg (% pt yr)	Warfarin (% pt yr)	Delta (% pt yr)	HR	ΔΔ (% pt yr)
All		14014	1.5	1.0	0.5	1.47	1.6	3.3	-1.7	0.47	-1.2
Age	<64 yrs	3264	1.2	0.7	0.5	1.76	0.6	1.7	-1.1	0.36	-0.6
	64 to <72	3554	1.3	0.8	0.5	1.67	1.5	3.2	-1.7	0.47	-1.2
	72 to <78	3685	1.6	1.2	0.4	1.28	2.0	3.5	-1.5	0.57	-1.1
	≥78	3511	1.9	1.4	0.5	1.38	2.2	5.2	-3.1	0.42	-2.6
Sex	Female	5347	1.7	1.1	0.7	1.62	1.5	3.3	-1.8	0.46	-1.1
	Male	8667	1.4	1.0	0.4	1.37	1.6	3.4	-1.8	0.48	-1.4
Elderly Female	<75 yrs	2835	1.5	0.7	0.7	2.01	1.1	2.3	-1.2	0.46	-0.5
	≥ 75	2512	2.0	1.5	0.5	1.39	2.1	4.5	-2.5	0.46	-1.9
Elderly Male	<75 yrs	5585	1.3	0.8	0.5	1.59	1.3	2.7	-1.4	0.48	-0.9
	≥ 75	3082	1.5	1.4	0.1	1.10	2.3	4.8	-2.5	0.48	-2.4
Weight	<70 kg	3365	2.3	1.2	1.0	1.85	1.6	3.6	-2.1	0.43	-1.0
	70 to <81.8	3634	1.4	1.4	0.1	1.05	1.6	3.5	-2.0	0.44	-1.9
	81.8 to <95	3389	1.3	0.9	0.3	1.39	1.6	3.3	-1.7	0.50	-1.3
	≥ 95	3626	1.1	0.6	0.5	1.95	1.5	2.9	-1.4	0.51	-0.9
Weight Female	<64 kg	1318	2.5	1.3	1.2	2.01	1.2	4.5	-3.3	0.27	-2.1
	64 to <74	1264	1.9	1.3	0.6	1.40	1.7	3.1	-1.4	0.56	-0.8
	74 to <86	1402	1.5	1.5	-0.1	0.95	1.5	3.2	-1.7	0.45	-1.8
	≥86.2	1363	1.2	0.3	0.9	5.20	1.5	2.4	-0.9	0.63	0.0
Weight Male	<75 kg	2160	2.2	1.4	0.9	1.62	1.7	3.8	-2.2	0.43	-1.3
	75 to <86	2151	1.1	1.0	0.1	1.08	1.8	3.5	-1.7	0.51	-1.7
	86 to <99	2199	1.3	0.9	0.3	1.34	1.5	3.0	-1.5	0.52	-1.1
	≥ 99.2	2157	0.9	0.7	0.3	1.41	1.5	3.3	-1.7	0.47	-1.5
CrCL (ml/min)	30 to ≤50.6	2700	2.4	1.3	1.0	1.75	2.0	5.1	-3.1	0.39	-2.1
	50.6< to 63.6	2794	1.7	1.6	0.1	1.05	2.1	3.8	-1.8	0.54	-1.6
	63.6 < to 77.9	2794	1.3	1.0	0.3	1.28	1.8	3.0	-1.1	0.63	-0.8
	77.9 < to 98.1	2822	1.2	0.8	0.5	1.59	1.0	3.1	-1.9	0.36	-1.4
	≥ 98.1	2731	1.0	0.5	0.5	2.10	1.2	2.2	-1.2	0.50	-0.7
VKA naive	No	8268	1.5	0.9	0.6	1.73	0.0	3.3	-3.3	0.46	-2.7
	Yes	5745	1.5	1.2	0.3	1.19	1.5	3.4	-1.9	0.49	-1.6
CHADS2	2-3	10988	1.2	0.8	0.4	1.55	1.4	3.0	-1.6	0.46	-1.2
	>3	3026	2.8	2.0	0.7	1.36	2.3	4.7	-2.4	0.49	-1.7
Stroke/TIA	No	10032	1.1	0.7	0.4	1.64	1.5	3.3	-1.8	0.46	-1.3
	Yes	3982	2.5	1.9	0.6	1.31	1.7	3.6	-1.8	0.49	-1.2
Diabetes	No	8965	1.5	1.1	0.4	1.38	1.5	3.1	-1.6	0.49	-1.1
	Yes	5049	1.4	0.8	0.6	1.71	1.7	3.8	-2.2	0.44	-1.6
Aspirin*	No	8760	1.1	0.7	0.4	1.56	1.2	2.6	-1.3	0.48	-0.9
	Yes	5254	2.1	1.5	0.6	1.37	2.2	4.8	-2.6	0.46	-2.0
PPI/h2 blocker*	No	11301	1.2	0.8	0.4	1.49	1.1	2.6	-1.5	0.42	-1.1
	Yes	2713	2.7	1.8	0.8	1.48	3.8	6.8	-3.0	0.57	-2.1
Dose Adj	No	10460	1.2	0.9	0.4	1.40	1.6	3.0	-1.3	0.55	-1.0
	Yes	3554	2.4	1.5	0.9	1.63	1.5	4.7	-3.2	0.31	-2.3
Location	Outside US	11409	1.6	1.1	0.5	1.45	1.3	3.1	-1.8	0.43	-1.3
	US	2605	1.0	0.6	0.4	1.62	2.8	4.5	-1.8	0.61	-1.4

Reviewer's Table. Source: the Applicant's dataset: DM, BASEGRP, POSTGRP, ADJEFFCA and BLDDATA

† A negative value indicates an absolute risk reduction (%/patient-year) of endpoint in the edoxaban group compared with warfarin.

ΔΔ (the net clinical benefit) was assessed based on equal weight of the efficacy and safety endpoint.

***Medication was taken at any time on or after the first dose through the last dose**

APPENDIX 2 Components of the CHADS2 Score (Source: ENGAGE AF Protocol)

$CHADS_2$ Item	Points
Congestive heart failure	1
Hypertension*	1
Age ≥ 75 years	1
Diabetes	1
History of Stroke or TIA	2

*Modified based on: Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70.

Congestive heart failure is defined as the current presence or prior history of clinical congestive heart failure Class C (structural heart disease with prior or current symptoms of heart failure, such as shortness of breath, fatigue, decreased exercise tolerance) or Class D (refractory heart failure requiring specialized interventions).

Hypertension defined as hypertension requiring pharmacologic therapy to maintain a BP < 140/85 mmHg or untreated hypertension documented by BP > 140 mmHg systolic or > 90 mmHg diastolic on two separate occasions.

Diabetes Mellitus includes diabetes requiring treatment with diet only or with pharmacologic therapy (insulin, oral hypoglycemic agents).

Stroke is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit that is generally in the distribution of a single brain artery (including the retinal artery) and that is not due to an identifiable non-vascular cause (i.e., brain tumor or trauma). The deficit must either be associated with symptoms lasting more than 24 hours or result in death within 24 hours of symptom onset.

TIA is defined as an abrupt onset, over minutes to hours, of a focal non-fatal, neurological deficit in the distribution of a single brain artery (including the retinal artery) that lasts less than 24 hours and that does not satisfy the definition of stroke above.

APPENDIX 3 Visit Schedule

Table 108: Visit Schedule Year 1

	SQ	Rand	Treatment Year One [a]															
	Day	Day	Day						Month									
	- 60	1	8	15	29	42	60	70	3	4	5	6	7	8	9	10	11	12
Visit Window (days) [b]	**n/a**	**n/a**	±3	±3	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7
Study Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Demographic Information	X																	
Medical/Surgical History	X																	
Alcohol and Tobacco Use	X																	
Physical Examination	X[c]																	
Vital Signs		X							X			X			X			X
12-lead ECG		X[c]			X													X
Hepatitis Serology		X[d]																
IXRS Randomization Visit Worksheet		X																
Liver function assessment includes ALT, AST, TBL, and ALP	X[d]	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Serum creatinine and body weight assessment	X[d]	X							X			X			X			X
Serum chemistry panel excluding creatinine		X			X				X			X			X			X
Hematology	X[d]	X			X				X			X			X			X
Urinalysis		X			X				X			X			X			X
AE Reporting [e]	••																	
SAEs, endpoints and other events of interest reporting [e](e.g., liver function abnormalities, new bone fractures, and neoplasms)	••																	

	SQ	Rand	Treatment Year One [a]															
	Day	Day	Day						Month									
	- 60	1	8	15	29	42	60	70	3	4	5	6	7	8	9	10	11	12
Visit Window (days) [b]	n/a	n/a	±3	±3	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7
QoL (questions 1 and 2)[f]		X							X			X			X			X
Prior and Concomitant Medication	X	X							X			X			X			X
In-clinic study drug administration					X													
Study drug dispensing[g]		X			X		X		X			X			X			X
Review and confirm study medication dosing with the subject using Subject Medication Dosing calendar		X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Review and confirm by telephone subject's understanding of the dosing instructions						X		X										
Study drug compliance					X		X		X			X			X			X
Contact IXRS for study drug assignment		X			X		X		X			X			X			X
Contact IXRS to enter subject status changes or for unscheduled drug assignments	---------- as needed ----------																	
INR[h] measurement with IXRS contact	X[i]	X[i]	X	X	X		X		X	X	X	X	X	X	X	X	X	X
D-dimer sampling		X							X									
PK Sampling					X[j]				X[k]									X[k]
Record date and time of subject's last dose (before PK sampling)					X				X									X
Pharmacogenomics informed consent (optional)	X																	

	SQ	Rand	Treatment Year One [a]															
	Day	Day	Day						Month									
	- 60	1	8	15	29	42	60	70	3	4	5	6	7	8	9	10	11	12
Visit Window (days) [b]	n/a	n/a	±3	±3	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7
Pharmacogenomic sampling (optional)		X[l]																

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CSED = common study end date; ECG = electrocardiogram; eCRF = electronic case report form; INR = international normalized ratio; IXRS = interactive voice and web response system; MI = myocardial infarction; PD = pharmacodynamics; PK = pharmacokinetics; QoL = quality of life; Rand = randomization; SAE = serious adverse event; SQ = study qualification; SEE = systemic embolic event; TBL = total bilirubin; TIA = transient ischemic attack; VKA = vitamin K antagonist.
a: Subjects no longer taking study drug will be followed for SAEs, endpoints, and other events of interest (e.g., liver function abnormalities, new bone fractures, and neoplasms) by visit or telephone contact every 3 months until the CSED Visit. The subjects with temporary study drug interruptions are expected to have eCRFs completed for study drug temporary interruptions. The targeted concomitant medications eCRF should also be completed every three months during study drug temporary interruptions or permanent discontinuations. The subjects with permanent study drug discontinuation prior to CSED Visit are expected to have both a Study Drug Discontinuation Visit and a CSED Visit.
b: Scheduling of visits within visit windows should be done with caution to the drug supply available in a dispensing unit.
c: Targeted physical exam performed by an Investigator or other healthcare professional designated by the Investigator. Physical examination at study qualification includes vital signs. If an ECG was done ≤ 4 days before randomization, it can serve as the baseline ECG and there is no need to repeat the ECG at the randomization visit.
d: Samples taken as part of routine care outside study auspices may be analyzed by local laboratories and the results used to qualify the subject provided the tests were performed ≤ 60 days before randomization. Alternatively, the central laboratory may be utilized for these laboratory tests. Although ALP is part of the liver panel at visits during the treatment period, it is not required as part of study qualification.
e: SAEs, endpoint events, and other events of interest should be reported as soon as site personnel learn of the event. Endpoint event reporting should occur throughout the study and not be restricted to specific visits. Also, AE reporting should occur throughout the study and not be restricted to specific visits.
f: QoL questions 1 and 2 are for outpatient evaluation and diagnostic tests.
g: Study drug assigned by the IXRS every 3 months may be dispensed as a 3 month supply or in smaller amounts sufficient to last until the next visit (e.g., one month supply).

h: INR assessment for adjustment of warfarin dosages will be done every month. Additional interim evaluations may be done at the discretion of the Investigator.
i: For subjects not taking any open-label VKA during the 60 days prior to randomization, INR must be ≤ 2.5 within 60 days prior to randomization, provided that the subject did not receive any VKA between that INR measurement and randomization. For subjects receiving open-label VKA at the time of randomization, INR value must be ≤ 2.5 within 48 hours prior to randomization, provided that the VKA dose had not been increased within those 48 hours.
j: Two PK samples will be collected during the Day 29 visit: a pre-dose sample (prior to administration of study drug) and a post-dose sample (1 to 3 hours post-dose). It is critical to record the date/time of the last dose the day before the PK sample, the date/time of the dose on Day 29, and the date/time of the PK sample collections.
k: One PK sample will be collected during the specified visits. It is critical to record the date/time of the last dose before the PK sample and the date/time of the PK sample collection.
l: Pharmacogenomics sample may be collected at any treatment visit if it was not obtained at Day 1 and a Pharmacogenomics Informed Consent has been obtained.
Source: ENGAGE AF, CSR

Table 109: Visit Schedule Year 2

Study Period	**Treatment Year Two [a, b]**												**Study Drug Discontinuation Visit [c]**	**Common Study End Date Visit [d]**
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**n/a**	**n/a**
Visit Window (days)[e]	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	**n/a**	**n/a**
Physical Examination[f]													X	X
Vital Signs			X			X			X			X	X	X
12-lead ECG												X	X	X
Liver function assessment includes ALT, AST, TBL, and ALP			X			X			X			X	X	X
Serum creatinine and body weight assessment			X			X			X			X	X	X
Serum chemistry panel excluding creatinine						X						X	X	X
Hematology						X						X	X	X
Urinalysis						X						X	X	X
AE Reporting [g]	••													
SAEs, endpoints, and other events of interest reporting [g] (e.g., liver function abnormalities, new bone fractures, and neoplasms)	••													
QoL (questions 1 and 2)[h]			X			X			X			X		
Prior and Concomitant Medication			X			X			X			X	X	X
Study drug dispensing[i]			X			X			X			X		
Review and confirm study medication dosing with the subject using the Subject Medication Dosing calendar	X	X	X	X	X	X	X	X	X	X	X	X		
Study drug compliance			X			X			X			X	X[j]	X[j]

Reference ID: 3642117

Study Period	Treatment Year Two [a, b]												Study Drug Discontinuation Visit [c]	Common Study End Date Visit [d]
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**n/a**	**n/a**
Visit Window (days)[e]	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	**n/a**	**n/a**
Contact IXRS for study drug assignment			X			X			X			X	X	X
Contact IXRS to enter subject status changes or for unscheduled drug assignments	---------- as needed ----------													
INR [k] measurement with IXRS contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sampling													X[l]	
Record date and time of subject's last dose (before PK sampling)													X[l]	X[l]

a: Subjects no longer taking study drug will be followed for SAEs, endpoints, and other events of interest (e.g., liver function abnormalities, new bone fractures, and neoplasms) by visit or telephone contact every 3 months until the CSED Visit. The subjects with temporary study drug interruptions are expected to have eCRFs completed for temporary study drug interruptions. The targeted concomitant medications eCRF should also be completed every three months during study drug temporary interruptions or permanent discontinuations. The subjects with permanent study drug discontinuation prior to CSED Visit are expected to have both a Study Drug Discontinuation Visit and a CSED Visit.
b: Subsequent treatment years will follow the same visit schedule as year two.
c: This visit is for subjects who permanently discontinue study drug before the CSED. Subjects who do not permanently discontinue study drug but have temporary study drug interruptions will not have this visit; however, the eCRF for temporary study drug interruption will be completed.
d: For all subjects, the CSED Visit will be performed. This includes subjects who temporarily interrupted or permanently discontinued study drug. All randomized subjects with final dose within 30 days of the CSED Visit or on the day of the CSED Visit will have a post-final-dose follow-up visit or telephone contact 30 to 37 days after the CSED Visit to collect data on SAEs, endpoints and other events of interest (e.g., liver function abnormalities, new bone fractures, and neoplasms). Subjects transitioning to open-label VKA should have INR testing on Day 4. In addition, INR testing is recommended as needed on Day 8 (window 7-9 days), Day 12 (window 11-14 days), Day 28, and at least monthly thereafter.

e: Scheduling of visits within visit windows should be done with caution to the drug supply available in a dispensing unit.
f: Full physical exam performed by an Investigator or other healthcare professional designated by the Investigator.
g: SAEs, endpoint events, and other events of interest should be reported as soon as site personnel learn of the event. Endpoint event reporting should occur throughout the study and not be restricted to specific visits. Also, AE reporting should occur throughout the study and not be restricted to specific visits.
h: QoL questions 1 and 2 are for outpatient evaluation and diagnostic tests.
i: Study drug assigned by the IXRS every 3 months may be dispensed as a 3 month supply or in smaller amounts sufficient to last until the next visit (e.g., one month supply).
j: Record date/time of last/final dose of study drug.
k: INR assessment for adjustment of warfarin dosages will be done every month. Additional interim evaluations may be done at the discretion of the Investigator.
l: One PK sample will be collected during the specified visits only if they occur before the Month 12 visit. It is critical to record the date/time of the last dose before the PK sample and the date/time of the PK sample collection. For the Study Drug Discontinuation Visit, PK sample will only be taken if the subject is still on study drug at the time of the visit and the visit occurs before the Month 12 visit.
Source: ENGAGE AF CSR

APPENDIX 4 Guidelines for INR-Based Dose Adjustments for Warfarin

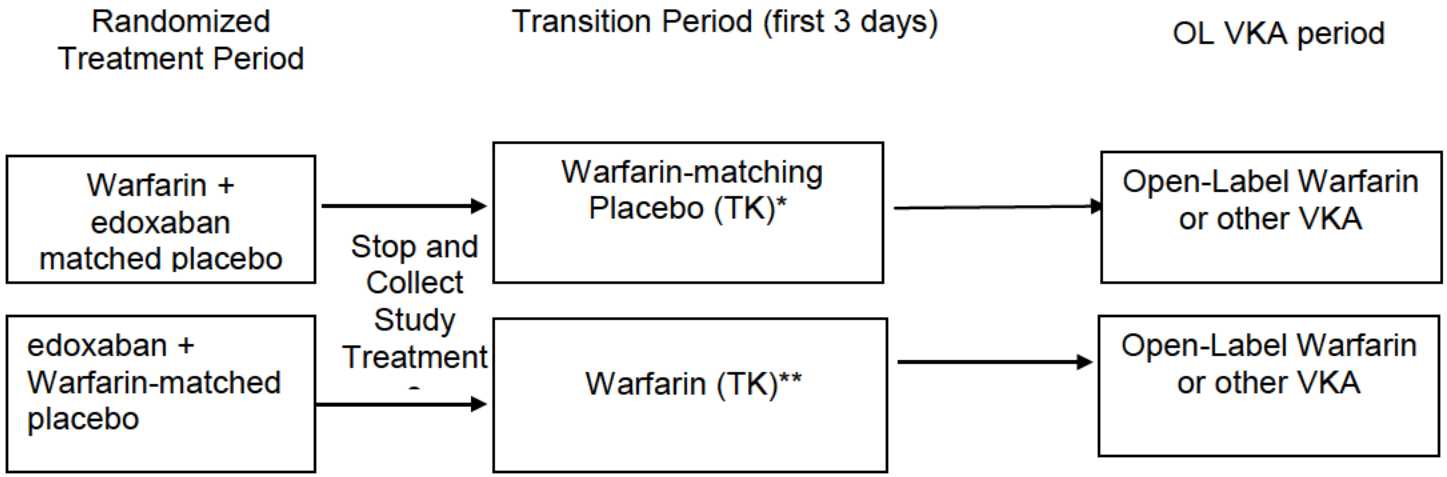
The following guidelines for adjusting the warfarin dose to maintain this INR were not meant to supersede the clinical judgment of the investigators or investigator designees.

INR	**Suggested Warfarin/Placebo Dose Adjustment**
< 1.5	Increase weekly dose of warfarin/placebo by 10% to 20%. Consider giving one extra dose of warfarin/placebo. Retest INR in 4 to 8 days or sooner per Investigator discretion.
1.5 to < 2	Increase weekly dose of warfarin/placebo by 5% to 10%. Retest INR in 7 to 14 days or sooner per Investigator discretion.
2.0 to 3.0	No Change
> 3.0 to 3.5	Decrease weekly dose of warfarin/placebo by 0% to 20%. Retest INR in 2 to 4 weeks or sooner per Investigator discretion.
> 3.5 to 4.0	Withhold 0 to 1 dose and/or decrease weekly dose of warfarin/ placebo by 0% to 20%. Retest INR in 1 to 2 weeks or sooner per Investigator Discretion.
> 4.0 but < 5.0	Withhold both double-blind study drugs for 1-2 days, and retest INR. When INR < 3.0 restart both study drugs with a 0-20% decrease in the warfarin/placebo study drug. Retest INR in 3 to 7 days or sooner per Investigator discretion.
5.0 to < 9.0 without significant bleeding	Withhold both double-blind study drugs for 1 to 2 days. Retest INR in 1 to 2 days or sooner per Investigator discretion. Resume dosing once INR < 3.0, but with weekly dose decreased by 5% to 20%. If the subject needs urgent surgery, then the subject should receive Fresh Frozen Plasma (FFP). If necessary, contact TIMI HOTLINE (US/Canada: 1-866-480- 1734; Other countries: +1-617-278-0900; Email: timiengage@partners.org) for consultation.
≥ 9.0 without significant bleeding	Withhold study drug. Give Vitamin K (single 2.5 to 5 mg oral dose) Repeat INR test daily until INR < 5.0. If INR remains too high, more Vitamin K doses can be considered. Resume dosing once INR < 3.0, but with weekly dose decreased by 10% to 20%. If the subject needs urgent surgery, then the subject should receive FFP. If necessary, contact TIMI HOTLINE (US/Canada: 1-866-480- 1734; Other countries: +1-617-278-0900; Email: timiengage@partners.org) for consultation.

Source: ENGAGE AF CSR

APPENDIX 5 Transition Plans and Study Stop Transition Plans

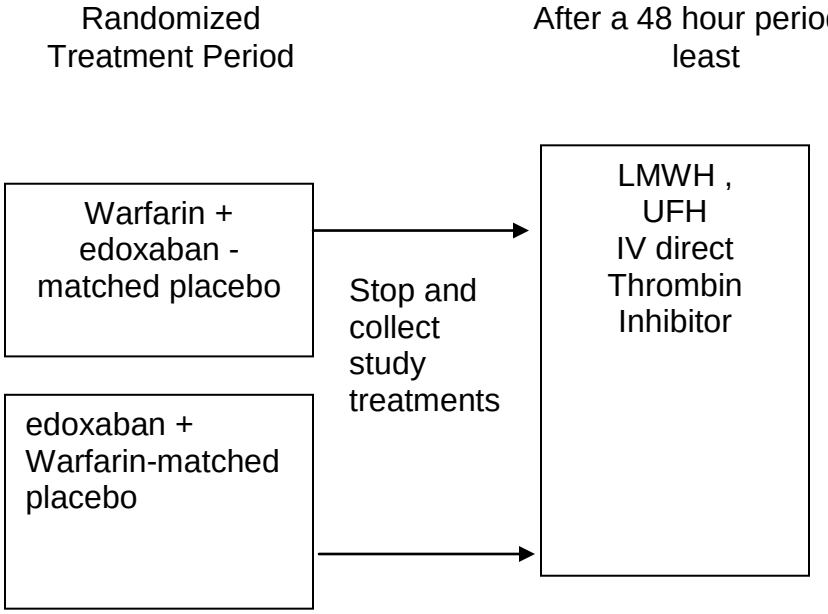
Figure 35: Temporary Transition to VKA



*Prescribed by Investigator; dose and duration of treatment at Investigator's discretion
**Use of TK was optional, at the Investigator's discretion

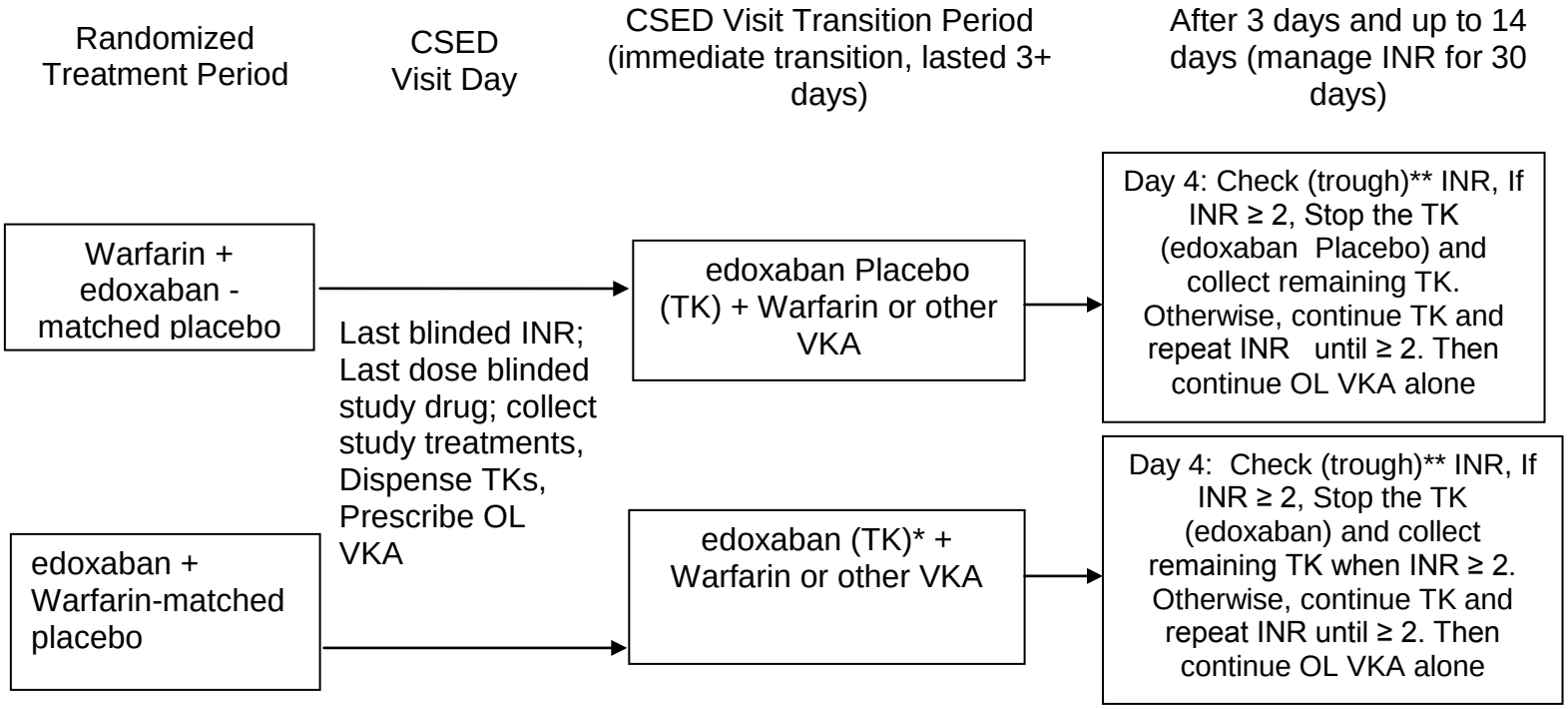
Source: Applicant Communication during review period

Figure 36: Temporary Transition to LMWH, UFH or IV direct Thrombin Inhibitor



Source: Applicant Communication during review period

Figure 37: Study Stop – Transition to VKA



* The schema used to determine the dose of edoxaban used in the EOS Transition Plan is shown in

Table 110. According to the applicant, this information was not included in the study protocol but was provided to the sites during the training for study closeout procedures.

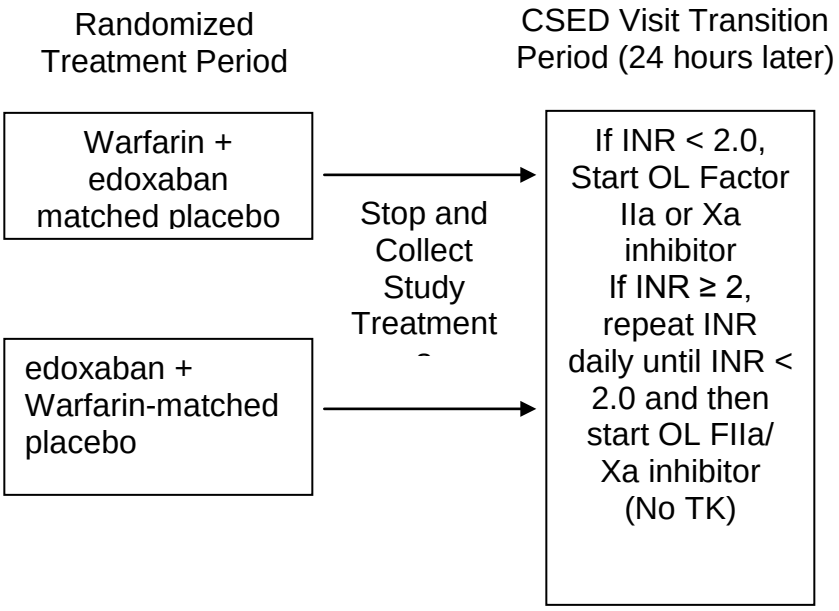
** The trough INR had to be taken at least 8 hours after the most recent dose of edoxaban/ edoxaban placebo + warfarin.Source: Applicant Communication during review period

Table 110: Dose used in end of study (EOS) transition plan

Treatment Group	Study Drug Dose at the Time of CSED Visit	Edoxaban Dose in the EOS Transition Plan
Edoxaban High Exposure	60 mg	30 mg
	30 mg (dose reduced)	15 mg
Edoxaban Low Exposure	30 mg	30 mg
	15 mg (dose reduced)	15 mg
Warfarin	Warfarin (INR based)	Edoxaban-matching Placebo

Source: Applicant Communication during review period

Figure 38: Study Stop – Transition to Factor IIa/Xa inhibitor



Source: Applicant Communication during review period

APPENDIX 6 Synopsis of CEC Definitions (source: CEC Charter):

1. Cerebrovascular Events
    a. Stroke

A stroke is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit that is generally in the distribution of a single brain artery (including the retinal artery) and that is not due to an identifiable non-vascular cause (i.e., brain tumor or trauma). The deficit must either be associated with symptoms lasting more than 24 hours or result in death within 24 hours of symptom onset. Since strokes may have variable clinical presentations (e.g., a large hemorrhagic stroke presenting with sudden syncope, embolic stroke with multiple deficits in >1 vascular territory), the use of supplementary information such as brain imaging, may be used by the CEC to determine if a stroke has occurred. CT and/or MRI scan reports, operative notes, autopsy results and other clinical data will be considered by the CEC to support the clinical impression, and to permit subclassification of the type of stroke.

All strokes will be sub-classified as “primary ischemic” or “primary hemorrhagic” based on imaging data, if available, or “uncertain cause” if imaging data is not available according to the definitions below. Primary ischemic strokes will be further subclassified by type in to the following categories:

- Ischemic Stroke with no hemorrhage
- Stroke without focal collections of intracerebral blood on a brain imaging. (This category will be sub-classified into atherosclerotic vs. lacunar, and embolic vs. other)
- Cerebral infarction with small foci (<10 mm) of hypointense signals on gradient-echo MRI sequences
- Ischemic Stroke with Hemorrhagic Conversion
- Cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage. Hemorrhagic conversion usually occurs on the cortical surface. Hemorrhagic conversion in the deeper brain requires evidence of nonhemorrhagic infarction in the same vascular territory
- Ischemic Stroke with Microhemorrhage (not considered to be consistent with a hemorrhagic conversion endpoint)

Primary hemorrhagic strokes will be classified by the location of bleeding (multiple locations may be checked if appropriate).

- Primary Hemorrhagic
    - Intracerebral Hemorrhage
    - Stroke with focal collections of intracerebral blood seen on a brain image (CT or MRI) or a postmortem examination, not likely to represent hemorrhagic conversion. Primary hemorrhages cause hematomas which are usually easily discriminated by their cortical location and rounded or elliptical shape. Microhemorrhages incidentally discovered on brain

imaging are not considered a primary hemorrhagic stroke endpoint event, and will be otherwise classified.

- Subarachnoid hemorrhage – High density fluid collection in subarachnoid space on brain images or blood in the subarachnoid space on autopsy
- Uncertain – Any stroke without brain image (CT or MRI), autopsy documentation, or other diagnostic information that permits sub-classification of the stroke, or if the tests are inconclusive

The severity of Stroke will be measured with the modified Rankin score at the next scheduled visit, i.e., 1-4 months after the event.

Stroke should be confirmed by either autopsy or brain imaging (CT or MRI); where these are unavailable the initial clinical presentation must be typical of stroke.

2. Subdural hematoma
   A subdural hematoma is defined as a high density fluid collection in subdural space on brain images or blood in the subdural space on autopsy. *NOTE: A subdural hematoma is considered an intracranial hemorrhage but will not be classified as a hemorrhagic stroke.*

3. Epidural hematoma
   An epidural (or extradural) hematoma is defined as a collection of high density fluid collection on brain images or blood occurring between the dura mater and the skull. *NOTE: An epidural hematoma is considered an intracranial hemorrhages but will not be classified as a hemorrhagic stroke.*

4. Microhemorrhages
   Microhemorrhages are defined as rounded foci of <10 mm that appear hypointense and that are distinct from other causes of signal loss on gradient-echo MRI sequences (e.g., vascular flow voids, leptomeningeal hemosiderosis, or non-hemorrhagic subcortical mineralization). Since epidemiological studies have shown as high as ~40% rate of microhemorrhage in stable asymptomatic elderly patients undergoing gradient echo MRI (but not other imaging modalities), and the clinical significance of these findings is not clear, findings of a microhemorrhage by itself will not be considered to satisfy the criteria for an ICH, stroke, or bleeding event. Instead microhemorrhages will be classified as either:
   a. Microhemorrhage in association with an ischemic stroke
   b. Isolated microhemorrhage (not an ICH, stroke, or bleed)

5. Transient ischemic attack (TIA)
   A TIA as an abrupt onset over minutes to hours of a focal non-fatal, neurological deficit in the distribution of a single brain artery (including the retinal artery) that lasts less than 24 hours and that does not satisfy the definition of stroke above.

For each case that the CEC confirms satisfies the protocol definition of TIA, the CEC Adjudicators will indicate whether brain imaging demonstrated evidence of a new ischemic brain injury or not.

6. Systemic Embolic Event (SEE) A Systemic Embolic Event is defined as an abrupt episode of arterial insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). Arterial embolic events involving the CNS (including the eye), coronary, and pulmonary arterial circulation are not considered SEEs, but will be classified respectively as stroke/TIA, myocardial infarction, and pulmonary embolism. In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.

7. Death Classification
    a. Death will be classified as *Cardiovascular, Malignancy,* or *Non-cardiovascular/Nonmalignancy*. The cause of death is determined by the principal condition that caused the death, not the immediate mode of death. All deaths will be assumed to be cardiovascular in nature unless a malignant or a non-cardiovascular cause can be clearly shown.

        i. Cardiovascular death is defined as death due to documented cardiovascular cause, including deaths due to bleeding. Causes of cardiovascular deaths include, but are not limited to, deaths resulting from atherosclerotic coronary heart disease (acute myocardial infarction, sudden cardiac death, non-sudden death with gradually worsening cardiac symptoms, unwitnessed death without clear alternate cause, procedural death related to cardiac surgery or coronary angiography), atherosclerotic vascular disease (cerebrovascular disease including stroke and hemorrhage, aortic, mesenteric, renovascular, peripheral arterial disease, or complication of a non-coronary vascular procedure), other cardiovascular (pulmonary embolism, endocarditis, congestive heart failure, valvular heart disease, arrhythmia), and deaths due to bleeding.

        ii. Malignancy-related deaths will include deaths that are directly a consequence of a malignancy, such as a brain tumor that causes herniation, coma, and respiratory arrest. Deaths due to malignancy will be further subclassified by organ system and timing of diagnosis (before vs. after randomization).

        iii. Non-cardiovascular/non-malignancy deaths include those caused primarily by infection, pulmonary, gastrointestinal, accidental, renal, trauma, or non-cardiovascular organ system failure.

b. For all deaths, the relationship of the death to bleeding and malignancy will be adjudicated as follows:
    i. Relationship to Bleeding (categories are mutually exclusive)
        - Fatal bleeding – death in which a bleeding event directly led to death within 7 days. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death must be either intracranial or nonintracranial bleeding.
        - Bleeding contributed to death – a death in which a bleeding event was part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but bleeding was not directly and/or immediately related to subject's death.
        - Deaths unrelated to a bleeding event – The case of death was unrelated to bleeding, either because there was no clinical significant bleeding in the month prior to death or the bleeding event did not contribute to the subject's death. In these cases, the cause of death cannot be intracranial / non-intracranial bleeding.

8. Relationship to Malignancy
    a. Death directly related to malignancy – Death in which the mode of death can be attributed to the direct effects of a malignancy. In such cases, the cause of death adjudicated by the CEC must be malignancy.
    b. Death due to a consequence related to malignancy. This would include deaths due to other processes (e.g., infection in a patient who becomes septic and neutropenic due to acute leukemia) that are a known complication of the malignancy. The underlying malignancy should be on the causal pathway leading to death, but not the immediate cause of death. In such cases, the cause of death adjudicated by the CEC cannot be malignancy, but instead should be the other process (e.g., infection).
    c. Death not related to a malignancy. Either no malignancy has been diagnoses or the malignancy that is present was not related to the cause of death. The cause of death must be something other than malignancy.
9. Sudden Cardiovascular Death
   Sudden CV death is defined as a sudden, unexpected death that was either:
    a. witnessed, occurring within 60 min from the onset of new symptoms, in the absence of a clear cause other than cardiovascular; or
    b. unwitnessed, within 24 hours of being observed alive, in the absence of pre-existing progressive circulatory failure or other non-cardiovascular causes of death;

10. Non-sudden Cardiovascular Death

This category refers to a patient who had symptoms of a cardiovascular nature and had gradual deterioration prior to death. It includes all patients with CV death who do not meet criteria for sudden death or unwitnessed CV death.

11. Unwitnessed CV Death -- Death that occurred unexpectedly, *without* patient being seen within 24 hours, and for which no known other major causes of death are identified.

APPENDIX 7 Overview of Bleeding Category Definition

Major bleeding event:

A clinically overt bleeding event (i.e., bleeding that is visualized by examination or radiologic imaging) that meets at least one of the following:

a) Fatal bleeding
b) Symptomatic bleeding in a critical area or organ such as:
- Retroperitoneal
- Intracranial
- Intraocular
- Intraspinal
- Intra-articular
- Pericardial
- Intramuscular with compartment syndrome

c) A clinically overt bleeding event that causes a fall in hemoglobin level of 2.0 g/dL (>1.24 mMol/L) or more, adjusted for transfusions. Each 1 unit of packed RBC or whole blood is counted as a 1.0 g/dL decrease in hemoglobin. In the case of surgical procedural related bleeding, the bleeding must be in excess of that normally associated with the surgery/procedure. In the absence of hemoglobin data, a fall of hematocrit of 6.0% or more, adjusted for transfusion, will satisfy the criteria for a major bleeding event.

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

A **life-threatening major bleed** is defined as a bleeding event that is either intracranial or is associated with hemodynamic compromise requiring intervention.

Intracranial hemorrhage :
Intracranial hemorrhage (ICH) included:
- Primary hemorrhagic stroke, including sub-arachnoid hemorrhage
- Primary ischemic stroke with major hemorrhagic conversion
- Subdural hematoma
- Epidural hematoma

Any ICH is major bleed. ICH could be fatal or non-fatal bleed.

Primary Hemorrhagic stroke included*:*
- Intracerebral Hemorrhage – Stroke with focal collections of intracerebral blood seen on a brain image (CT or MRI) or a postmortem examination, not likely to represent hemorrhagic conversion. Primary hemorrhages cause hematomas which are usually easily discriminated by their cortical

location and rounded or elliptical shape. Microhemorrhages incidentally discovered on brain imaging are not considered a primary hemorrhagic stroke endpoint event, but will be otherwise classified (see below 6.1.4).

- Subarachnoid hemorrhage – High density fluid collection in subarachnoid space on brain images or blood in the subarachnoid space on autopsy

Primary ischemic stroke with Hemorrhagic Conversion – Cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage. Hemorrhagic conversion usually occurs on the cortical surface. Hemorrhagic conversion in the deeper brain requires evidence of nonhemorrhagic infarction in the same vascular territory. Microhemorrhages evident on MRI, whether in the cortex or deep brain structures, are not considered to be consistent with a hemorrhagic conversion endpoint.

Subdural hematoma: A subdural hematoma is defined as a high density fluid collection in subdural space on brain images or blood in the subdural space on autopsy. NOTE: A subdural hematoma is considered an intracranial hemorrhage but will not be classified as a hemorrhagic stroke.

Epidural hematoma: An epidural (or extradural) hematoma is defined as a collection of high density fluid collection on brain images or blood occurring between the dura mater and the skull. NOTE: An epidural hematoma is considered an intracranial hemorrhages but will not be classified as a hemorrhagic stroke.

Fatal bleed:

Fatal bleed includes both fatal ICH and fatal non-ICH. Any fatal bleed is major bleed. or all deaths, the relationship of the death to bleeding was adjudicated as follows Relationship to Bleeding (categories are mutually exclusive)

Fatal bleeding – death in which a bleeding event directly led to death within 7 days. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death must be either intracranial or non-intracranial bleeding.

Bleeding contributed to death – a death in which a bleeding event was part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but bleeding was not directly and/or immediately related to subject's death. An example of bleeding contributing to death is a large retroperitoneal bleed that leads to surgical evacuation, development of a subsequent abscess in the area of bleeding that leads to sepsis, multiorgan failure and death 10 days after the onset of bleeding. If bleeding has contributed to death (but the bleeding was not categorized as "fatal"), then the cause of death must be recorded as something other than intracranial / non-intracranial bleeding.
Deaths unrelated to a bleeding event – The case of death was unrelated to bleeding,

either because there was no clinical significant bleeding in the month prior to death or the bleeding event did not contribute to the subject's death. An example of a death unrelated to bleeding is an episode of guaiac positive stools in a patient who dies of postobstructive pneumonia due to lung cancer. In these cases, the cause of death cannot be intracranial / non-intracranial bleeding.

Clinically relevant non-major bleeding events (CRNM):

A clinically overt bleeding event that requires medical attention. Examples of bleeding requiring medical attention include, but are not limited to, bleeding events that result in the following:

- Diagnostic or therapeutic measures:
- Requires or prolongs hospitalization
- Laboratory evaluation
- Imaging studies
- Endoscopy, colonoscopy, cystoscopy, or bronchoscopy
- Nasal packing
- Compression
- Ultrasound guided closure of an aneurysm
- Coil embolization
- Inotropic support
- Surgery
- Interruption or stopping study medication at the advice of a physician
- Changing concomitant therapies (e.g., reducing the dose of or discontinuing aspirin) at the advice of a physician
- Note: an outpatient visit without any of the above or similar diagnostic/therapeutic measures does not satisfy the criteria for "requiring medical attention"

Clinically relevant non-major bleeding will be classified according to site as follows:

- Cutaneous or soft tissue
- Epistaxis
- Ear-nose-throat (ENT)
- Gastrointestinal (subclassified as upper vs lower)
- Hemoptysis
- Hematuria (macroscopic only) / urethral
- Oral / Pharyngeal
- Puncture site
- Surgical site
- Vaginal
- Other (including any other bleeding event considered clinically significant by the CEC)

Clinically overt bleeding requires visualization of bleeding by examination or radiologic imaging.

Minor (not clinically relevant) bleeding events:

Other overt bleeding events that do not fulfill the criteria of a major bleeding event or a clinically relevant non-major bleeding event (e.g., epistaxis that does not require medical attention) will be classified as a minor bleeding event.

Minor bleeding events that do not result in changes in therapy, medical evaluation, testing, or medical treatment / management by a physician or other health care provider as identified by the actions taken on the bleeding eCRF form will not be sent for review to the CEC. The final status for these events will be “minor bleed.”

APPENDIX 8 Screening Failures

Table 111: Tabular Listing of Reasons for Screening Failure

	Overall n(%)
Screen Failure Subjects	4392 (17.2)
Reasons for Screen Failure:	
Protocol Eligibility Not Met	2523 (57.4)
INR>2.5	129 (2.9)
Inclusion/Exclusion Criteria	1693 (38.5)
Other	701 (16.0)
Investigator's decision	619 (14.1)
Subject's decision	1245 (28.3)
Reason not available	5 (< .01)
Subjects with Exclusion Criteria:	
Severe Renal Failure (CrCL <30 mL/min)	333 (7.6)
HGB <10g/dL, Platelets <100k or WBC <3k	207 (4.7)
Conditions Associated with High Bleeding Risk	149 (3.4)
Active Liver Disease or Persistent Liver Enzyme Elevation	147 (3.3)
Non-Compliant to Study Protocol	99 (2.3)
Medical Conditions (e.g., Active Cancer, Chemotherapy), Life Expectancy <12 Mths	96(2.2)
Clinically Relevant Lab Abnormalities	45 (1.0)
Acute Cardiac Events Within Previous 30Days (AMI or ACS or PCI)	37 (0.8)
Pre-planned Invasive Procedures/Surgeries With Anticipated Bleeding	37 (0.8)
Structural Factors (MS, Atrial Myxoma, or Mechanical Valve)	35 (0.8)
History of Positive Hepatitis B Antigen or Hepatitis C Antibody Prior to Randomization	28 (0.6)
Receiving Concomitant Prohibited Therapy	24 (0.5)
Increased Safety Risk Due to Medical Conditions as deemed by the Investigator	20 (0.5)
History of Left Atrial Appendage Exclusion (Surgery or Procedure)	17 (0.4)
Receiving/Planned Dual Antiplatelet Agents During Study	16 (0.4)
Chronic OAC Therapy Not Warranted	14 (0.3)
Previously Randomized in an Edoxaban Study	14 (0.3)
Transient AF Due to Reversible Factors	12 (0.3)
Alcohol/Drug Dependence in Past 12 Months	9 (0.2)
Intracardial Mass or LV Thrombus	9 (0.2)
Contraindicated for OAC Therapy	8 (0.2)
Females with Childbearing Potential	8 (0.2)
Receiving Investigational Agent (Drugs/Device) Within 30 Days Prior to Randomization	6 (0.1)
Receiving Concomitant Cyclosporine Therapy	2 (<0.2)
Known History of Positive HIV	1 (<0.1)

	Overall n(%)
Subjects Failed Inclusion Criteria:	
History of Documented AF by ECG Within Past 12 months and OAC Planned for Duration of the Study	277 (6.3)
$CHADS_2$ Score >=2	100 (2.3)
Male or Female With Age >= 21yrs	6 (0.1)
Able to Provide Written IC	1 (<0.1)
Investigator's decision	619 (14.1)
Subject's decision	1245 (28.3)
Reason not available	5 (< .01)

Reviewer's Table; Data Source: ENGAGE AF Clinical Study Report

APPENDIX 9 PRT-018, Dose-finding phase 2 study

Title: A Phase 2, randomized, parallel group, multi-center, multi-national study for the evaluation of safety of four fixed dose regimens of DU-176b in subjects with non-valvular atrial fibrillation

Important Study Dates:
Date First Subject Enrolled: First subject randomized date: 02 Jul 2007
Date Last Subject Completed: Last subject last follow-up date: 10 Jun 2008

Primary Objective:
The stated primary objective was to evaluate the safety of four fixed dose regimens of edoxaban (30 mg qd, 30 mg bid, 60 mg qd, and 60 mg bid) in subjects with NVAF. Warfarin was included as an active control. Evaluation of bleeding events and liver enzymes/bilirubin were the primary safety endpoints.

Study Design:
This was a randomized, double-blind (DU-176b) and open-label (warfarin), parallel group, multi-center, multi-national study.

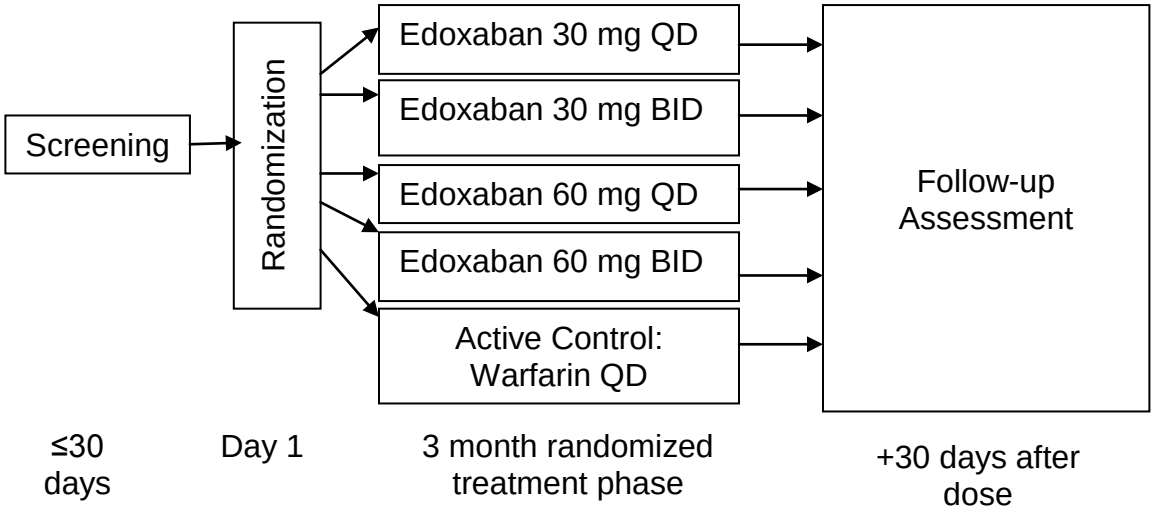
Treatments and Doses:
Edoxaban 30 mg qd, edoxaban 30 mg bid, edoxaban 60 mg qd, and edoxaban 60 mg bid, (only subjects randomized before 14 Jan 2008), and warfarin tablets (open-label) qd with dose adjusted to maintain an INR between 2.0 and 3.0.

Data from previous PK and PD studies of edoxaban supported qd and bid dosing regimens.

The doses of edoxaban used in this study, 30 mg and 60 mg, administered either once or twice daily, had been studied previously in healthy volunteers and in subjects undergoing hip replacement surgery. These doses and higher (up to 180 mg daily) had been previously studied but the studies were small and the longest duration of administration in these previous studies was 14 days.

Population:
Male and female subjects, 18 to 85 years of age, inclusive, with NVAF and at least a moderate yearly risk of stroke (based on the $CHADS_2$ index score of ≥2).

Schema:



Note: Edoxaban 60 mg bid dose regimen was terminated by IDMC recommendation on 14 Jan 2008. Before the IDMC recommended termination of the 60 mg bid edoxaban dose regimen, subjects were randomized in a 1:1:1:1:1 ratio to treatment with one of four edoxaban dose regimens or warfarin. After the IDMC recommendation, subjects were randomized to one of the remaining three edoxaban dose regimens or warfarin.

PD sampling occurred before dosing on the Day 1 visit and on Day 28 ± 2 days. AEs were collected throughout the trial. PK samples were acquired between 1 and 3 hours after dosing on day 28± 2 days.

Primary safety endpoints: ALT or AST elevations ≥3 times the upper limit of normal (ULN) and/or total bilirubin (TBL) elevations ≥2 times the ULN and major plus other clinically relevant non-major bleeding events.

The definition of major bleeding events in this study was derived from the International Society on Thrombosis and Hemostasis. Analysis of bleeding events was based on the adjudication provided by the blinded and independent CEC.

Main enrollment criteria:

1. Male or female and 18 to 85 years of age, inclusive.
2. Persistent NVAF
3. A $CHADS_2$ index score of at least 2
4. Not have a condition associated with high risk of bleeding or other acute or serious chronic condition

Blinding:

Subjects, the Investigator, and the Sponsor were blinded to the edoxaban dose regimen (i.e., 30 mg qd, 30 mg bid, 60 mg qd, or 60 mg bid), but not to randomization to edoxaban or warfarin, which was administered open-label. To maintain the edoxaban dose regimen blind, matching placebo for edoxaban was used for the second dose of the day for those subjects randomized to the qd regimens.

Primary Safety Variables:

1. Major bleeding events, clinically relevant non-major bleeding events, or both.
2. ALT or AST ≥3 x ULN, TBL ≥2 x ULN, or both (not necessarily simultaneously)

Primary Efficacy Analysis:
Although the study was not designed to evaluate efficacy, MACEs were recorded. The proportion of subjects experiencing MACE during the 3-month treatment period was summarized by treatment group with a 95% Clopper-Pearson confidence interval (CI) for the Safety Analysis Set. MACE was defined as stroke (ischemic or hemorrhagic), SEE, MI, cardiovascular death, and hospitalization for any cardiac condition.

Clinical Events Committee:
The CEC followed its own charter for processing and adjudicating bleeding events. The CEC adjudicated bleeding events independently of the Investigators' assessments and were blinded to the subject's treatment.

Amendments:
There were 5 amendments but only amendment # 3 (23 Jan 2008) is important to include in this summary because it substantively altered the conduct of the study. The amendment stated that in accordance with the recommendation of the IDMC (14 Jan 2008), randomization to the 60 mg bid dose regimen group was discontinued and Investigators were notified that subjects previously randomized to the 60 mg bid dose regimen were to discontinue study medication immediately and be evaluated at an end-of-treatment visit. The reason for the IDMC recommendation was an increased incidence of bleeding in the 60 mg bid regimen relative to the other treatment arms.

Disposition of Subjects:
There was an average of 242 (minimum 235 to maximum 251) subjects randomized to all treatment groups except for the edoxaban 60 mg bid group which had only 180 subjects, less than expected because of the IDMC's recommendation to discontinue this group before the completion of the study for excessive major bleeding rates. Almost all subjects were in the per protocol analysis and in the pharmacodynamic analysis set.

Study completion status of subjects in the safety analysis set is shown in Table 112. Most subjects completed except in the 60 mg bid arm. Approximately 30% of the subjects who were randomized to the 60 mg bid arm had completed before the IDMC decision to discontinue the arm of the study. The rest of the subjects in that arm (~70%) were withdrawn prematurely. There were more withdrawals in the edoxaban groups than in the warfarin group, mostly because of "withdrawal of consent" or adverse

events. Because warfarin was open-label subjects and investigators knew if they were on or dispensing edoxaban. This along with the knowledge that the IDMC recommended discontinuation of one of the edoxaban treatment arms probably biased the early withdrawals.

Table 112: Disposition of Subjects: Safety Analysis Set

	Edoxaban Daily Dose				
Variable	**30 mg qd (N = 235)**	**30 mg bid (N = 244)**	**60 mg qd (N = 234)**	**60 mg bid (N = 180)**	**Warfarin (N = 250)**
n (%) Completed	200 (85.1)	207 (84.8)	204 (87.2)	52 (28.9)	226 (90.4)
n (%) Withdrawn	35 (14.9)	37 (15.2)	30 (12.8)	128 (71.1)	24 (9.6)
During Treatment	34 (14.5)	35 (14.3)	27 (11.5)	118 (65.6)	23 (9.2)
After Treatment	1 (0.4)	2 (0.8)	3 (1.3)	10 (5.6)	1 (0.4)
Reasons for Withdrawal					
Adverse Event [a]	11 (4.7)	11 (4.5)	14 (6.0)	13 (7.2)	5 (2.0)
Protocol Violation	1 (0.4)	3 (1.2)	2 (0.9)	1 (0.6)	2 (0.8)
Death	3 (1.3)	3 (1.2)	1 (0.4)	0 (0.0)	2 (0.8)
Lost to Follow-up	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.6)	1 (0.4)
Withdrawal of Consent	16 (6.8)	16 (6.6)	7 (3.0)	8 (4.4)	12 (4.8)
Administrative	0 (0.0))	2 (0.8)	2 (0.9)	1 (0.6)	2 (0.8)
Not meet entry criteria	2 (0.9)	0 (0.0)	1 (0.4)	1 (0.6)	0 (0.0)
Other	2 (0.9)	2 (0.8)	2 (0.9)	103 (57.2)	0 (0.0)
IDMC Decision	N/A	N/A	N/A	100 (55.6)	N/A

Source: PRT018 clinical study report, p. 55

Most subjects except for those in the 60 mg BID group had ≥ 84 days of treatment. Aside from the 60 mg BID treatment group, the exposure among groups was relatively well matched.

Table 113: Extent of Exposure: Number (%) of subjects in Safety Analysis Set

	DU-176b Daily					
Statistics	**Any Dose (N = 893)**	**30 mg qd (N = 235)**	**30 mg bid (N = 244)**	**60 mg qd (N = 234)**	**60 mg bid (N = 180)**	**Warfarin (N = 250)**
Cumulative days on treatment						
≥1 - <7	37 (4.1)	10 (4.3)	10 (4.1)	6 (2.6)	11 (6.1)	6 (2.4)
≥7 - <15	36 (4.0)	3 (1.3)	7 (2.9)	5 (2.1)	21 (11.7)	5 (2.0)
≥15 - <21	13 (1.5)	4 (1.7)	2 (0.8)	2 (0.9)	5 (2.8)	1 (0.4)
≥21 - <28	19 2.1)	5 (2.1)	4 (1.6)	5 (2.1)	5 (2.8)	2 (0.8)
≥28 - <42	37 (4.1)	6 (2.6)	4 (1.6)	4 (1.7)	23 (12.8)	5 (2.0)
≥42 - <56	41 (4.6)	2 (0.9)	5 (2.0)	4 (1.7)	30 (16.7)	1 (0.4)
≥56 - <70	22 (2.5)	3 (1.3)	2 (0.8)	1 (0.4)	16 (8.9)	4 (1.6)
≥70 - <84	201 (22.5)	54 (23.0)	62 (25.4)	55 (23.5)	30 (16.7)	87 (34.8)
≥84	487 (54.5)	148 (63.0)	148 (60.7)	152 (65.0)	39 (21.7)	137 (54.8)
Mean duration (Days)	71.5	75.8	76.0	77.5	52.3	79.6
Mean daily dose, mg	63.3	29.8	59.2	59.7	117.1	4.5
Mean Compliance (%)	98.4	98.8	98.4	98.8	97.3	98.2

Source: PRT018 clinical study report, p. 65

Demographic Characteristics:

The demographic and other baseline characteristics were well matched across treatment groups. However, the demographic and baseline characteristics were somewhat different than what was seen in ENGAGE AF with the subjects in PRT-018 being younger, more often Caucasian, and almost entirely from Eastern Europe. Also, subjects in PRT-018 were more likely to be on aspirin at baseline, and have more ischemic heart disease and heart failure. However, they were at lower risk for endpoint events (fewer subjects with $CHADS_2$ scores ≥ 3).

Table 114: Demographic Characteristics of the Phase 2 and 3 trials (Safety analysis set)

Characteristic	PRT-018 Range by treatment group	ENGAGE AF Range by treatment group
Caucasian	97.2% to 98.0%	80.7% -81%
Eastern European	90.6% to 93.3%	33.8% -33.9%
Male	59.6% to 65.2%	61.2% -62.5%
Age	64.7 to 66.0 years	70.5 -70.6 years
Warfarin naïve	57.4% to 67.7%	40.8% -41.2%
Aspirin at baseline	49.6% to 52.8%	28.7% -29.7%
Mean weight	87.75 kg to 88.95 kg	83.7 kg -84.2 kg
CHADS2 score ≥ 3	36% to 37.2%	52.6% -54%
Prior Diabetes	17.9% -25%	35.9% - 36.4%
Prior Stoke or TIA	16.8% - 21.7%	28.1% - 28.5%
Prior Ischemic Heart Disease	62.7% -69.6%	32.9% - 33.7%
Prior Congestive Heart Failure	87.2% -88.8%	56.6% - 58.3%

Source: PRT-018 CSR, p. 57, 58 and source for ENGAGE AF data is CSR, p. 108 and 130.

Efficacy Endpoint: This study was neither designed nor powered to evaluate efficacy. Nevertheless, it is interesting to examine the major adverse cardiovascular events (MACE) that occurred during the treatment period. MACE, a secondary endpoint, was defined as the composite of stroke [ischemic or hemorrhagic], SEE, MI, CV death, and hospitalization for any cardiac condition. No central adjudication was done for these events. The analysis was based on Investigators' interpretations.

Subjects with MACEs during the treatment period are summarized in Table 115. The treatment period was defined as the time from the first dose of study drug through the day after the last dose. The numbers in the rows are events; a subject with multiple MACEs will show up in multiple rows and a subject with one MACE that fits multiple categories will appear in multiple rows. The number of MACEs during the treatment period was low in each treatment group but the lowest frequency of events was seen in

the 60 mg bid group suggesting the possibility of a dose relationship. Because of the low number of overall events, the applicant felt that conclusions regarding the dose of edoxaban could not be made based on this endpoint. Nevertheless, if they were aiming for noninferiority on efficacy for their Phase 3 trial, the 30 mg and 60 mg qd doses appeared to have similar rates of MACE compared to warfarin.

Table 115: Major Adverse Cardiovascular Events in Study PRT-018

	Edoxaban Daily Dose				
	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]
Acute pulmonary edema	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Angina pectoris	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Angina unstable	1 (0.4)	1 (0.4)	3 (1.3)	0 (0.0)	0 (0.0)
Aortic aneurysm	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Cardiac failure	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiomyopathy	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intestinal angina	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: PRT-018 CSR

Safety: It is important to note that the exposure to the 60 mg bid was less than exposure in the other treatment groups and this should be kept in mind when evaluating the results. The mean duration of exposure was about 77 days in all treatment groups except for the 60 mg bid group which was 52.3 days because the IDMC recommended early termination of this group. Compliance was close to 99%.

All reported bleeding events were centrally adjudicated by the CEC and categorized as major, clinically relevant non-major, or minor based on prespecified criteria (Table 116).

The incidence of 3 different categories of bleeding in PRT-018 (overall, major bleeding and major bleeding or clinically relevant non-major bleeding) is shown in Table 117. The edoxaban 60 mg bid group had the highest incidence of bleeding events during the treatment period. The differences between the edoxaban 60 mg bid group and the

warfarin group in the incidences of overall bleeding events, major and major or clinically relevant non-major bleeding events were statistically significant.

The edoxaban 30 mg bid group also had a statistically higher observed incidence than the warfarin group for major or clinically relevant non-major bleeding events, but not for major bleeding alone or overall bleeding.
The edoxaban 30 and 60 mg qd groups were comparable in bleeding rates to warfarin.

Table 116: Bleeding Event Adjudication

Major bleeding events:	Symptomatic bleeding in critical areas or organs: • Retroperitoneal • Intracranial • Intraocular • Intraspinal • Intra-articular • Pericardial • Intramuscular with compartment syndrome Any other overt bleeding event associated with one of the following outcomes: • Fatal • Hemoglobin drop of ≥2 g/dL (1.24 mmol L^{-1}) • Transfusion ≥2 units of packed red blood cells or whole blood • Hemoglobin drop of ≥1 g/dL AND transfusion ≥1 unit of packed red blood cells or whole blood
Clinically relevant non-major bleeding events:	• Any bleeding event reported as an SAE that does not fit the definition of a major bleeding event • Any bleeding event resulting in temporary discontinuation of study medication or other anti-platelet agent • Any bleeding event resulting in permanent discontinuation of study medication or other anti-platelet agent • Spontaneous skin hematoma ≥25 cm^2 • Spontaneous ear-nose-throat (ENT) bleeding ≥5 minutes requiring medical attention • Macroscopic hematuria or urethral bleeding requiring medical attention • Spontaneous gastrointestinal (GI) or rectal bleeding requiring medical attention • Gingival bleeding ≥5 minutes requiring medical attention • Any other bleeding event reported by the Investigator, considered clinically significant by the CEC
Minor bleeding events:	Minor bleeding events that do not fulfill the criteria of a major bleeding event or a clinically relevant non-major bleeding event

Source: PRT-018 CSR, p. 33

Table 117: Incidence of Bleeding in PRT-018 during the treatment period

	Edoxaban Daily					
	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

Warfarin management:

It is important to evaluate how well the warfarin group was managed in order to ensure comparability of treatment arms. The time in target INR, below target and above target is shown in Table 118. It took half the treatment period to achieve time in therapeutic range (TTR) over 50%. TTR ranged from a minimum of 6.6% at baseline to a maximum of 50.4% at Day 42. Most of the subjects outside of therapeutic range were subtherapeutic (ranging from 93% at time 0 to 40.5% at the last week of treatment), with supratherapeutic values occurring much less often (ranging from 0.4% at time 0 to 11% at Day 21). It is hard to evaluate the comparability of the bleeding rates in the edoxaban arms to coumadin when the warfarin arm was not managed well. Nevertheless, the sponsors decided to use this dose ranging trial to select their dose. A more prudent approach may have been to redo this trial and add a higher QD dose.

Table 118: Time in Target INR, below target INR and above target INR in the warfarin treatment group

INR Range	Number (%) of Subjects in the Warfarin Group								
	Baseline (N = 243)	**Day 7 (N= 234)**	**Day 14 (N = 227)**	**Day 21 (N = 228)**	**Day 28 (N = 229)**	**Day 42 (N = 228)**	**Day 56 (N = 224)**	**Day 70 (N = 224)**	**Day 84 (N = 215)**
< 2.0	226 (93.0)	174 (74.4)	129 (56.8)	122 (53.5)	106 (46.3)	93 (40.8)	93 (41.5)	93 (41.5)	87 (40.5)
≥ 2.0 to ≤ 3.0 (target)	16 (6.6)	50 (21.4)	74 (32.6)	81 (35.5)	98 (42.8)	115 (50.4)	114 (50.9)	110 (49.1)	108 (50.2)
> 3.0	1 (0.4)	10 (4.3)	24 (10.6)	25 (11.0)	25 (10.9)	20 (8.8)	17 (7.6)	21 (9.4)	20 (9.3)

Note: Investigators adjusted warfarin doses based on local laboratory INR readings.
Source: Table 10.2 of Clinical Study Report DU176b-PRT018. Percentages are based on number of subjects at each visit.

APPENDIX 10 Comparison between ENGAGE AF and other trials with novel anticoagulants (NOACs) and warfarin/ placebo trials

Table 119: Constancy Assumption Table comparing ENGAGE-AF to other NOAC Trials

	Apix vs. W ARISTOTLE (53 mos/1.7 yr med tx duration)	**Riva vs. W ROCKET (46 mos/ 1.4 yr med. tx duration)**	**Dabi vs. W RE-LY (40 months/ 1.8 yr med treatment duration)**	**Edox vs. W ENGAGE AF (53 mos/2.5 yr med tx duration)**
N(ITT)	18201	14171	12098	21105
Blinding	Double dummy (DD)	DD	Open-label	DD
% female	35	40	36	38
% with h/o stroke/TIA/SEE	19	55	22	28
Mean $CHADS_2$ Score	2.1	3.5	2.1	2.5
% w prior VKA therapy	56	62	61	59
Mean TTR (%)	62	56	64	65
Study Drug Int. (%)	39.8 (counted > 3 d)	35.2 (counted >3d)	29 (counted all)	63.3 (counted > 3d)
Study Drug Discontinuation (%)	26.4	35	17.9	34
Primary endpoint	Stroke/SEE	Stroke/SEE	Stroke/SEE	Stroke/SEE in mITT/on Tx
Stroke/SEE Event rate warfarin (%/yr)	1.60	2.4	1.71	1.5
Stroke/SEE Event rate test agent (%/yr)	1.27	2.1	1.11	1.18
HR or Δ (95% CI)	0.79 (95% CI=0.66, 0.95)	0.88(95% CI=(0.74, 1.03)	0.65 (95% CI=0.52, 0.81)	0.79 (97.5% CI=0.63, 0.99)

Reviewer's Table

Table 120: Constancy Assumption Table comparing ENGAGE-AF to Warfarin/Placebo Trials

	5 primary prevention studies (W vs. Pbo)	**EAFT (W vs. pbo)[33]**	**ENGAGE-AF**
N (ITT)	2461	439	21105
% female	0-47	43	38
% with h/o stroke/TIA/SEE	6	100	28
Target INR	1.4-2.8 to 2.0-4.5	2.5-4.0	2-3
Mean TTR or % in range	42-83	59	65
Endpoint	Ischemic stroke; to Str/TIA/SEE	Stroke	Stroke + SEE
Event rate W (%/yr)	0.62 – 3.08	4	1.5
Event rate Experimental Drug or Pbo (%/yr)	2.99-8.2	12	1.18
HR (95% CI)	0.21 – 0.65	0.34 (0.2, 0.57)	0.79 (97% CI=0.63, 0.99)

Reviewer's Table

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

APPENDIX 11 SAEs results during the overall study period

Table 121 Incidence of SAEs by SOC (≥ 0.5% more frequently in the Edoxaban group) and related PT terms during overall period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Subjects with at least one SAE	3031 (43.3%)	2979 (42.5%)	3118 (44.5%)
Blood And Lymphatic System Disorders	89 (1.3%)	128 (1.8%)	83 (1.2%)
Anemia	53 (0.8%)	70 (1.0%)	45 (0.6%)
Iron Deficiency Anemia	13 (0.2%)	29 (0.4%)	11 (0.2%)
Any Anemia Related PT*	77 (1.1%)	113 (1.6%)	68 (0.9%)
Respiratory, Thoracic And Mediastinal Disorders	306 (4.4%)	297 (4.2%)	270 (3.9%)
Chronic Obstructive Pulmonary Disease	105 (1.5%)	93 (1.3%)	88 (1.3%)
Dyspnea related PT*	28 (0.4%)	27 (0.4%)	12 (0.3%)
Respiratory Failure	26 (0.4%)	29 (0.4%)	20 (0.3%)
Pleural Effusion	23(0.3%)	14 (0.2%)	19 (0.3%)
Pulmonary Edema	12 (0.2%)	11 (0.2%)	8 (0.1%)
Interstitial Lung Disease	8 (0.1%)	9 (0.1%)	4 (0.06%)

Reviewer's analysis using the Applicant's dataset: AEEV1, DM and CDER CSC MAED tool
*Anemia-related PT include hematocrit abnormal, hematocrit decreased, hemoglobin decreased, red blood cell count decreased, and any PT term containing anemia

Table 122 Incidence of SAEs by SMQ of interest† during the overall study period

	Edoxaban 30mg N = 7002	Edoxaban 60mg N = 7012	Warfarin N = 7012
Hematopoietic erythropenia (SMQ)	58 (0.8%)	76 (1.1%)	53 (0.8%)
Acute central respiratory depression (SMQ)	111 (1.6%)	144 (2.1%)	117 (1.7%)
Interstitial lung disease (SMQ)	18 (0.3%)	24 (0.3%)	12 (0.2%)
Acute Renal Failure (SMQ)	94 (1.3%)	97 (1.4%)	107 (1.5%)
Hypersensitivity reactions[a]	175 (2.5%)	189 (2.7%)	173 (2.5%)
Torsade de pointes/QT prolongations (SMQ)	205 (2.9%)	199 (2.8%)	239 (3.4%)
Hepatic Disorder			
Liver function test elevation PTs[b]	13 (0.2%)	24 (0.3%)	16 (0.2%)
Drug related hepatic disorders-comprehensive search (SMQ)	84 (1.2%)	72 (1.0%)	134 (1.9%)
Drug related hepatic disorders-comprehensive search (SMQ), excluding INR increased PT	61 (0.9%)	59 (0.8%)	63 (0.9%)
Drug related hepatic disorders-severe events only— (SMQ)	37 (0.5%)	32 (0.5%)	33 (0.5%)
Hepatitis, non-infectious (SMQ)	9 (0.1%)	9 (0.1%)	3 (<0.1%)

Reviewer's analysis using the Applicant's dataset: AEEV1, DM and CDER CSC MAED tool

† SMQ broad terms were used for the analysis

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

b. PTs include alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, blood bilirubin unconjugated increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, liver function test abnormal and transaminases increase

APPENDIX 12 OSE review of hepatic cases in ENGAGE AF

USUBJID	AGE	SEX	BMI	country	Txt	pALTx	pASTx	pALPx	pTBLx	severity	most likely cause
1004.0015	70	M	44.82	USA	E 30	11.27	7.6	2.8	3.67	moderate	common duct stone most likely
1031.0002	83	M	31.39	USA	E 30	3.65	2.8	3.4	5.33	serious	CA pancreatic head; later fatal
1130.0051	85	F	30.58	Argentina	E 30	5.54	2.94	1.6	4.25	fatal	pancreatic CA
1143.0042	72	M	28.69	Argentina	warf	7.63	8.47	3.7	6.08	serious	unexplained; cholestasi;,warfarin unlikely
1167.0011	83	M	26.4	Argentina	E 60	9.17	12.6	2.37	2.67	fatal	myocardial infarction, pulmonary embolus
1726.0001	78	M	24.38	Germany	E 60	11.02	8.56	1.19	2.17	moderate	unexplained; negative rechallenge, Gilbert's
1905.0024	54	M	33.06	Czech R	warf	4.4	2.44	2.34	5.75	moderate	unexplained; negative rechallenge
1905.0052	74	F	32.87	Czech R	E 60	14.07	9.77	1.28	2.5	serious	no cause found; edoxaban 2 yrs. unlikely
1913.0028	70	M	34.72	Czech R	E 30	3.02	1.71	1.15	5.5	mild	common duct sludge, stone
2908.0071	74	M	24.84	Brazil	E 60	9.21	6.49	1.52	9.42	serious	common duct stone after 2 yrs edoxaban
3013.0002	58	M	25.16	Russia	E 60	3.33	2.52	0.59	2.02	mild	heart failure; Gilbert's syndrome
3018.0014	54	M	25.42	Russia	E 60	7.31	7.22	2.07	8.83	serious	gallbladder stones; cholecystectomy
3022.004	54	F	41.58	Russia	warf	3.62	8.56	1.33	3.83	serious	congestive heart failre
3061.0013	66	F	34.97	Russia	warf	10.65	4.39	5.95	2.92	mild	possile amiodarone-hepatitis
3108.0013	66	M	26.51	Columbia	warf	13.73	10.04	0.88	3.33	serious	heart failure; Gilbert's syndrome
3506.0006	65	M	29.83	Italy	E 60	5.23	8.04	8.29	9.58	serious	bile duct CA; died later
4005.0015	54	M	34.09	Ukraine	E 60	7.88	14.53	0.83	2.25	moderate	alcoholic hepatitis; negative rechallenge
4012.0038	34	M	28.62	Ukraine	warf	5.23	4.09	0.53	2.08	moderate	occult alcoholic hepatitis; not warfarin
4039.0006	63	M	22.98	Ukraine	E 60	3.98	4.91	0.58	2.67	moderate	uncertain; autoimmune hepatitis
4042.0013	68	M	26.18	Ukraine	E 60	4.08	3.54	1.72	2.5	fatal	heart failure, after 2 yrs on edoxaban
4335.0015	76	M	26.99	China	warf	8.25	2.51	1.4	3.58	serious	pneumonia, heart failre; no warfarin
4402.0012	46	M	31.35	India	E 60	**23.73**	**25.11**	1,57	3.92	serious	acute viral hepatitis E
4411.0004	70	M	20.2	India	warf	19.9	5.51	1.11	2.17	fatal	sepsis, heart failure, shock
4411.005	40	M	20.31	India	E 60	**50.21**	**83.78**	2.82	2.5	fatal	pneumonia, heart failure, shock
5003.0007	75	M	27.99	Poland	E 30	**28.35**	**59.91**	0.82	2.75	life-threatening	heart failure, shock - recovered
5031.0093	80	F	26.03	Poland	E 30	18.08	**22.03**	2.28	2.33	serious	probable heart failure
5032.0034	76	F	29.62	Poland	E 60	16.59	16.14	2.01	4.33	moderate	uncertain; negative rechallenge 3 yrs.
5033.0057	80	F	27.82	Poland	E 60	3.18	3.56	2.48	9.75	serious	pancreatic CA; later died

5056.0039	77	M	26.9	Poland	E 60	16.54	11.24	1.17	2.08	serious	common duct stone; not edoxaban
5304.001	64	M	24.45	Bulgaria	E 30	5.63	7.62	1.04	2.25	mild	Gilbert syndrome; mild heart failure
5404.001	64	M	30.46	Hungary	E 30	19.77	**22.13**	2.49	3.83	serious	worse heart failure; Gilbert's syndrome
5409.001	64	M	38.4	Hungary	E 30	9	7.11	1.39	2.17	moderate	alcoholic hepatitis
5513.0004	79	M	33.5	Israel	warf	6.54	5.96	1.26	3.67	serious	gallbladder stones;later fatal sepsis
5609.0006	80	M	23.7	Romania	E 60	17.46	**25.04**	1.21	3.5	moderate	increased alcohol + acute viral hepatitis E
5622.0012	63	F	25.64	Romania	E 60	11.86	18.92	1.05	2.17	mild	uncertain; ?CHF; negative E rechallenge
6117.0011	76	M	27.11	Japan	E 60	7.06	7.93	1.72	4.17	serious	common duct stone
6186.0002	77	M	22.14	Japan	warf	4.67	2.84	16.23	7.25	serious	pancreatic CA; lost to follow-up
7003.0011	77	F	29.84	UK	E 60	3.54	2.92	3.73	7.75	serious	pancreatic CA; later fatal
7035.0002	66	M	32.2	UK	E 60	10.81	10.11	1.04	2.17	mild	uncertain; possible E-DILI;
7101.0002	43	M	31.24	USA	E 60	7.73	6.38	1.37	2.56	moderate	possible amiodarone; E rechallange neg
7155.0004	82	F	19.18	USA	warf	4.24	3.56	2.42	2.92	mild	uti, poss nitrofur tox; E rechallenge neg
7306.0006	84	M	21.48	USA	warf	3.1	0.25	0.43	2.67	mild	uncertain; unlikely W; Gilbert's syndrome
7406.0039	68	F	32.44	India	warf	12.97	**29.17**	1.32	17.83	moderate	acute viral hepatitis B
1014.0005	78	M	31.63	USA	E 60	5.17	3.76	0.47	6.25	serious	not edoxaban; probable CA pancreas
1016.001	83	F	26.9	USA	E 60	5.84	5.31	6.35	**23.58**	serious	CA head of pancreas
1022.003	73	M	25.1	USA	Warf	**66.56**	**109.04**	0.72	2.67	fatal	acute heart failure, sepsis
1041.0011	78	F	35.94	USA	E 60	7.46	16.47	3.56	4.17	serious	very unlikely E; probable autoimmune hepatitis
1041.0035	73	M	38.35	USA	E 30	5.77	9.13	1.32	3.42	serious	probable heart failure; Klebsiella pneumonia
1095.0007	52	F	26.71	USA	Warf	12.7	8.72	1.37	4.17	serious	not warfarin, probable common duct stones
1127.0008	66	M	27.92	Argentina	E 60	6.23	8.67	0.93	2.5	fatal	heart failure, ischemic hepatopathy
1129.0045	73	M	24.5	Argentina	E 30	7.13	9.27	2.83	**29.5**	fatal	heart failure, ischemic hepatopathy
1408.0008	70	M	34.6	Peru	E 60	7.96	8.71	2.94	7	serious	not edoxaban; probable common duct stones
1627.0005	82	M	23.09	Canada	E 30	6	7.78	1.24	3.42	serious	common duct stones,
1908.0062	68	M	30.07	Czech R	E 30	3.25	1,62	0.65	2.17	mild	Gilbert syndrome; gallbladder stones
2035.0027	53	F	39.79	Canada	E 30	6.97	3.22	5.31	9.33	mild	very unlikely edoxaan; possible viral hepatitis
2045.0004	63	F	33.63	Canada	E 60	**168.78**	**284.28**	0.87	2.93	fatal	acute heart failure, shock
7440.0005	76	M	24.03	India	E 30	**33.75**	n.d.	2.61	3.75	fatal	cardiac arrest

Reviewer's Table. Source: OSE Hepatology Consultation

APPENDIX 13 Reported MedDRA Prefer Terms (PTs) for (a) Acute Renal Failure, SMQ (broad term), (b) Acute Renal Failure, SMQ (narrow term)

(a)

SMQ or PT Terms	Edoxaban 30mg (15mg DosAdj)	Edoxaban 60mg (30mg DosAdj)	Warfarin
Acute Renal Failure, SMQ	735 (10.50%)	741 (10.57%)	668 (9.53%)
Acute Prerenal Failure	3 (0.04%)	7 (0.10%)	3 (0.04%)
Albuminuria	2 (0.03%)	1 (0.01%)	0 (0.00%)
Anuria	0 (0.00%)	1 (0.01%)	0 (0.00%)
Azotemia	9 (0.13%)	3 (0.04%)	8 (0.11%)
Blood Creatinine Abnormal	0 (0.00%)	1 (0.01%)	0 (0.00%)
Blood Creatinine Increased	120 (1.71%)	129 (1.84%)	119 (1.70%)
Blood Urea Increased	70 (1.00%)	80 (1.14%)	82 (1.17%)
Creatinine Renal Clearance Abnormal	2 (0.03%)	1 (0.01%)	2 (0.03%)
Creatinine Renal Clearance Decreased	225 (3.21%)	242 (3.45%)	208 (2.97%)
Glomerular Filtration Rate Decreased	5 (0.07%)	12 (0.17%)	10 (0.14%)
Hypercreatininemia	3 (0.04%)	1 (0.01%)	2 (0.03%)
Nephritis	1 (0.01%)	0 (0.00%)	0 (0.00%)
Oliguria	1 (0.01%)	1 (0.01%)	2 (0.03%)
Proteinuria	86 (1.23%)	87 (1.24%)	86 (1.23%)
Renal Failure	117 (1.67%)	130 (1.85%)	136 (1.94%)
Renal Failure Acute	81 (1.16%)	65 (0.93%)	70 (1.00%)
Renal Function Test Abnormal	2 (0.03%)	1 (0.01%)	4 (0.06%)
Renal Impairment	144 (2.06%)	159 (2.27%)	99 (1.41%)
Renal Tubular Necrosis	1 (0.01%)	0 (0.00%)	1 (0.01%)
Tubulointerstitial Nephritis	2 (0.03%)	1 (0.01%)	2 (0.03%)
Urine Output Decreased	4 (0.06%)	0 (0.00%)	1 (0.01%)

Reviewer's Table, the Applicant's dataset: DM & AEEV1

(b)

SMQ or PT Terms	Edoxaban 30mg (15mg DosAdj)	Edoxaban 60mg (30mg DosAdj)	Warfarin
Acute Renal Failure, SMQ	346 (4.94%)	355 (5.06%)	305 (4.35%)
Acute Prerenal Failure	3 (0.04%)	7 (0.10%)	3 (0.04%)
Anuria	0 (0.00%)	1 (0.01%)	0 (0.00%)
Azotemia	9 (0.13%)	3 (0.04%)	8 (0.11%)
Oliguria	1 (0.01%)	1 (0.01%)	2 (0.03%)
Renal Failure	117 (1.67%)	130 (1.85%)	136 (1.94%)
Renal Failure Acute	81 (1.16%)	65 (0.93%)	70 (1.00%)
Renal Impairment	144 (2.06%)	159 (2.27%)	99 (1.41%)

Reviewer's Table, the Applicant's dataset: DM & AEEV

9.1 Literature Review/References

All references are in footnotes.

9.2 Labeling Recommendations

Possible labeling recommendations related to the observed elevated risk of stroke compared to warfarin in subjects with normal renal function are discussed Sec. 1 above, starting on p. 19.

9.3 Advisory Committee Meeting

A meeting of the CRDAC to discuss this NDA is scheduled for October 30, 2012. The expected focus of the meeting will be the observed increased relative risk of stroke compared to warfarin in subjects with normal renal function.

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/s/

MELANIE J BLANK
10/09/2014

MARTIN ROSE
10/09/2014

TZU-YUN C MCDOWELL
10/10/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206316
Priority or Standard	Standard
Submit Date(s)	01/08/2014
Received Date(s)	01/08/2014
PDUFA Goal Date	01/08/2015
Division / Office	DHP/OHOP/OND
Reviewer Name(s)	Saleh Ayache, MD
Review Completion Date	09/08/2014
Established Name	edoxaban
(Proposed) Trade Name	SAVAYSA™
Therapeutic Class	Factor Xa inhibitor
Applicant	DAIICHI SANKYO, INC.
Formulation(s)	Tablet for oral administration
Dosing Regimen	60 mg once daily orally
Indication(s)	For the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) (b) (4)
Intended Population(s)	Patients with venous thromboembolism

Template Version: March 6, 2009

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Table of Abbreviations

AE	Adverse event
AF	Atrial fibrillation
ALP	Alkaline phosphatase
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
BID	Twice daily
CVA	Cerebrovascular accident
CEC	Clinical Events Committee
CrCL	Creatinine clearance
CRNM	Clinically Relevant Non-Major
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
DHP	Divisions of Hematology Products
DCRP	Division of Cardiovascular and Renal products
eCTD	Electronic Common Technical Document
ECG	Electrocardiogram
FXa	Factor Xa
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
HR	Hazard ratio
Hb	Hemoglobin
ICH	Intracranial hemorrhage
INR	International normalized ratio
IXRS	Interactive voice/web response system
LMWH	Low molecular weight heparin
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
MI	Myocardial infarction
NOAC	New oral anticoagulants
NT-proBNP	N-terminal pro Brain Naturetic Peptide
PD	Pharmacodynamic
PREA	Pediatric Research Equity Act
PP	Per Protocol
P-gp	P-glycoprotein
PK	Pharmacokinetic
PE	Pulmonary embolism
QD	Once daily
RV	Right ventricular
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System Organ Class

SEE	Systemic embolic event
TTR	Time in Therapeutic Range
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WNL	Within normal limits

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical review team finds a favorable benefit-risk profile for edoxaban for the treatment of VTE. Edoxaban should be approved for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (b) (4)

1.2 Risk Benefit Assessment

The overall benefit of edoxaban treatment is considered to outweigh the risk for the treatment of DVT and/or PE.

Edoxaban is a selective Factor Xa (FXa) inhibitor. Approval is being sought for the use of edoxaban for the treatment and (b) (4) of venous thromboembolic disease (VTE), including deep vein thrombosis and pulmonary embolization, in patients who have been diagnosed with VTE and initiated therapy with parenteral anticoagulant, (b) (4) for 5-10 days. In support of (b) (4) standalone indications (treatment of VTE (b) (4) the Applicant has submitted the data from one clinical trial (Hokusai-VTE). (b) (4) (b) (4) The Applicant added that treatment for patients with VTE begins with the diagnosis and continues (b) (4)

In the Hokusai VTE trial, edoxaban was shown to be non-inferior to warfarin for the treatment of DVT and/or PE. The primary efficacy endpoint was symptomatic recurrent VTE (i.e., the composite of DVT, non-fatal PE, and fatal PE). The rate of recurrent symptomatic VTE was 3.2% in the edoxaban group compared to 3.5% in the warfarin group. The estimated hazard ratio was 0.89 (0.70-1.13) for the comparison of edoxaban to warfarin. The upper 95% confidence limits of 1.13 demonstrated that treatment with heparin/edoxaban retained about 91% treatment effect of heparin/warfarin.

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

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant 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) (b) (4) 2) a single dose PK/PD study in pediatric patients age birth to <18 years and 3) (b) (4)

The request for deferral is reasonable and should be granted.

The sponsor is pursuing the development of an antidote to the anticoagulant effect of edoxaban.

2 Introduction and Regulatory Background

2.1 Product Information

Edoxaban (DU-176b) is an oral, selective, reversible factor Xa (FXa) inhibitor developed as an anticoagulant by Daiichi Sankyo Co. Ltd., Japan. Factor Xa is the serine protease located in the final common pathway of the coagulation cascade which catalyzes the conversion of prothrombin to thrombin. Inhibition of FXa reduces thrombin generation and prolongs clotting time, and reduces the risk of thrombus formation.

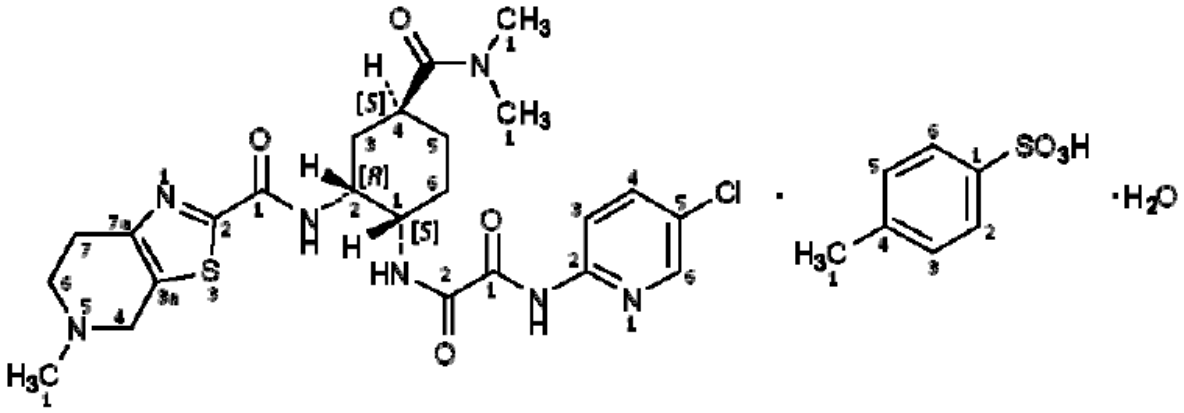
Edoxaban tosylate is a crystalline solid. Edoxaban is slightly soluble in water. Edoxaban is available for oral administration as a 60 mg, 30 mg, or 15 mg round shaped, non-scored, film coated tablet. The inactive ingredients are: mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, magnesium stearate, talc, and carnauba wax.

Molecular Formula: $C_{24}H_{30}ClN_7O_4S \cdot C_7H_8O_3S \cdot H_2O$ (as edoxaban tosylate monohydrate)
(C24H30ClN7O4S as edoxaban anhydrous free form)

Molecular Weight: 738.27 (as edoxaban tosylate monohydrate)
(548.06 as edoxaban anhydrous free form)

Structural Formula: Edoxaban tosylate monohydrate

Figure 1: Edoxaban structure



Source: NDA submission, module 2.3.S, P.3

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are multiple approved anti-coagulant drugs indicated for the treatment of venous thromboembolism (VTE) as seen in the Table 1. There are two groups of approved anti-coagulants based on the route of administration (oral and parenteral).

Xarelto and Eliquis are direct Fxa inhibitors. Xarelto was approved in 2011 for treatment of VTE and reduction of recurrence of VTE and Eliquis was approved on 8/21/2014 for the treatment and prevention of VTE. In addition, Pradaxa (anti-thrombin) and

Coumadin (anti-vitamin K) are oral anticoagulants approved for treatment and prevention of VTE.

Table 1: Currently Approved Products for VTE

Approved drug	Route of Administration	Reduce risk of stroke and SE in nonvalvular afib	Treatment of DVT or PE	Reduction risk of recurrence of VTE	Prophylaxis of DVT after surgery
Xarelto (rivaroxaban)	Oral	X	X	X	X^
Eliquis (apixaban)		X	X	X	X^
Pradaxa* (dabigatran)		X	X	X	
Coumadin (warfarin)		X	X	X	
Lovenox* (enoxaparin sodium)	Parenteral		Acute DVT not PE		X
Arixtra (Fondaparinux sodium)			X In conjunction with warfarin		X
Fragmin (deltaparin sodium)			X in patients with cancer	X	X
Heparin		X	X	X	

2.3 Availability of Proposed Active Ingredient in the United States

No product containing edoxaban is approved in the U.S. Edoxaban received approval in Japan on 22 April 2011 for prevention of VTE in patients undergoing any of the following orthopedic procedures: total hip or knee replacement or hip fracture surgery.

2.4 Important Safety Issues With Consideration to Related Drugs

The main safety issue with anticoagulant products is bleeding. In addition hepatotoxicity safety concern has been associated with oral anticoagulants.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 63266 (27 May 2004): Submitted to the Division of Hematology Products (DHP) for the treatment of Deep Vein Thrombosis (DVT), the treatment of Pulmonary Embolism (PE), (b) (4)

Special Protocol Assessment for phase 3 study was initially submitted on 23 June 2009 and no agreement letter was sent to the Sponsor on 04 August 2009. The main reason

for disagreement was the inability for the FDA to concur with the non-inferiority margin proposed for the primary endpoint's analysis. FDA agreed with the applicant on the primary endpoint of composite of DVT, non-fatal and fatal PE during the 12 month study period in the modified intent-to-treat (mITT) population using adjudicated events to support the proposed indication.

Type B meeting (EOP2) was held on 29 April 2009. In this meeting FDA reminded the Applicant of the risk of proceeding with only a 60 mg dose and noted that with a 30 mg dose safety may be preserved but if the incidence of bleeding is exceeded using the 60 mg dose, they may need to redo the entire study. The Applicant felt that its goal to achieve maximum efficacy while maintaining the safety profile is better achieved using only the 60 mg dose. FDA emphasized that the sponsor has proposed a single study and will need extra effort to manage the INRs in the warfarin arm and will have to ensure control. FDA does not believe that the goal of 60% of percent of time in therapeutic range is adequate for optimal warfarin dosing.

Type B Meeting End of Phase 2 Meeting (EOP2): Held between the applicant and Divisions of Hematology Products (DHP) and Division of Cardiovascular and Renal products (DCRP) on 6 November 2008.

Type B Meeting (Pre-NDA18) was held with DHP on 18 September 2013.

The sponsor submitted an initial Pediatric Study Plan (PSP) to DHP on 4 June 2013 (IND 63266). The Division of hematology Products (DHP) reached agreement with the Applicant on the initial Pediatric Study Plan (iPSP) on 31 October 2013. The iPSP includes (b) (4) clinical studies.

2.6 Other Relevant Background Information

The Applicant has concurrently submitted an application for proposed indication to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. That submission is under review in Division of Cardiovascular and Renal Products (DCRP).

Edoxaban was approved in Japan on 22 Apr 2011 for the prevention of VTE following total knee arthroplasty (TKA), total hip arthroplasty (THA), and hip fracture surgery (HFS), and it was launched in Japan as LIXIANA® on 19 Jul 2011.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA submission contains the required components of the electronic Common Technical Document (eCTD). The overall quality and integrity of the application appear reasonable.

The initial filing review of the submission revealed the following:

- The Applicant submitted one trial to support [redacted] (b) (4) 1) for the treatment of DVT and PE and 2) [redacted] (b) (4)
- No dose ranging study was done in patients with VTE.

During the application review we identified the following issues:

- [redacted] (b) (4)
- There was a numerically higher incidence of all-cause mortality in patients treated with edoxaban.
- There was a numerically increased incidence of gastrointestinal (GI) and vaginal major bleeding events among patients treated with edoxaban.
- Edoxaban may have a potential to be hepatotoxic based on observed numerical increased in abnormal changes in liver enzymes (ALT and or AST) and bilirubin compared to warfarin.

3.2 Compliance with Good Clinical Practices

Informed consent was required from patients in all clinical trials. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

The following sites were selected for an auditing review to be conducted by the Office of Compliance.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Schellong, Sebastian Friedrichstr. 41 Dresden, SN 1067 DEU Western Europe	1707	144	Treatment of VTE (DVT or PE) (b) (4) [redacted]
Jacobson, Barry 7 York rd, Parktown Johannesburg, 2000 ZAF Africa phone:27 11 4898414	4905	130	Treatment of VTE (DVT or PE) (b) (4) [redacted]
Lyons, Roger 4411 Medical Drive, Suite 100 San Antonio, TX 78229 USA United States	1002	50	Treatment of VTE (DVT or PE) (b) (4) [redacted]
Kingsley, Edwin Comprehensive Cancer Centers of Nevada 3730 S. Eastern Avenue Las Vegas NV 89169	1039	24	Treatment of VTE (DVT or PE) (b) (4) [redacted]

3.3 Financial Disclosures

In accordance with 21 CFR 54.4, the applicant submitted the required financial disclosure requirements and certification for the pivotal Phase 3 study, DU176b-D-U305 (Hokusai VTE).

The Applicant certified that there was no financial arrangement with clinical investigators who conducted the clinical studies (Form FDA 3454). (b) (6) [redacted] disclosed a payment of $71,528; (b) (6) [redacted] disclosed a payment of $30,000; and (b) (6) [redacted] disclosed a payment of $51,000. (b) (6) [redacted]

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Edoxaban tosylate is synthesized in a [redacted] (b) (4) The manufacturing process will be performed at Daiichi Sankyo Propharma Co., Ltd. (DSPP) Akita Plant.

For further details refer to CMC review.

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

Edoxaban (DU-176b) is an anti-coagulant exerting its pharmacodynamics effects mainly via inhibition of activated coagulation factor X (FXa). The three metabolites of edoxaban (D21-1402-0201, D21-2135-0101, D21-2393) also had anti-FXa activity and caused clotting time prolongation.

Edoxaban inhibited platelet aggregation induced by thrombin, possibly via inhibition of thrombin, since edoxaban did not affect ADP, U46619 or collagen-induced platelet aggregation.

In studies on rats, edoxaban showed dose-dependent prevention of venous thrombus and prolonged prothrombin time, but did not affect the APTT values.

For further details refer to Pharmacology/Toxicology review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Edoxaban is a selective inhibitor of factor Xa (FXa), the serine protease located in the final common pathway of the coagulation cascade which catalyzes the conversion of prothrombin to thrombin. It does not require antithrombin III for antithrombotic activity. Edoxaban inhibits free FXa, and prothrombinase activity. Inhibition of FXa reduces

thrombin generation and prolongs clotting time, and reduces thrombus formation. In *in vitro* studies, edoxaban tosylate hydrate prolonged PT and APTT with a similar potency.

4.4.2 Pharmacodynamics

Edoxaban tosylate hydrate prolonged the clotting time of human plasma in a concentration-dependent manner. As a result of FX_a inhibition, edoxaban prolongs clotting time tests such as prothrombin time (PT), and activated partial thromboplastin time (aPTT). Changes observed in PT, INR, and aPTT at the expected therapeutic dose, however, are small, subject to a high degree of variability and not useful in monitoring the anticoagulant effect of edoxaban.

For further details information refer to Clinical Pharmacology review.

4.4.3 Pharmacokinetics

The following is a brief summary of edoxaban pharmacokinetics and ADME based on the sponsor's submission. For detailed presentation and review refer to the clinical pharmacology review.

In single dose studies, edoxaban displayed approximately dose-proportional pharmacokinetics for doses of 15 to 60 mg in healthy subjects.

Absorption
Edoxaban is absorbed with peak plasma concentrations within 12 hours. Absolute bioavailability is 62%. Edoxaban is predominantly absorbed in the upper gastrointestinal tract with approximately 12% absorbed in the colon. Food increases peak exposure to varying degrees, but has minimal effect on total exposure. SAVAYSA was administered with or without food in the ENGAGE AF TIMI 48 (atrial fibrillation) and Hokusai VTE studies. Edoxaban is poorly soluble at pH of 6.0 or higher. Thus, drugs or disease conditions that increase the stomach pH or increase gastric emptying and gut motility have the possibility of reducing edoxaban dissolution and absorption. However, co-administration of proton pump inhibitors did not impact edoxaban exposure.

Distribution

Disposition is biphasic. The volume of distribution is 107 (19.9) L [mean (SD)]. In vitro plasma protein binding is approximately 55%. There is no clinically relevant accumulation of edoxaban (accumulation ratio 1.14) with once daily dosing. Steady state concentrations are achieved within 3 days.

Metabolism

Unchanged edoxaban is the predominant form in plasma. Edoxaban is metabolized via hydrolysis (mediated by carboxylesterase 1), conjugation or oxidation by CYP3A4

(<10%). The predominant metabolite M 4, formed by hydrolysis, is human-specific and active and reaches less than 10% of the exposure of the parent compound in healthy subjects. Exposure to the other metabolites is less than 5% of exposure to edoxaban.

Elimination

In healthy subjects, the total clearance of edoxaban is estimated as 22 (±3) L/hour; 50% is renally cleared (11 L/hour). Renal clearance accounts for approximately 35% of the administered dose. Metabolism and biliary/intestinal excretion account for the remaining clearance. The terminal t½ for oral administration is 10 to 14 hours.

For further details information refer to Clinical Pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Clinical Trials

Trial ID/ Trial Type	Objectives	Study Design	Dose/Rout of administration	Subjects	Duration
C-U301 (ENGAGE AF-TIMI 48) Efficacy and Safety	Efficacy and safety, Non-inferiority versus warfarin	Phase 3, randomized, multicenter, double-blind, double dummy, parallel group, active controlled	Edoxaban: 30 mg QD PO; 60 mg QD PO	Patients with AF N=21,026 treated Edoxaban: 30 mg QD (n=7002); 60 mg QD (n=7012) Warfarin: (n=7012)	Median of 916, 904, and 904 days for Edoxaban 30 mg, Edoxaban 60 mg, and warfarin, respectively
D-U305 (Hokusai VTE) Efficacy and Safety	Efficacy and safety, Non-inferiority versus warfarin	Phase 3, randomized, multicenter, multinational, double-blind, matching placebo, parallel group, active controlled	LMWH/Edoxaban: LMWH SC for ≥5days, followed by PO edoxaban 60 mg QD LMWH/Warfarin: LMWH SC and warfarin QD PO for ≥5days, followed by warfarin QD PO	Patients with symptomatic DVT and/or PE 8240 treated Edoxaban: (n=4118) Warfarin: (n=4122)	A minimum of 3 months up to 12 months
PRT018, C-J225 and C-J226	Safety versus warfarin	Phase 2, randomized, parallel group, multicenter, double-	Edoxaban: 30 to 120 mg (QD and BID regimens)	Patients with non-valvular AF Edoxaban:	3 months (12 weeks)

Safety Trials		blind edoxaban, open-label active controlled	Warfarin: QD PO	(n=1446) Warfarin (n=250)	
J-03 and J-05 Safety Trials	Safety versus warfarin	Phase 2 AF Uncontrolled Studies	Edoxaban: 60-120 mg BID PO; 5-30 mg QD PO;	Patients with non-valvular Edoxaban: (n=56)	10 weeks 6 weeks
PRT007, PRT011, J-04, B-J209 (phase 2) B-J302, B-J303, B-J304 (Phase 3)	Safety and efficacy	Phase 2/3 VTE Prophylaxis trials. P3 trial was randomized, open label trial in subjects undergoing total hip or knee replacement or hip fracture surgery	Edoxaban: 5 to 120 mg (QD and BID regimens) 30 mg (QD regimen)	(n= 2638) patients None (PRT007) Dalteparin (PRT011; 172); Placebo (J-04; 102); Enoxaparin (B-J209; 87) Enoxaparin 679	7 to 10 days (PRT007, PRT011) 11 to 14 days (J-04, B-J209) 11 to 14 days
36 Phase I, Trials in healthy subjects	PK/PD trials	Healthy subjects (PK, PK/PD, drug-drug interaction studies)	Single dose 10 to 180 mg Multiple dose 60 to 120 mg (QD and BID regimens)	N= 1360 1201 subjects exposed to edoxaban	1 day 2 to 14 days
A-U120	PK/PD	Phase 1 Study in Subjects w/Renal Impairment (1 study/ 40 subjects)	Single Dose 15 mg	32 renally impaired (8 healthy)	
A-E134	PK/PD	Phase 1 Study in Subjects w/Hepatic Impairment	Single Dose 15 mg	17 hepatically impaired (16 healthy)	

Modified from NDA submission 2.7.4 Summary of Clinical Safety, Table A-1.2, P21-2

5.2 Review Strategy

This review is focused on safety and efficacy evidence that the applicant provided to support the proposed indications. Therefore, this review is driven by the proposed indications, including:

- Review focused on the phase 3 randomized controlled trial Hokusai VTE (DU176b-D-U305) for efficacy.
- Safety data from pivotal trial DU176b-D-U305, supportive phase 3 studies (B-J302, B-J303, B-J304 in patients undergoing total hip or knee replacement or hip fracture surgery) and phase 2 studies (PRT007, PRT011, J-04, B-J209 in patients undergoing total hip or knee replacement or hip fracture surgery) will be reviewed for safety.
- Examination of the study population eligibility to enter the trials.

- Reproduction or auditing of major efficacy and safety analyses.
- Review the Applicant's justification to conduct one trial to support (b) (4) .
- Survey of current literature on diagnosis, treatment (b) (4) of DVT and PE, using standard textbooks, reviews, references submitted by the sponsor and publications listed in PubMed.

5.3 Discussion of Individual Studies/Clinical Trials

Protocol DU176b-D-U305

Title: A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multi-Center, Multi-National Study for the Evaluation of Efficacy and Safety of (LMW) Heparin/Edoxaban versus (LMW) Heparin/Warfarin in Subjects with Symptomatic Deep-Vein Thrombosis and/or Pulmonary Embolism.

Objectives:
Primary: The primary objective is to evaluate whether initial low molecular weight (LMW) (or unfractionated) heparin followed by edoxaban is non-inferior to initial LMW (or unfractionated) heparin overlapping with warfarin, followed by warfarin only in the treatment of subjects with acute symptomatic VTE for the prevention of recurrent VTE during a12 month study period.

Secondary objectives:

- To compare the treatments for the incidence of the combination of major and clinically relevant non-major bleeding during and for 3 days after completion of study drug.
- To compare the treatments for the composite outcome of recurrent DVT, non-fatal recurrent PE and all-cause mortality during the treatment period.

Other objectives include comparisons of major bleeding, "net clinical outcome", any bleeding, major adverse cardiovascular events (MACE), liver abnormalities for both treatment arms, the time in therapeutic range (TTR) in the warfarin treated patients, and population pharmacokinetics and pharmacodynamics (PK/PD) of edoxaban in relation to efficacy and safety endpoints.

Trial Design:

This phase 3 trial was designed as an event-driven, multi-national, multicenter, randomized, double-blind, matching placebo, parallel-group, non-inferiority trial. The maximal treatment period was to be 12 months. However, some of the patients were likely to be treated for the minimum 3 month period consistent with current American College of Physicians Guidelines resulting in a range of 3 to 12 months treatment in the study. Investigators had the ability to decide on continuation or discontinuation of maintenance anti-thrombotic therapy at 3 and 6 months of treatment.

It was anticipated that 10% of subjects would be discontinued at 3 months, an additional 40% at 6 months and the remainder would complete the entire 12 month treatment period. The Steering Management Coordinating Committee (SMCC) was to ensure that the indicated proportions will complete the times projected.

Regardless of the total duration of drug therapy, efficacy and safety data were to be collected on all subjects (including those who temporarily or permanently discontinue study drug) during the entire 12 month period after randomization. All efficacy and safety endpoints required confirmatory testing. All subjects were to have a safety follow-up visit approximately 14 days after the last dose of study drug.

Eligible subjects were stratified by:

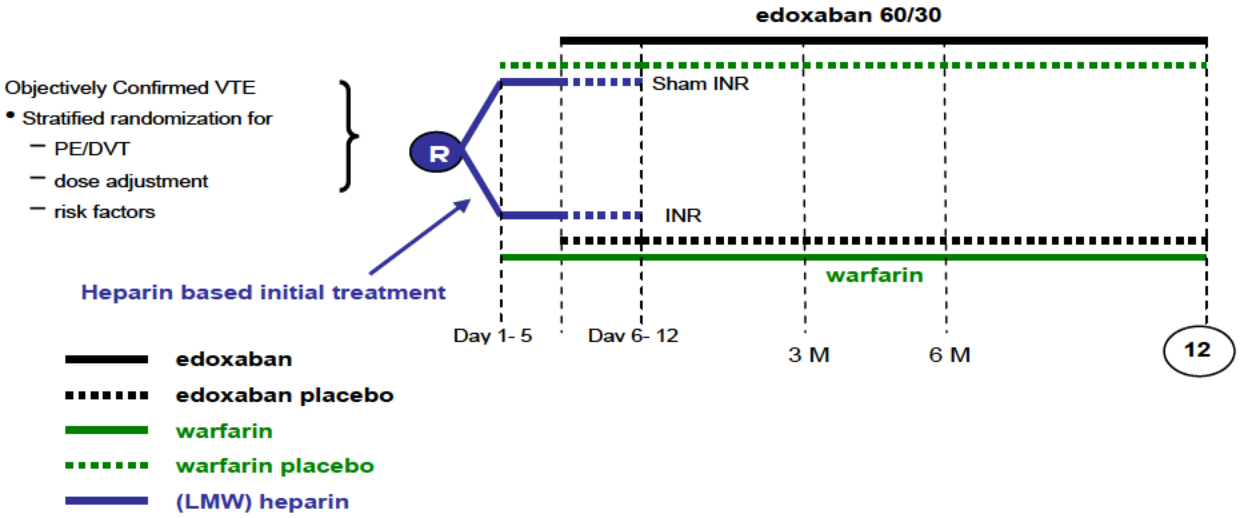
1. Presenting diagnosis
    a. PE with or without DVT (41%) and
    b. DVT only (59%)
2. Baseline risk factors: Temporary risk factors only (such as trauma, surgery, immobilization, estrogen therapy, etc.) versus all others
3. Need for dose edoxaban/edoxaban placebo 30 mg allocation
    a. Body weight ≤ 60 kg;
    b. Creatinine clearance (CrCL) between 30 and 50 mL/min; and
    c. Concomitant use of the P-glycoprotein (P-gp) inhibitors verapamil or quinidine.

After stratification and confirmation of eligibility, subjects were to be randomized via an interactive voice/web response system (IXRS) to a randomization schedule generated by an independent biostatistician employed by the system in a 1:1 ratio to one of the following:

- **Group A:** Initial LMWH plus placebo warfarin for at least 5 days until sham INR >2.0 on 2 consecutive occasions at least 24 hours apart. At that point, LMWH (or UFH) was to be stopped and the subject commenced edoxaban at a dose of 60 mg/d and continued placebo warfarin adjusted to maintain a sham INR between 2.0 -3.0.
- **Group B:** Initial LMWH (or UFH) plus warfarin for at least 5 days until the INR >2.0 on 2 consecutive measurements at least 24 hours apart. At that point, LMWH was to be stopped, and the subject started placebo edoxaban and continued warfarin adjusted to maintain INR between 2 to 3.

Figure 2 shows a schema of the study design.

Figure 2: Hokusai VTE Study Design



Source: NDA submission, Protocol DU176b-D-U305, Version 1.0, Figure 3.1, P.43.

Anticoagulation treatment, including up to a single dose of a Vitamin K antagonist (VKA) is allowed for a maximum of 48 hours prior to randomization.

Patients were excluded from the trial if they required thrombectomy, insertion of a caval filter, or use fibrinolytic agent, had a creatinine clearance of <30 ml/min, significant liver disease or active bleeding.

The study was to continue until 256 primary efficacy endpoint events (i.e., recurrent VTE) occur while "on-treatment" or within 3 days of discontinuation of treatment in the Per Protocol (PP) analysis set across both treatment groups. The total study drug treatment period for any individual subject after randomization was to be ≤ 12 months.

Study governance was at the direction of several committees:

- Steering Management Coordinating Committee provided oversight for the study and included sponsor representatives
- Independent Data Monitoring Committee monitored safety and gave recommendations to the SMCC. Stopping guidelines were to be defined by the sponsor prior to commencement of the study.
- Clinical Events Committee adjudicated and categorized index diagnosis and endpoints

Study Endpoints:

Primary Efficacy Endpoints:
The primary efficacy endpoint is symptomatic recurrent VTE (i.e., the composite of DVT, non-fatal PE, and fatal PE). CEC adjudication results will be the basis for the final analyses.

Diagnosis of symptomatic recurrent PE requires meeting one or more of the following criteria:

- A (new) intraluminal filling defect in (sub)-segmental or more proximal branches on spiral CT scan,
- A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram,
- A (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy (VPLS),
- A nondiagnostic lung scan accompanied by documentation of new deep vein thrombosis by ultrasonography or venography.

In the absence of previous DVT investigations at baseline, diagnosis of symptomatic recurrent DVT requires one of the following:

- A noncompressible venous segment on ultrasonography,
- An intraluminal filling defect on venography,
- An intraluminal filling defect on spiral/contrast CT of the leg.

When DVT investigations are performed at baseline, diagnosis of symptomatic recurrent DVT requires one of the following:

- Abnormal compression ultrasound (CUS) where compression had been normal or, if non-compressible during screening, a substantial increase (≥ 4 mm) in diameter of the thrombus during full compression,
- An extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography.
- An extension of an intraluminal filling defect, or a new intraluminal filling defect on spiral/contrast CT of the leg

Diagnosis of fatal PE is based on one or more of the following:

- Objective diagnostic testing,
- Autopsy,
- Death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out.

Secondary Efficacy Endpoint:
The secondary efficacy endpoints include composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period.

Safety Endpoints:
The primary safety endpoint is clinically relevant bleeding occurring during administration of study drug and for 3 days following its discontinuation. Definitions are

provided for major, clinically relevant non-major, life-threatening and nuisance bleeding as follows:

- Major bleeding (sub-classified into life-threatening [either intracranial or associated with hemodynamic compromise requiring intervention] or not) is overt bleeding with one or more of the following:
    - Fall in Hgb of 2 g/dL or more
    - Leading to the need for transfusion or 2 or more units of PRBCs or equivalent
    - Occurring in any of the following sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal
    - Contributing to death
- Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician temporary cessation of study treatment, or impairment of activities of daily living and are exemplified by the following:
    - Epistaxis lasting more than 5 minutes or having other characteristics
    - Gingival bleeding lasting more than 5 minutes
    - Macroscopic hematuria
    - Macroscopic GI bleeding
    - Rectal bleeding of more than a few spots
    - Hemoptysis of more than a few speckles
    - Intramuscular hematoma
    - Subcutaneous hematoma greater than 25 cm2 or 100 cm2 depending on whether unproved or not, respectively
- Nuisance bleeding is defined as all other bleeding

Additional endpoints include all deaths, major adverse cardiovascular events and hepatic laboratory functional abnormalities. Major adverse cardiovascular events will be adjudicated by the CEC according to internationally accepted criteria.

Safety
Subjects will be assessed for the following events:

- VTE
- Bleeding
- Major adverse cardiovascular events (myocardial infarction, stroke, systemic emboli, cardiovascular death)
- Death
- Liver enzyme abnormalities/liver dysfunction
- New bone fractures
- Cancers
- Adverse reactions (seriousness, severity, causality, action taken regarding study drug, outcome and treatment required)

Selection of Dosage Regimens:

The use of initial (LMW) heparin with warfarin is based upon current guidelines. Heparins permitted for the initial (LMW) heparin treatment are the following:

- enoxaparin 1 mg/Kg SC bid,
- enoxaparin 1.5 mg/Kg SC qd, or

UFH (started with 5000 IU bolus and 1300 IU/h IV infusion, with adjustment to keep aPTT in the therapeutic range).

The warfarin regimen (dosages adjusted to maintain INR 2.0 - 3.0) is based on standard of care.

Eligibility Criteria:

Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

1. Male or female subjects older than the minimum legal adult age (country specific);
2. Acute symptomatic proximal DVT and/or symptomatic PE confirmed at the site by appropriate diagnostic imaging;
3. Able to provide written informed consent.

Exclusion Criteria

1. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE;
2. Indication for warfarin other than DVT and/or PE;
3. More than 48 hours pretreatment with therapeutic dosages of anticoagulant treatment (LMWH, UFH, and fondaparinux per local labeling) or more than a single dose of a VKA prior to randomization to treat the current episode;
4. Treatment with any investigational drug within 30 days prior to randomization;
5. Calculated CrCL < 30 mL/min
6. Significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis) or alanine transaminase (ALT) ≥ 2 times the upper limit of normal (ULN), or total bilirubin (TBL) ≥ 1.5 times the ULN;
7. Subjects with active cancer for whom long term treatment with (LMW) heparin was anticipated;
8. Life expectancy < 3 months;
9. Active bleeding or high risk for bleeding contraindicating treatment with (LMW) heparin or warfarin;
10. Uncontrolled hypertension as judged by the Investigator (e.g., systolic blood pressure > 170 mm Hg or diastolic blood pressure > 100 mm Hg despite antihypertensives);
11. Women of childbearing potential without proper contraceptive measures, and women who were pregnant or breast feeding;
12. Any other contraindication listed in the local labeling of LMWH, UFH, or warfarin;
13. Chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 (COX-1) and cyclooxygenase 2 (COX-2) inhibitors for ≥ 4 days/week anticipated to continue during the study

14. Treatment with aspirin in a dosage of more than 100 mg/per day or dual antiplatelet therapy (any two antiplatelet agents including aspirin plus any other oral or IV antiplatelet drug) anticipated to continue during the study;
15. Treatment with the potent P-glycoprotein (P-gp) inhibitors ritonavir, nelfinavir, indinavir, or saquinavir anticipated to continue during the study;
16. Systemic use of the anti-arrhythmic drug dronedarone at the time of randomization (subjects randomized to study prior to Amendment 2 were to have their edoxaban dose reduced);
17. Systemic use of the P-gp inhibitors ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin at the time of randomization; subsequent use was permitted;
18. Known history of positive Hepatitis B antigen or Hepatitis C antibody;

Treatment:

Eligible subjects will be stratified by 1) presenting diagnosis (a. PE with or without DVT and b. DVT only), 2) baseline risk factors (a. temporary risk factors [such as trauma, surgery, immobilization, estrogen therapy, etc.] vs. b. all others), and 3) need for dose adjustment (body weight ≤ 60 Kg; creatinine clearance [CrCL] between 30 and 50 mL/min, and concomitant use of strong P-glycoprotein inhibitors). At randomization, the investigator provides the IXRS with the study center number; the subject's presenting diagnosis, date of birth, CrCL, and body weight category (≤ 60 Kg or > 60 Kg); and whether the subject is receiving concomitant treatment with the strong P-gp inhibitors verapamil or quinidine.

Initial (LMW) heparin treatment should be administered as soon as possible after randomization. The day of the first dose of study (LMW) heparin and (placebo) warfarin will be considered Day 1.

Anti-coagulation treatment, including a single dose of vitamin K antagonist (VKA), is allowed for a maximum of 48 hours prior to randomization. If pre-randomization treatment was given, the initiation of study (LMW) heparin should be scheduled in relation to the type of pre-randomization regimen used:

- As close as possible to the next scheduled injection if pre-randomization treatment with LMWH or fondaparinux was administered:
  - 12 ± 3 hours after the last injection of LMWH with a bid regimen,
  - 24 ± 3 hours after the last injection of LMWH with a qd regimen,
- Four (±3) hours after bolus injection or stopping infusion with UFH if the subject is switching to LMWH.
- Continue the UFH infusion if the subject is staying on UFH.

Concomitant with starting study (LMW) heparin, the subject should also start on warfarin or placebo warfarin. Placebo or warfarin dosages were to be adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 to 3.0, inclusive).

Edoxaban or placebo edoxaban treatment should not start until both of the following occur:

- Subject has been on (LMW) heparin/(placebo) warfarin for ≥ 5 days.
- Subject has a (sham) INR ≥ 2.0 on two consecutive occasions (second occasion on or after Day 5) at least 24 hours apart.

Once these conditions are met, the (LMW) heparin should be discontinued, and the edoxaban or placebo edoxaban started according to the following schedule:

- If the subject was on an enoxaparin bid regimen start edoxaban dosing 12 ± 3 hours after the last enoxaparin dose
- If the subject was on an enoxaparin Qd regimen start edoxaban dosing 24 ± 3 hours after the last enoxaparin dose
- If the subject was on an UFH regimen start edoxaban dosing 4 ± 1 hours after the last heparin dose

During the study, if the subject experienced life-threatening bleed (bleeding resulting in hemodynamic compromise requiring intervention or any intracranial hemorrhage) all antiplatelets/anticoagulants and study drugs were to be withheld. In addition, investigators were to consider the following:

- Institution of standard of care for life-threatening bleeding (large bore IV or central venous line, type and crossmatch blood, admit to the intensive care unit, provide hemodynamic and respiratory support);
- Administration of antidotes if applicable (e.g., administer protamine if the subject had recently received heparin);
- Administration of red blood cells (or whole blood) as needed;
- Administeration of fresh frozen plasma (FFP) and Vitamin K (10 mg IV administered slowly over 20 to 30 minutes), particularly if the INR is known to be > 2.5.

The treatment period began with the first dose of (LMW) heparin and (placebo) warfarin and ended with the last dose of study drug prior to permanent discontinuation of study drug. Subjects who permanently discontinued study drug were to be followed for primary and secondary efficacy and safety endpoints and SAEs by visit or telephone contact at least once every three months until Month 12.

Prohibited Concomitant Medications:

- Use of antiplatelet medication, including aspirin, as single agent antiplatelet therapy was allowed while on study drug.
- Oral anticoagulants including VKAs (non-study warfarin, dicumarol, coumarin derivatives), Factor IIa inhibitors (e.g., dabigatran), and FXa inhibitors (e.g., rivaroxaban, apixaban) were prohibited.
- Parenteral anticoagulants such as heparin, low molecular weight heparins, direct thrombin inhibitors, and FXa inhibitors were prohibited except as a bridge when resuming study drug.

- If a subject required treatment with a fibrinolytic agent, then study drug was to be interrupted while the subject was taking the fibrinolytic drug and at least 24 hours after administration of a fibrinolytic agent.
- While on study drug, NSAIDS or Cox-2 inhibitors could not be taken for ≥ 4 days per week.
- At randomization treatment with strong P-gp inhibitors, except for quinidine and/or verapamil was prohibited.

Statistical Plan

The following analysis sets were planned:

- Modified intent-to-treat (mITT) Set: All randomized subjects who receive at least one dose of study drug. Analyses were to be based on the randomized treatment even if he/she received the incorrect study drug.
- Per-protocol (PP) Analysis Set: All randomized subjects who received at least one dose of the study drug, in whom the index DVT/PE event at baseline was confirmed by the CEC. Analyses were based on the randomized treatment even if a subject inadvertently received the incorrect study drug.
- Safety Analysis Set: All randomized subjects who received at least one dose of randomized study drug. Analyses were to be based on the randomized treatment, unless a subject inadvertently received the incorrect drug during the entire study, in which case, the subject was to be grouped according to the treatment actually received.

Subjects in both the mITT and the PP sets were included in the efficacy analyses for non-inferiority and superiority.

All subjects in the safety set were included in the safety analyses.

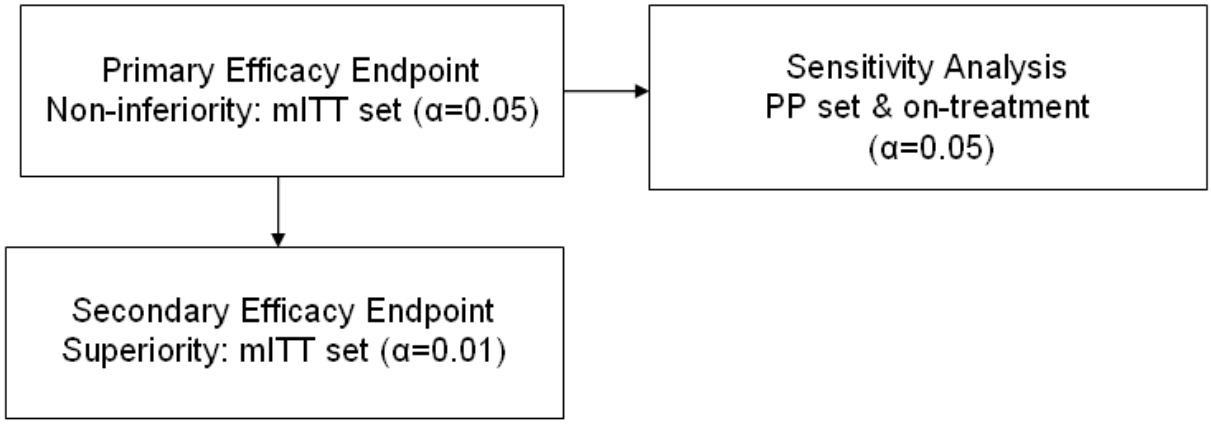
Subjects in each analysis set were presented by strata and treatment group.

The time (after termination of initial heparin) in therapeutic range (TTR) was estimated for each subject randomized to the comparator arm using the interpolation method of Rosendaal. The proportion of TTR as well as the proportion of time subjects had significant deviations (INR <1.5 or INR >4) was presented.

Efficacy Analyses:

The trial was tested for non-inferiority and if edoxaban was not inferior to warfarin, then was to be tested for superiority (shown in Figure 3).

Figure 3: Non-Inferiority and Superiority Testing of Edoxaban vs. Warfarin



Source: NDA submission, Module 5.3.5.1, Figure 11.1, P.86.

The primary efficacy analysis was assessed based on the mITT analysis set. The time to first event of the composite primary efficacy outcome was analyzed using a Cox's proportional hazard model including treatment, age and stratification factors as covariates. Subjects who did not encounter an efficacy outcome were censored at 365 days, or the last day that the subject had a complete assessment for study outcomes, whichever came first. Subjects lost to follow-up, who died for reasons other than DVT/PE or who withdrew informed consent before the end of the study period and did not have a primary efficacy outcome were censored on the last day of complete assessment.

Edoxaban would be considered non-inferior to warfarin if the upper limit of the two-sided 95% CI of the hazard ratio was below 1.5.

A sensitivity analysis was performed based on the PP analysis set with the "on treatment" approach using the same proportional hazard model as for the primary efficacy analysis. For this analysis, however, only the endpoint reached while on treatment or within 3 days of drug discontinuation was counted (allowing for drug efficacy to wear off). The time to first event was the number of days at risk from the initial dose of study drug to the first event experienced while at risk.

Patients were censored if they had not experienced an efficacy endpoint while on treatment or for the 3 days following drug discontinuation. The edoxaban arm to comparator arm comparison will be computed with 95% CI (2-sided testing). (For discussion of statistical methods refer to statistical review).

Subjects in the mITT analysis set were categorized into 2 groups based on DVT without PE and PE with or without DVT and analyses of VTE rates were performed for each group.

Summary statistics for the primary endpoint were prepared using the mITT and PP analysis sets with the "on treatment" approach. The event rate and the risk ratio were estimated with a 95% CI for each arm. The event rates and the relative risk ratio for each component were estimated with a 95% CI.

If non-inferiority in the primary endpoint was established, edoxaban was to be compared to warfarin for superiority (α=0.01, 2-sided) with regard to the time to an event in the composite clinical outcome, but using all-cause, rather than VTE-related, mortality during the 12 month study period. The superiority analysis was performed on the mITT analysis set.

Summary statistics for the secondary efficacy endpoint were based on the mITT and the PP analysis sets. The event rate and the risk ratio were calculated with a 95% CI for each treatment group. Event rates and relative risk ratios were also calculated for each component of the composite secondary endpoint.

Exploratory Efficacy Analyses: Event rate and risk ratio of net clinical outcome defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, major bleeding and all-cause mortality were summarized by treatment with a 95% CI.

Safety Analyses:

All safety analyses were to be performed on the safety population.

The primary endpoint of time to major or clinically relevant non-major bleeding were compared between treatment groups for superiority (α=0.05, 2-sided) using a similar Cox's proportional hazard model as in the primary efficacy analysis. Subjects were censored 3 days after the day of permanent study drug discontinuation. If the comparison favors edoxaban, time to major bleeding was also tested in the same manner.

Bleeding events were summarized and analyzed for the following categories:

- Major bleeding,
- Major and clinically relevant non-major bleeding,
- Nuisance bleeding,
- Any bleeding (all bleeding categories combined).

The number and percentage of patients with persistent elevation of liver enzymes (including various levels) were summarized by treatment group. A separate analysis would be performed for patients who had elevated transaminase and elevated bilirubin in the absence of elevated alkaline phosphatase. The proportion of subjects within treatment groups and the difference in proportions between treatment groups were estimated with 95% CIs.

The incidence of MACE (composite of non-fatal myocardial infarction, non-fatal stroke, non-fatal systemic embolic events and cardiovascular deaths) were summarized by treatment with 95% CI.

Other safety analyses to be performed were adverse events, clinical laboratory evaluations, vital signs and physical findings.

No formal interim analyses were planned. Risk-benefit was to be evaluated by the DMC.

Efficacy and safety analyses were to be performed on multiple subgroups as explorations.

Sample Size Determination:

The sample size was based on the accumulation of 256 “on treatment” primary efficacy events in the PP analysis set. Assuming equal efficacy, a total of 256 events will give a power of 90% to demonstrate that edoxaban would be non-inferior to the comparator with a non-inferiority upper CI margin for the hazard ratio of 1.5 (2-sided, α=0.05). It was determined that a total of 7,500 subjects needed to randomize in the study.

Protocol Amendments:
There were 4 amendments and 12 addenda to the original protocol dated 24 Aug 2009.

1. Amendment # 1 (Dated 26-Aug-2010): Tablet colors were added in descriptions of warfarin tablets throughout the protocol. The 5 mg dose strength was removed from the clinical supply to decrease the possibility of dosing errors.
2. Amendment # 2 (Dated 17-Feb-2011): The concomitant use of dronedarone was made an exclusion criterion based on the results of phase 1 dronedarone DDI study that showed the plasma levels of edoxaban increases significantly. However, any subjects randomized prior to this amendment who were taking dronedarone concurrently had their edoxaban dose reduced.
3. Amendment # 3 (Dated 11-Apr-2011):
    a. Changed to the INR measurements requirement from 2 consecutive measurements to two separate measurements one calendar day apart would prompt the change from the initial treatment to the edoxaban or warfarin treatment.
    b. Added clarification that in the event of decrease in CrCL > 20% in repeat measurements, the edoxaban dosage should be reduced.
    c. Added that all documentations of clinically significant hepatic enzyme abnormalities and/or hepatic events should prompt submission of adjudication dossier.
    d. Added that optional off-site INR unscheduled measurement may be considered during the initial treatment period after randomization.
4. Amendment # 4 (Dated 16-Apr-2012):
    a. Revised the protocol to reduce the number of events needed to support the primary efficacy analyses of the Hokusai VTE trial to 220 Overall events in the mITT Analysis Set instead of 256 On-Treatment events in

the original protocol. The rationale for this amendment was a lower incidence of the recurrent VTE events.

b. Increased the minimum duration of study treatment from 3 to 6 months once the last subject(s) had been randomized to the study.
c. Added an additional analysis of Treatment +30 Days for the PP and Safety Analysis Sets based on regulatory request.
d. Revised the definition of the "Per Protocol" Analysis Set was to exclude subjects who had a treatment misallocation.

6 Review of Efficacy

Efficacy Summary

One randomized controlled trial DU176b-D-U305 (Hokusai VTE) was conducted to support the proposed indications for the treatment of VTE (b) (4) The trial was conducted from January 28, 2010, to June 12, 2013.

Hokusai VTE was a phase 3 randomized, multi-national, multi-center, randomized, double-blind, matching placebo, parallel-group, events-driven, noninferiority trial. The trial was designed to compare initial heparin followed by edoxaban to concurrent initial heparin and warfarin to support the indications for treatment and prevention of recurrent DVT and PE.

A total of 8292 patients were randomized. Randomization was stratified by presenting VTE diagnosis, the need for dose adjustment (if the weight less than 60 kg or the creatinine clearance between 30 and 50 mL/min or receiving P-glycoprotein (P-gp) inhibitors) and by presence or absence of temporary risk factor. Subjects were then randomized in 1:1 ratio to receive either edoxaban (60 mg once daily or 30 mg if they qualify for dose reduction) or warfarin (titrated to INR 2.0 - 3.0). Subjects were to receive initial heparin therapy with low molecular weight heparin (LMWH) or unfractionated heparin for at least 5 days and until INR (sham or real) was ≥ 2.0 on two measurements. Warfarin patients were started concurrently with initial heparin therapy, and edoxaban patients were started after discontinuation of initial heparin. The treatment duration was from 3 months up to 12 months determined by investigator based on patient clinical features.

The primary efficacy outcome was symptomatic VTE, defined as the composite of recurrent DVT including a new non-fatal symptomatic PE, and fatal PE during the 12 month study period adjudicated by the clinical events committee (CEC).

The secondary efficacy endpoint was the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period.

In the Hokusai VTE trial, edoxaban was shown to be non-inferior to warfarin for the treatment of DVT and PE. The primary efficacy analysis was based on 276 events of recurrent VTE or VTE-related death observed at the study cutoff date. The rate of recurrence of VTE (primary efficacy endpoint) was 3.2% in the edoxaban treatment group compared to 3.5% in the warfarin treatment group during the study (on-treatment period). The estimated hazard ratio for time to primary endpoint was 0.89 (95% CI: 0.703, 1.13) for edoxaban group versus warfarin group. The upper 95% CI confidence limit of 1.13 demonstrated that treatment with edoxaban retained about 91% treatment effect of warfarin.

The primary efficacy results for treatment of DVT and PE are summarized in Table 11, below.

(b) (4)

6.1 Indication

- Treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and
- (b) (4)

6.1.1 Methods

One pivotal trial, DU176b-D-U305 (Hokusai VTE), was conducted to support the proposed indications for the treatment of VTE (b) (4)

Study Design

Hokusai VTE was an event-driven, phase 3, multi-national, multi-center, randomized, double-blind, matching placebo, parallel-group, non-inferiority study to evaluate the efficacy and safety of edoxaban for the treatment of subjects with acute symptomatic VTE and for the prevention of symptomatic recurrent VTE.

Prior to randomization, treatment with therapeutic dosages of anticoagulant (LMWH, UFH, and fondaparinux per local labeling) was allowed for maximum 48 hours. Only a single pre-randomization dose of a VKA was allowed. A total of 8292 subjects enrolled at 439 sites across 37 countries around the globe. Subjects were stratified by 1) presenting diagnosis (PE with or without DVT, or DVT only), 2) baseline risk factors (temporary risk factors vs others) and 3) need for allocation to edoxaban reduced dose of 30 mg (body weight ≤ 60 kg, or CrCL ≥ 30 to ≤ 50 mL/min, or concomitant use of the

pre-specified P-glycoprotein inhibitors (e.g., verapamil or quinidine). Subjects were then randomized in 1:1 ratio to receive either edoxaban (60 mg once daily or 30 mg if they qualify for dose reduction) or warfarin (titrated to INR 2.0 - 3.0). Subjects were to receive initial heparin therapy with low molecular weight heparin (LMWH) or unfractionated heparin for at least 5 days and until INR (sham or real) was ≥ 2.0 on two measurements. Warfarin patients were started concurrently with initial heparin therapy, and edoxaban patients were started after discontinuation of initial heparin. The treatment duration was from 3 months up to 12 months determined by investigator based on patient clinical features.

Study Patients

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.

A total of 8292 subjects who met the eligibility criteria and none of the exclusion criteria were randomly assigned via interactive voice/web response system (IXRS) in a 1:1 ratio to receive edoxaban dose of 60 mg once daily (or 30 mg daily if they qualified for dose reduction) or warfarin dose titrated to INR 2.0 - 3.0). There were 4143 subjects assigned to the edoxaban arm and 4149 subjects were assigned to the warfarin arm.

Twenty five subjects randomized to edoxaban and 27 subjects randomized to warfarin arms did not receive treatment (mITT= 8240 subjects). Of the 8,240 subjects (4118 in edoxaban arm and 4122 in warfarin arm) in the mITT analysis set, 65 (0.8%) subjects withdrew consent and 11 (0.1%) were lost to follow up.

The number and percentage of subjects with an index event that was not confirmed by CEC adjudication was 61 (1.5%) in the edoxaban group and 44 (1.1%) in the warfarin group. Therefore, the PP Analysis Set consisted of 4057 (97.9%) subjects in the edoxaban arm and 4078 (98.3%) subjects in the warfarin arm.

No subjects experienced treatment misallocation; therefore the Safety population is identical to the mITT population.

The following Table 3 summarizes the study populations used for data analysis.

Table 3: Number of Subjects in Analysis Sets – All Randomized Subjects

	Edoxaban N=4143	**Warfarin N=4149**
Randomized subjects, n (%)	4143	4149
Never received study drug, n (%)	25 (0.6)	27 (0.7)
mITT (Treated) Analysis Set, n (%)	4118 (99.4)	4122 (99.3)
Experiencing treatment misallocation, n (%)	0 (0.0)	0 (0.0)
Index event not confirmed by CEC adjudication, n (%)	61 (1.5)	44 (1.1)
Per Protocol Analysis set, n (%)	4057 (97.9)	4078 (98.3)
Safety Analysis Set, n (%)	4118 (99.4)	4122 (99.3)

Source: NDA submission, Module 5.3.5.1, Table 11.1, P97.

The inclusion criteria were adult subjects presenting with acute, symptomatic proximal DVT involving the popliteal, femoral or iliac veins, and/or PE requiring anticoagulant therapy.

Study Treatment

Subjects randomized to heparin/edoxaban group (N=4143) received initially LMW heparin plus placebo warfarin for at least 5 days until the sham INR reached ≥ 2.0 on two separate measurements at least one calendar day apart or a single supra-therapeutic sham INR measurement ≥ 3.0 was achieved (with the reasonable assumption that a therapeutic INR, i.e., ≥ 2 had been achieved for at least 24 hours). At that point the LMW heparin was stopped, and the subject started on edoxaban (60 mg or 30 mg once daily [QD]) and continued placebo warfarin (adjusted to maintain a sham INR ≥ 2.0 and ≤ 3.0).

Subjects randomized to LMW heparin/warfarin group (N=4122) received initially LMW heparin plus warfarin for at least 5 days until the INR was ≥ 2.0 on two separate measurements at least one calendar day apart or after a single supra-therapeutic INR measurement ≥ 3.0 was achieved (with the reasonable assumption that a therapeutic INR, i.e., ≥ 2 had been achieved for at least 24 hours). Then the LMW heparin was stopped, and the subject started on placebo edoxaban (60 mg QD) and continued warfarin (adjusted to maintain an INR ≥ 2.0 and ≤ 3.0).

Subjects were allowed to interrupt and resume treatment with study drug on multiple occasions, if necessary, but all subjects were to be followed continuously until the end of the study (12-months post-randomization or until study truncation).

Efficacy Endpoints

The primary efficacy endpoint was symptomatic recurrent VTE, defined as the composite of non-fatal PE, and fatal PE events during the 12 month study period adjudicated by the clinical events committee (CEC).

The secondary efficacy endpoint was the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period.

Statistical Methods

See Statistical review for discussion of statistical methods.

The Sponsor defined the following:
Modified Intent-to-Treat (mITT) Set: All randomized subjects who received at least 1 dose of study drug. Analyses were based on the randomized treatment even if a subject inadvertently received the incorrect study drug.

Per Protocol (PP) Analysis Set: All randomized subjects who received at least 1 dose of study drug, who did not have treatment misallocation, and for whom the index DVT or PE event at baseline was confirmed by the CEC. Treatment misallocation was defined as a subject taking incorrect treatment during the entire study period.

Safety Analysis Set: All randomized subjects who received at least 1 dose of study drug. Analyses were based on the randomized treatment, unless a subject inadvertently received the incorrect drug during the entire study, in which case, the subject was grouped according to the treatment actually received.

Overall Study Period: The time from the reference date (randomization date/initial dose of study drug date) to the last study follow-up visit.

On-Treatment Period: The time period the subject was taking study drug up to 3 days after their last dose for that time period. A subject may have had multiple periods of study drug use if they temporarily interrupted and resumed study drug during the study.

Treatment +30 Days Period: The time period from randomization up to 30 days after last dose of study drug.

Subjects in both the mITT and PP Analysis Sets were included in the efficacy analyses for non-inferiority (primary endpoint) and superiority (secondary endpoint). The planned efficacy analyses for the primary endpoint (symptomatic recurrent VTE) were performed using the mITT Analysis Set for the Overall Study Period. Sensitivity analyses included the Per Protocol (PP) Analysis Set for the On-Treatment period, Treatment +30 Days, and events occurring in the first 90 days. In addition, an “imputation under the non-inferiority null” method was used to examine the impact of missing data for the mITT Analysis Set for the Overall Study Period.

All safety analyses are based on subjects in the Safety Analysis Set.

The trial was designed to accumulate approximately 220 primary efficacy events in the modified intent-to-treat (mITT) Analysis Set, Overall Study Period. Assuming equal efficacy (hazard ratio = 1.00), a total of 220 events gave a power of 85% to demonstrate that (LMW) heparin/edoxaban was non-inferior to the comparator, considering a relative non-inferiority margin of 1.5 (two-sided α=0.05). Derivation of the non-inferiority margin was based on the indirect confidence interval (CI) comparison method.

The noninferiority margin of 1.5 in the Hokusai VTE study corresponds to retention of 70% of the warfarin treatment effect.

The primary efficacy endpoint analysis was based on the mITT population (i.e., all randomized subjects who received at least one dose of study drug). All primary efficacy events that occurred in the 12-month Overall Study Period were included in the primary efficacy analysis, regardless of whether the subject was receiving study treatment at the time of the event. The time to the first event of adjudicated symptomatic recurrent VTE was analyzed using a Cox proportional hazards regression model including treatment and the stratification factors (presenting diagnosis, baseline risk factor, and dose allocation at randomization) as covariates. The edoxaban/warfarin hazard ratio was computed with a 95% CI (two-sided testing) based on this model. Edoxaban was considered non-inferior to the comparator if the upper limit of the 95% CI was less than 1.5.

The incidence of adjudicated symptomatic recurrent VTE events was estimated for subjects with PE (with or without DVT) and for subjects with DVT only. The incidence of each component of the composite primary efficacy endpoint (fatal PE, non-fatal PE, or DVT only) was also estimated. Secondary efficacy and key safety endpoints were analyzed using the same covariates as used in the primary Cox proportional hazards model for the primary endpoint.

Missing data were imputed only for sensitivity analyses.

The DMC performed one unblinded formal interim review of major bleeding and recurrence of symptomatic VTE when approximately 128 symptomatic VTE events had been observed.

The statistical plan was to test the primary efficacy endpoint for non-inferiority using mITT set at α=0.05. If the upper limit of the two-sided 95% CI of the hazard ratio was below 1.5, then non-inferiority to warfarin group was to be established. If non-inferiority was achieved, then the secondary efficacy endpoint would be tested for superiority using mITT set at α=0.01.

Reviewer Comments: The design of the trial, the population included, and the endpoints selected seem appropriate to determine the relative benefits/risks of the use of edoxaban and warfarin for the treatment of VTE over the period of time

of the trial. (b) (4) [redacted]

6.1.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics (including risk factors) were based on the mITT population.

Demographics

The mean age in the edoxaban and warfarin treatment groups was 55.7 and 55.9 years, respectively. Most of subjects were males (57.3% in the edoxaban group and 57.2% in the warfarin group). The majority of subjects were white (70%) followed by Asian (21%), Black (4%) and other (5%) which was similar between the two arms.

The percentage of subjects who required the 30 mg edoxaban and placebo edoxaban at randomization was comparable between the two treatment groups (17.8% and 17.4%, respectively). The percentages of subjects that had body weight ≤ 60 kg (10.7% vs 10.3%), CrCL 30 to 50 mL/min (4.5% and 4.3%) and used quinidine/verapamil (0.5% and 0.4%) were similar between the edoxaban and warfarin groups, respectively. Post-randomization requirement for 30 mg edoxaban/edoxaban placebo occurred in 123 subjects (68 for edoxaban and 55 for edoxaban placebo (active warfarin).

Demographic and baseline characteristics of the study population are summarized in Table 4 below.

Table 4: Patients Demographic and Baseline Characteristics, mITT Analysis Set

	Edoxaban (N=4118)	**Warfarin (N=4122)**
Age (years)		
Median Age (years) (Min, Max)	57 (18,106)	57 (18,95)
<65 years, n (%)	2784 (68)	2752 (67)
≥ 65 years, n (%)	1334 (32)	1370 (33)
≥ 75 years, n (%)	560 (13.6)	544 (13.2)
Gender, n	4118	4122
Male, n (%)	2360 (57)	2356 (57)
Female, n (%)	1758 (43)	1766 (43)
Race		
Caucasian, n (%)	2867 (70)	2895 (70)
Black, n (%)	156 (4)	144 (4)
Asian, n (%)	866 (21)	861 (21)
Other, n (%)	220 (5)	211 (5)
Edoxaban 30 mg dose at randomization		
Yes, n (%)	733 (18)	719 (17)
No, n (%)	3385 (82)	3403 (83)
Weight at randomization (kg)		
≤ 60, n (%)	524 (13)	519 (13)
> 60, n (%)	3594 (87)	3603 (87)
CrCL at randomization (mL/min)		
≥30 to ≤50, n (%)	268 (7)	273 (7)
> 50, n (%)	3850 (93)	3849 (93)
Verapamil or Quinidine Use at Randomization		
Yes, n (%)	26 (1)	25 (1)
No, n (%)	4092 (99)	4097 (99)
Edoxaban 30 mg dose at randomization		
Yes, n (%)	733 (18)	719 (17)
No, n (%)	3385 (82)	3403 (83)
Risk factors		
Temporary Factors only, n (%)	1132 (27)	1140 (28)
Other, n (%)	2986 (73)	2982 (72)
Verapamil or Quinidine Use at Randomization		
Yes	26 (0.6)	25 (0.6)
No	4092 (99.4)	4097 (99.4)

Source: NDA submission, Module 5.3.5.1, Table 10.2, Page 83.

The demographic and baseline characteristics were comparable between the edoxaban 30 mg and edoxaban placebo 30 mg (active warfarin) treatment groups. The

demographic and baseline characteristics were comparable between the edoxaban 60 mg and edoxaban placebo 60 mg dose (active warfarin) treatment groups.

Demographic and baseline characteristics for the two dose strata are shown in Table 5 below.

Table 5: Demographic and Baseline Characteristics by Edoxaban Dose at Randomization, mITT Analysis Set

	Active Edoxaban		**Active Warfarin**	
	Edoxaban 30 mg N=733	**Edoxaban 60 mg N=3385**	**Edoxaban Placebo 30 mg N=719**	**Edoxaban Placebo 60 mg N=3403**
Age (years), N	733	3385	719	3403
Mean (SD)	59.9 (19.19)	54.7 (15.43)	60.2 (19.45)	55.0 (15.24)
Median (Min,Max)	64 (18,106)	56 (18,93)	64 (19,95)	56 (18,93)
<65 years	372 (50.8)	2412 (71.3)	363 (50.5)	2389 (70.2)
≥65 years	361 (49.2)	973 (28.7)	356 (49.5)	1014 (29.8)
Gender, N	733	3385	719	3403
Male, n (%)	245 (33.4)	2115 (62.5)	241 (33.5)	2115 (62.2)
Female, n (%)	488 (66.6)	1270 (37.5)	478 (66.5)	1288 (37.8)
Race	730	3379	718	3397
Caucasian, n (%)	326 (44.5)	2541 (75.1)	323 (44.9)	2572 (75.6)
Black, n (%)	22 (3.0)	134 (4.0)	22 (3.1)	122 (3.6)
Asian, n (%)	337 (46.0)	529 (15.6)	331 (46.0)	530 (15.6)
Other, n (%)	45 (6.1)	175 (5.2)	42 (5.8)	169 (5.0)
Presenting Diagnosis, N	733	3385	719	3403
Pulmonary Embolism, n (%)	311 (42.4)	1360 (40.2)	309 (43.0)	1370 (40.3)
with DVT, n (%)	97 (13.2)	514 (15.2)	80 (11.1)	480 (14.1)
without DVT, n (%)	214 (29.2)	846 (25.0)	229 (31.8)	890 (26.2)
DVT Only, n (%)	422 (57.6)	2025 (59.8)	410 (57.0)	2033 (59.7)
Risk Factors, N	733	3385	719	3403
Temporary, n (%)	206 (28.1)	926 (27.4)	206 (28.7)	934 (27.4)
Other, n (%)	527 (71.9)	2459 (72.6)	513 (71.3)	2469 (72.6)
Weight at Randomization (kg), N	733	3385	719	3403
≤ 60, n (%)	524 (71.5)	0 (0.0)	519 (72.2)	0 (0.0)
> 60, n (%)	209 (28.5)	3385 (100)	200 (27.8)	3403 (100)
Creatinine Clearance at Randomization (IXRS) (mL/min), N	733	3385	719	3403
≥30 to ≤ 50, n (%)	268 (36.6)	0 (0.0)	273 (38.0)	0 (0.0)
>50, n (%)	465 (63.4)	3385 (100)	446 (62)	3403 (100)
Verapamil or Quinidine Use at Randomization	733	3385	719	3403
Yes, n (%)	26 (3.5)	0 (0.0)	25 (3.5)	0 (0.0)
No, n (%)	707 (96.5)	3385 (100)	694 (96.5)	3403 (100)

Source: NDA submission, Module 5.3.5.1, Table 10.3, P. 85.

The enrollment by region was balanced between the two arms with most of subjects from Eastern and Western Europe. Approximately 10% of subjects enrolled were from North America (US and Canada). Table summarized the enrollment by region.

Table 6: Enrollment Summary by Region, Country, and Treatment Group Safety Analysis Set

Region	Edoxaban N=4118	Warfarin N= 4122
Western Europe, n (%)	1133 (27.5)	1120 (27.1)
Eastern Europe, n (%)	1084 (26.3)	1098 (26.6)
Nordic, n (%)	174 (4.2)	180 (4.4)
Asian, n (%)	850 (20.7)	847 (20.5)
Australia/New Zealand, n (%)	145 (3.5)	145 (3.5)
South Africa/South America, n (%)	316 (7.7)	312 (7.6)
USA/Canada, n (%)	416 (10.1)	420 (10.2)
USA, n (%)	307 (7.5)	311 (7.5)

Source: NDA submission, Module 5.3.5.1, Table 14.1.1.2, P.86.

Baseline disease characteristics:

The presenting diagnoses of index event of subjects were similar and of similar frequency among the edoxaban and the warfarin treatment groups. Approximately 41% of the subjects in each arm had diagnoses of pulmonary embolism with or without DVT prior to trial entry and approximately 59% of subjects in each arm had diagnoses of DVT only at the trial entry. There were 61 subjects (1.5%) in the edoxaban arm and 44 subjects (1.1%) in the warfarin arm for whom the index event was not confirmed by CEC adjudication.

The percentage of subjects randomized by the intended treatment duration at study entry was balanced between the two arms. Approximately 5% of the subjects in each arm were to receive treatment for three months and 38% in each arm to receive the drug for 6 months and 57% to receive the study drug for up to 12 months.

Table 7: Patients' baseline disease characteristics, mITT Analysis Set

	Edoxaban (N=4118)	**Warfarin (N=4122)**
Presenting diagnosis		
Pulmonary embolism, n (%)	1671 (41)	1679 (41)
With DVT, n (%)	611 (15)	560 (14)
Without DVT, n (%)	1060 (26)	1119 (27)
DVT only, n (%)	2447 (59)	2443 (59)
Intended treatment duration		
3 months, n (%)	221 (5)	245 (6)
6 months, n (%)	1555 (38)	1502 (36)
12 months, n (%)	2339 (57)	2371 (58)

Source: NDA submission, Module 5.3.5.1, Table 10.2, Page 83.

Baseline risk factors for thromboembolism

The underlying risk factors were similar between the two groups. More than half of the subjects in both arms had reported at least one risk factor for VTE. The most common risk factors for VTE were recent surgery, trauma or previous episodes of PE or DVT.

Table 8: Baseline risk factors for thromboembolism, mITT Analysis Set

	Edoxaban (N=4118)	**Warfarin (N=4122)**
Risk factors for VTE, n (%)		
No Risk Factors Reported, n (%)	1963 (47.7)	1983 (48.1)
Risk Factors Reported, n (%)	2155 (52.3)	2139 (51.9)
Recent Surgery, Trauma or Immobilization, n (%)	760 (19)	769 (19)
Use of Estrogen Containing Drugs, n (%)	272 (7)	300 (7)
Puerperium, n (%)	9 (0.2)	14 (0.3)
Active Cancer, n (%)	106 (3)	95 (2)
Previous Episodes of PE/DVT, n (%)	784 (19)	736 (18)
Prolonged sitting for more than 4 Hours, n (%)	288 (7)	284 (7)
Known Thrombophylic Condition, n (%)	168 (4)	176 (4)
Antithrombin Deficiency, n (%)	6 (0.1)	4 (<0.1)
Factor V Leiden, n (%)	105 (3)	106 (3)
Hyperhomcysteinanemia, n (%)	16 (0.4)	28 (0.7)
Antiphospholipid Antibodies, n (%)	12 (0.3)	14 (0.3)
Protein C Deficiency, n (%)	14 (0.3)	12 (0.3)
Protein S Deficiency, n (%)	17 (0.4)	15 (0.4)
Prothrombin Gene Mutation, n (%)	18 (0.4)	16 (0.4)
Other Thrombophylic Condition, n (%)	60 (2)	70 (2)
Other Risk Factors, n (%)	199 (5)	171 (4)

Source: NDA submission, Module 5.3.5.1, Table 14.1.3.1

Reviewer comments: Approximately half of the subjects in both arms had underlying risk factors at the time of entry. Risks factors such as recent surgery, trauma, embolization, prolonged sitting for more than 4 hours, or use of estrogen drug were similar between the two arms. Also, the percentages of subjects with risk factors such as previous episode of DVT/PE or known thrombophylic condition were similar between the two arms.

Medical History:

There were numerically higher numbers of subjects randomized to warfarin than edoxaban with clinically relevant medical history at baseline in the following categories:

1. History of bleeding (25 [0.6%] in edoxaban vs. 37 [0.9%] in warfarin),
2. Hypertension (1590 [39%] in edoxaban vs. 1672 [40.6%] in warfarin),
3. Diabetes (422 [10.3%] in edoxaban vs. 442 [10.7%] in warfarin),
4. Valvular disease (133 [3.2%] in edoxaban vs. 147 [3.6%] in warfarin), and
5. Cardiovascular disorder (546 [13.3%] in edoxaban vs. 576 [14.0%] in warfarin).

However, there were differences in baseline medical history, including the following categories that had a slightly higher percentage of subjects randomized to edoxaban:

1. Heart rhythm disorder (284 [6.9%] in edoxaban vs. 255 [6.2%] in warfarin),
2. Hepatic disease (427 [10.4%] in edoxaban vs. 412 [10.0%] in warfarin),
3. Osteoporosis (204 [5.0%] in edoxaban vs. 180 [4.4%] in warfarin), and
4. Cerebrovascular disease (178 [4.3%] in edoxaban vs. 146 [3.5%] in warfarin).

6.1.3 Subject Disposition

A total of 8292 subjects were randomized in the trial; 4143 subjects in the edoxaban and 4149 subjects in warfarin treatment groups.

The mITT analyses included all randomized subjects who received at least 1 dose of study drug. Twenty five subjects in the edoxaban and 27 subjects in warfarin group did not receive any treatment. Therefore there were 8240 subjects in the mITT set (4118 in the edoxaban group and 4122 in warfarin group).

The PP analyses included all randomized subjects who received at least 1 dose of study drug, who did not have treatment misallocation, and for whom the index DVT or PE event at baseline was confirmed by the CEC. The number of subjects with an index event that was not confirmed by CEC adjudication was 61 (1.5%) in the edoxaban group and 44 (1.1%) in the warfarin group.

A total of 7892 (96%) subjects completed the study; 3937 (96%) in the edoxaban group and 3955 (96%) in warfarin group. Among the 348 (4%) subjects who did not complete the follow up there were 181 subjects in the edoxaban and 167 subjects in the warfarin groups. There were a total of 263 deaths in the trial (136 in edoxaban and 127 in

warfarin group). Sixty five subjects withdrew their consent and 11 (0.1%) were lost to follow up.

Table 9: Study Completion Status

	Edoxaban (N= 4118)	Warfarin (N=4122)
Subjects Completing Study, n (%)	3937 (96)	3955 (96)
Subjects completed 12-month follow-up, n (%)	3937 (96)	3955 (96)
Subjects completed <12 Month follow-up due to study truncation, n (%)	879 (21)	881 (21)
Subjects did not complete study follow-Up, n (%)	181 (4)	167 (4)
Death, n (%)	136 (3.3)	127 (3.1)
Withdrawn consent, n (%)	32 (1)	33 (1)
Lost to follow-up, n (%)	7 (0.2)	4 (<0.1)
Other, n (%)	6 (0.1)	3 (<0.1)

Source: NDA submission, Module 5.3.5.1, Table 14.1.1.6, P.12.

Reviewer Comments: The completion rate for the trial was high (96%). There did not appear to be any significant differences in subject disposition between the two arms of the trial.

Protocol Deviations:
No data/cases were identified that should have been excluded from any of the Analysis Sets. A summary of major protocol deviations is provided in Table 10.

Table 10: Protocol deviations, mITT Analysis set

	Edoxaban (N=4118)	Warfarin (N=4122)
At least one protocol deviation, n (%)	953 (23.1)	943 (22.9)
Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the index VTE episode, n (%)	16 (0.4)	27 (0.7)
Receiving non-study warfarin for an indication other than DVT and/or PE, n (%)	28 (0.7)	21 (0.5)
Had more than 48 hours pre-treatment with therapeutic dosages of anticoagulant treatment or more than a single dose of VKA prior to randomization to treat the index episode, n (%)	162 (4)	168 (4)
Received disallowed concomitant medications that impacts the evaluation of primary endpoints for efficacy or safety, n (%)	863 (21)	830 (20)
NSAIDs, n (%)	651 (15.8)	640 (15.5)
Aspirin use > 100 mg QD, n (%)	39 (0.9)	29 (0.7)
Dual antiplatelet therapy, n (%)	30 (0.7)	20 (0.5)
Any other prohibited medications, n (%)	143 (2.5)	141 (2.4)
CrCL <30 at randomization, n (%)	10 (0.2)	10 (0.2)
Subjects at sites for which subject data authenticity is suspect and cannot be confirmed, n (%)	16 (0.4)	8 (0.2)

Source: NDA submission, Module 5.3.5.1, Table 14.1.2.1, P. 16.

Reviewer comments: There were 32 patients most from in India sites (16 in the edoxaban arm and 8 in the warfarin arm), who had protocol deviations of subject data authenticity unable to be confirmed and who were not excluded from the trial. The applicant did not provide explanation of the deviations or reason to retain these subjects the analysis data set. Given the small number of patients with the deviation (32 patients), we think this did not have a significant impact on the trial results.

6.1.4 Analysis of Primary Endpoint(s)

Primary Efficacy Endpoint: Time to the first occurrence of recurrent VTE or VTE-related death during the 12-month study period.

Primary efficacy analysis was based on mITT population (patients who received at least one dose of study treatment).

The non-inferiority margin of the upper 95% confidence limit was set for HR < 1.5 (Edoxaban vs. Warfarin) with retention of ~70% warfarin treatment effect. Non-inferiority will be tested at α=0.05 (two-sided).

For the primary endpoint event of symptomatic recurrent VTE, there were 130 (3.2%) events that occurred in the edoxaban arm and 146 (3.5%) in the warfarin arm. The HR for the edoxaban group vs. the warfarin group was 0.89 (95% CI: 0.703, 1.128). The upper bound of the 95% CI is 1.128, which was below the pre-specified non-inferiority margin of 1.5 with a p-value of <0.0001. However, testing the primary endpoint of recurrent VTE for superiority failed to show statistical differences (p=0.33) between the two arms.

Among the 130 subjects with primary endpoint events of recurrent VTE, 73 (1.8%) subjects in the edoxaban arm had recurrent PE with or without DVT and 57 (1.5%) DVT only compared to 83 (2.0%) subjects had recurrent PE with or without DVT and 63 (1.5%) DVT events in the warfarin arm. However, the results showed that the number of subjects with fatal PE was similar between the two arms (24 events in each arm).

The results of primary endpoint analysis are summarized in Table 11.

Table 11: Primary Endpoint (Adjudicated Symptomatic Recurrent VTE), mITT Analysis Set – Overall Study Period

Primary Efficacy Endpoint	Edoxaban N=4118	Warfarin N=4122
Subjects with recurrent VTE, n (%)	130 (3.2)	146 (3.5)
HR (95% CI) p-value (for non-inferiority)	0.89 (0.70, 1.13) <0.0001*	
p-value (for superiority)	0.33	
Type of First Recurrent VTE		
PE With/Without DVT, n (%)	73 (1.8)	83 (2.0)
PE-Related Death, n (%)	24 (0.6)	24 (0.6)
Non-Fatal PE, n (%)	49 (1.2)	59 (1.4)
With DVT, n (%)	2 (<0.1)	2 (<0.1)
Without DVT, n (%)	47 (1.1)	57 (1.4)
DVT Only, n (%)	57 (1.4)	63 (1.5)

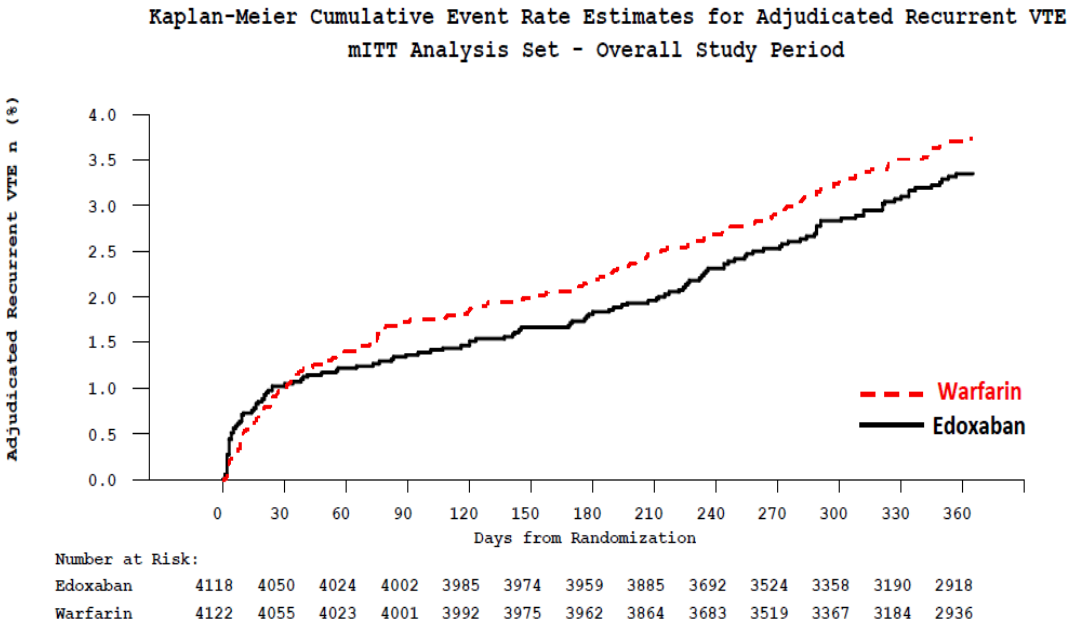
* The p-value is for the pre-defined non-inferiority margin of 1.5.
Source: NDA submission, Module 5.3.5.1, U305 Table 11.2, P 28.

Kaplan-Meier cumulative event rate estimates for the primary endpoint in the mITT Analysis Set, Overall Study Period are shown in Figure 4. The adjudicated symptomatic recurrent VTE events in edoxaban subjects exceeded those in warfarin subjects for the first 10 days. In the first 10 days of the trial there were 30 (0.7%) events of recurrent

VTE (9 PE and 21 DVT) in the edoxaban arm vs 22 (0.5%) events (7 PE and 15 DVT) in the warfarin arm.

The Applicant explanation of the numerical imbalance of higher incidence of event in the edoxaban arm in the first 10 days of the trial is that subjects randomized to edoxaban arm received initial heparin only but those randomized to warfarin received two active anticoagulants treatment of heparin and warfarin initially.

Figure 4: Kaplan-Meier Cumulative Event Rate Estimates for Primary Endpoint (Adjudicated Symptomatic Recurrent VTE) – mITT Analysis Set, Overall Study Period



Source: NDA submission, Module 5.3.5.1, U305 Figure 14.2.1.33, Page 101.

Reviewer comments: Trial met its non-inferiority margin. An excess of recurrent VTE events occurred among edoxaban group in the first 10 days. However, the rate of the events was less in the edoxaban group after the first 30 days and continued to be lower up to 12 months.

Sensitivity Efficacy Analyses:

The sensitivity efficacy analyses for non-inferiority for the time to the first occurrence of adjudicated symptomatic recurrent VTE was performed by the Sponsor on the PP Analysis Set, using the On-Treatment and Treatment +30 Days Study Periods. The sensitivity analysis results were consistent with those from the primary analysis.

Table 12: Sensitivity Analysis Results Of Primary Efficacy Endpoint, PP Population

	Edoxaban N=4057	**Warfarin N=4078**
On-Treatment Study Period, n (%)	64 (1.6)	80 (2.0)
Edoxaban vs. Warfarin HR (95% CI)	0.80 (0.58, 1.11)	
Treatment+30 Days, Study Period, n (%)	87 (2.1)	102 (2.5)
Edoxaban vs. Warfarin HR (95% CI)	0.85 (0.64, 1.14)	
Treatment+30 Days excluding unexplained deaths, n (%)	74 (1.8)	89 (2.2)
Edoxaban vs. Warfarin HR (95% CI)	0.83 (0.61, 1.13)	

Source: NDA submission, Module 5.3.5.1, Table 11.5, P105

The sensitivity analysis performed on PP analysis set reported in the initial 90 days study period revealed that the primary endpoint event of symptomatic recurrent VTE occurred in 54 (1.3%) in the edoxaban arm vs. 71 (1.7%) in the warfarin arm. The HR for the edoxaban group vs. the warfarin group was 0.85 (95% CI: 0.64, 1.14).

Table 13: Analysis of Adjudicated Recurrent VTE event PP Analysis Set - Initial 90-Day Study Period

Primary Efficacy Endpoint	**Edoxaban N=4057**	**Warfarin N=4078**
Subjects with recurrent VTE, n (%)	54 (1.3)	71 (1.7)
Edoxaban vs. Warfarin HR (95% CI) p-value	0.85 (0.64, 1.14) p-value <0.0001	
PE With/Without DVT, n (%)	35 (0.9)	44 (1.1)
PE-Related death, n (%)	12 (0.3)	12 (0.3)
Non-Fatal PE, n (%)	23 (0.6)	32 (0.8)
DVT Only, n (%)	19 (0.5)	27 (0.7)

Source: NDA submission, Module 5.3.5.1, Table 14.2.1.5, P164

Primary Efficacy Analysis by Edoxaban Dose:

Subjects with moderate renal impairment (CrCL 30-50 ml/min), low weight ≤ 60 kg or pre-specified concomitant use of P-gp inhibitors at randomization received edoxaban after the initial heparin at a reduced dose of 30 mg.

In the mITT Analysis Set, the active edoxaban and active warfarin groups were well balanced with respect to the numbers of subjects requiring edoxaban/edoxaban placebo 30 mg at randomization (edoxaban: N=733; warfarin: N=719).

The primary efficacy endpoint of recurrent VTE was reported in 22 subjects (3.0%) in the active edoxaban 30 mg vs. 30 subjects (4.2%) of the edoxaban placebo 30 mg (active warfarin). However, the percentage of symptomatic recurrent VTE events in the active edoxaban 30 mg and active edoxaban 60 mg dose cohorts were 3.0% and 3.2%, respectively.

Table 14: Adjudicated Symptomatic Recurrent VTE by Edoxaban Dose at Randomization, mITT Analysis Set – Overall Study Period

	Active Edoxaban		**Active Warfarin**	
	Edoxaban 30 mg N=733	Edoxaban 60 mg N=3385	Placebo 30 mg N=719	Placebo 60 mg N=3403
Subjects With Recurrent VTE, n (%)	22 (3.0)	108 (3.2)	30 (4.2)	116 (3.4)
PE With/Without DVT, n (%)	14 (1.9)	59 (1.7)	19 (2.6)	64 (1.9)
DVT Only, n (%)	8 (1.1)	49 (1.4)	11 (1.5)	52 (1.5)

Source: NDA submission, Module 5.3.5.1, Table 11.3, P. 102

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoint for superiority of edoxaban treatment compared to warfarin treatment for the time to the first occurrence of recurrent VTE and all-cause mortality was performed on mITT population for the overall study period of 12 months.

The composite secondary endpoint of recurrent VTE and all-cause mortality occurred in 228 (5.5%) of subjects in the edoxaban group and 228 (5.5%) subjects in the warfarin group (HR: 1.00; 95% CI: 0.832, 1.200, p=0.99). The results showed that treatment with edoxaban is not superior to warfarin in reducing the incidence of recurrent VTE or all-cause mortality.

There was a slightly increased incidence of mortality in the edoxaban group compared to that in the warfarin group 3.0% vs 2.6%. Although, there were no differences in VTE-related death between the two treatment groups, there was a numerical increase in infection related death among edoxaban treated patients.

Table 15: Adjudicated Secondary Endpoint (Recurrent VTE and All-cause Mortality), mITT Analysis Set - Overall Study Period

Secondary Efficacy Endpoint	Edoxaban N=4118	Warfarin N=4122
Subjects with recurrent VTE or all-cause mortality, n (%)	228 (5.5)	228 (5.5)
HR (95% CI)	1.00 (0.83, 1.20)	
p-value (Superiority)	0.99	
Recurrent non-fatal VTE, n (%)	106 (2.5)	122 (3.0)
All-cause mortality, n (%)	122 (3.0)	106 (2.5)
VTE-related death, n (%)	24 (0.6)	24 (0.6)
Fatal PE	4 (<0.1)	3 (<0.1)
Unexplained Death (VTE can't be r/o)	20 (0.5)	21 (0.5)
Infectious Disease related death, n (%)	25 (0.6)	12 (0.2)
Other death, n (%)	73 (1.8)	76 (1.8)

Source: NDA submission, Module 5.3.5.1, Table 11.10, P.115.

Reviewer comments: Generally, the rate of events of the composite secondary endpoint of recurrent VTE or all-cause mortality was similar between the two groups. There was a higher incidence of mortality from all causes in edoxaban mainly due infection related mortality (unrelated to VTE-related mortality) but numbers of these events were small.

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

Pre-specified subgroup analyses were performed for the primary efficacy endpoint using the mITT Analysis Set, Overall Study Period.

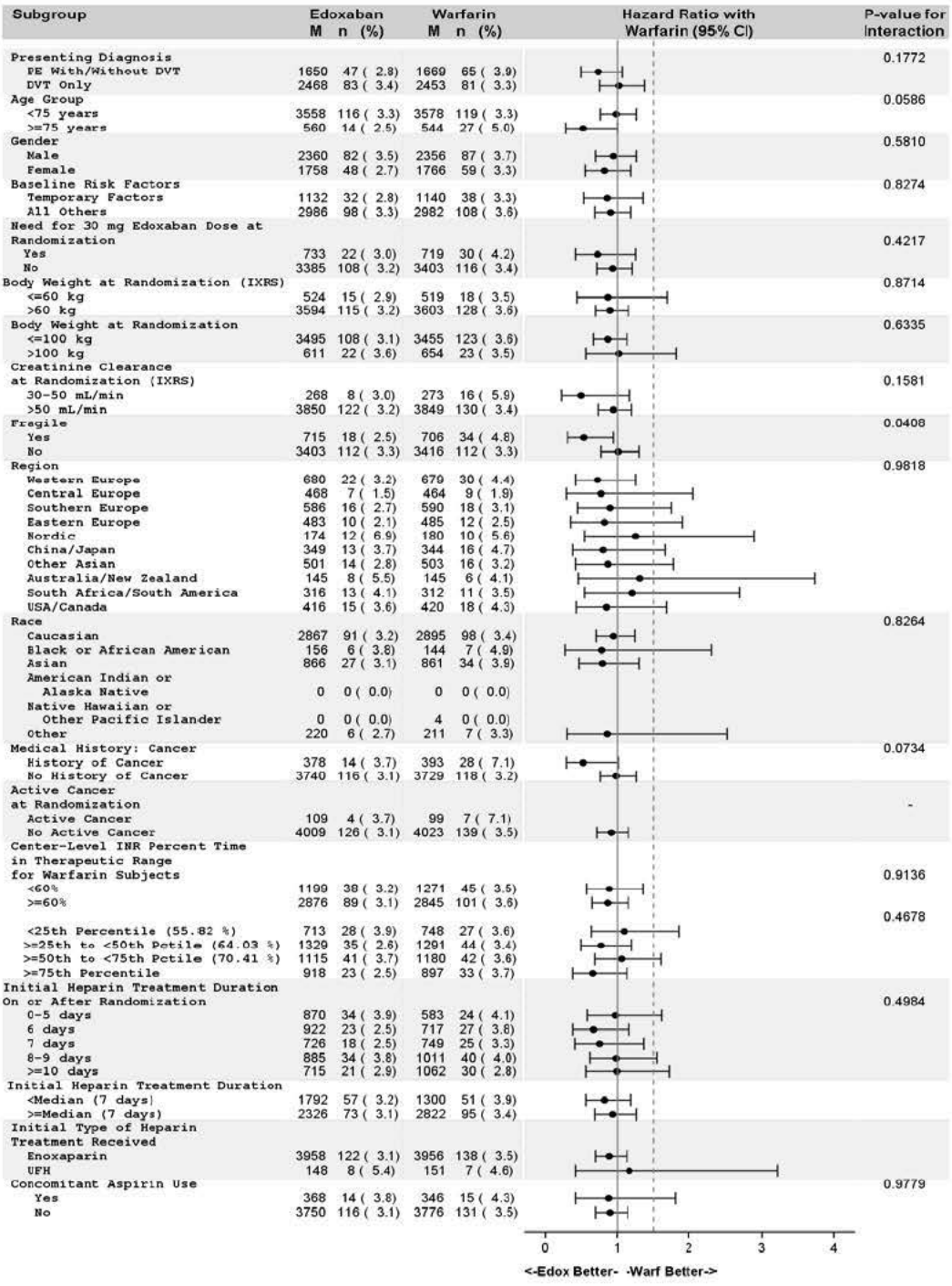
The following pre-specified subgroup analyses were performed.

1. Presenting diagnosis (PE with/without DVT, DVT only). If the CEC was unable to confirm the diagnosis the investigators' diagnosis was used).
2. Age: < 75 years, ≥ 75 years
3. Gender: male, female
4. Baseline Risk factor: temporary, other
5. Need for 30 mg edoxaban dose at randomization - edoxaban 30 mg: yes/no
6. Body weight at randomization
    a. ≤ 60 kg, > 60 kg,

   b. ≤ 100 kg, > 100kg
7. CrCL at randomization: 30 to 50 mL/min, > 50 mL/min
8. Fragile population (at randomization: age ≥ 75 years and/or body weight ≤ 50 kg and/or CrCL 30 to 50 mL/min)
9. Region and/or specific countries
10. Race
11. Medical History of Cancer at randomization: yes/no
12. Active Cancer at randomization: yes/no
13. Center Level INR Percent Time in Therapeutic Range for Warfarin subjects:
   a. < 60%, ≥ 60%
   b. by TTR quartiles
14. Initial Heparin Treatment Duration
   a. 0-5, 6, 7, 8-9, ≥ 10 days
   b. < median (7 days), ≥median (7 days)
15. Initial Type of Heparin Treatment received: enoxaparin/UFH
16. Concomitant Aspirin use: yes/no

The results of subgroups analyses were shown in the Forest plots in Figure 5.

Figure 5: Forest Plot of Primary Endpoint (Recurrent VTE) by Subgroup, mITT Analysis Set – Overall Study Period



Fragile population = at randomization: age ≥75 years and/or body weight ≤50 kg and/or CrCL 30-50 mL/min

Source: NDA submission, Module 5.3.5.1, Figure 11.4 P108.

Subgroup Analyses by Index PE and PE Severity

A total of 3319 subjects presented with an index PE (with or without DVT) (confirmed by CEC adjudication, or by the investigator if CEC could not adjudicate), 1650 subjects (49.7%) were randomized to the edoxaban group and 1669 subjects (50.3%) were randomized to the warfarin group. In a total of 35 subjects (26 in the edoxaban and 9 in the warfarin) the index PE were not confirm by the adjudicated CEC.

In the mITT analysis set for the overall period, the primary endpoint (symptomatic recurrent VTE) occurred in 47 (2.8%) of the edoxaban subjects with an index PE compared to 65 (3.9%) in the warfarin subjects with an index PE for a relative reduction in risk of 27% (HR: 0.73; 95% CI: 0.50, 1.06).

PE severity was further assessed by protocol pre-specified assessments of baseline anatomic extent, baseline serum NT-proBNP, and baseline right ventricular dysfunction (as measured by computed tomography).

Results for these analyses are shown in the Sponsor's Table 16 below.

Table 16: Primary Endpoint (Adjudicated Symptomatic Recurrent VTE) by Index PE and by PE Severity

	Edoxaban N= 4118	**Warfarin N= 4122**
Subjects with an index PE, n (%)	1650 (49.7%)	1669 (50.3)
Recurrent VTE, n_1*/n (%)	47 (2.8)	65 (3.9)
Edoxaban vs. Warfarin, HR (95% CI)	0.73 (0.50,1.06)	
Subjects with extensive anatomic PE, n (%)	743 (18)	778 (18.9)
Recurrent VTE, n_1/n (%)	24 (3.2)	30 (3.9)
Edoxaban vs. Warfarin, HR (95% CI)	0.84 (0.48, 1.43)	
Subjects with NT-proBNP ≥500 pg/ml	447 (10.9)	483 (11.7)
Recurrent VTE, n_1/n (%)	14 (3.1)	30 (6.2)
Edoxaban vs. Warfarin, HR (95% CI)	0.50 (0.26, 0.93)	
Subjects with RV dysfunction, n (%)	171 (4.2)	179 (4.3)
Recurrent VTE, n_1/n (%)	5 (2.9)	12 (6.7)
Edoxaban vs. Warfarin, HR (95% CI)	0.42 (0.14, 1.19)	

* n1= number of patients with recurrent VTE

Source: NDA submission, Module 5.3.5.1, Table 11.6, P110.

PE severity based on baseline serum NT-proBNP

There were 447 subjects in the edoxaban arm and 483 subjects in the warfarin arm who met the criteria for severe PE based on BNP at the baseline. The primary endpoint (symptomatic recurrent VTE) occurred in 14 (3.1%) of the edoxaban subjects compared

to 30 (6.2%) in the warfarin subjects for a relative reduction in risk of 50% (HR: 0.50; 95% CI: 0.26, 0.94).

Reviewer comments: (b) (4) [redacted]

Subgroup Analyses by Index DVT

From the total of 4921 subjects who presented with DVT only based on diagnosis as confirmed by CEC adjudication (or by the investigator if the CEC could not adjudicate), 2468 (50.2%) randomized to edoxaban and 2453 (49.8%) were randomized to warfarin.

In the mITT population during the 12-month study period, the primary endpoint of adjudicated symptomatic recurrent VTE occurred in 83 (3.4%) of subjects with an index DVT in the edoxaban group compared to 81 (3.3%) in the warfarin group (HR: 1.02; 95% CI: 0.75, 1.38). With respect to the PP population, analyses for the on-treatment and treatment +30 days study periods showed comparable results.

Table 17: Primary Endpoint (Adjudicated Symptomatic Recurrent VTE) by Index DVT

Recurrent VTE by Index DVT	**Edoxaban**	**Warfarin**
mITT Analysis Set- Overall Study Period, n/N* (%)	83/2468 (3.4)	81/2453 (3.3)
Edoxaban vs. Warfarin HR (95% CI)	1.02 (0.75, 1.38)	
PP Analysis Set – On- Treatment Study Period, n/N (%)	47/2433 (1.9)	50/2418 (2.1)
Edoxaban vs. Warfarin HR (95% CI)	0.94 (0.63, 1.39)	
PP Analysis Set – Treatment +30 Days Study Period, n/N (%)	59/2433 (2.4)	60/2418 (2.5)
Edoxaban vs. Warfarin HR (95% CI)	0.98 (0.68, 1.40)	

N* = number of subjects who presented with DVT diagnosis.
Source: NDA submission, Module 5.3.5.1, U305 Table 11.7

Reviewer comments: The analysis of the primary endpoint of recurrent VTE in subjects with presenting diagnosis of DVT suggested no statistically significant differences between the two groups.

Subgroup Analyses by Age Group

In subgroup analysis of subjects age 75 years or older in mITT population, a total of 1104 subjects (13.4%) were ≥ 75 years old, including 560 (13.6%) subjects in the edoxaban group and 544 subjects (13.2%) in the warfarin group.

The primary efficacy endpoint of recurrent VTE in subjects ≥ 75 years of age, occurred in 14 subjects (2.5%) in the edoxaban group compared to 27 subjects (5.0%) in the warfarin group, (HR: 0.52; 95% CI: 0.27, 0.99).

Subgroup Analyses by History of Cancer

In subgroup analysis of subjects with cancer in mITT population, a total of 771 (9.4%) subjects had a medical history of cancer, including 378 subjects in the edoxaban group and 393 subjects in the warfarin group. The adjudicated symptomatic recurrent VTE was observed in 14 (3.7%) edoxaban subjects with a cancer history compared to 28 (7.1%) warfarin subjects with a cancer history, (HR: 0.53; 95% CI: 0.28, 1.00).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended edoxaban dose is 60 mg taken orally once daily (b) (4) However, the recommended dose of edoxaban should be reduced to 30 mg once daily in patients with one or more of the following:

- Moderate to severe renal impairment (CrCL 15 - 50 mL/min)
- Low body weight ≤60 kg (132 lbs)
- Concomitant use of P glycoprotein (P gp) inhibitors (b) (4)

In the phase 3 trial (Hokusai VTE) at randomization, in the mITT population, a total of 1452 (17.6%) subjects met the pre-specified criteria requiring allocation to edoxaban 30 mg (or matching placebo), including 733 (17.8%) subjects in the edoxaban group and 719 (17.4%) subjects in the warfarin group.

The primary endpoint of adjudicated symptomatic recurrent VTE was observed in 22 (3.0%) of subjects assigned to edoxaban 30 mg compared to 30 (4.2%) of the corresponding warfarin subgroup (i.e., subjects receiving warfarin and the matching placebo for edoxaban 30 mg). The rate of recurrent VTE was comparable btween subjects receiving edoxaban 30 mg (3%) and those receiving edoxaban 60 mg (3.2%).

The efficacy of edoxaban by dose is summarized in Table 14.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The efficacy of edoxaban was persistent during the treatment period and no tolerance effects were identified in the clinical trial. The Sponsor did not provide information about increase in VTE events after the drug stopped.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The review of safety for the proposed indications of the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), (b) (4) was primarily based on the safety results from Hokusai VTE. The safety findings are the follows.

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 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%).

7.1 Methods

The review of safety for the proposed indications of the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), (b) (4) was primarily based on the safety results from the phase 3 trial, Hokusai VTE. The safety data includes data from all completed clinical studies, and ongoing studies and post-marketing data with a cutoff date of 30 Jun 2013, 31 May 2013, and 30 Sep 2013, respectively.

However, the primary safety data is data from two pivotal trials:

- Study DU176b-C-U301 (ENGAGE AF-TIMI 48): This was a randomized, controlled, double-blind, double-dummy, multi-national, multi-center study designed to evaluate the efficacy and safety of edoxaban for reducing the risk of stroke and systemic embolic events (SEE) in subjects with atrial fibrillation (AF). A total of 21,105 subjects were randomized in this trial (21,026 treated). The median treatment durations were 916, 904, and 904 days in the edoxaban 30 mg, edoxaban 60 mg, and warfarin treatment groups, respectively.
- Study DU176b-D-U305 (Hokusai VTE): This was a randomized, controlled, double-blinded, double-dummy, multi-national, multi-center study designed to evaluated the efficacy and safety of edoxaban for the treatment and secondary prevention of venous thromboembolism (VTE) in subjects with acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE). A total of 8292 subjects were randomized in this trial (8240 treated). The median treatment durations were 267 and 266 days in the edoxaban and warfarin treatment groups, respectively.

Five supportive phase 2 safety studies in subjects with non-valvular AF (NVAF): These studies were designed primarily to evaluate the safety of various dosage regimens of edoxaban in subjects with NVAF.

- Controlled studies: A total of 1446 subjects were treated with 30 to 120 mg edoxaban daily (30 mg, 45 mg, or 60 mg QD; 30 mg or 60 mg BID) for 12 weeks in 3 warfarin controlled studies (PRT018, C-J225 and C-J226); 450 subjects were treated with warfarin.
- Uncontrolled studies: A total of 56 subjects were treated with edoxaban in 2 studies, for either 6 weeks (J-05; 5 mg, 15 mg, or 30 mg edoxaban QD) or 10

weeks (J-03; 30 mg, 45 mg, or 60 mg twice daily [BID]). Data from these studies are not pooled with each other or with data from the controlled studies.

- (b) (4)
- Safety data from phase I clinical pharmacology studies.
- Post-marketing experience as of the data cutoff date for this submission (30 Sep 2013).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In the Hokusai VTE trial, all safety analyses were performed using the safety analysis set population which consisted of all subjects who received at least one dose of drug after randomization.

The primary safety outcome was clinically relevant bleeding, defined as the composite of major or clinically relevant non-major bleeding that occurred during or within three days of stopping study treatment.

Major bleeding was defined as any overt bleed associated with

- Fall in hemoglobin of 2 g/dL or more or
- Require more than two units of RBCs transfusion or
- Bleed in critical site such as intracranial, intraspinal, intraocular pericardial, intramuscular with compartment syndrome, intra-articular or retroperitoneal or
- Bleeding leading to death.

Clinically relevant non-Major (CRNM) bleed was defined as one of the following:

- Epistaxis lasting more than 5 minutes
- Gingival bleeding lasting more than 5 minutes
- Macroscopic hematuria
- Macroscopic GI bleeding or rectal bleeding of more than a few spots
- Hemoptysis of more than a few speckles
- Intramuscular hematoma or subcutaneous hematoma greater than 25 cm^2.

If a substantial number of the subjects experienced multiple Major or CRNM bleeding events, time to recurrent events was used to analyze the bleeding events.

The analysis of bleeding events focused primarily on those events occurring during treatment or within 3 days after interrupting or stopping treatment.

For ENGAGE AF-TIMI 48 the safety analyses are being reviewed (final review pending) by the Division of Cardiovascular and Renal Product (DCRP).

7.1.2 Categorization of Adverse Events

MedDRA terminology version 14.1 was used in the Hokusai VTE and the integrated analysis. However, all post-marketing AE data were coded using MedDRA version 16.1.

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

The adverse events from clinical trials were pooled in groups based on phases of the study and study population.

7.2 Adequacy of Safety Assessments

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

Hokusai VTE:

In the Hokusai VTE trial, the baseline demographic characteristics of the safety population were similar to those of the mITT population and were balanced between the treatment groups.

Treatment duration was similar between the two arms. The median treatment duration was 267 days for the edoxaban group and 266 days in the warfarin group (approximately 9 months). The mean treatment duration was 251.9 days for the edoxaban group and 250.3 days for the warfarin group.

Duration of drug exposure was also comparable in the two arms. The median drug exposure duration was 265 days for edoxaban and 261 days for warfarin. The mean drug exposure duration was 250.3 days for edoxaban and 248.4 days for warfarin.

The percentage of subjects who stopped after three months of treatment (11.8% in the edoxaban group and 12.8% in the warfarin group) was double that expected prior to start treatment (5.4% in the edoxaban and 6% in the warfarin).

The percentage of subjects who received >3 months to ≤ 6 months of treatment was 26.1% in the edoxaban arm and 26.3% in the warfarin arm.

The percentage of subjects who received > 6 months of treatment was 62.1% in the edoxaban arm and 60.9% in the warfarin arm.

The percentage of patients who received ≥12 months of treatment was 40.3% in the edoxaban arm and 40.2% in the warfarin arm.

The summary of treatment duration and drug exposure durations are presented in Table 18.

Table 18: Treatment Duration and Study Drug Exposure, Safety Analysis Set

	Edoxaban (N=4118)	Warfarin (N=4122)
Duration of Actual Treatment (days)		
Mean (±SD) (days)	251.9 (112.0)	250.3 (113.0)
Median (min, max) (days)	267 (1, 407)	266 (1, 422)
Intended treatment duration		
3 months, n (%)	221 (5.4)	245 (6.0)
6 months, n (%)	1555 (37.8)	1502 (36.5)
12 months, n (%)	2339 (56.8)	2371 (57.6)
Actual treatment duration		
≤ 3 Months, n (%)	485 (11.8)	528 (12.8)
> 3 to ≤ 6 Months, n (%)	1076 (26.1)	1084 (26.3)
> 6 Months, n (%)	2557 (62.1)	2510 (60.9)
≥ 12 Months, n (%)	1661 (40.3)	1659 (40.2)
Total Number of Days Exposed to Study Drug		
Mean (±SD) (days)	250 (111.8)	248.4 (112.6)
Median (days)	265	261

Source: NDA submission, Module 5.3.5.1, Table 12.1, P 124.

Reviewer Comments: Time of observation and mean and median exposure to study drug were similar in the two groups of the trial. The number of subjects who stopped treatment after 3 months was double that expected prior to start treatment (as planned by investigators).

The median and the mean of initial heparin treatment duration were comparable between the edoxaban and warfarin treatment groups (7 and 8 days for median, 7.5 and 8.5 for mean, respectively). The duration of initial heparin exposure during the study treatment is summarized in Table 19.

Table 19: Initial Heparin Treatment Duration, Safety Analysis Set

	Edoxaban (N=4118)	**Warfarin (N=4122)**
Initial Heparin Treatment Duration, Days		
Mean (SD)	7.5 (2.85)	8.5 (3.99)
Median (Min, Max)	7 (0, 54)	8 (0, 64)
Number of Days, n (%)		
0 - 6 days	1792 (43.5)	1300 (31.5)
7 days	726 (17.6)	749 (18.2)
8 days	532 (12.9)	638 (15.5)
≥ 9 days	1068 (26.0)	1435 (34.8)

Source: NDA submission, Module 5.3.5.1, Table 12.2, P 125.

Reviewer comments: The median and mean of initial heparin treatment in the warfarin group were one day longer than in the edoxaban group.

There was a similar percentage of subjects in the edoxaban and warfarin groups received a reduced dose of 30 mg of edoxaban/edoxaban placebo at randomization (17.8% and 17.4%, respectively). The most frequent reason for 30 mg edoxaban/edoxaban placebo assignment at randomization was body weight ≤ 60 kg (10.7% for edoxaban and 10.3% for warfarin, respectively).

A total of 123 of subjects (68 in the edoxaban group and 55 in the warfarin group) had their edoxaban or edoxaban placebo dose adjusted from 60 mg to 30 mg after randomization, mainly due to impaired renal function.

Table 20: Edoxaban Dose Adjustment Summary, Safety Analysis Set

	Edoxaban N=4118	**Warfarin N=4122**
Subjects with 60 mg dose at randomization, n (%)	3385 (82.2)	3403 (82.6)
Subjects with 30 mg dose at randomization, n (%)	733 (17.8)	719 (17.4)
Weight only (≤ 60 kg)	442 (10.7)	425 (10.3)
CrCL only (≤ 50 - ≥ 30 mL/min)	184 (4.5)	179 (4.3)
Quinidine and/or Verapamil Use only	22 (0.5)	18 (0.4)
CrCL and Quinidine/Verapamil Use	3 (<0.1)	3 (<0.1)
Weight and CrCL	81 (2.0)	90 (2.2)
Weight and Quinidine/Verapamil Use	1 (<0.1)	3 (<0.1)
Weight, CrCL and Quinidine/Verapamil Use	0 (0.0)	1 (<0.1)
Subjects with 30 mg dose post-randomization, n (%)	68 (2.0)	55 (1.6)
Weight only (≤ 60 kg)	7 (0.2)	5 (0.1)
CrCL only (≤ 50 - ≥ 30 mL/min)	29 (0.9)	24 (0.7)
Quinidine and/or Verapamil Use only	3 (<0.1)	0 (0.0)
CrCL and Quinidine/Verapamil Use	2 (<0.1)	1 (<0.1)
Weight and CrCL	2 (<0.1)	1 (<0.1)
Weight and Quinidine/Verapamil Use	0 (0.0)	1 (<0.1)
Other	25 (0.7)	23 (0.7)

Source: NDA submission, Module 5.3.5.1, Table 14.1.5.13, P139

Reviewer comments: The number of patients who required dose adjustment post randomization was small (2%).

7.2.2 Explorations for Dose Response

The edoxaban dose selection for the Hokusai VTE study (edoxaban 60 mg once daily) was based on the results of phase 1 pharmacokinetic (PK) and drug-drug interaction studies, phase 2 studies in subjects with non-valvular AF and subjects undergoing lower-limb orthopedic surgeries, and pharmacometric analyses.

Study PRT018 was a phase 2, randomized, parallel group, multi-center, multi-national study for the evaluation of safety of four fixed dose regimens of DU-176b in subjects with non-valvular atrial fibrillation. A total of 1146 subjects were randomly assigned to one of the following five treatment groups in a 1:1:1:1:1 ratio to edoxaban 30 mg QD, 30 mg BID, 60 mg QD, 60 mg BID, or warfarin dosage adjusted to maintain INR between 2.0 and 3.0, inclusive. The duration of treatment for an individual subject was 3 months.

The results from the phase 2 (PRT018) study showed that bleeding incidences were higher at a dose of 30 mg and 60 mg twice daily regimens compared to edoxaban 30 mg and 60 mg once daily.

7.2.3 Special Animal and/or In Vitro Testing

In vitro, metabolism of edoxaban is predominantly mediated by cytochrome P450 (CYP) 3A4, involved in the formation of D103-2684, D21-1402, and a hydroxylated metabolite; and carboxylesterase 1 (CES1), involved in the formation of D21-2393, a human-specific metabolite. Edoxaban is a substrate of the efflux transporter, P glycoprotein (P-gp), but not a substrate for uptake transporters such as organic anion transporter (OATP1B1, organic anion transporters OAT1 and OAT3, or organic cation transporter OCT2).

The *in vitro* total plasma protein binding (individual protein binding not identified) for edoxaban at concentrations from 0.2 µg/mL to 5 µg/mL is about 55%, whereas the human-specific metabolite, D21-2393, is about 80% bound to plasma proteins over a concentration range of 0.2 µg/mL to 2 µg/mL. Edoxaban partitions almost equally in blood and plasma with a ratio of about 46%.

Refer to Clinical Pharmacology review for further details.

7.2.4 Routine Clinical Testing

Routine clinical testing obtained while on the trial included, liver function test (at day 1 then monthly) serum chemistry panel (at Day 1 and 30 then every 3 months), hematology and urinalysis (at Day 1 then every 3 months), and INR measurement (Day 1, Day 2-12 then monthly).

7.2.5 Metabolic, Clearance, and Interaction Workup

Edoxaban is the active moiety and is the predominant circulating drug-related moiety. In healthy volunteers, edoxaban is primarily eliminated unchanged in urine (35% of the administered dose and 50% of the absorbed dose) and the bile (49% can be recovered from the feces), with a minor contribution (<10%) of metabolism via CYP3A4 towards the total clearance of edoxaban.

Edoxaban is metabolized via hydrolysis (mediated by carboxylesterase 1), conjugation or oxidation by CYP3A4. Three of the metabolites [D21-2393 (M-4), D21-2135 (M-8), and D21-1402 (M-6)] are pharmacologically active with anticoagulant activity similar to that of edoxaban.

Edoxaban is a substrate of the efflux transporter P-gp, drug interaction studies were conducted with several P-gp inhibitors; many of these drugs are also inhibitors of

CYP3A4. A 50% dose reduction is recommended if edoxaban is coadministered with quinidine, ketoconazole, verapamil, erthomycine, cyclosporine or dronedarone. No dose reduction is recommended for edoxaban when co-administered with atorvastatin or esomeprazole.

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

Gastrointestinal and vaginal bleeding: In a recent meta-analysis of the six contemporary randomized clinical trial results using the new oral anticoagulants (NOAC) other than edoxaban: 2 direct thrombin-inhibitors and 4 Factor Xa inhibitors trials, gastrointestinal bleeding was more prominent in the NOAC group vs. warfarin (HR for NOAC: 1.30, 95% CI: 0.97, 1.73)[(1)]. A sex-based meta-analysis also recently documented that bleeding complications occur more frequently in women receiving new oral anticoagulants for VTE than men [(2)].

Liver injury: Hepatotoxicity safety concern has been associated with oral anticoagulant.

7.3 Major Safety Results

The incidence rates of treatment emergent adverse events (TEAEs) that occurred during the on-treatment study period (includes during study drug administration or during the first three days after a study drug temporary interrupted or permanent discontinued), were comparable between the treatment groups. TEAEs were reported in 69% of subjects in the edoxaban group and 71% of the warfarin group. However, the rate of drug related TEAEs occurred in edoxaban group (14%) was lower than that in warfarin group (21%).

The percentage of subjects with treatment-emergent serious adverse events (TESAEs) was comparable between the edoxaban group and warfarin group (12% vs. 13%, respectively). The TESAEs that were associated with a fatal outcome were 68 (1.7%) in the edoxaban group vs. 61 (1.5%) in the warfarin group.

The rate of TEAEs that led to interruption of study drug was lower in the edoxaban group (7%) than warfarin group (11%).

TEAEs that caused permanent discontinuation of study drug were comparable between the edoxaban and warfarin groups (4.7% and 4.5%, respectively).

TEAEs that occurred during on-treatment and overall study period are summarized in Table 21.

Table 21: Treatment Emergent Adverse Events, Safety Analysis Set – On-Treatment and Overall Study Period

	Edoxaban N=4118	**Warfarin N=4122**
On-Treatment Period		
Subjects with at least one TEAE, n (%)	2821 (69)	2928 (71)
Drug-Related, n (%)	583 (14)	856 (21)
Severe adverse event, n (%)	289 (7)	295 (7)
Serious adverse events (TESAE), n (%)	503 (12)	544 (13)
Drug-Related, n (%)	27 (0.7)	101 (2.5)
Fatal TESAEs, n (%)	68 (1.7)	61 (1.5)
TEAEs led to Interruption of study drug, n (%)	295 (7)	467 (11)
Drug-Related, n (%)	60 (1.5)	229 (5.6)
TESAEs, n (%)	155 (3.8)	215 (5.2)
TEAEs led to permanent discontinuation, n (%)	195 (4.7)	185 (4.5)
Drug-Related, n (%)	41 (1.0)	51 (1.2)
TESAEs, n (%)	121 (2.9)	105 (2.5)
Overall Study Period		
Subjects with at least one TEAE, n (%)	2951 (72)	3041 (74)
Drug-Related, n (%)	592 (14)	865 (21)
Severe adverse event, n (%)	390 (10)	384 (9)
Serious adverse events (TESAE), n (%)	654 (16)	678 (16)
Drug-Related, n (%)	28 (1)	102 (3)
Fatal TESAEs, n (%)	119 (3)	107 (3)

Source: NDA submission, Module 5.3.5.1, Table 12.17, P 148.

Reviewer comments: There was higher incidence of SAEs related to the study drug among the warfarin group (2.5%) than in the edoxaban group (0.7%) mainly due to high incidence of increased INR in the warfarin group (1.7% in warfarin vs <0.1% in edoxaban).

7.3.1 Deaths

All deaths occurring during the study were adjudicated by the independent CEC.

The analysis of all-cause mortality for the Overall Study Period (OSP) suggested that the number and percentage of death was slightly higher in edoxaban arm compared to warfarin arm. There were 136 (3.3%) deaths reported in the edoxaban arm compared to 130 (3.2%) deaths reported in the warfarin arm. However, the percentage of VTE related death was similar between the two arms (0.7%).

The cardiovascular deaths observed in the edoxaban group were comparable to that in the warfarin group (0.4% and 0.3%, respectively). However, the number of deaths due to ischemic stroke was double in edoxaban arm (6 patients) of that occurred in warfarin arm (3 patients).

Cancer deaths were 51 (1.2%) in the edoxaban group vs. 59 (1.4%) in the warfarin group.

Deaths attributable to infectious disease were more pronounced in the edoxaban group than in the warfarin group (0.6% and 0.3%, respectively). The infectious disease deaths were due mostly to "typical infections" for this subject population such as pneumonia, sepsis, and septic shock.

Adjudicated primary cause of death reported during overall study period is summarized in Table 22.

Table 22: Adjudicated Primary Cause of Death– OSP- Safety Analysis Set

Cause of Death	Edoxaban N=4118	Warfarin N=4122
All-cause Mortality, n (%)	136 (3.3)	130 (3.2)
VTE-Related Death, n (%)	27 (0.7)	28 (0.7)
PE, n (%)	4 (<0.1)	3 (<0.1)
Unexplained Death and VTE can't be r/o, n (%)	23 (0.6)	25 (0.6)
Cardiovascular Death, n (%)	15 (0.4)	13 (0.3)
MI, n (%)	2 (<0.1)	2 (<0.1)
Ischemic stroke, n (%)	6 (0.1)	3 (<0.1)
Other Cardiac Death, n (%)	7 (0.2)	8 (0.2)
Other Known Cause, n (%)	94 (2.3)	89 (2.2)
Cancer, n (%)	51 (1.2)	59 (1.4)
Bleeding (including Hemorrhagic Stroke), n (%)	6 (0.1)	10 (0.2)
Infectious Disease, n (%)	25 (0.6)	12 (0.3)
Other, n (%)	12 (0.3)	8 (0.2)

Source: NDA submission, Module 5.3.5.1, Table 12.21, P155

The analysis of all-cause mortality for the On-treatment study period suggested that the number and percentage of death was comparable between the two groups. There were 35 (0.8%) deaths reported in the edoxaban group and 33 (0.8%) deaths reported in the warfarin group. However, there was a numerical increase in the VTE-related mortality in the edoxaban arm compared to the warfarin arm. The difference in mortality between the edoxaban arm and the warfarin arm was due to cardiovascular-related death (ischemic stroke) and infection disease-related death (7 and 6 in the edoxaban vs. 4 and 3, in the warfarin, respectively). Mortality due to bleeding was reported in 5 patients in the warfarin arm compared to 2 patients in the edoxaban arm.

Adjudicated primary cause of death that occurred during on-treatment study period is summarized in Table 23.

Table 23: Adjudicated Primary Cause of Death, Safety Analysis Set – On-Treatment Study Period

Cause of Death	Edoxaban N=4118	Warfarin N=4122
All-cause Mortality, n (%)	35 (0.8)	33 (0.8)
VTE-Related Death, n (%)	13 (0.3)	10 (0.2)
PE, n (%)	2 (<0.1)	0 (0.0)
Unexplained Death (VTE can't r/out), n (%)	11 (0.3)	10 (0.2)
Cardiovascular Death, n (%)	6 (0.1)	3 (<0.1)
MI, n (%)	1 (<0.1)	2 (<0.1)
Ischemic stroke, n (%)	2 (<0.1)	0 (0.0)
SEE, n (%)	0 (0.0)	0 (0.0)
Other Cardiac Death[a], n (%)	3 (<0.1)	1 (<0.1)
Other Known Cause, n (%)	16 (0.4)	20 (0.5)
Cancer, n (%)	4 (<0.1)	7 (0.2)
Bleeding (including hemorrhagic stroke), n (%)	3 (<0.1)	5 (0.1)
Infections Disease, n (%)	7 (0.2)	4 (<0.1)
Other, n (%)	3 (<0.1)	4 (<0.1)

[a] Other cardiac deaths were postoperative tamponade, heart failure, ruptured aortic aneurysm (edoxaban) and arrhythmia (warfarin).

Source: NDA submission, Module 5.3.5.1, Table 12.20, P. 153.

Treatment-emergent adverse events with fatal outcome by system organ class and preferred term in the safety population during on-treatment period are summarized in Table 24.

Table 24: Treatment-Emergent Adverse Events with Fatal Outcome – by SOC and Preferred Term, Safety Analysis Set – On-Treatment Period

SOC/Preferred Term with 2 or more Subjects with AE with Fatal Outcome	**Edoxaban N=4118**	**Warfarin N=4122**
Infections and infestations, n (%)	17 (0.4)	8 (0.2)
Sepsis	5 (0.1)	3 (<0.1)
Pneumonia	3 (<0.1)	0 (0.0)
Septic shock	3 (<0.1)	2 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	31 (0.8)	40 (1.0)
Metastases to liver	4 (<0.1)	0 (0.0)
Lung neoplasm malignant	2 (<0.1)	2 (<0.1)
Metastases to central nervous system	2 (<0.1)	0 (0.0)
Pancreatic carcinoma	2 (<0.1)	4 (<0.1)
Prostate cancer	2 (<0.1)	1 (<0.1)
Uterine cancer	2 (<0.1)	0 (0.0)
Adenocarcinoma	1 (<0.1)	2 (<0.1)
Bladder cancer	1 (<0.1)	2 (<0.1)
Pancreatic carcinoma metastatic	1 (<0.1)	2 (<0.1)
Cervix cancer metastatic	0 (0.0)	3 (<0.1)
Lung adenocarcinoma	0 (0.0)	2 (<0.1)
Metastatic malignant melanoma	0 (0.0)	2 (<0.1)
Cardiac disorders, n (%)	6 (0.1)	2 (<0.1)
Cardiac arrest	2 (<0.1)	0 (0.0)
Cardiac failure	0 (0.0)	2 (<0.1)
Respiratory, thoracic and mediastinal disorders, n (%)	7 (0.2)	2 (<0.1)
Acute respiratory distress syndrome	2 (<0.1)	0 (0.0)
Acute respiratory failure	2 (<0.1)	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)	2 (<0.1)
General disorders and administration site, n (%)	4 (<0.1)	6 (0.1)
Death	4 (<0.1)	4 (<0.1)

Source: NDA submission, Module 5.3.5.1, Table 12.22, P. 156.

Reviewer comments: The safety analysis of adjudicated death occurring during treatment +3 days period suggested that the rate of the death was comparable between the two arms. However, there were numerical increases in VTE-related, cardiovascular-related and infectious disease related mortality in the edoxaban arm.

7.3.2 Nonfatal Serious Adverse Events

Hokusai VTE Trial:

There were 503 subjects in the edoxaban group and 544 subjects in the warfarin group who had treatment emergent serious adverse events (TESAE) during the on-treatment period. The rate of serious adverse events reported in the edoxaban and warfarin group were comparable (12.2% and13.2%, respectively). However, the rates of reported infectious disease TESAEs were higher in edoxaban group then warfarin group (2.6% and 2%) with pneumonia, bronchitis and sepsis were the most common.

Most frequently reported TESAEs by SOC among the edoxaban group during the on-treatment period were infections and infestations (2.6%), benign neoplasms, malignant and unspecified SOC (1.9%), respiratory, thoracic and mediastinal disorders (1.4%), Injury, poisoning and procedural complications (1.2%), and cardiac disorders (1.1%).

Table 25: Treatment-Emergent Serious Adverse Events by SOC and Preferred Term Reported by at Least 0.2% Subjects, Safety Analysis Set – On-Treatment Period

SOC/Preferred Term	**Edoxaban N=4118**	**Warfarin N=4122**
Subjects with at least one TESAE, n (%)	503 (12.2%)	544 (13.2%)
Infections and infestations, n (%)	108 (2.6)	84 (2.0)
Pneumonia, n (%)	30 (0.7)	17 (0.4)
Bronchitis, n (%)	8 (0.2)	1 (<0.1)
Urinary tract infection, n (%)	8 (0.2)	6 (0.1)
Sepsis, n (%)	7 (0.2)	4 (<0.1)
Cellulitis, n (%)	5 (0.1)	11 (0.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps), n (%)	80 (1.9)	99 (2.4)
Colon cancer, n (%)	2 (<0.1)	7 (0.2)
Blood and lymphatic system disorders, n (%)	12 (0.3)	18 (0.4)
Anemia, n (%)	3 (<0.1)	10 (0.2)
Nervous system disorders, n (%)	39 (0.9)	25 (0.6)
Syncope, n (%)	8 (0.2)	3 (<0.1)
Cardiac disorders, n (%)	45 (1.1)	38 (0.9)
Cardiac failure, n (%)	8 (0.2)	6 (0.1)
Cardiac failure congestive, n (%)	4 (<0.1)	8 (0.2)
Respiratory, thoracic and Mediastinal disorders, n (%)	58 (1.4)	52 (1.3)
Dyspnea, n (%)	14 (0.3)	5 (0.1)
Chronic obstructive pulmonary disease, n (%)	8 (0.2)	12 (0.3)
General disorders and administration site, n	38 (0.9)	37 (0.9)
Chest pain, n (%)	14 (0.3)	9 (0.2)
Non-cardiac chest pain, n (%)	7 (0.2)	5 (0.1)
Psychiatric disorders, n (%)	8 (0.2)	15 (0.4)
Vascular disorders, n (%)	24 (0.6)	14 (0.3)
Gastrointestinal disorders, n (%)	39 (0.9)	24 (0.6)
Hepatobiliary disorders, n (%)	14 (0.3)	16 (0.4)
Skin and subcutaneous tissue disorders, n (%)	12 (0.3)	6 (0.1)
Musculoskeletal and connective tissue, n (%)	29 (0.7)	30 (0.7)
Renal and urinary disorders, n (%)	27 (0.7)	20 (0.5)
Investigations, n (%)	17 (0.4)	88 (2.1)
International normalized ratio increased, n (%)	4 (0.1)	77 (1.9)
Injury, poisoning and procedural, n (%)	49 (1.2)	59 (1.4)

Source: NDA submission, Module 5.3.5.1, Table 12.23, P.158

Reviewer comments: The rate of reported serious adverse events during treatment +3 were comparable between the two groups. Note that approximately 2% of warfarin group reported TESAE of increased INR.

7.3.3 Dropouts and/or Discontinuations

In the analysis of the Hokusai VTE trial, the percentage of subjects who discontinued study drug for any reason was comparable between the edoxaban and warfarin groups (17%).
The incidence of adverse events that lead to premature discontinuation was 368 (8.8%) in the edoxaban arm and 367 (8.9%) in the warfarin arm. Comparable percentage of subjects in each arm discontinued treatment due to either suspected VTE, bleeding or other treatment emergent adverse events. However, the number of subjects who discontinued treatment due to death was higher in the edoxaban arm (53 vs 41 deaths).

Permanent discontinuations of study drug are summarized in Table 26.

Table 26: Permanent Discontinuations of Study Drug, Safety Analysis Set

	Edoxaban (N=4118)	**Warfarin (N=4122)**
Subjects Completing Study Drug Treatment, n (%)	3423 (83.1)	3404 (82.6)
All subjects permanently discontinue study drug, n (%)	695 (16.9)	718 (17.4)
Subjects discontinue study drug due to AEs, n (%)	364 (8.8)	367 (8.9)
Suspected endpoint, n (%)	138 (3.4)	158 (3.8)
Death, n (%)	53 (1.3)	41 (0.8)
Bleeding, n (%)	58 (1.4)	57 (1.4)
Other TEAEs, n (%)	115 (2.8)	111 (2.7)
Discontinue due to elective surgery, n (%)	17 (0.4)	18 (0.4)
Concomitant use of prohibited medication, n (%)	4 (<0.1)	2 (<0.1)
Subject Withdrew Consent, n (%)	21 (0.5)	22 (0.5)
Subject Lost to Follow-up, n (%)	2 (<0.1)	3 (<0.1)
Pregnancy, n (%)	8 (0.2)	4 (<0.1)
Protocol Violation, n (%)	22 (0.5)	22 (0.5)
Other*, n (%)	255 (6.2)	279 (6.8)

* Most common reason was subject preference n= 435 (81.5% of Other)
Source: NDA submission, Module 5.3.5.1, Table 12.4, P 127.

Reviewer comments: The frequency of adverse events that led to drug discontinuation of study drug was similar in the edoxaban group (8.8%) and in the warfarin group (8.9%).

The percentage of study drug discontinuations was similar between the edoxaban and warfarin treatment arms when comparing subjects in the 30 mg dose edoxaban and edoxaban placebo (warfarin) groups (26.3% and 24.3%, respectively). However, the percentage of subjects who discontinued study drug in the 30 mg group was almost twice as much as for those in the 60 mg group, 26.3% and 14.8%, respectively. Note

that the percentage of subjects who discontinued warfarin with 30 mg placebo edoxaban was also higher than for those who received warfarin with 60 mg placebo edoxaban, 24.3% vs. 16%, respectively.

Permanent discontinuations of study drug by dose are summarized in Table 27.

Table 27: Study Drug Discontinuations by Edoxaban Dose, Safety Analysis Set

	Active Edoxaban		Active Warfarin	
Number of Subjects	Edoxaban 30 mg N=733	Edoxaban 60 mg N=3385	Edoxaban Placebo 30 mg N=719	Edoxaban Placebo 60 mg N=3403
Completed Study Treatment, n (%)	540 (73.7)	2883 (85.2)	544 (75.7)	2860 (84.0)
Subjects Permanently Discontinue, n (%)	193 (26.3)	502 (14.8)	175 (24.3)	543 (16.0)
Reason For Permanent Discontinuation				
Suspected Endpoint/Adverse Event	107 (14.6)	257 (7.6)	88 (12.2)	279 (8.2)
Suspected Endpoint, n (%)	33 (4.5)	105 (3.1)	35 (4.9)	123 (3.6)
Adverse Event, n (%)	77 (10.5)	156 (4.6)	56 (7.8)	166 (4.9)
Elective Surgery, n (%)	5 (0.7)	12 (0.4)	4 (0.6)	14 (0.4)
Concomitant Use of Prohibited Study Medication, n (%)	2 (0.3)	2 (<0.1)	1 (0.1)	1 (<0.1)
Subject Withdrew Consent, n (%)	7 (1.0)	14 (0.4)	5 (0.7)	17 (0.5)
Subject Lost to Follow-up, n (%)	1 (0.1)	1 (<0.1)	0 (0.0)	3 (<0.1)
Pregnancy, n (%)	1 (0.1)	7 (0.2)	0 (0.0)	4 (0.1)
Protocol Violation, n (%)	5 (0.7)	17 (0.5)	5 (0.7)	17 (0.5)
Other*, n (%)	64 (8.7)	191 (5.6)	71 (9.9)	208 (6.1)

* Most common reason was subject preference n= 435 (81.5% of Other)

Source: NDA submission, Module 5.3.5.1, Table 12.5, P 128.

7.3.4 Significant Adverse Events

The primary composite safety endpoint of major bleeding and clinically relevant non-major bleeding occurred in 349 (8.5%) subjects in the edoxaban arm and 423 (10.3%) subjects in the warfarin arm. Edoxaban was superior to warfarin for the primary safety composite endpoints with HR of 0.81 for the edoxaban group vs. the warfarin group (95% CI: 0.71, 0.94) with the p value of <0.004 for superiority.

However, the analysis of major bleeding, which was reported in 56 subjects (1.4%) in the edoxaban arm and 66 subjects (1.6%) in the warfarin arm, failed to show statistical differences between the two arms p-value = 0.35.

There was a numerical increase in bleeding related fatality in the warfarin treated group (10 fatal bleeding cases reported in warfarin vs 3 fatal bleeding cases reported in edoxaban arm).

The primary safety analysis of adjudicated bleeding events is summarized in Table 30.

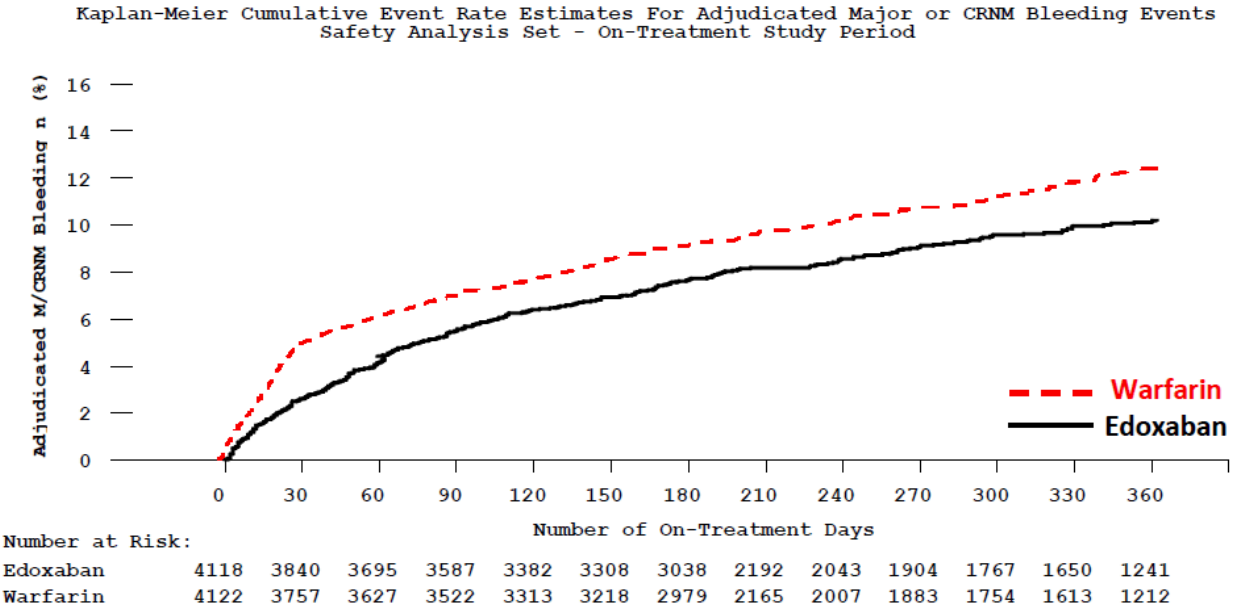
Table 28: Primary Safety Analysis of Adjudicated Bleeding Events, (Safety Analysis) On-Treatment

Adjudicated Bleeding	**Edoxaban N= 4118**	**Warfarin N= 4122**
Major/CRNM Bleeding, n (%)	349 (8.5)	423 (10.3)
HR Edoxaban vs. Warfarin (95% CI) p-value	0.81 (0.71, 0.94) P value= 0.004	
- Major Bleeding, n (%)	56 (1.4)	66 (1.6)
HR Edoxaban vs. Warfarin (95% CI) p-value	0.84 (0.59, 1.21) P value= 0.35	
Fatal, n (%)	3 (0.1)	10 (0.3)
- CRNM Bleeding, n (%)	298 (7.2)	368 (8.9)
Nuisance Bleeding, n (%)	663 (16.1)	787 (19.1)
All bleeding events, n (%)	895 (21.7)	1056 (25.6)

Source: NDA submission, Module 5.3.5.1, Table 12.6, P.130

Cumulative Kaplan-Meier event rate estimates for major plus CRNM bleeding shows that edoxaban group had lower events rate than warfarin group Figure 6.

Figure 6: Kaplan-Meier Cumulative Event Rate Estimates for Primary Safety Endpoint (Adjudicated Major/CRNM Bleeding), Safety Analysis Set – On-Treatment Study Period



Source: NDA submission, Module 5.3.5.1, Figure 12.1, P.131

The primary safety outcome was the composite of major and clinically relevant non-major bleeding events. Additional safety outcomes were all deaths and other cardiovascular events (i.e., ischemic stroke, TIA, non-central nervous system systemic embolism, cardiovascular death, acute coronary syndromes [MI, unstable angina]).

Major bleeding events were comprised of fatal bleeding events, non-fatal critical organ bleeding events and non-fatal non-critical organ bleeding events.

Major Adverse Cardiovascular Events (MACE)

The analysis of the composite adjudicated endpoint of MACE which includes non-fatal myocardial infarction (MI), non-fatal stroke, non-fatal systemic embolic events (SEE), and cardiovascular death revealed a numerically higher rate of the events in the edoxaban group 49 (1.2%) than in the warfarin group 40 (1%).

However the differences in rate of MACE incidence was statistically insignificant with p-value = 0.35. The main reason for imbalances of MACE incidence was due to a higher rate of MI event and rate of cardiovascular related death among subjects treated with edoxaban.

The composite endpoint of MACE (non-fatal MI, non-fatal stroke, non-fatal SEE, and Cardiovascular Death) are summarized in the Table 29.

Table 29: Summary of Adjudicated MACE, Safety Analysis Set – On-Treatment Study Period

	Edoxaban N=4118	**Warfarin N=4122**
Subjects with MACE Events, n (%)	49 (1.2)	40 (1.0)
Edoxaban vs. Warfarin HR (95%CI) P value	1.22 (0.80, 1.85) P= 0.35	
- Myocardial infarction, n (%)	20 (0.5)	13 (0.3)
Edoxaban vs. Warfarin HR (95%CI)	1.54 (0.76, 3.08)	
Fatal MI	1 (<0.1)	2 (<0.1)
- Stroke, n (%)	26 (0.6)	26 (0.6)
Fatal Ischemic Stroke, n (%)	2 (<0.1)	0 (0.0)
- SEE (systemic embolic events), n (%)	4 (<0.1)	0 (0.0)
Cardiovascular Death*, n (%)	6 (0.1)	3 (<0.1)

* Includes total of fatal MI, ischemic stroke, SEE and other cardiac deaths.
Source: NDA submission, Module 5.3.5.1, Table 12.15, P.146.

7.3.5 Submission Specific Primary Safety Concerns

In addition to bleeding events of special interest in Hokusai-VTE trial included cardiovascular events and liver-related events.

Bleeding:

All reported bleeding events were adjudicated and served as the basis of the all safety bleeding analyses. The on-treatment Study Period represented the primary period for all safety analyses, including bleeding.

The primary composite safety endpoint of major bleeding and clinically relevant non-major bleeding occurred in 349 (8.5%) subjects in the edoxaban arm and 423 (10.3%) subjects in the warfarin arm. Edoxaban was superior to edoxaban for the primary safety composite endpoints with HR of 0.81 for the edoxaban group vs. the warfarin group (95% CI: 0.71, 0.94) with the p value of <0.004 for superiority.

However, the analysis of major bleeding which reported in 56 subjects (1.4%) in the edoxaban arm and 66 subjects (1.6%) in the warfarin arm, failed to show statistical differences between the two arms p-value = 0.35.

There was numerically less bleeding related fatality among edoxaban treated group (3 fatal bleeding cases reported in edoxaban vs 10 fatal bleeding cases reported in warfarin arm).

The primary safety analysis of adjudicated bleeding events is summarized in Table 30.

Table 30: Primary Safety Analysis of Adjudicated Bleeding Events, (Safety Analysis) On-Treatment

Adjudicated Bleeding	**Edoxaban N= 4118**	**Warfarin N= 4122**
Major/CRNM Bleeding, n (%)	349 (8.5)	423 (10.3)
HR Edoxaban vs. Warfarin (95% CI) p-value	0.81 (0.71, 0.94) P value= 0.004	
- Major Bleeding, n (%)	56 (1.4)	66 (1.6)
HR Edoxaban vs. Warfarin (95% CI) p-value	0.84 (0.59, 1.21) P value= 0.35	
Fatal, n (%)	3 (0.1)	10 (0.3)
- CRNM Bleeding, n (%)	298 (7.2)	368 (8.9)
Nuisance Bleeding, n (%)	663 (16.1)	787 (19.1)
All bleeding events, n (%)	895 (21.7)	1056 (25.6)

Source: NDA submission, Module 5.3.5.1, Table 12.6, P.130

In subgroup analysis comparing the primary safety endpoint of the rate of major bleeding and clinically relevant non major bleeding, between subjects who received an edoxaban dose of 30 mg versus those who received it at a dose of 60 mg, the results suggested that the safety of the two dosing regimens are comparable. Major/CRNM bleeding in the 30 mg edoxaban group was 7.9% vs. 8.6% in the 60 mg edoxaban group. Major bleeding in subjects received 30 mg of edoxaban was 1.5% and 1.3% in subjects who received 60 mg edoxaban.

Table 31: Adjudicated Bleeding Events by Edoxaban Dose at Randomization, Safety Analysis Set – On-Treatment Study Period

	Active Edoxaban		Active Warfarin	
	Edoxaban 30 mg N=733	Edoxaban 60 mg N=3385	Placebo 30 mg N=719	Placebo 60 mg N=3403
All Bleeding, n (%)	154 (21.0)	741 (21.9)	215 (29.9)	841 (24.7)
Major/CRNM Bleeding, n (%)	58 (7.9)	291 (8.6)	92 (12.8)	331 (9.7)
Major Bleeding, n (%)	11 (1.5)	45 (1.3)	22 (3.1)	44 (1.3)
Fatal bleeding, n (%)	1 (0.1)	1 (<0.1)	4 (0.6)	6 (0.2)
CRNM Bleeding, n (%)	47 (6.4)	251 (7.4)	76 (10.6)	292 (8.6)
Nuisance Bleeding, n (%)	117 (16.0)	546 (16.1)	162 (22.5)	625 (18.4)

Source: NDA submission, Module 5.3.5.1, Table 12.7 P. 132.

There were 349 subjects (8.5%) in the edoxaban group and 423 subjects (10.3%) in the warfarin group who had an overt (major or CRNM) bleeding during the on-treatment period of the study. Fatal bleeding was reported in three edoxaban subjects (< 0.1%) and 10 of warfarin subjects (0.2%). Overt bleeding associated with fall in hemoglobin ≥ 2 g/dL occurred in 40 (1.0%) of the edoxaban treated subjects vs. 33 (0.8%) of the warfarin treated subjects. Two of the edoxaban subjects and 6 of the warfarin subjects had bleeding with hemodynamic compromise. Overt bleeding required transfusions ≥ 2 units occurred in 28 (0.7%) of the edoxaban treated subjects vs. 22 (0.5%) warfarin treated subjects.

Table 32: Adjudicated Major or CRNM Bleeding Event Characteristics, Safety Analysis Set – On-Treatment Study Period

Adjudicated Major or CRNM Bleeding	**Edoxaban N=4118**	**Warfarin N=4122**
Clinically Overt	349 (8.5)	423 (10.3)
Fatal Bleeding	3 (<0.1)	10 (0.2)
Fall in Hemoglobin ≥2 g/dL	40 (1.0)	33 (0.8)
Transfusions ≥2 units	28 (0.7)	22 (0.5)
Hemodynamic Compromise	1 (<0.1)	6 (0.1)
Requiring Surgery	3 (<0.1)	2 (<0.1)

Source: NDA submission, Module 5.3.5.1, Table 12.8 CSR, P.133

Major/CRNM bleeding by location:
Analysis of adjudicated major/CRNM bleeding by location during on-treatment period suggested higher or similar rate of the events among warfarin treatment group compared to edoxaban treatment group with the exception of vaginal bleeding which was numerically higher among edoxaban treatment group.

Major Bleeding by Location: The analysis of major bleeding suggested higher incidence of GI and vaginal major bleeding events and lower incidence of intracranial hemorrhage (ICH) and fatal bleeding in the edoxaban arm.

Fatal bleeding occurred in 2 subjects in the edoxaban arm (one fatal case of GI bleed and one fatal case of intramuscular bleed) vs in 10 subjects in the warfarin arm (six fatal cases of intracranial hemorrhage, two fatal cases of GI bleed, one intramuscular bleed and one fatal case of retroperitoneal).

In the edoxaban treatment group, major intracranial bleeding events occurred in 5 subjects with no fatality vs. 18 subjects with 6 fatalities in the warfarin arm. In addition at all other sites the major bleeding events were numerically less or the same number compared with the warfarin treatment group except for the following: GI tract and vaginal bleeding occurred more frequently in the edoxaban arm.

GI tract major bleeding events were 27 (0.7%) with one resulting in fatality in the edoxaban group vs. 18 (0.4%) with two resulting in fatality in the warfarin group. Vaginal major bleeding events were 9 (0.5%) in the edoxaban group vs. 3 (0.2%) in the warfarin group. Upper GI major bleeding and lower GI major bleeding reported in 16 and 11 subjects in the edoxaban compared to 12 and 6 subjects in the warfarin arm, respectively.

Adjudicated Major/CRNM bleeding events by location are summarized in Table 33.

Table 33: Adjudicated Major/CRNM Bleeding Events by Location, Safety Analysis Set – On-Treatment Study Period

	Edoxaban N=4118	Warfarin N=4122
Adjudicated Major/CRNM Bleed, n (%)	349 (8.5)	423 (10.3)
Gastrointestinal Tract, n (%)	98 (2.4)	94 (2.3)
Vaginal, n (%)	81 (4.6)	56 (3.2)
Macroscopic Hematuria/Urethral, n (%)	76 (1.8)	109 (2.6)
Cutaneous Soft Tissue, n (%)	32 (0.8)	77 (1.9)
Epistaxis, n (%)	45 (1.1)	37 (0.9)
Oral/Pharyngeal, n (%)	11 (0.3)	20 (0.5)
Intracranial Hemorrhage, n (%)	5 (0.1)	18 (0.4)
Intramuscular, n (%)	4 (<0.1)	10 (0.2)
Intra-Articular	4 (<0.1)	4 (<0.1)
Intraocular	1 (<0.1)	4 (<0.1)
Conjunctiva/Scleral	1 (<0.1)	8 (0.2)
Other, n (%)	11 (0.3)	22 (0.5)
Adjudicated Major Bleed, n (%)	56 (1.4)	66 (1.6)
ICH, n (%)	5 (0.1)	18 (0.4)
Fatal, n (%)	0 (0.0)	6 (0.1)
Retroperitoneal, n (%)	0 (0.0)	4 (<0.1)
Fatal, (%)	0 (0.0)	1 (<0.1)
Pericardial, n (%)	1 (<0.1)	1 (<0.1)
Intraocular, n (%)	1 (<0.1)	4 (<0.1)
Intra-Articular, n (%)	4 (<0.1)	4 (<0.1)
Gastrointestinal Tract, n (%)	27 (0.7)	18 (0.4)
Fatal, (%)	1 (<0.1)	2 (<0.1)
Vaginal, n (%)	9 (0.5)	3 (0.2)
Intramuscular, n (%)	2 (<0.1)	4 (<0.1)
Fatal, n (%)	1 (<0.1)	1 (<0.1)
Other, n (%)	2 (<0.1)	0 (0.0)

Source: NDA submission, Module 5.3.5.1, Table 12.9, P. 134-136.

The most common bleeding adverse reactions reported in at least 1% of subjects during on treatment period in edoxaban and warfarin were vaginal hemorrhage (9.0% vs. 7.1%), cutaneous soft tissue hemorrhage (5.9% vs. 10%), epistaxis (4.7% vs. 5.7%) oral/pharyngeal hemorrhage (3.4% vs. 3.9%), lower gastrointestinal hemorrhage (3.4% vs. 3.1%), macroscopic hematuria/urethral (2.2% vs. 2.8%), and puncture site hemorrhage (1.4% vs. 2.4%), respectively.

Table 34: Adjudicated Bleeding Events in ≥ 1% of Subjects by Location, Safety Analysis Set - On-Treatment Study Period

	Edoxaban N=4118	Warfarin N=4122
Adjudicated all bleeding events, n (%)	895 (21.7)	1056 (25.6)
Gastrointestinal Tract, n (%)	171 (4.2)	150 (3.6)
Vaginal, n/M* (%)	158 (9.0)	126 (7.1)
Macroscopic Hematuria/Urethral, n (%)	91 (2.2)	117 (2.8)
Cutaneous Soft Tissue, n (%)	245 (5.9)	414 (10)
Puncture site, n (%)	56 (1.4)	91 (2.4)
Epistaxis, n (%)	195 (4.7)	237 (5.7)
Oral/Pharyngeal, n (%)	138 (3.4)	162 (3.9)
Conjunctiva/scleral, n (%)	29 (0.7)	62 (1.5)

*M is number of female (M=1758 in edoxaban and M= 1766 in warfarin)
Source: NDA submission, Module 5.3.5.1, Table 14.3.1.10, P391.

Subgroup Analysis by Index PE or DVT

Out of a total of 8240 subjects randomized in the trial, 3319 subjects presented with PE (with or without DVT) and 4921 presented with DVT only. Of subjects who presented with an index PE 1650, (49.7%) were randomized to the edoxaban group and 1669 (50.3%) were randomized to the warfarin group. Of subjects presented with an index DVT only, 2468 (59.7%) were randomized to the edoxaban group and 2453 (49.8%) were randomized to warfarin group.

The results from subgroup analyses by presenting diagnosis of PE or DVT of adjudicated major/CRNM bleeding occurred during on treatment period revealed that the rate of major bleeding or CRNM bleeding was lower in the edoxaban group (10.1 in subjects with PE and 7.4 % in subjects with DVT) than in the warfarin group (11.2 in subjects with PE and 9.6 % in subjects with DVT).

Table 35: Adjudicated Major/CRNM Bleeding by Index PE or DVT, On-Treatment Period, Safety Analysis Set

Adjudicated Major or CRNM Bleeding	Edoxaban	Warfarin
Index PE with/without DVT	1650	1669
Subject with major bleeding, (%)	166 (10.1)	187 (11.2)
Edoxaban vs. Warfarin, HR (95% CI)	0.88 (0.711, 1.079)	
Index DVT only	2468	2453
Subject with major bleeding, (%)	183 (7.4)	236 (9.6)
Edoxaban vs. Warfarin, HR (95% CI)	0.76 (0.629, 0.926)	

Source: NDA submission, Module 5.3.5.1, Table 12.11, P.140.

Subgroup analysis by edoxaban dose at randomization:
At randomization, subjects with low body weight (≤60kg), moderate renal impairment

(CrCL 30 to 50 ml/min), and/or pre-specified concomitant P-gp inhibitors received both active edoxaban 30 mg and placebo warfarin (n =733), or placebo edoxaban 30 mg and active warfarin (n =719).

In subgroup analysis comparing the rate of major bleeding and clinically relevant non major bleeding between subjects who received edoxaban dose of 30 mg versus those who received it at dose of 60 mg, the results suggested that the safety of the two dosing regimens are comparable (7.9% vs 8.6%). The incidences of clinically overt bleeding (major and CRNM) in subjects who received 30 mg or 60 mg of edoxaban were less than that in warfarin group.

Summary of the subgroup analysis by edoxaban dose are summarized in Table 36.

Table 36: Subgroup Analysis by Edoxaban Dose at Randomization, (Safety Analysis) On-Treatment

	Active Edoxaban		**Active Warfarin**	
	Edoxaban 30 mg N=733	Edoxaban 60 mg N=3385	Placebo 30 mg N=719	Placebo 60 mg N=3403
All Bleeding, n (%)	154 (21.0)	741 (21.9)	215 (29.9)	841 (24.7)
Fatal, n (%)	1 (0.1)	1 (<0.1)	4 (0.6)	6 (0.2)
Major/CRNM Bleeding, n (%)	58 (7.9)	291 (8.6)	92 (12.8)	331 (9.7)
Major Bleeding, n (%)	11 (1.5)	45 (1.3)	22 (3.1)	44 (1.3)
CRNM Bleeding, n (%)	47 (6.4)	251 (7.4)	76 (10.6)	292 (8.6)
Nuisance Bleeding, n (%)	117 (16.0)	546 (16.1)	162 (22.5)	625 (18.4)

Source: NDA submission, Module 5.3.5.1, Table 12.7, P 132.

Liver-related Events:

The analysis of suspected hepatic events that occurred during On-treatment Period suggested that the percentage of patients with hepatic events was similar between the two arms, (8.6% in each arm). The number and percentage of patients with liver injury event confirmed by the independent CEC hepatic adjudication were low, 62 patients (1.5%) in the edoxaban arm and 52 patients (1.3%) in the warfarin arm. Two thirds of cases were classified as mild in severity in both arms. Severe cases of confirmed liver injury were reported in 10/62 (16%) of subjects in the edoxaban arm and 8/52 (15%) in the warfarin arm.

The incidence of the event of serum aminotransferase elevations (ALT or AST ≥3 times of upper limits of normal [ULN] and ≥5xULN) was comparable in edoxaban and warfarin groups (2.6% vs 2.4%, respectively).

The incidence of events of total bilirubin level (TBL) elevations of ≥2xULN was numerically higher in the edoxaban group than in the warfarin groups (1.1% vs 0.6%, respectively).

The incidence of potentially more serious liver injury with whole-organ dysfunction, as shown by serum bilirubin elevations of ≥3xULN, was very low: 9 (0.2%) for edoxaban and 4 (0.1%) for warfarin.

Liver enzyme and bilirubin abnormality data from the start of randomization are summarized in Table 37.

Table 37: Liver Test Abnormalities, Safety Analysis Set – On-Treatment Period

Liver enzyme and bilirubin abnormalities that occurred at least one day after the first dose of edoxaban or edoxaban placebo	**Edoxaban N=4118**	**Warfarin N=4122**
Subjects with ALT or AST, N	3901	3903
≥3 x ULN	106 (2.7)	100 (2.6)
≥5 x ULN	36 (0.9)	34 (0.9)
≥8 x ULN	14 (0.4)	15 (0.4)
≥10 x ULN	9 (0.2)	5 (0.1)
≥20 x ULN	1 (<0.1)	0 (0.0)
Subjects with TBL, N	3901	3905
≥2 x ULN	41 (1.1)	24 (0.6)
≥3 x ULN	9 (0.2)	4 (0.1)
Subjects with Alkaline Phosphatase (ALP), N	3901	3905
≥2 x ULN	38 (1.0)	48 (1.2)
≥3 x ULN	13 (0.3)	16 (0.4)
Subjects with ALT or AST ≥3 x ULN and TBL ≥2 x ULN	9 (0.2)	4 (0.1)
Subjects with ALT or AST ≥3 x ULN and concurrent TBL ≥2 x ULN	6 (0.2)	3 (<0.1)
Subjects with ALT or AST ≥3 x ULN and concurrent TBL ≥2 x ULN and concurrent ALP ≥2 x ULN	3 (<0.1)	2 (<0.1)
Subjects with ALT or AST ≥3 x ULN and concurrent TBL ≥2 x ULN and concurrent ALP < 2 x ULN	3 (<0.1)	1 (<0.1)

Source: NDA submission, Module 5.3.5.1, Table 14.3.1.105, P 1434.

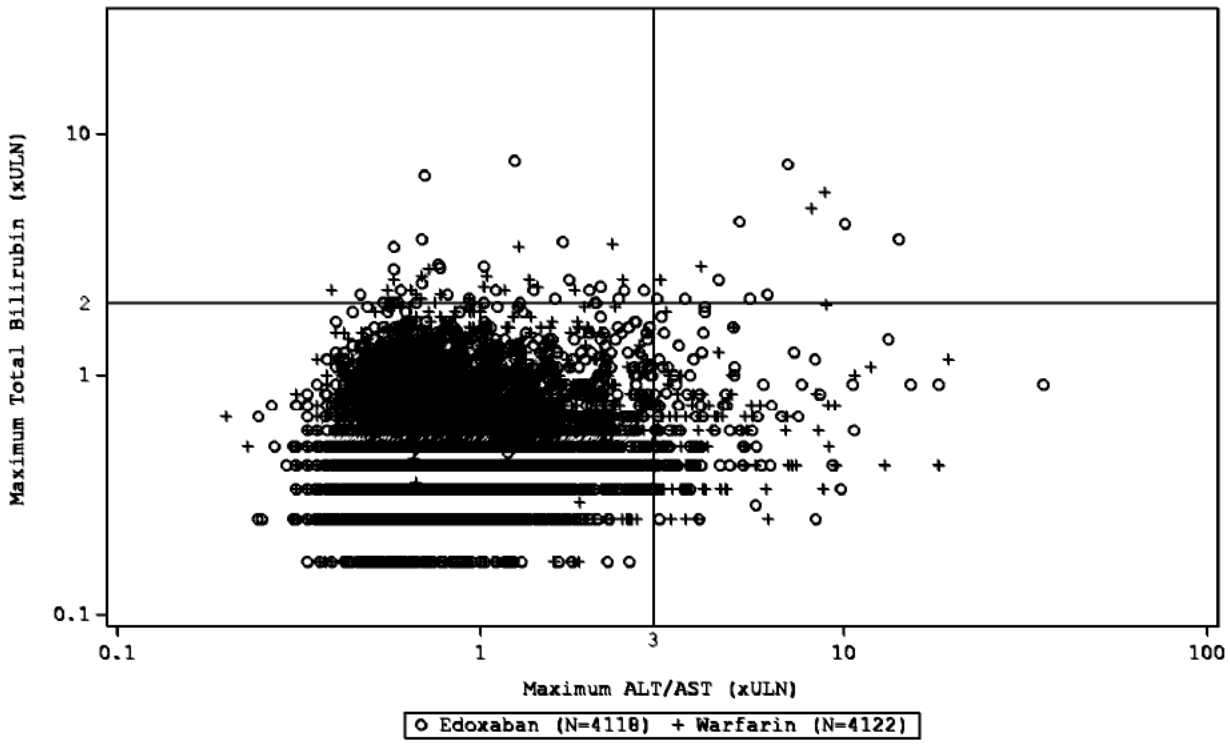
When the cases with both ALT and TBL elevations above 3xULN and 2xULN were evaluated in detail, using the eDISH (drug-induced serious hepatotoxicity) program to inspect the time course of all liver tests (ALT, TBL, AST, ALP) over their entire periods of observation, plus a narrative describing all pertinent clinical factors observed and

recorded, there were no cases found of probable Hy's Law cases of drug-induced hepatocellular jaundice, from either drug treatment.

Shown in Figure 7 below is the scatter plot of the peak ALT and TBL values for each of the randomized subjects, one point for each, in four quadrants as separated by ALT 3xULN and TBL 2xULN. The upper-right quadrant shows only 9 edoxaban and 4 warfarin-treated patients for incidence of about of less than 0.2%. None of the 13 cases identified to had an elevation of AST or AST of ≥3 x ULN concurently with elevation of total bilirubin of ≥2 x ULN concluded to meet the criteria for Hy's law. All cases of potential liver abnormalities had an alternative explanation for liver enzymes elevation were identified (confounder underlying disease) except for one case that occurred in the edoxaban arm where no alternative explanation was found.

The case was for a 65 year-old male who presented with an acute diagnosis of symptomatic proximal DVT of the left leg. Approximately 4 months on treatment his AST (7x ULN) and bili (1.8 direct and 2.6 indirect) were found to be elevated followed with elevation of gamma-glutamyltransferase (GGT) and subject discontinued the study drug. Two months later all liver enzymes returned within normal limits and the subject resumed treatment for anther 5 months without any changes in his liver enzymes.

Figure 7: Scatter Plot of Peak ALT and TBL for Each Randomized Subject, Safety Analysis Set – On-Treatment Period



Note: Includes liver enzyme and bilirubin abnormalities that occurred at least one day after the first dose of edoxaban or edoxaban placebo, and excludes abnormalities during the open-label heparin treatment period.

Source: NDA submission, Module 5.3.5.1, Figure 12.3, P163.

Reviewer comments: Although there were fairly frequent serum aminotransferase (ALT and AST) elevations, there was no notable difference between the incidence in the edoxaban and in the warfarin-treated subjects. None of the edoxaban subject's hepatic events were concluded to be meeting Hy's rule for liver injury.

7.4 Supportive Safety Results

Supportive safety data included all completed clinical studies. However, the main source of the safety data came from than the two pivotal trials (ENGAGE AF-TIMI 48 and Hokusai VTE). Data generated from phase 1 through phase 3 supportive studies (other than the ENGAGE AF-TIMI 48 and Hokusai VTE trials) are grouped and summarized based on each study's objectives, subject population, duration of treatment with study drug, and the indication for which edoxaban was used in that study.

7.4.1 Common Adverse Events

Hokusai-DVT

The rate of TEAEs were comparable between the two arms with more than two thirds of subjects reported at least one adverse events.

The most common TEAEs in the edoxaban treatment group by preferred term were headache (5.8% and 4.9%, edoxaban vs. warfarin, respectively) and nasopharyngitis (5.6% each). The most common TEAE in the warfarin group by Preferred Term was INR increased (0.5% and 8.2%, edoxaban vs. warfarin, respectively).

The most frequently reported TEAEs (those that occurred in at least 2% of subjects by Preferred Term) for the Safety Analysis Set On-Treatment Period is summarized in Table 38.

Table 38: The most frequently reported TEAEs (occurred in at least 2% of subjects by Preferred Term) for the Safety Analysis Set On-Treatment Period

SOC/Preferred Term	**Edoxaban N=4118**	**Warfarin N=4122**
Subjects With at Least One TEAE	2821 (68.5)	2928 (71)
Infections and infestations, n (%)	1049 (25.5)	1076 (26.1)
Nasopharyngitis, n (%)	230 (5.6)	231 (5.6)
Urinary tract infection, n (%)	165 (4.0)	149 (3.6)
Bronchitis, n (%)	113 (2.7)	90 (2.2)
Influenza, n (%)	101 (2.5)	91 (2.2)
Upper respiratory tract infection, n (%)	85 (2.1)	93 (2.3)
Psychiatric disorders, n (%)	218 (5.3)	172 (4.2)
Insomnia, n (%)	83 (2.0)	66 (1.6)
Nervous system disorders, n (%)	518 (12.6)	478 (11.6)
Headache, n (%)	240 (5.8)	201 (4.9)
Dizziness, n (%)	113 (2.7)	124 (3.0)
Vascular disorders, n (%)	262 (6.4)	305 (7.4)
Hypertension, n (%)	110 (2.7)	121 (2.9)
Respiratory, thoracic and mediastinal, n (%)	496 (12.0)	468 (11.4)
Cough, n (%)	127 (3.1)	109 (2.6)
Epistaxis, n (%)	195 (4.7)	237 (5.7)
Dyspnea, n (%)	112 (2.7)	92 (2.2)
Gastrointestinal disorders, n (%)	763 (18.5)	746 (18.1)
Diarrhea, n (%)	159 (3.9)	170 (4.1)
Constipation, n (%)	119 (2.9)	111 (2.7)
Nausea, n (%)	112 (2.7)	103 (2.5)
Skin and subcutaneous tissue disorders, n (%)	417 (10.1)	388 (9.4)
Cutaneous soft tissue hemorrhage, n (%)	245 (5.9)	414 (10.0)
Rash, n (%)	85 (2.1)	89 (2.2)
Musculoskeletal and connective tissue, n (%)	699 (17.0)	714 (17.3)
Pain in extremity, n (%)	203 (4.9)	190 (4.6)
Back pain, n (%)	134 (3.3)	154 (3.7)
Arthralgia, n (%)	114 (2.8)	104 (2.5)
General disorders and administration site, n (%)	523 (12.7)	569 (13.8)
Edema peripheral, n (%)	141 (3.4)	170 (4.1)
Puncture Site bleeding, n (%)	56 (1.4)	99 (2.4)
Chest pain, n (%)	92 (2.2)	108 (2.6)
Pyrexia, n (%)	87 (2.1)	70 (1.7)
Macroscopic Hematuria/Urethral	91 (2.2)	117 (2.8)
Investigations, n (%)	588 (14.3)	861 (20.9)
Hepatic enzyme increased, n (%)	118 (2.9)	118 (2.9)
Blood creatine phosphokinase increased, n (%)	66 (1.6)	86 (2.1)
International normalized ratio increased, n (%)	21 (0.5)	336 (8.2)

Source: NDA submission, Module 5.3.5.1, Table, 12.18, P. 150

Reviewer Comments: The incidence of TEAEs occurred during on treatment period were similar between the two arms.

ENGAGE AF-TIMI 48

The trial was a multi-national, double-blind study comparing the efficacy and safety of edoxaban 60 mg and edoxaban 30 mg to warfarin (titrated to INR 2.0 to 3.0) to reduce the risk of stroke and systemic embolic events in patients with nonvalvular atrial fibrillation.

A total of 21,105 patients were randomized in 1:1:1 ratio to edoxaban 30 mg, edoxaban 60 mg and warfarin. Subjects were followed on study treatment for a median of 2.8 years. Subjects in all 3 treatment groups had a median age of 72 years.

The most frequent TEAEs that were reported by subjects were urinary tract infections (9.8%, 10.0%, and 10.0%, respectively), nasopharyngitis (8.8%, 9.2%, and 8.8%, respectively), bronchitis (8.1%, 8.3%, and 8.2%, respectively), dizziness (7.3%, 7.7%, and 8.4%, respectively), and peripheral edema (8.2%, 8.3%, and 9.6%, respectively).

Table 39 summarizes the most frequently reported TEAEs (in at least 5% of subjects in any treatment group) for the Safety Analysis Set On-Treatment period

Table 39: Treatment-Emergent Adverse Events Reported by at Least 5% of Subjects by SOC and Preferred Term, Safety Analysis Set – On-Treatment Period (ENGAGE AF-TIMI 48)

System Organ Class/Preferred Term	Edoxaban 30mg (15mg DosAdj) (N=7002) n (%)	Edoxaban 60mg (30mg DosAdj) (N=7012) n (%)	Warfarin (N=7012) n (%)
Infections and Infestations	3129 (44.7)	3126 (44.6)	3142 (44.8)
Urinary Tract Infection	698 (10.0)	688 (9.8)	703 (10.0)
Nasopharyngitis	645 (9.2)	620 (8.8)	620 (8.8)
Bronchitis	584 (8.3)	567 (8.1)	572 (8.2)
Upper Respiratory Tract Infection	443 (6.3)	411 (5.9)	445 (6.3)
Blood And Lymphatic System Disorders	486 (6.9)	632 (9.0)	475 (6.8)
Anemia	261 (3.7)	368 (5.2)	242 (3.5)
Nervous System Disorders	1484 (21.2)	1454 (20.7)	1481 (21.1)
Dizziness	537 (7.7)	514 (7.3)	592 (8.4)
Headache	356 (5.1)	334 (4.8)	336 (4.8)
Cardiac Disorders	1759 (25.1)	1711 (24.4)	1784 (25.4)
Atrial Fibrillation	528 (7.5)	474 (6.8)	491 (7.0)
Cardiac Failure	373 (5.3)	425 (6.1)	448 (6.4)
Vascular Disorders	990 (14.1)	985 (14.0)	992 (14.1)
Hypertension	475 (6.8)	481 (6.9)	438 (6.2)
Respiratory, Thoracic And Mediastinal Disorders	1370 (19.6)	1382 (19.7)	1395 (19.9)
Dyspnea	434 (6.2)	456 (6.5)	470 (6.7)
Cough	416 (5.9)	383 (5.5)	365 (5.2)
Gastrointestinal Disorders	1934 (27.6)	2005 (28.6)	1947 (27.8)
Diarrhea	486 (6.9)	482 (6.9)	499 (7.1)
Musculoskeletal and Connective Tissue Disorders	1826 (26.1)	1790 (25.5)	1843 (26.3)
Back Pain	496 (7.1)	476 (6.8)	478 (6.8)
Arthralgia	417 (6.0)	385 (5.5)	386 (5.5)
General Disorders and Administration Site Conditions	1490 (21.3)	1476 (21.0)	1589 (22.7)
Edema Peripheral	578 (8.3)	577 (8.2)	675 (9.6)
Injury, Poisoning and Procedural Complications	1259 (18.0)	1216 (17.3)	1410 (20.1)
Fall	452 (6.5)	453 (6.5)	565 (8.1)

Source: NDA submission, Module 2.7, summary of clinical safety, P.57.

Reviewer Comments: Generally TEAEs were similar for edoxaban and warfarin treated subjects.

For further details of the safety in ENGAGE AF TIMI trial refer to DCRP review.

Controlled Phase 2 AF Studies:
A total of 1917 subjects were randomized in the 3 controlled Phase 2 AF studies, PRT018, C-J225 and C-J226, and 1896 subjects were treated with study drug. Of these, 1022 subjects were treated with an edoxaban QD regimen, 424 with an edoxaban BID regimen, and 450 with warfarin. The primary objective of these studies was to evaluate the safety of various dose regimens of edoxaban, compared with that of warfarin, in subjects with non-valvular AF. The duration of treatment was 12 weeks.

Treatment emergent adverse events in the controlled phase 2 AF studies:
Edoxaban QD vs Warfarin: The most common TEAEs (those with an incidence of ≥2%) in the edoxaban QD group vs warfarin were blood urine present (8.6% vs 5.3%), nasopharyngitis (6.7% vs 5.1%), epistaxis (4.9% vs 3.3%), γ-glutamyltransferase (GGT) increased (3.1% vs 1.6%), AST increased (2.9% vs 0.7%), ALT increased (2.8% vs 0.9%), headache (2.6% vs 1.3%), hematuria (2.4% vs 3.1%), gingival bleeding (2.3% vs 1.1%), subcutaneous hemorrhage (2.1% vs 1.3%), dizziness (2.0% vs 0.7%) and glucose urine present (2.0% vs 1.8%).

Edoxaban BID vs Warfarin: The most common TEAEs (incidence of ≥2%) in both the edoxaban 30 mg BID and 60 mg BID groups in Study PRT018 were hematuria (2.9% and 6.1%, respectively, vs 1.6% in the warfarin group), epistaxis (2.0% and 3.9% vs 2.4%), and gingival bleeding (2.0% and 2.2%, respectively, vs 0 in the warfarin group).

Reviewer comments: The 30 to 60 mg BID regimens were associated with increased incidences of Clinically Relevant Non-Major and Minor Bleeding, and with higher incidences of discontinuation due to TEAEs.

Phase 2 and phase 3 VTE prophylaxis studies in subjects undergoing orthopedic surgery:

The 6 controlled studies evaluated edoxaban QD regimens with doses ranged from 5 mg up to 90 mg. Study PRT007 was uncontrolled study in this subject population that also included edoxaban BID regimens with a dose range from 15 mg to 60 mg BID or dose escalating from 30 mg up to 120 mg QD. A total of 3722 subjects were randomized in these studies; 3678 subjects were treated with edoxaban or control drug. These studies were similar in study design, length of exposure (7 to 14 days) and subject population. The safety data of all subjects receiving edoxaban QD regimens in the 6 controlled and 1 uncontrolled study were pooled.

The most common TEAEs overall in the edoxaban Total QD group (incidence of ≥3%) were γ-glutamyltransferase (GGT) increased (6.3% vs 22.1% in the enoxaparin group), ALT increased (4.9% vs 33.4%), procedural pain (4.8% vs 0%), hematuria (3.5% vs 2.2%), nausea (3.3% vs 0.7%), pyrexia (3.2% vs 1.7%), blood lactate dehydrogenase increased (3.1% vs 3.0%), AST increased (3.0% vs 27.5%) and constipation (3.0% vs 0.5%).

The combined incidences of hematuria and blood urine present were similar between the edoxaban Total QD and enoxaparin groups (5.2% vs 5.0%).

Reviewer comments: The safety analysis from the phase 2 and 3 trials in patients undergone orthopedic surgery with short term exposure to edoxaban (two weeks) suggested that the risk of bleeding associated with edoxaban was comparable to that of enoxaparin in that setting. Consistent with Hokusai VTE results.

Phase I Studies:
Safety data from the following trials where analyzed as a group:

- Healthy volunteers (N=1201): Pooled safety data of the healthy volunteers from the integrated Phase 1 studies, including healthy volunteers from the special population studies A-U120 and A-E134;
- Subjects (N=32) with renal impairment from Study A-U120;
- Subjects (N=17) with hepatic impairment from Study A-E134;
- Subjects (N=10) with end-stage renal disease (undergoing hemodialysis) from Study A-U146;

Subjects in Phase 1 studies received single doses of edoxaban from 10 to 180 mg or multiple daily doses of 60, 90, or 120 mg. A total of 866 healthy subjects received edoxaban single dose treatments. A total of 335 healthy subjects received edoxaban multiple dose treatment for up to 14 days. The maximum period of study drug administration was 14 days.

Common TEAEs (≥1%) in edoxaban-treated healthy subjects were headache (7%), dizziness (4%), and nausea (3%). Two of the common TEAEs were bleeding-related: occult blood positive (2%) and gingival bleeding (1%).

The most common TEAEs (>10%) in the 32 renally impaired subjects were international normalized ratio (INR) increased (34%), prothrombin time prolonged (31%), and activated partial thromboplastin time prolonged (22%).

Headache and vomiting (1 subject, 6% each) were the only TEAEs in the 17 hepatically impaired subjects. Laboratory analyses of liver enzymes and TBL did not result in any concerns about potential drug-induced liver injury.

Reviewer Comments: The analyses of the phase 1 trials in healthy and renal and hepatic impaired subjects suggested that short term exposure to edoxaban was associated mainly with headache, nausea, positive occult blood and gingival bleeding. Consistent with Hokusai VTE results.

7.4.2 Laboratory Findings

The following laboratory tests were monitored during the trial, liver function test (AST, ALT, bilirubin, alkaline phosphatase), renal function test (creatinine, creatinine clearance, protein in urinalysis, and blood in urinalysis) and hematological test (platelets, leukocytes, hematocrit, hemoglobin) and creatine kinase and clinical chemistry (glucose and cholesterol).

The analysis for ALT and AST suggested that, there was an elevation in the Day 2-12 sample reflecting the blood sample obtained following (LMW) heparin treatment prior to the start of the edoxaban study drug (active or placebo edoxaban).

For the edoxaban subjects: The mean/median of ALT was 24.8 IU/L / 20.0 IU/L (at baseline), 75.5 IU/L / 52.0 IU/L (Day 2 to 12 visit), and 24.3 IU/L / 20.0 IU/L (Day 30 visit). The mean/median of AST was 49.8 IU/L / 42.0 IU/L (at baseline), 57.7 IU/L / 43.0 IU/L (Day 2 to 12 visit), and 28.1 IU/L / 23.0 IU/L (Day 30 visit).

For warfarin subjects: The mean/median of ALT was 25.9 IU/L / 20.0 IU/L (at baseline), 71.1 IU/L / 51.0 IU/L (Day 2 to 12 visit) and 24.6 IU/L / 21.0 IU/L (Day 30 visit). The mean/median of AST was 52.3 IU/L / 41.0 IU/L (at baseline), 50.6 IU/L / 41.0 IU/L (Day 2 to 12 visit) and 27.2 IU/L / 24.0 IU/L (Day 30 visit).

Similarly, among subjects entering into the study with elevated ALT or AST at baseline, with the exception of Day 2 to 12 sample, the mean and median changes over time for ALT and AST were similar for the two treatment groups with drifting of the mean/median to lower than at baseline.

Of edoxaban subjects with a normal baseline ALT, 84.4% had a normal value at last assessment and 5.2% had a high value at last assessment. Of warfarin subjects with a baseline normal ALT value, 83.7% had a normal value at last assessment and 4.8% had a high value at last assessment. Similar findings were seen for subjects with a normal baseline AST value in both treatment groups.

The analyses for hemoglobin and hematocrit showed that the mean/median values at baseline to last visit were similar between the 2 groups. For the edoxaban subjects:

The mean/median hemoglobin was 133.1 g/L /135.0 g/L (at baseline) and 137.8 g/L /139.0 g/L (at last assessment). For warfarin subjects: The mean/median Hemoglobin was 133.2 g/L /135.0 g/L (at baseline) and 139.0 g/L /140.0 g/L (at last assessment).

The mean/median for hematocrit at baseline was 40.1%/41.0% for edoxaban subjects and 40.1%/40.0% for warfarin subjects. The hematocrit mean/median at last assessment was 41.9%/42.0% for edoxaban subjects and 42.2%/42.0% for warfarin subjects.

The hematocrit value at baseline was normal in 72.1% of edoxaban subjects and 73.2% in the warfarin subjects. The percentage of subjects who had a normal hematocrit value at their last assessment was 73.3% in the edoxaban group and 73.4% in the warfarin group. However, 6.5% of edoxaban subjects vs. 4.9% of warfarin subjects with a normal baseline hematocrit had a low Hematocrit as their worst assessment. In addition, 4.1% of edoxaban subjects vs. 2.9% of warfarin subjects went from a normal baseline hematocrit to a low hematocrit value at last assessment.

The analyses for CrCL, mean/median values at baseline to last visit were similar between the two groups.

For edoxaban subjects: mean/median CrCL was 105.23 mL/min/100.50 mL/min (at baseline) and 102.10 mL/min/98.30 mL/min (at last assessment). For warfarin subjects: mean/median CrCL was 104.90 mL/min/100.90 mL/min (at baseline) and 102.29 mL/min/98.35 mL/min (at last assessment).

7.4.3 Vital Signs

The changes from baseline by visit in vital signs (systolic blood pressure, diastolic blood pressure, pulse, and weight) for the Safety Analysis Set during On-Treatment Study Period were submitted and reviewed. The changes in vital signs were comparable among the treatment groups.

Reviewer comments: Review of the vital signs changes during the treatment suggested that the changes were small and similar between the edoxaban and warfarin group.

7.4.4 Electrocardiograms (ECGs)

During the Hokusai-DVT trial a twelve-lead electrocardiogram (ECG) data was collected Day 1, Day 30, and at the follow-up visit. The analysis of the shifts (defined as changes from normal, abnormal/not clinically significant, and abnormal/clinically significant at baseline to normal, abnormal/not clinically significant, and abnormal/clinically significant post baseline) suggested that the shifts in ECGs were comparable between the treatment groups.

Edoxaban therapeutic and supratherapeutic plasma exposures effects on QTc interval was assessed in Study PRT021. The trial was a phase 1, randomized, single-dose,

placebo and active controlled four-period crossover in healthy male and female subjects.

A total of 64 healthy subjects between the ages of 18 to 45 were enrolled and received the following treatments on 4 different occasions:

A. DU-176b single oral 90 mg dose
B. DU-176b single oral 180 mg dose
C. Placebo
D. Moxifloxacin single oral 400 mg dose used as positive control

The duration of subject treatment (from first to last dose) was approximately 26 days.

The results suggested that both single clinical (90 mg) and supra-therapeutic (180 mg) doses of edoxaban had no clinically relevant (>10 msec increase) effect on individually corrected QT interval (QTcI) in this thorough QTc study.

For more details refer to clinical pharmacology review.

7.4.5 Special Safety Studies/Clinical Trials

This section is not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The incidences of any bleeding, major bleeding, CRNM bleeding or nuisance bleeding were similar in the subjects who received 30 mg or 60 mg of edoxaban in the Hokusai-VTE trial.

There was no dose dependency for bleeding seen in Hokusai-VTE trial (Table 31).

7.5.2 Time Dependency for Adverse Events

The incidence of major/CRNM bleeding reported during 30 days following completing treatment was 0.8% in the edoxaban arm vs 0.4% in the warfarin arm in the Hokusai-VTE trial. Also, the incidence of drug related treatment emergent adverse events reported during 30 days following completing treatment was similar between the two groups (0.1%).

7.5.3 Drug-Demographic Interactions

The incidence of clinically relevant bleeding (major/NMCR bleeding) was less in male patients compared to female patients in the edoxaban arm (6.1% in male vs 11.7% in female).

There were a total of 1104 subjects (17.3%) were ≥ 75 years old in Hokusai-VTE trial, 715 in the edoxaban group and 706 in the warfarin group. Of the 1421 subjects ≥ 75 years old, 424 (38.4%) received 30 mg edoxaban (208 in the active edoxaban group, and 216 in the edoxaban placebo [active warfarin] group). Major/CRNM bleeding was observed in 70 (12.5%) of the edoxaban subjects compared to 82 (15.1%) of the warfarin subjects for a relative reduction in risk of 18% (HR: 0.82; 95% CI: 0.59, 1.12). Of the 1104 subjects ≥ 75 years, 424 (38.4%) received 30 mg edoxaban (208 in the active edoxaban group, and 216 in the edoxaban placebo [active warfarin] group).

The incidences of major/CRNM bleeding were comparable among regions and were comparable between the two arms of the study.

Reviewer comment: In the Hokusai-VTE trial, the bleeding incidence between the two arms based on age and region suggested no clinically significant differences. There was less bleeding incidence in male compared to female mainly due to vaginal bleeding in female patients in the Hokusai-VTE trial.

7.5.4 Drug-Disease Interactions

The subgroup analysis on patients with moderate renal impairment with CrCL between 30-50 mL/min at randomization, major/CRNM bleeding was observed in 28/268 (10.4%) of edoxaban subjects compared to 321/3850 (8.3%) observed in subjects with CrCL >50 mL/min.

In the analysis of subgroup on patients with medical history of cancer at randomization, major/CRNM bleeding was observed in 47/378 (12.4%) of edoxaban subjects with a cancer history compared to 74/393 (18.8%) of warfarin subjects with a cancer history for a relative reduction in risk of 36% (HR: 0.64; 95% CI: 0.45, 0.92).

Within the population of subjects reporting history of cancer at randomization, 208 subjects (2.5%) also reported the cancer as active at the time of randomization. In this active cancer at randomization group, 20/109 (18.3%) edoxaban subjects had Major/CRNM bleeding vs. 25/99 (25.3%) in the warfarin group for a relative reduction in risk of 28% (HR: 0.72; 95% CI: 0.40, 1.30).

Reviewer comment: In the Hokusai-VTE trial, there was a higher bleeding incidence in subjects with moderate renal impairment than those with mild or normal renal function. The results of the analysis of major/CRNM bleeding in patients with medical history of cancer and those who have active cancer at

randomization suggested that no clinical significant differences in the incidence of bleeding between edoxaban group and warfarin group in the Hokusai-VTE trial.

7.5.5 Drug-Drug Interactions

In Hokusai-VTE trial concomitant use of low dose ≤100 mg/day aspirin with edoxaban resulted in increased incidence of major/CRNM bleeding compared to those who did not use aspirin (15% vs 8%, respectively). Also concomitant use of antiplatelet (excluding aspirin) with edoxaban resulted in increased incidence of major/CRNM bleeding compared to those who did not use antiplatelet (18% vs 8%, respectively).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to Pharmacology/Toxicology review.

7.6.2 Human Reproduction and Pregnancy Data

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.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant submitted an initial Pediatric Study Plan (PSP) to DHP on 6/4/2013. On 10/31/2013 DHP issued a letter to the sponsor confirming DHP agreement to the submitted Agreed-Upon Initial PSP.

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

The proposed pediatric studies include the following:

- (b) (4)
- 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 (b) (4) The trial will enroll (b) (4) pediatric patients with documented VTE. The objective of the trial is (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In Hokusai-VTE there were 41 cases of overdose reported as an adverse events, 17 (0.4) cases in the edoxaban and 24 (0.6) in the warfarin. From the 17 reported cases in the edoxaban arm were assessed by the investigator to be considered 14 mild, 2 moderate and 1 severe. None of the overdoses cases were associated with another adverse event or bleeding event.

Edoxaban does not enhance thrombin generation in vitro and aggravate coagulation status in a rat model of hypercoagulation [3, 4]. These findings suggest that edoxaban has a low risk of the activation of coagulation pathway and potentially a low risk of relevant rebound effect.

Study PRT009, in which healthy subjects received edoxaban 60 mg BID for 4 days, showed no evidence of hypercoagulation or rebound as assessed by biomarkers.

7.7 Additional Submissions / Safety Issues

The applicant submitted the 120-day safety update on April 17, 2014. The submission contained safety data at a cutoff date of 31 Dec 2013 from the following:

1) Phase 2 ongoing clinical studies D-U211 (eTRIS) and E-U210 (ePAD),
    a. eTRIS a randomized, open label, multi-center study designed to investigate the efficacy and safety of edoxaban 90 mg once daily (QD) for 10 days, followed by edoxaban 60 mg QD for 3 months, in the treatment of acute, symptomatic DVT, compared with LMW heparin/warfarin. As of 13DEC2013, there were 56 in the edoxaban group and 28 in the LMWH/warfarin group.
    b. ePAD a randomized, open label, active control, multi-center study designed to assess the safety and potential efficacy of edoxaban 60 mg QD plus aspirin (100 mg QD) given for 3 months, in comparison with clopidogrel (75 mg QD) plus aspirin, in subjects with symptomatic peripheral arterial disease (PAD) who have undergone successful femoropopliteal endovascular intervention (with or without stent placement). As of 13DEC2013, there were 47 in the edoxaban group and 47 in the clopidogrel groups.
2) Phase 1 completed (A-U154) and ongoing (A-E155, A-U158, PER977-01-001, A-A144) studies
3) Post-marketing data for LIXIANA®, 4) other safety information from ENGAGE AF-TIMI 48 trial, pregnancy updates from Hokusai VTE and Literature search for publications related to edoxaban.

Death

There were 2 deaths reported during the safety update period from 01 Jun 2013 to 31 Dec 2013. One fatal case from hemorrhagic stroke was treated with the edoxaban/aspirin (ePAD) and other fatal case from subdural hematoma was treated with warfarin/heparin (eTRIS). Both deaths were adjudicated in a blinded manner by CEC as not related to edoxaban.

Serious Adverse Events:

A total of 23 subjects had SAEs. Of these, SAEs reported among 6 subjects in E-U210 (ePAD) were considered to be related to the study drug by the Investigator (vascular pseudoaneurysm in 2 subjects, hematuria, epistaxis, retroperitoneal hematoma, and post procedural hematoma in 1 subject each).

Adverse Events led to study drug discontinuation:

A total of 11 subjects discontinued treatment due to AEs. Adverse events leading to permanent discontinuations that were considered drug related by the Investigators were hepatic enzyme increased, vascular pseudoaneurysm, epistaxis, and prolonged menstruation.

Bleeding Events in eTRIS and ePAD:
There were 13 cases of bleeding including one major bleeding reported in the edoxaban group in both trials.

Reviewer comments: The 120-day Safety Update data were consistent with that of the safety data reported in the NDA.

8 Postmarket Experience

Edoxaban was approved in Japan on 22 Apr 2011 for the prevention of VTE following total knee arthroplasty (TKA), total hip arthroplasty (THA), and hip fracture surgery (HFS), and it was launched in Japan as LIXIANA® on 19 Jul 2011.

Adverse events reported between the launch and 30 Sep 2013 were collected from post-marketing data sources such as spontaneous reports including regulatory authority and literature as well as Drug Use Survey.

Exposure Status:

- Data from Drug Use Survey (LIX-011-011) was collected from 247 sites participated in the enrollment. A total of 2419 patients completed the survey up to 31 Jan 2013.
- Spontaneous Reports: The sales figures provided are distribution data of when LIXIANA® was shipped from Daiichi Sankyo to distributors. The figure between the launch and September 2013 was used. Assuming a dosing period per patient of 14 days regardless of strength, the number of patients who were exposed to LIXIANA® is estimated to be approximately (b) (4) An approximately (b) (4) additional patients were estimated to be treated during the reporting period from 01 Oct 2013 through 31 Dec 2013 (120 days safety update).

A total of 1065 AEs were reported in 837 patients from approximately total of (b) (4) patients exposed to the edoxaban. The most frequent AEs occurred in the system organ class were: Vascular disorders (157 cases), followed by Investigations (139 cases), Skin and subcutaneous tissue disorders (164 cases), and Injury, poisoning and procedural complications (121 cases). Hemorrhage subcutaneous (146 cases) was the

most frequent adverse event, followed by Deep vein thrombosis (93 cases), Hepatic function abnormal (76 cases), Hemorrhage (61 cases), and Hemoglobin decreased (59 cases).

A total of 105 SAEs were reported in 82 patients. Subcutaneous hemorrhage (11 cases) was the most frequent SAE, followed by hemorrhage (8 cases), pulmonary embolism (6 cases), wound hemorrhage (6 cases), anemia (5 cases), and post procedural hemorrhage (5 cases).

During postmarketing, overdose was reported in 11 patients with varying dosage (maximum reported was 90 mg per day) and duration (maximum reported was 3 days), of which only one reported an associated adverse event and in 10 cases reported as not associated with adverse events. In a case, a 77 year old man receiving post-operative LIXIANA® 45 mg/day for an unknown number of days reported non-serious subcutaneous hemorrhage, vomiting, and rash. Concomitant therapy also included loxoprofen and heparin. The events resolved after LIXIANA® was discontinued and the patient was switched to warfarin.

Three fatal cases were reported: 2 cases of aspiration pneumonia and 1 case of acute myocardial infarction. In all cases, the patients were enrolled in the Drug Use Survey and died after discontinuation of LIXIANA® for 9, 17 or 27 days, respectively. All cases were assessed as not related to LIXIANA® by the reporter.

There were no actions taken or label changes by the Regulatory Authority or the Manufacturer for LIXIANA® for safety or other reasons since launch.

9.1 Literature Review/References

1. Adam SS, McDuffie JR, Ortel TL, Williams JWJCINAIMA, Pmid. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. Ann Intern Med. 2012;157(11):796-807.
2. Alotaibi GS, Almodaimegh H, McMurtry MS, Wu C. Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? A sex-based metaanalysis. Thromb Res. 0049;2013 Jul 26:doi 10.
3. Furugohri T, Fukuda T, Tsuji N, Kita A, Morishima Y, Shibano T. Melagatran, a direct thrombin inhibitor, but not edoxaban, a direct factor Xa inhibitor, nor heparin aggravates tissue factor-induced hypercoagulation in rats. Eur J Pharmacol. 2012;686(1-3):74-80.
4. Furugohri T, Sugiyama N, Morishima Y, Shibano T. Antithrombin-independent thrombin inhibitors, but not direct factor Xa inhibitors, enhance thrombin generation in plasma through inhibition of thrombin-thrombomodulin-protein C system. Thromb Haemost. 2011;106(6):1076-83.

9.2 Labeling Recommendations

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)

9.3 Advisory Committee Meeting

No advisory committee was convened to review this application.

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SALEH AYACHE
09/08/2014

KATHY M ROBIE SUH
09/08/2014

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SALEH AYACHE
09/09/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 206316 **Applicant: Daiichi Sankyo, Inc.** **Stamp Date: January 8, 2014**

Drug Name: Savaysa ™ (edoxaban) **NDA Type: NME**

On initial overview of the NDA/BLA application for filing: Note: The NDA submission includes two indications. This review addresses the indications "for the treatment of venous thromboembolism (VTE) including deep vein thrombus (DVT) and pulmonary embolism (PE) (b) (4) For the indication "to reduce risk of stroke in patients with non-valvular atrial fibrillation," see review by the Division of Cardiovascular and Renal Products.

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD/STDM submission
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: DU176b-PRT018 Study Title: A Phase 2, randomized, parallel group, multi-center, multi-national study for the evaluation of safety of four fixed dose regimens of DU-176b in subjects with non-valvular atrial fibrillation		X		No dose ranging study was done in patients with VTE.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 1146 subjects Arms: Five arms trial (30mg QD, 30mgBID, 60mg QD, 60mg BID, warfarin QD adjusted) Location in submission: Module 5.3.5.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: **D-U305 (Hokusai VTE)** Study title: A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multi-Center, Multi-National Study for the Evaluation of Efficacy and Safety of (LMW) Heparin/Edoxaban Versus (LMW) Heparin/Warfarin in Subjects With Symptomatic Deep-Vein Thrombosis and/or Pulmonary Embolism. Sample Size: 8292 Arms: double-blind, active controlled trial Location in submission: Module 5.3.5.1 Indication: for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and (b) (4)	X			Only a single pivotal study was submitted for the desired indications.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Study DU176b-PRT021 assessed the effect of edoxaban single doses on QTc (completed November 2007).
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			See DCRP for atrial fibrillation indication. Although anticoagulation is not commonly used for lifelong treatment for VTE, long-term treatment of several months is common and repeated treatment courses occur. Therefore, safety data for chronic use is relevant to the VTE indication.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The initial Pediatric Study Plan (PSP) agreed on October 11, 2013
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	applicability of foreign data in the submission to the U.S. population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				See statistics
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				See statistics
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				See statistics
34.	Are all datasets to support the critical safety analyses available and complete?				See statistics
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				See statistics
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
The following information has been requested from the Applicant:

Provide an abbreviated data analysis of primary endpoint by geographic region for your Hokusai VTE Study.

Provide a rationale for assuming the applicability of foreign data in the submission to the U.S. population for treatment of VTE.

Saleh Ayache, MD

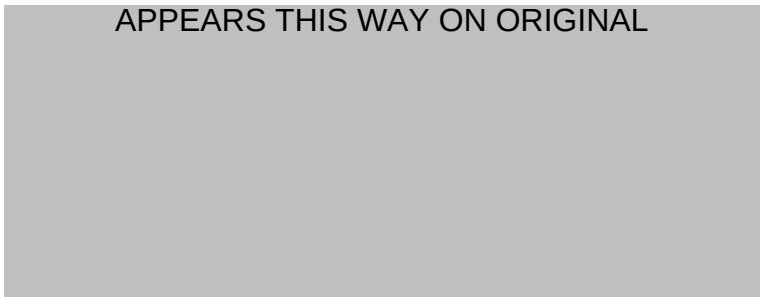
Reviewing Medical Officer Date

Kathy Robie-Sue, M.D, PhD

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement



File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement

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SALEH AYACHE
02/19/2014

KATHY M ROBIE SUH
02/19/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206316 **Applicant: Daiichi-Sankyo** **Stamp Date: 1/8/2014**

Drug Name: Edoxaban (Savaysa™) **NDA/BLA Type: 1**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD/STDM submission
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			It takes long time to load xml data define file for the pivotal trial. The Sponsor submitted a pdf define file upon our request.
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?				
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: PRT018; Study Title: A Phase 2, Randomized, parallel group, multi-center, multi-national study for the evaluation of safety of four fixed dose regimens of DU-176b in subjects with non-valvular atrial fibrillation Sample Size: 1146; Arms: 5-- E 30 mg OD, E 30 mg BID, E 60 mg OD, E 60 mg BID, Warfarin OD titrated to INR 2 to 3 Location in submission: Mod. 5.3.5.1 Study Number: U301; Study Title: ENGAGE AF	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 21,105 Arms: 3-- E 60 mg OD, E 30 mg OD, Warfarin OD titrated to INR 2 to 3 Location in submission: Mod. 5.3.5.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 U301 - ENGAGE AF Indication: Reduction in the risk of stroke and SE in patients with nonvalvular A Fib	X			This was the only Phase 3 trial for the A Fib indication
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			TQT study was submitted: PRT021
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			The Sponsor had submitted information about 4 post-marketing cases indicating liver disorder or abnormal liver function (2 serious and 2 non-serious) upon our request
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Bleeding and hepatic events were evaluated
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			The Sponsor submitted the requested datasets. However, the adjudication dataset ADJINV.xpt is incomplete
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?		X		It is noted that the detail bleeding dataset requested by FDA in the pre-NDA meeting does not contain all the requested elements
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms		X		The Division

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	in a legible format (deaths, serious adverse events, and adverse dropouts)?				requested CRFs for death, discontinuation due to AEs, withdrawals due to AEs, SAEs and adjudicated events in the ENGAGE AF-TIMI 48 study. For events that had more than one adjudication, the Sponsor did not submit all the adjudication forms.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?		X		The FD submission was incomplete. We contacted the Sponsor, and they have agreed to submit all the information that is required. We expect the documents to arrive in a few days.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? NO

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

1. For many of the events with more than on adjudication, the submitted adjudication package did not include all the adjudication forms and results.
2. For events that were adjudicated using paper forms, there is no information in the ADJINV database regarding the names of individual adjudicators or their adjudication determinations.
3. We noted that in one case out of the small number reviewed, an adjudication package named the identity of the study drug a patient received. Such information should have been redacted. We do not know how frequently such information was not redacted from the packages.
4. Changes in transfusion-adjusted hemoglobin levels in the adjudication results were not consistent with hemoglobin and transfusion information in adjudication packages in 3 of the approximately 10 bleeding event packages that were closely reviewed. Changes in transfusion-adjusted hemoglobin levels are an important component of the primary safety endpoint, the rate of major bleeding. If the observed inconsistencies represent calculation errors or methodological errors, and these errors are widespread, the safety results in the NDA may be unreliable.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

(Note: comments to the sponsor are being drafted by the clinical team).

Tzu-Yun McDowell Marty Rose	2/14/14
Reviewing Medical Officer	Date
Marty Rose	2/14/14
Clinical Team Leader	Date

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

/s/

TZU-YUN C MCDOWELL
02/14/2014

MARTIN ROSE
02/14/2014
Signed as efficacy reviewer and team leader