



Daiichi Sankyo, Inc.

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT

SAVAYSA™ (EDOXABAN TOSYLATE)

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

1.0 EXECUTIVE SUMMARY

1.1 Overview

On 8 January 2014, Daiichi Sankyo submitted a New Drug Application (NDA) for SAVAYSA (edoxaban tosylate) tablets (NDA 206316) requesting approval of an indication to reduce the risk of stroke and systemic embolism (SEE) in nonvalvular atrial fibrillation (AF). On 17 September 2014, the Federal Register published the announcement for a Cardiovascular and Renal Drugs Advisory Committee meeting to be held on 30 October 2014 to discuss the Daiichi Sankyo NDA currently under review for reducing the risk of stroke and SEE in patients with AF.

The submission is based on data from more than 40 clinical pharmacology studies, a large Phase 2 program, and the Phase 3 trial known as ENGAGE AF-TIMI 48, which recruited more than 21,000 subjects with AF who were at medium to high risk for stroke or SEE based on a CHADS₂ (congestive heart failure [CHF], hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack [TIA] or thromboembolism [doubled]) score ≥ 2 . In addition, the submission included the results of a full preclinical program as well as the Chemistry, Manufacturing and Controls data for edoxaban tablets.

ENGAGE AF-TIMI 48 included 2 dosing regimens, and the results with both regimens met the prespecified objectives. In this study, edoxaban met its primary objective of noninferiority to warfarin on the protocol-defined primary efficacy endpoint of stroke (ischemic or hemorrhagic) or SEE. Edoxaban was also shown to be superior to warfarin with respect to the principal safety endpoint of International Society of Thrombosis and Haemostasis (ISTH)-defined major bleeding. In addition, the results of ENGAGE AF-TIMI 48 demonstrated similarly consistent results across numerous prespecified secondary analyses, sensitivity analyses, and net clinical outcomes. Overall, ENGAGE AF-TIMI 48 met all the prespecified statistical primary efficacy and principal safety endpoints, thereby fulfilling those hypotheses, and met all the conditions stipulated in the United States (US) Special Protocol Assessment compared with well-managed warfarin.

In addition to the primary and secondary efficacy and safety endpoints, the Study Protocol and Statistical Analysis Plan (SAP) for ENGAGE AF-TIMI 48 outlined an extensive plan aimed at confirming and supporting the main study outcomes including subgroup analyses for multiple baseline characteristics. The results of those subgroup analyses were consistent with the overall study results. However, a subgroup analysis for stroke or SEE (primary endpoint) by renal function across 4 prespecified categories of creatinine clearance (CrCL; normal renal function [≥ 80 mL/min]; mild renal impairment [> 50 to < 80 mL/min]; moderate renal impairment [30 - 50 mL/min], and severe renal impairment [< 30 mL/min]) demonstrated a significant interaction for heterogeneity for both the edoxaban 60/30 mg ($P < 0.0002$) and 30/15 mg ($P = 0.0077$) regimens. The hazard ratio (HR) for stroke or SEE in the subgroup with CrCL ≥ 80 mL/min treated with the higher dose regimen was 1.41 (95% CI: 0.97, 2.06; $P = 0.070$). This observation will be discussed in greater depth in this briefing document (**Section 1.9** and **Section 9.4**).

Based on the overall results of ENGAGE AF-TIMI 48, Daiichi Sankyo considers NDA 206316, as submitted, to be appropriate to support the safe and effective use of edoxaban for the treatment of AF in the prevention of stroke and SEE. The recommended dose for edoxaban as

submitted is 60 mg once daily (QD) with dose modification to 30 mg QD for patients with risk factors for bleeding (as prespecified in the protocol).

1.2 Proposed Indication and Dosage

Data presented in this briefing document support the following proposed indication for edoxaban in the US:

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

The recommended dose of edoxaban is 60 mg QD. The recommended dose is 30 mg QD in patients with 1 or more of the following:

- Moderate to severe renal impairment (CrCL 15 to 50 mL/min)
- Low body weight (≤ 60 kg or 132 lbs)
- Concomitant use of P-glycoprotein (P-gp) inhibitors except amiodarone

1.3 Therapeutic Landscape

For patients with AF and an average CHADS₂ score similar to that of patients enrolled in the ENGAGE AF-TIMI 48 study, published data suggest that treatment with a vitamin K antagonist (VKA) reduces the rate of stroke or SEE by approximately 65% (from an estimated absolute annual rate of approximately 5.7% if untreated to approximately 1.6% per year if treated with VKA).^{1,2} Warfarin continues to be the most commonly used oral anticoagulant for the past 50 years even after approval of 3 novel oral anticoagulants (NOACs) targeting thrombin/Factor IIa (dabigatran) or Factor Xa (rivaroxaban and apixaban). The use of these new therapeutic agents is increasing but remains generally low despite the continuing challenges associated with warfarin and other VKAs. In particular, VKA therapy is the leading cause of hospitalizations due to bleeding complications.³ After considering all the warfarin limitations, the single most important factor to explain the significant underutilization of anticoagulants is the fear of hemorrhage.⁴

Anticoagulation therapy requires achieving a delicate balance between preventing ischemic events and mitigating the risk of bleeding complications. The need to achieve this balance remains true with the NOACs and all oral anticoagulants. Recent clinical studies with oral anticoagulants in AF patients showed that the NOACs are generally as effective as warfarin in preventing strokes and SEEs. The main advantage NOACs offer is in their ability to reduce bleeding, especially hemorrhagic stroke, compared to warfarin. Recently, a relationship linking NOAC-related bleeding to mortality has been proposed, placing further emphasis on achieving an appropriate balance between ischemic protection and the risk of bleeding.⁵ The NOACs also have a wide therapeutic index, rapid onset of action, and are cleared usually within 24 hours.

Although available NOACs significantly address some of the concerns associated with warfarin therapy, each has its unique limitations. Further evidence and therapeutic options will facilitate the adoption of newer therapies for the increasing number of patients who are currently in need and are untreated because of the fear of bleeding complications. The results of ENGAGE AF-TIMI 48 clearly demonstrate that edoxaban would provide physicians with a QD therapeutic option with a better bleeding profile than that provided by warfarin while maintaining a favorable reduction in the risk of stroke or SEE. In addition, edoxaban has a low

potential for interactions with drugs metabolized by cytochrome P450 (CYP) variants and, specifically, with the relatively common CYP3A4 variants. The drug interaction with P-gp inhibitors has been shown to be manageable. Importantly, ENGAGE AF-TIMI 48 evaluated and demonstrated the safety and efficacy of the edoxaban regimen for AF subjects with renal impairment; this population was identified as being at a significantly higher risk for stroke, SEE, and bleeding complication compared to warfarin.

1.4 Study ENGAGE AF-TIMI 48

ENGAGE AF-TIMI 48 enrolled subjects (age ≥ 21 years) with documented AF within the preceding 12 months and in whom anticoagulant therapy was indicated. Eligible subjects were at a medium to high risk for stroke and SEE (CHADS₂ score ≥ 2). Key exclusion criteria were secondary AF, severe renal insufficiency (calculated CrCL < 30 mL/min) conditions associated with high bleeding risk (e.g., past history of intracranial or spontaneous intraocular, spinal, retroperitoneal, or intra-articular bleeding), or dual-antiplatelet therapy.

The dose selection and design of ENGAGE AF-TIMI 48 was driven by the goal to achieve noninferior stroke and SEE prevention while achieving at least a 10% reduction in ISTH-predefined major bleeding compared with well-controlled warfarin. The inclusion of 2 dosing regimens in ENGAGE AF-TIMI 48 as well as the specific dosing regimens selected was based on five Phase 2 studies in AF subjects that investigated the safety of different doses in ethnically diverse populations. The largest Phase 2 AF study (n=1143) included 4 doses (30 mg QD, 30 mg twice daily [BID], 60 mg QD, and 60 mg BID). Based on the outcomes of the comprehensive development program for edoxaban, QD administration of the 60 mg and 30 mg dose regimen, and the direction to use half of these doses in a prespecified group of subjects with a likely increased risk for bleeding, were developed for the Phase 3 AF program. ENGAGE AF-TIMI 48 is the only double-blind study to evaluate 2 dosing regimens with a prespecified dose-modification strategy intended to mitigate the anticoagulant-associated bleeding risk while maintaining an effective stroke risk protection.

Compared to other contemporary programs with oral anticoagulants, ENGAGE AF-TIMI 48 had the longest on-treatment subject exposure (median, 2.5 years; representing approximately 15,500 subject-years per treatment arm) as well as the longest follow-up overall (2.8 years and approximately 19,000 subject-years per treatment arm). This controlled clinical trial accrued the largest number of adjudicated primary efficacy endpoints (667 stroke or SEE in the modified Intent-to-Treat [mITT] On-treatment data set) and principal safety endpoints (1196 major bleeds in the Safety On-treatment data set) as well as the largest number of primary efficacy endpoints in the overall study period (1016 in the Intent-to-Treat [ITT] Overall data set). Further, even with its long follow-up, ENGAGE AF-TIMI 48 had a low rate of withdrawal of consent (1.2%), and an extremely low rate of missing final vital status (1 subject). ENGAGE AF-TIMI 48 also achieved a very high rate of international normalized ratio (INR) within the therapeutic range of 2 to 3 in the group of subjects treated with warfarin. The median Time in Therapeutic Range (TTR) of 68.4% exceeded that achieved in other contemporary NOAC studies.

Eligible subjects were stratified by CHADS₂ risk score at randomization: Stratum 1—CHADS₂ risk score 2 and 3; and Stratum 2—CHADS₂ risk score 4, 5, and 6 (see **Section 5.3.1.1, Figure 5-2**). Within each CHADS₂ stratum, subjects were further stratified based on whether they required edoxaban dose reductions (from 60 to 30 mg QD or from 30 to 15 mg QD) for moderate renal impairment (CrCL ≥ 30 and ≤ 50 mL/min), low body weight (≤ 60 kg), or concomitant use

of specific P-gp inhibitors (quinidine, verapamil, dronedarone). After the second stratification, subjects were randomized (1:1:1) either to the edoxaban 60/30 mg QD regimen, the edoxaban 30/15 mg QD regimen, or warfarin QD (dose adjusted to maintain INR 2.0-3.0). At the end of the study, subjects transitioned to open-label oral anticoagulant therapy (VKA or NOAC) using a prospectively defined and comprehensive transition plan (see **Section 5.3.1.4**).

The primary efficacy endpoint was time to first stroke (ischemic or hemorrhagic) or SEE. The principal safety endpoint was major bleeding (as defined by the ISTH), including fatal bleeding, and/or symptomatic bleeding in a critical area or organ, and/or bleeding causing a reduction in hemoglobin level of 2 g/dL adjusted for transfusion. Secondary efficacy endpoints were the composite of stroke, SEE, and cardiovascular (CV) mortality; major adverse cardiovascular event (MACE); and the composite of stroke, SEE, and all-cause mortality. Net clinical outcome composite endpoints included stroke, SEE, major bleeding, and death. All prespecified key efficacy and safety outcomes were adjudicated by an independent Clinical Events Committee (CEC), blinded to treatment assignment.

Endpoints were analyzed using mITT, ITT and safety populations for both the overall and on-treatment and study periods described in **Table 1-1**. For the noninferiority analysis of the primary efficacy endpoint, time to first event was analyzed using a Cox proportional hazards regression model. The 2-sided 97.5% CIs for the HRs (each edoxaban treatment regimen versus warfarin) were estimated. If the upper limit of the CI of the HR was below 1.38, noninferiority to warfarin was established for the edoxaban treatment regimen. If noninferiority was established for the edoxaban 60/30 mg regimen, superiority testing was performed for edoxaban 60/30 mg versus warfarin. Time to first event was compared between edoxaban and warfarin using a log-rank test, at a pairwise comparison significance level of $\alpha = 0.01$. If superiority of edoxaban 60/30 mg versus warfarin was established for the primary efficacy endpoint, the secondary efficacy endpoints were tested for superiority versus warfarin in a hierarchical sequence with each test performed at $\alpha = 0.01$.

The study was event-driven. All subjects were to be treated and followed until approximately 672 primary efficacy endpoint events were collected. The target number of events provided 87% power for confirming noninferiority for each edoxaban regimen.

Table 1-1 Analysis Populations by Study Period and Analysis (Endpoint)

Analysis Sets (Definitions)	Analysis (Endpoint) by Study Period	
	Overall Study Period ^a	On-Treatment Period ^b
mITT (treated subjects as per randomization)	Noninferiority	Noninferiority (Primary efficacy)
ITT (all randomized subjects)	Superiority	Not applicable
Safety (treated subjects as per actual treatment received)	Not applicable	Superiority (Principal safety)

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat.

^a Overall study period was defined as the time from the reference date (randomization date or initial dose of study drug date, depending on analysis set) to the common study end date (CSED) visit.

^b On-treatment period was defined as the time period the subject was taking study drug up to 3 days after the subject's last dose for that time period. Subjects may have had multiple periods of study drug use if they temporarily interrupted and resumed study drug during the study.

1.5 Study Population

Overall, 21,105 subjects were randomly assigned to edoxaban 60/30 mg (n = 7035), edoxaban 30/15 mg (n = 7034), or warfarin (n = 7036). Of these subjects, 21,026 received at least 1 dose of edoxaban 60/30 mg (n = 7012), edoxaban 30/15 mg (n = 7002), or warfarin (n = 7012). These 21,026 treated subjects constituted the mITT/Safety analysis set. A similar percentage of subjects in the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin treatment groups completed the common study end date (CSED) visit (88.5%, 88.9%, and 87.5%, respectively). Reasons for not completing this study visit were death prior to CSED announcement (10.5% overall) or withdrawal of consent (1.2% overall). One subject in the edoxaban 30/15 mg group had unknown vital status at end of study. The median duration of exposure was 2.5 years, and the median duration of follow-up was 2.8 years.

The subject cohort enrolled in ENGAGE AF-TIMI 48 is consistent with the AF population seen in clinical practice. Subjects were a median age of 72 years and had a mean CHADS₂ score of 2.8; approximately 53% of subjects had a CHADS₂ score ≥ 3 . In all 3 treatment groups, CrCL was ≥ 30 to ≤ 50 mL/min in approximately 18% of subjects, and 41% of subjects were VKA naive. Approximately 25% of subjects had their dose reduced at randomization based on at least 1 of the prespecified criteria.

Compliance with study treatment, as measured by pill count, was high (~98% of subjects were > 80% compliant) and consistent across the treatment groups. Furthermore, double-blind warfarin therapy was administered and closely monitored to maintain INR 2.0-3.0. The median time in TTR of 68.4% exceeds that achieved in other contemporary NOAC trials in AF, indicating excellent clinical management of warfarin.

1.6 Summary of Primary Clinical Outcomes

Overall, the efficacy and safety of edoxaban compared favorably with warfarin and was similar across multiple endpoints, populations, and analyses (**Figure 1-1**). Both edoxaban 60/30 mg and 30/15 mg regimens were noninferior to well-managed warfarin for prevention of stroke (ischemic and hemorrhagic) or SEE (primary efficacy endpoint), with lower rates reported with the edoxaban 60/30 mg regimen. The edoxaban 60/30 mg regimen was equally effective as well-managed warfarin at reducing the risk of ischemic stroke (HR = 0.94); however, the edoxaban 30/15 mg regimen was associated with a higher risk of ischemic stroke than warfarin. The study confirmed that there was a favorable reduction in hemorrhagic strokes with both edoxaban dosing regimens. In addition, consistent clinical benefit was observed across a variety of other efficacy endpoints. Compared with warfarin, edoxaban was associated with consistently lower rates of all types of bleeding, including major bleeding (principal safety endpoint), intracranial hemorrhage (ICH), and life-threatening bleeding. The only exception was gastrointestinal (GI) bleeding, which occurred slightly more frequently with the edoxaban 60/30 mg regimen, but less frequently with the 30/15 mg regimen than with warfarin. Finally, the net clinical outcome composite of stroke, SEE, major bleed, or all-cause mortality supported the superiority of both dose regimens of edoxaban compared with warfarin. Overall, the primary efficacy and principal safety findings were consistent across most of the subgroups.

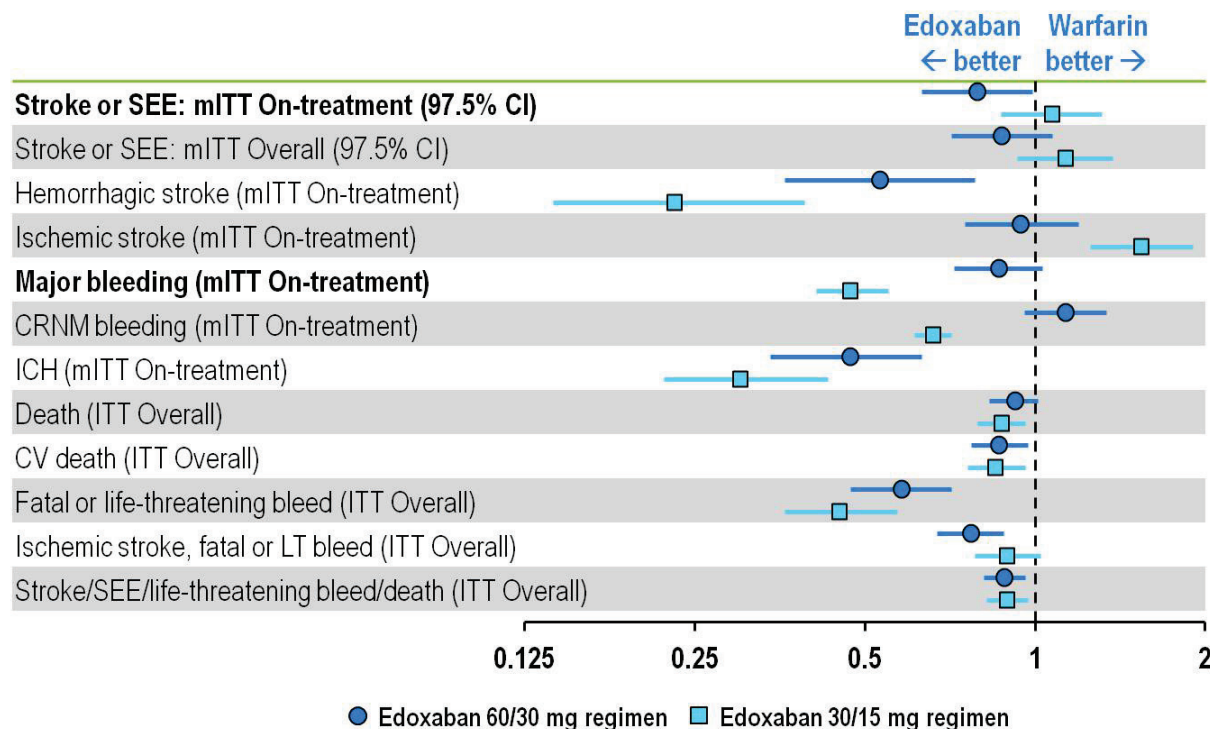


Figure 1-1 Summary of Key Outcomes

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial hemorrhage; ITT, intent-to-treat; LT, life-threatening; mITT, modified intent-to-treat; SEE, systemic embolic event. 95% confidence intervals are shown unless otherwise noted.

1.6.1 Primary Efficacy Analysis

In the prespecified noninferiority efficacy analysis of the mITT on-treatment data set, the edoxaban 60/30 mg regimen demonstrated a lower event rate for stroke or SEE than warfarin (1.18% vs 1.50% per year, respectively), with a clinically meaningful treatment effect as demonstrated by a relative risk reduction of 21% (HR = 0.79, 97.5% CI: 0.63, 0.99; $P < 0.001$ for noninferiority; **Figure 1-1**). In contrast, the edoxaban 30/15 mg regimen had a slightly higher annual event rate (1.61%) compared to warfarin but still met the criteria for noninferiority (HR = 1.07, 97.5% CI: 0.87, 1.31; $P = 0.006$ for noninferiority).

In the prespecified superiority analysis for efficacy performed in the ITT analysis set overall study period, there was a trend favoring the edoxaban 60/30 mg regimen versus warfarin (HR = 0.87, 99% CI: 0.71, 1.07; $P = 0.081$).

The annualized event rate for ischemic stroke was similar in both the edoxaban 60/30 mg and warfarin groups (0.87% vs 0.93% per year, respectively; HR = 0.94, 95% CI: 0.75, 1.19). In contrast, more subjects in the edoxaban 30/15 mg group experienced ischemic stroke compared with the warfarin group (1.43% vs 0.93% per year, respectively; HR = 1.54).

1.6.2 Principal Safety Analysis

Edoxaban-treated subjects experienced significantly lower rates of major, ICH, fatal, and clinically relevant non-major (CRNM) bleeding events than those treated with warfarin. The annualized rates of major bleeding (principal safety endpoint) in the edoxaban 60/30 mg and warfarin groups were 2.75% and 3.43%, respectively (HR = 0.80, 95% CI: 0.71, 0.91; $P < 0.001$) and 1.61% in the edoxaban 30/15 mg group (HR = 0.47, 95% CI: 0.41, 0.55; $P < 0.001$; **Figure 1-2**). Annualized event rates for major plus CRNM bleeding in the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin groups were 11.1%, 8.0%, and 13.0%, respectively. Rates of ICH and fatal bleeding were higher in the warfarin group (0.85% and 0.38%, respectively) than in either the edoxaban 60/30 mg group (0.39% and 0.21%, respectively) or the edoxaban 30/15 mg group (0.26% and 0.13 %, respectively).

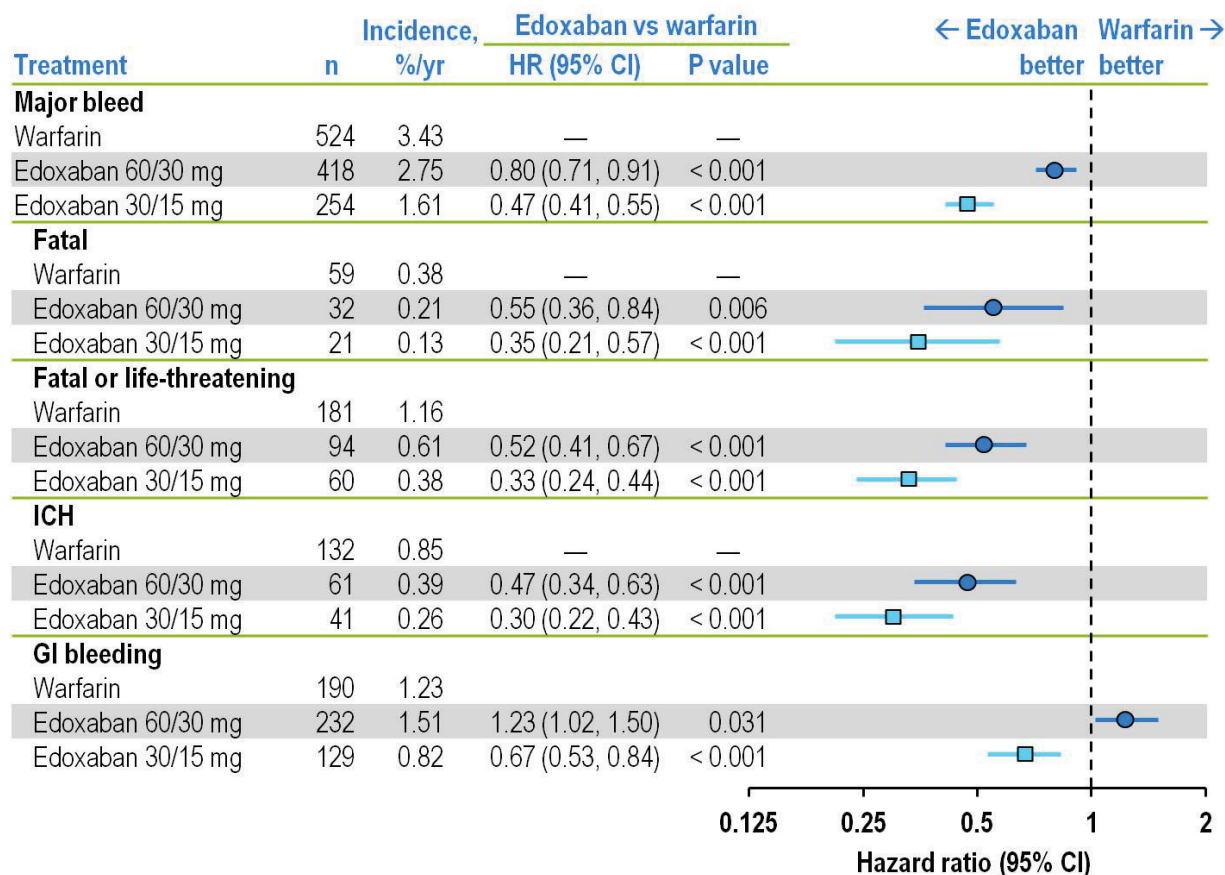


Figure 1-2 Principal Safety Endpoint: Major Bleeding (Safety Analysis Set, On-Treatment Period)

Abbreviations: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage; yr, year.

While the bleeding rate was generally lower for edoxaban for most anatomic locations, this was not observed for GI bleeding. The annualized rate of major GI bleeding was higher in the

edoxaban 60/30 mg group than in the warfarin group (1.51% vs 1.23% per year, respectively), but lower in the edoxaban 30/15 mg group (0.82% per year).

1.6.3 Key Secondary Endpoints

Subjects in the edoxaban 60/30 mg group had a clinically significantly reduced risk of experiencing any of the 3 predefined secondary efficacy endpoints compared to those in the warfarin group, with edoxaban 60/30 mg demonstrating a significant relative risk reduction of 10% or more for all 3 endpoints: composite of stroke, SEE, and CV mortality (HR = 0.87; 95% CI: 0.79, 0.96); MACE (HR = 0.89; 95% CI: 0.81, 0.97); and composite of stroke, SEE, and all-cause mortality (HR = 0.90; 95% CI: 0.82, 0.98). Subjects in the edoxaban 30/15 mg group had a numerically lower risk of all 3 secondary endpoints compared with the warfarin group, but the risk reduction was smaller than that observed in the edoxaban 60/30 mg group.

Edoxaban-treated subjects had lower CV mortality and lower all-cause mortality than those treated with warfarin. Compared with warfarin, both the edoxaban 60/30 mg and 30/15 mg regimens resulted in a relative risk reduction in CV mortality of 14% and 15%, respectively, and a relative risk reduction in all-cause mortality of 8% and 13%, respectively. As expected for this study population (median age, 72 years; average CHADS₂ score, 2.8), approximately 70% of deaths were due to CV events.

1.6.4 Efficacy Subgroups

Primary Efficacy Endpoint (Stroke or SEE) by Subgroups

The primary efficacy findings for subgroups based on demographic and baseline characteristics (such as age, gender, race, body weight, CrCL, CHADS₂ score, dose reduced or not, warfarin naive or not, etc.) were generally consistent with the overall study results. For almost all subgroups, the event rate for stroke or SEE was lower in the edoxaban 60/30 mg group than in the warfarin group (HR < 1.0). A statistically significant interaction for heterogeneity was observed for subgroups based on CrCL and based on geographic regions. In the subgroup analysis by CrCL, subjects with moderate renal impairment (30 to 50 mL/min) had a relative risk of stroke or SEE of 0.88 (95% CI: 0.58, 1.32), and subjects with mild renal impairment (> 50 to < 80 mL/min) had a relative risk of 0.53 (95% CI: 0.40, 0.70), while subjects with normal renal function (≥ 80 mL/min) had a relative risk of 1.41 (95% CI: 0.97, 2.06) compared with warfarin (see **Section 1.9** for further details).

Principal Safety Endpoint (Major Bleeding) by Subgroups

Edoxaban-treated subjects had lower bleeding rates compared with the warfarin group across all prespecified subgroups based on demographic and baseline characteristics such as age, gender, body weight, renal function, CHADS₂ score (risk stratification scheme for stroke), or past history of stroke or TIA. No treatment group-by-subgroup interaction was observed when the same sensitivity analyses were conducted for the principal safety endpoint of major bleeding ($P = 0.25$). A similar advantage for lower bleeding rates with edoxaban was also observed in subjects receiving concomitant medications such as aspirin, antiplatelet agents, and nonsteroidal anti-inflammatory drugs (NSAIDs), although the bleeding event rates were higher in these subgroups.

1.6.5 Net Clinical Outcomes

The balance between risk of bleeding and prevention of ischemic stroke is always critical when managing patients with AF, particularly for patients at a higher risk of bleeding. To evaluate the overall risk/benefit of edoxaban, net clinical outcome composite endpoints were evaluated by comparing each edoxaban regimen with warfarin for efficacy and safety events (such as the composite of stroke, SEE, major bleed or all-cause mortality) that may lead to significant morbidity or mortality. For all of these endpoints, both edoxaban dosing regimens were numerically higher than well-managed warfarin (**Figure 1-3**).

Based on these results, Daiichi Sankyo concluded that the edoxaban 60/30 mg regimen offered the best balance between efficacy and safety, and thus recommended that this regimen be approved by the US Food and Drug Administration (FDA) for use in patients with AF.

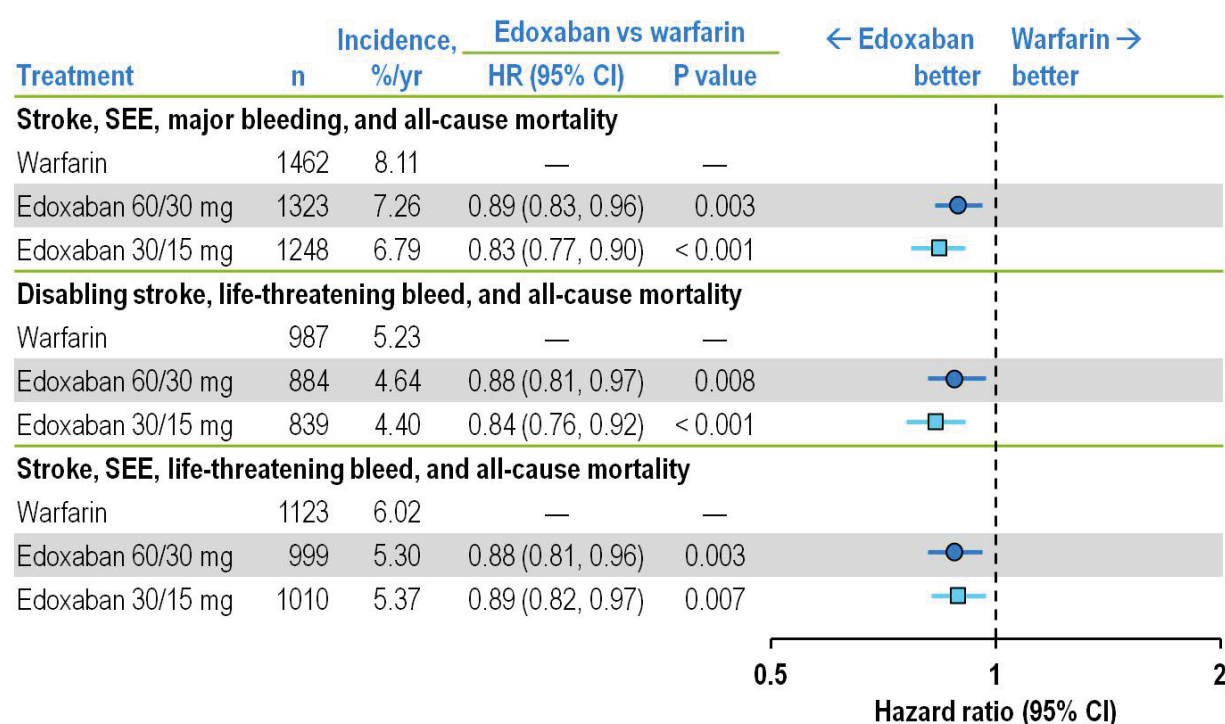


Figure 1-3 Net Clinical Outcomes (ENGAGE AF-TIMI 48)

Abbreviations: CI, confidence interval; HR, hazard ratio; SEE, systemic embolic event.

The primary net clinical outcome is a composite of stroke, SEE, major bleeding, and all-cause mortality.

1.7 Transition Period Outcomes

At the end of the ENGAGE AF-TIMI 48 after the final dose of study drug, subjects were transitioned to open-label anticoagulant therapies in accordance with a prespecified transition algorithm. The transition scheme was effective, as judged by: fewer events during the transition period, no increase in the risk of stroke or SEE, and no increase in the risk of all-cause mortality, or major bleeding when subjects in the edoxaban groups transitioned to open-label anticoagulant

therapies at the end of the study. Seven subjects (0.2%) in each treatment group had a stroke before Day 30 of the transition period.

1.8 Summary of Other Safety Parameters

Non-Bleeding Treatment-Emergent Adverse Events

A comprehensive review of non-bleeding safety, including hepatic safety, did not identify any safety signals. Overall, the incidence of non-bleeding treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events were similar for both edoxaban and warfarin-treated subjects. Non-bleeding TEAEs leading to study drug interruptions or discontinuations were also similar in both edoxaban and warfarin-treated subjects.

The most common TEAEs across the edoxaban 60/30 mg and warfarin groups were urinary tract infections (9.8% vs 10.0%), nasopharyngitis (8.8% for both groups), bronchitis (8.1% vs 8.2%), and peripheral edema (8.2% vs 9.6%). Anemia was the only non-bleeding TEAE reported by $\geq 5\%$ of subjects in any treatment group and occurring more frequently ($> 1\%$) in the edoxaban 60/30 mg group than in the warfarin group (5.2% and 3.5%, respectively). This finding could be due to a higher incidence of GI bleeding events in the edoxaban 60/30 mg group.

Hepatic Safety

Hepatic abnormalities or hepatic cases of special interest meeting any of the prespecified criteria were forwarded to independent CEC hepatic specialists for assessment and adjudication. Review of the laboratory data for liver enzyme and bilirubin abnormalities showed that alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations $\geq 3 \times$ upper limit of normal (ULN) were comparable. Additionally, cases that were adjudicated by 2 independent hepatic specialists in a blinded manner did not indicate any clinically concerning signal for drug-induced liver injury. Two subjects in the edoxaban 60/30 mg group and 1 subject in the edoxaban 30/15 mg group were adjudicated as having met Hy's Law criteria. In each case, there were additional mitigating factors or circumstances potentially contributing to the liver enzyme and bilirubin elevations (see **Section 8.1.5.1** for details). In the global Phase 3 edoxaban program, there were 5 cases adjudicated as Hy's law (3/18,010 subjects treated with edoxaban and 2/11,010 subjects treated with warfarin). There were no Hy's law cases in any other edoxaban studies.

1.9 Subgroup Analyses by Baseline CrCL

Numerous prespecified subgroup efficacy and safety analyses were conducted for multiple baseline characteristics (see **Section 9.4**). As noted above (**Section 1.6.4**), for almost all subgroups, the event rate for stroke or SEE was lower in the edoxaban 60/30 mg group than in the warfarin group ($HR < 1.0$). In contrast, a prespecified subgroup analysis by renal function across 4 categories of CrCL (normal renal function [≥ 80 mL/min]; mild renal impairment [> 50 to < 80 mL/min]; moderate renal impairment [30 to 50 mL/min], and severe renal impairment [< 30 mL/min]) demonstrated a significant interaction for heterogeneity for both the edoxaban 60/30 mg ($P < 0.001$) and 30/15 mg regimens ($P = 0.008$). The relative risk of stroke or SEE was observed to be higher with edoxaban than with warfarin in the subgroup of subjects with normal renal function ($CrCL \geq 80$ mL/min) and lower in the edoxaban subgroup with mild renal function than in the warfarin group. These findings prompted additional post-hoc analyses to

further understand what may have contributed to the observed HRs. The results of those analyses are described below and also described in further detail in **Section 9.4.3**.

1. *Exposure analysis:* A pharmacokinetic (PK) analysis showed that exposure to edoxaban varied by renal function, as described in **Section 11.0**. Subjects with CrCL ≥ 80 mL/min (i.e., normal renal function) had slightly lower exposure compared to subjects with CrCL > 50 to < 80 mL/min (i.e., mild renal impairment), although mean exposure in the subgroup with CrCL ≥ 80 mL/min remained within the therapeutic range for benefit based on exposure-response modeling. The mean exposure achieved in the subgroup with CrCL 30 to 50 mL/min (i.e., moderate renal impairment) receiving a reduced dose of 30 mg was lower than that achieved in subjects with normal renal function receiving 60 mg, and yet the HR observed in the moderately impaired subgroup was 0.88, favoring edoxaban 60/30 mg. Additionally, using modeling and simulation analysis, the predicted benefit of increased exposure to edoxaban in the normal renal function subgroup to a level equal to that achieved in the mildly impaired subgroup would result in a reduction of the annual stroke or SEE event rate of 0.08%, a reduction that would have minimal effect on the HR.
2. *Event rate analysis:* Comparison of the annualized event rates for stroke or SEE in the subgroups with normal renal function and mild renal impairment (**Figure 1-4**) demonstrated that the event rates in the edoxaban 60/30 mg group were very similar (1.06%/year and 1.07%/year, respectively). In contrast, the event rates in the warfarin groups were different (0.76%/year and 2.0%/year, respectively). This represents a 62% reduction in the event rate between the mild renal impairment and the normal renal function subgroups treated with warfarin. This magnitude of difference has not been seen in other contemporary NOAC studies.⁶⁻⁸ Moreover, the similar event rates in the two 60/30 mg edoxaban groups (mild vs normal) was unexpected considering that these 2 groups differed with respect to their median CHADS₂ score at baseline (2.6 in the normal renal function subgroup and 2.9 in the mild renal impairment subgroup).

In contrast to those observed in the edoxaban 60/30 mg group, the observed rates of stroke or SEE increased in the edoxaban 30/15 mg group, as expected, in a near linear manner across the 3 renal subgroups (1.23%/year for normal renal function, 1.67%/year for mild renal impairment, and 2.32%/year, for moderate renal impairment). This is consistent with the nearly linear increase in baseline CHADS₂ score across the renal subgroups (2.6, 2.9, and 3.1, respectively).

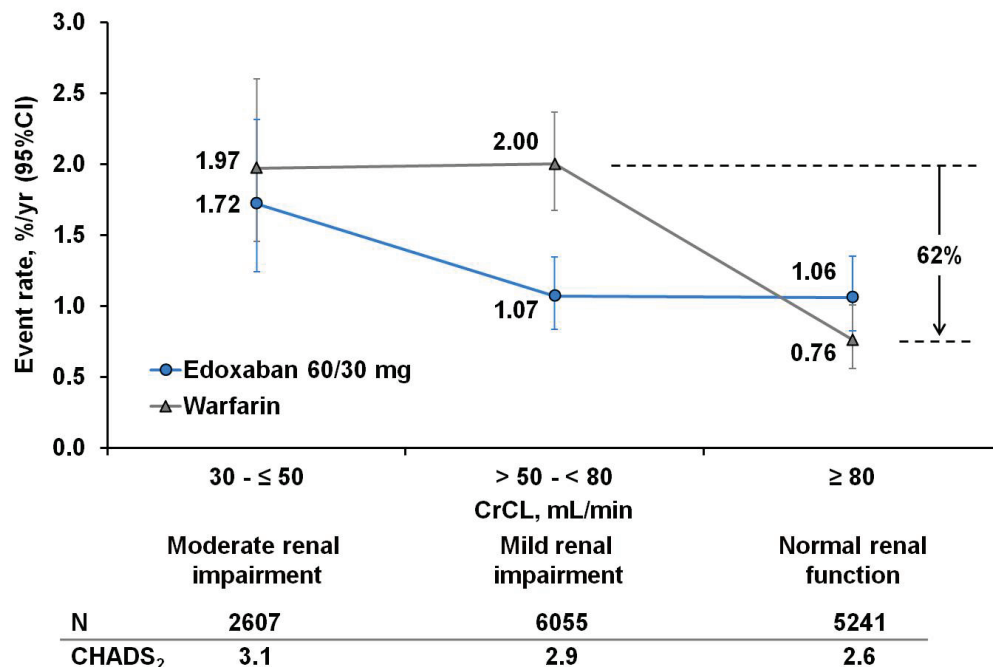


Figure 1-4 Annualized Event Rates for Stroke or SEE by Renal Subgroup

Abbreviations: CI, confidence interval; CHADS₂, congestive heart failure (CHF), hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack (TIA) or thromboembolism (doubled); CrCL, creatinine clearance; SEE, systemic embolic event; yr, year.

3. *Myocardial infarction analysis:* The observed annualized event rates for MI, another prespecified ischemic endpoint that should reflect similar benefit of anti-coagulation, were inconsistent with the observed imbalance in the normal renal function subgroup and favored edoxaban with a yearly event rate of 0.4%/year in the 60/30 mg group compared to 0.5%/year in the warfarin group.
4. *Analysis of the Hokusai VTE Study:* A similar subset analysis of the primary efficacy parameter (prevention of recurrence of VTE) conducted in the Hokusai VTE study, a large Phase 3 study comparing edoxaban 60/30 mg to warfarin in 8240 subjects with VTE for 12 months, demonstrated that there was no imbalance in the CrCL ≥ 80 mL/min group. The observed HR for VTE was 1.05 for edoxaban 60/30 mg compared to warfarin in the normal renal function subgroup, lending support to the benefit of edoxaban across all CrCL subsets.
5. *Subgroup population profile:* Finally, one cannot exclude random variability as an explanation for the observed differences between these subgroups. Due to the lack of stratification by renal function as analyzed using 4 categories of CrCL, there may have been some unidentifiable sources of bias across treatment groups within the renal subgroups in terms of baseline characteristics, demographics, concomitant medication, and geographic recruitment that could have contributed to differences in event rates for stroke or SEE. When data were analyzed by the CrCL categories used for dose modification as well as for stratification (≤ or > 50 mL/min), no significant interaction was observed.

In summary, a variety of factors, including exposure to edoxaban, an unusually low event rate in the warfarin group, and potential imbalances between treatment groups due to randomization not being performed within subgroups, could have contributed to the observed HR for stroke or SEE compared with warfarin in the subgroup of subjects with normal renal function. Because exposure does not fully account for the HR difference and because similar results were not seen in the Hokusai VTE study, the HR should be interpreted in the context of (1) a low absolute event rate for stroke or SEE, and (2) the small differences between treatment groups.

1.10 Clinical Utility Analyses

Results from ENGAGE AF-TIMI 48 showed the edoxaban 60/30 mg regimen is safe and effective in the subject population studied. As part of the edoxaban AF program, comprehensive pharmacometric analyses were conducted to develop edoxaban exposure-response models on important efficacy and safety outcomes and then to characterize edoxaban's clinical utility using the ENGAGE AF-TIMI 48 primary endpoints. Analyses revealed a correlation between outcomes and exposure, with stroke or SEE decreasing and major bleeding increasing, dependent on exposure level.

The clinical utility assessments provided guidance for the appropriate edoxaban dose regimen to be recommended by Daiichi Sankyo for AF patients on the basis of different weighting for efficacy and safety endpoints.

1.11 Clinical Perspectives and Benefit-Risk

In summary, a need remains for an alternative oral anticoagulant that safely and effectively reduces the risk of stroke or SEE and the bleeding risk in patients with AF while addressing the limitations of currently available anticoagulants. Data presented in this briefing document from ENGAGE AF-TIMI 48 demonstrate that edoxaban reduced the risk of stroke or SEE similar to warfarin while significantly reducing the risk of major bleeding, including ICH and life-threatening bleeding. Clinical outcomes in ENGAGE AF-TIMI 48 with respect to risk of stroke and major bleeding, as well as CV and all-cause mortality, were favorable both in absolute terms and relative to warfarin. The data from ENGAGE AF-TIMI 48 supports edoxaban 60 mg QD (with dose reduction to 30 mg in select patients) as a safe and effective regimen, which provides a favorable benefit-risk balance for the proposed AF indication.

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ACE	angiotensin-converting enzyme
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
AF	atrial fibrillation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
aPTT	activated partial thromboplastin time
ARB	angiotensin II receptor blocker
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
AT	antithrombin
AUC _{0-∞}	area under the concentration-time curve from time zero to infinity
AUC _{0-24,ss}	area under the concentration-time curve from time zero to 24 hours at steady-state
AUC _{ss}	area under the concentration-time curve at steady-state (total exposure)
AUC _{tau}	steady-state area under the concentration-time curve
BID	twice daily
BMI	body mass index
C _{av}	average concentration
CEC	Clinical Events Committee
CES1	carboxylesterase 1
CHADS ₂	congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism
CHA ₂ DS ₂ -VASc	congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, female gender
CHF	congestive heart failure
CI	confidence interval
CL/F	oral clearance
CL _{nr} /F	non-renal clearance
CL _r	renal clearance
CL _r /F	oral renal clearance
C _{max}	maximum observed concentration
C _{max,ss}	maximum observed concentration at steady-state (steady-state peak concentration)
CMC	Chemistry, Manufacturing and Controls
C _{min}	minimum observed concentration
C _{min,ss}	minimum observed concentration at steady-state (steady-state trough concentration)
CMV	cytomegalovirus
CrCL	creatinine clearance

CRNM	clinically relevant non-major
CSED	common study end date
CUI	clinical utility index
CV	cardiovascular
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DosAdj	dose adjustment
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic Case Report Form
EP	endpoint
ePAD	Edoxaban in Peripheral Arterial Disease
ESRD	end-stage renal disease
ETP	endogenous thrombin potential
eTRIS	Edoxaban Thrombus Reduction Imaging Study
F ₁₊₂	fibrinogen 1 + 2/prothrombin fragment 1 + 2
FDA	Food and Drug Administration
FIIa	factor IIa
FXa	factor Xa
GGT	gamma-glutamyltransferase
GI	gastrointestinal
h	hour
HR	hazard ratio
HRS	Heart Rhythm Society
IC ₅₀	50% inhibitory concentration
ICH	intracranial hemorrhage
IgM	immunoglobulin M
INN	International Nonproprietary Name
INR	international normalized ratio
INR 2.0-3.0	INR between 2.0 and 3.0, inclusive
ISTH	International Society of Thrombosis and Haemostasis
ITT	intent-to-treat
IU	international unit
IV	intravenous
IXRS	Interactive Voice and Web Response System
JAN	Japanese Accepted Name
K _i	inhibition constant
KM	Kaplan-Meier
LFT	liver function test
LMWH	low-molecular weight heparin
LSM	least-squares mean
LT	life-threatening
MACE	major adverse cardiac event
MI	myocardial infarction

min	minute
min, max	minimum, maximum
MiRI	mild renal impairment
mITT	modified intent-to-treat
NC	not calculated
NDA	new drug application
NOAC	novel oral anticoagulant
NSAID	nonsteroidal anti-inflammatory drug
OAC	oral anticoagulant
PBO	placebo
PCC	prothrombin complex concentrate
PD	pharmacodynamics(s)
PE	pulmonary embolism
P-gp	P-glycoprotein
P_{int}	P value for the interaction
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic
PP	per protocol
PT	prothrombin
QD	once daily
QTcI	QTc interval based on an individual correction
rVIIa	activated recombinant factor VII
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SEE	systemic embolic event
SOC	system organ class
SPA	Special Protocol Assessment
SRI	severe renal impairment
Subj Yr Expo	subject year exposure
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TG	thrombin generation
TIA	transient ischemic attack
TK	transition kit
T_{max}	time to maximum observed concentration
TTR	time in therapeutic range
ULN	upper limit of normal
US	United States
USAN	United States Adopted Name
VKA	vitamin K antagonist
VTE	venous thromboembolism
yr	year

2.0 PRODUCT DEVELOPMENT RATIONALE

2.1 Clinical Background

Atrial fibrillation (AF) is the most common serious cardiac arrhythmia in adults. A recent systematic review of global epidemiologic data on AF confirms the emergence of this disease as a major public health burden, with significant and progressive effects on disability and mortality.⁹ In the United States (US), an estimated 2.4 million adults have paroxysmal or persistent AF and that number is projected to reach 5.6 million in the year 2050.¹⁰⁻¹⁴ Nonvalvular AF is the most common type of AF, accounting for more than 70% of all AF cases.¹⁵ The overall prevalence of AF ranges from 2.3% to 3.4% and increases with age, with an estimated life-time risk of approximately 25%.¹⁶ The age-adjusted prevalence of AF is higher in men than women.^{17,18}

Atrial fibrillation is a source of significant morbidity and mortality because it increases the risk of stroke and systemic embolic events (SEE; **Figure 2-1**).¹⁹ Atrial fibrillation causes enlargement of the atria, endothelial damage, myocyte hypertrophy, and fibrosis. The lack of atrial systolic contraction associated with AF promotes blood stasis, with an associated local increase in procoagulant factors, and thrombocyte activation facilitates thrombus formation.²⁰ Thrombus formation within the left atrium and subsequent emboli to the cerebral circulation account for most AF-related strokes. In the US and Europe, subjects with AF have a 5-fold increased risk of ischemic stroke compared with individuals of the same age in sinus rhythm. Approximately 1 in 5 of all strokes is attributed to AF.²¹⁻²⁶ Over the past 2 decades, AF-related hospital admissions have increased by 66% due to the aging population and more frequent diagnosis of AF.²⁷⁻³⁰

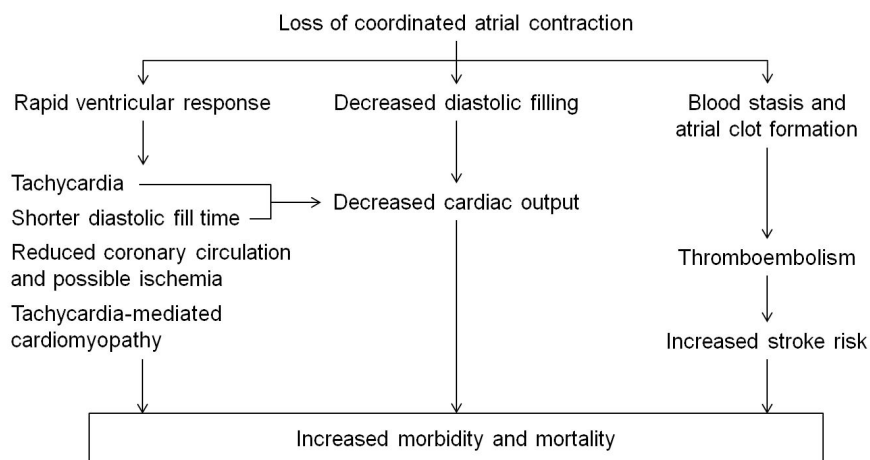


Figure 2-1 Clinical Implications of Atrial Fibrillation

Reprinted with permission from Gutierrez C, Blanchard DG. *Am Fam Physician*. 2011;83:61-8.¹⁹

Stroke in AF patients is a serious, incapacitating, and life-threatening condition. Cardioembolic strokes in AF patients are associated with increased mortality and greater morbidity from longer hospital stays, more severe functional impairment, and a lower rate of return to home.³¹⁻³⁵ Given the high risk of disabling and fatal stroke in patients with AF and the healthcare costs associated

with long-term care, antithrombotic therapy is used to minimize the risk of stroke in this patient population.

2.2 Current Treatment Landscape in Atrial Fibrillation

According to management guidelines for patients with AF, the choice of antithrombotic therapy should be based on the risk of thromboembolism.³⁶ In the United States, approved therapies for reducing the risk of stroke or SEE in AF patients with at least 1 risk factor (as assessed by the CHADS₂ [congestive heart failure (CHF), hypertension, age \geq 75 years, diabetes mellitus, prior stroke or transient ischemic attack (TIA) or thromboembolism (doubled)] score) are vitamin K antagonists (VKAs; e.g., warfarin) and novel oral anticoagulants (NOACs), including direct thrombin inhibitors (e.g., dabigatran) and factor Xa (FXa) inhibitors (e.g., rivaroxaban and apixaban). Aspirin is still used for the prevention of stroke and SEE in AF patients with no risk factors.²⁸ The CHADS₂ score, which has been the most widely used thromboembolic risk assessment scheme and was used in ENGAGE AF-TIMI 48 to select subjects and score their risk,^{1,2} incorporates 1 point each for CHF/left ventricular dysfunction, hypertension, age \geq 75 years, and diabetes mellitus, and 2 points for prior stroke. Based on this schema, the recommendation is aspirin for a risk score of 0, aspirin or oral anticoagulants (OACs) for a risk score of 1, and OACs for a risk score \geq 2.³⁷

Recent AF guideline updates (2014 American Heart Association/American College of Cardiology/Heart Rhythm Society and 2012 focused update of the European Society of Cardiology) introduced the risk stratification by CHA₂DS₂-VASc score, which includes congestive heart failure, hypertension, age \geq 75 years (doubled), diabetes mellitus, prior stroke or TIA or thromboembolism (doubled), vascular disease, age 65 to 74 years, and female gender in the point score system.^{21,36} The updated 2012 European Society of Cardiology guidelines recommend anticoagulant therapy based on the risk assessment by CHA₂DS₂-VASc score.

Warfarin, a VKA, is the most commonly used OAC. Randomized controlled studies have shown that warfarin reduces the risk of ischemic stroke in subjects with AF by approximately 65% when no other treatment is used.^{24,25,38} Management of warfarin therapy, however, is challenging for both physicians and patients.

The warfarin dose often requires frequent adjustment to maintain an international normalized ratio (INR) between 2.0 and 3.0, inclusive (INR 2.0-3.0).³⁹ Out of range INR increases the risk for either an ischemic or a bleeding event. Numerous drug and food interactions can affect the metabolism of warfarin.⁴⁰ Therefore, maintaining INR within the narrow therapeutic window can be challenging, requiring close laboratory monitoring and frequent warfarin dose adjustments. Moreover, a delayed onset of the anticoagulant effect,⁴¹ and a prolonged pharmacodynamic (PD) effect after cessation of treatment add to the difficulty of warfarin management in patients requiring treatment interruption for invasive procedures or a bleeding event. However, even after considering all the warfarin limitations, the single most important factor to explain the significant underutilization of anticoagulants is the fear of hemorrhage.⁴

Currently available NOACs have been shown in controlled clinical trials to be noninferior or superior (in the case of apixaban and dabigatran 150 mg twice daily [BID]) to warfarin in reducing the incidence of stroke and SEE in patients with nonvalvular AF. When used at appropriate doses, the NOACs provide similar protection against ischemic stroke while reducing the incidence of hemorrhagic stroke compared with warfarin. With the exception of

gastrointestinal (GI) bleeding, the NOACs reduce bleeding events irrespective of their severity compared with warfarin. In addition, NOACs have been shown to reduce mortality compared with warfarin,⁴² and they can be administered as a convenient, once daily (QD) or BID, oral, fixed dose, with a wide therapeutic index that does not require frequent monitoring or adjustment. These agents also have a rapid onset of action. The primary limitations of NOACs are the current lack of a specific reversal agent and the lack of a PD test to assess the extent of anticoagulation.

For chronic OAC therapy, patient adherence and the ability to adapt to changing clinical status (such as renal impairment, concomitant medications, and body weight) are important. Although available NOACs address some of the concerns associated with warfarin therapy, each one has its unique limitations. For example, dabigatran and apixaban require BID dosing, which is known to affect patient adherence, and rivaroxaban has significant drug interactions with combined P-glycoprotein (P-gp)/cytochrome P450 (CYP) 3A4 inhibitors.

A medical need remains for an alternative OAC that safely and effectively reduces the risk of stroke and SEE and improves upon the bleeding risk in patients with AF while addressing the limitations of currently available anticoagulants. Edoxaban addresses many of these limitations with a QD dosing regimen, minimal food effect, and minimal drug interactions with CYP3A4 inhibitors/inducers. Edoxaban does not require frequent monitoring, and specific dosing guidance can be provided for patients with moderate and severe renal impairment (SRI). This would provide physicians with an alternative therapeutic option for chronic anticoagulant therapy.

3.0 EDOXABAN OVERVIEW

3.1 Drug Description

Edoxaban tosylate (DU-176b) is an anticoagulant agent, an FXa inhibitor. The recommended nomenclature of the drug substance is edoxaban (International Nonproprietary Name [INN]), edoxaban and edoxaban tosylate (United States Adopted Name [USAN]), and edoxaban tosilate hydrate (Japanese Accepted Name [JAN]). The molecular formula of edoxaban tosylate is $C_{24}H_{30}ClN_7O_4S \cdot C_7H_8O_3S \cdot H_2O$, and its molecular mass is 738.27 (548.06 as edoxaban, the anhydrous free base of edoxaban tosylate).

The structural formula of edoxaban tosylate is shown in **Figure 3-1**.

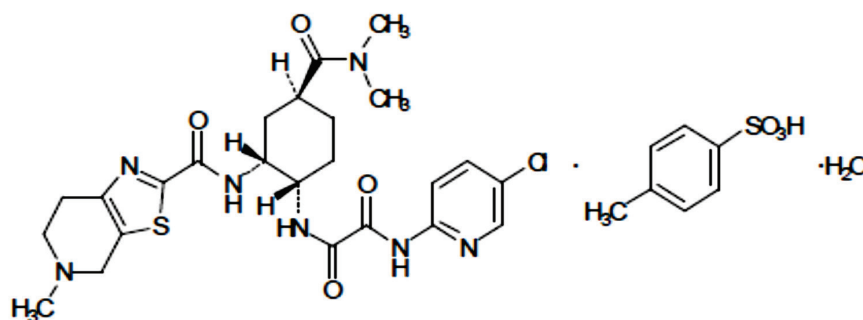


Figure 3-1 Chemical Structure of Edoxaban Tosylate

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).

3.2 Mechanism of Action

Edoxaban is a highly selective, direct and reversible inhibitor of FXa, the serine protease located in the final common pathway of the coagulation cascade. Edoxaban inhibits free FXa and prothrombinase activity (**Figure 3-2**). Inhibition of FXa in the coagulation cascade reduces thrombin generation (TG), prolongs clotting time, and reduces the risk of provoked thrombus formation.

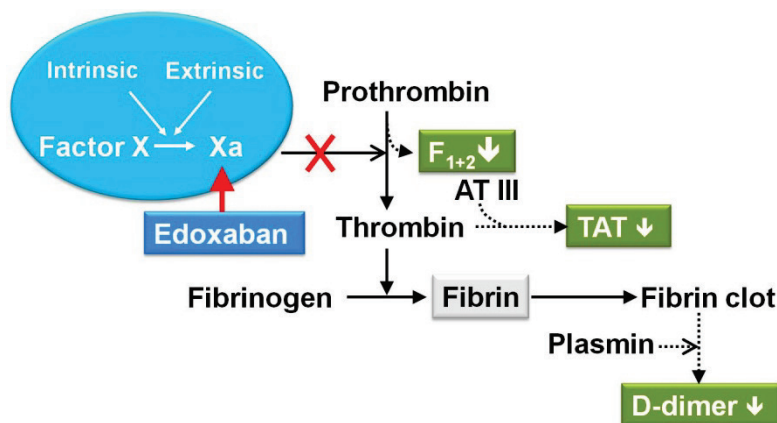


Figure 3-2 Mechanism of Action of Edoxaban

Abbreviations: AT, antithrombin; F₁₊₂, fibrinogen 1+2; TAT = thrombin-antithrombin complex.

3.3 Development and Early Studies

3.3.1 Regulatory History

Daiichi Sankyo consulted with the US Food and Drug Administration (FDA) as well as several other global health authorities throughout the edoxaban clinical development program. The pivotal Phase 3 study in subjects with AF, ENGAGE AF-TIMI 48 (DU176b-C-U301), was a global study conducted under a Special Protocol Assessment (SPA) with the FDA's Division of Cardiovascular and Renal Drug Products. Edoxaban is also under simultaneous review by the Division of Hematology Products for venous thromboembolism (VTE) based on the pivotal Phase 3 Hokusai VTE study (DU176b-D-U305).

Edoxaban marketing applications are currently under review by multiple global health authorities (European Union, Switzerland, Brazil, Taiwan, and South Korea) for AF and VTE based on the results of these same pivotal Phase 3 studies.

Edoxaban has been marketed in Japan as LIXIANA® (since 22 April 2011) for prevention of VTE in patients undergoing any of the following orthopedic procedures on the lower limb: total knee replacement, total hip replacement, and hip fracture surgery. The recommended oral dose for adults is 30 mg QD, with a recommended dose reduction to 15 mg QD for patients with moderate renal impairment (creatinine clearance [CrCL] 30 to 50 mL/min). Currently, Japan is the only market to have approval for edoxaban globally. The AF and VTE indications in Japan based on the global edoxaban program including ENGAGE AF-TIMI 48 and Hokusai VTE were approved for marketing on 26 September 2014.

3.3.2 Nonclinical Overview

The nonclinical profile of edoxaban has been investigated in a comprehensive series of pharmacology, pharmacokinetics (PK), and toxicology studies. Safety pharmacology and pivotal toxicology studies were conducted in accordance with Good Laboratory Practice guidelines.

Pharmacology studies demonstrated that edoxaban is a potent and selective inhibitor of FXa *in vitro* with inhibition of rat FXa about 12 times less than that for rabbit, monkey, or human

FXa. The anticoagulant properties of edoxaban *in vivo* were established in several rat thrombosis models: venous thrombosis, venous stasis thrombosis, arterial-venous shunt, disseminated intravascular coagulation, and venous thrombosis treatment models. The minimally effective single oral doses in the *in vivo* models were 0.1 to 2.5 mg/kg in rats yielding plasma edoxaban concentrations of approximately < 5 to 190 ng/mL. Plasma concentrations were generally proportional to the administered doses.

Nonclinical PK studies adequately characterized the absorption, distribution, metabolism, and elimination (ADME) of edoxaban in rats and cynomolgus monkeys. The results of these studies indicated that edoxaban was absorbed rapidly, had a broad tissue and organ distribution, and was eliminated via multiple pathways mainly as the parent compound via hepatic/renal excretion and with limited metabolic elimination.

Overall, nonclinical toxicology data did not reveal any unique hazards for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, or phototoxicity. A unique human metabolite, D21-2393, was detected and evaluated in separate toxicity studies. No clinically relevant adverse effects were evident in the repeated-dose oral toxicity studies in rats at doses up to either 2000 mg/kg or 600 mg/kg. In the *in vitro* and *in vivo* genotoxicity studies, D21-2393 induced numerical chromosomal aberrations in Chinese hamster lung cells, but was negative in human lymphocytes. In addition, D21-2393 showed neither mutagenic potential in the bacterial reverse mutation test nor *in vivo* genotoxic potential in bone marrow micronucleus tests in rats at oral doses up to 2000 mg/kg. Hence, D21-2393 is considered not to pose any genotoxic risk to humans. In a reproductive and developmental toxicity study, D21-2393 showed no effects on fertility and early embryonic development at doses up to 1000 mg/kg/day. In a juvenile toxicity study in rats with direct dosing of metabolite, D21-2393 showed no effects on postnatal development and growth, organ development, skeletal development, or sexual maturation at doses up to 200 mg/kg/day.

3.4 Proposed Indication and Dosage

3.4.1 Proposed Indication

Data presented in this briefing document support the following proposed indication for edoxaban in the United States:

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

3.4.2 Dosage and Administration

The recommended dose of edoxaban is 60 mg taken orally QD.

The recommended dose of edoxaban is 30 mg QD in patients with 1 or more of the following:

- Moderate to severe renal impairment (CrCL 15 to 50 mL/min)
- Low body weight \leq 60 kg (132 lbs)
- Concomitant use of P-gp inhibitors except amiodarone (see **Section 7.4.3**)

4.0 CLINICAL PHARMACOLOGY

The edoxaban PK and PD profiles were investigated in a large program of 43 clinical pharmacology studies. Phase 1 studies were conducted to elucidate the single- and multiple-dose PK and PD effects of edoxaban, drug-drug interactions (DDIs), an approach to switching from other anticoagulant drugs, and reversal of the anticoagulant effect of edoxaban. Pharmacometric analyses included population pharmacokinetic (PopPK) and exposure-response analyses from the pivotal Phase 3 trials (ENGAGE AF-TIMI 48 and Hokusai VTE) as well as PopPK analyses of Phase 1 and Phase 2 data to address specific questions related to dose proportionality, PK/PD relationships, and the effect of SRI, as well as to provide data, to guide dose selection in the Phase 3 trials. An overview of the key data from these studies and analyses is presented. ENGAGE AF-TIMI 48 exposure-response modeling is further detailed in **Section 11.0**.

4.1 Pharmacokinetics

4.1.1 Absorption, Distribution, Metabolism, and Elimination (ADME)

Edoxaban is both the active moiety and the major circulating drug-related moiety. On oral administration, approximately 62% of the drug is absorbed. Edoxaban is predominantly absorbed in the upper GI tract, with approximately 12% absorbed in the colon. Food increases peak exposure to varying degrees but has minimal effect on total exposure. Esomeprazole decreases peak exposure by approximately 33% but has minimal effect on total exposure. Given the shallow exposure-response relationship across the Phase 3 dose range, no restrictions are recommended for dosing of edoxaban with food or esomeprazole.

In healthy human subjects, edoxaban undergoes both Phase 1 and Phase 2 metabolism. Phase 1 metabolism is predominantly mediated by carboxylesterase 1 (CES1) and CYP3A4/5. Metabolism by CES1 results in the formation of a human-specific metabolite, D21-2393, accounting for < 10% of total edoxaban exposure in healthy adults. Seven metabolites (six Phase 1 and one Phase 2) have been identified in humans. Three (D21-2393, D21-2135, and D21-1402) are pharmacologically active with anticoagulant activity. However, because of low abundance, these metabolites are not expected to contribute significantly to the overall pharmacologic activity of edoxaban in subjects with normal renal function and in the absence of CYP inducers. No individual metabolic pathway is expected to contribute > 10% to total clearance.

The postulated human metabolic pathway of edoxaban is shown in **Figure 4-1**.

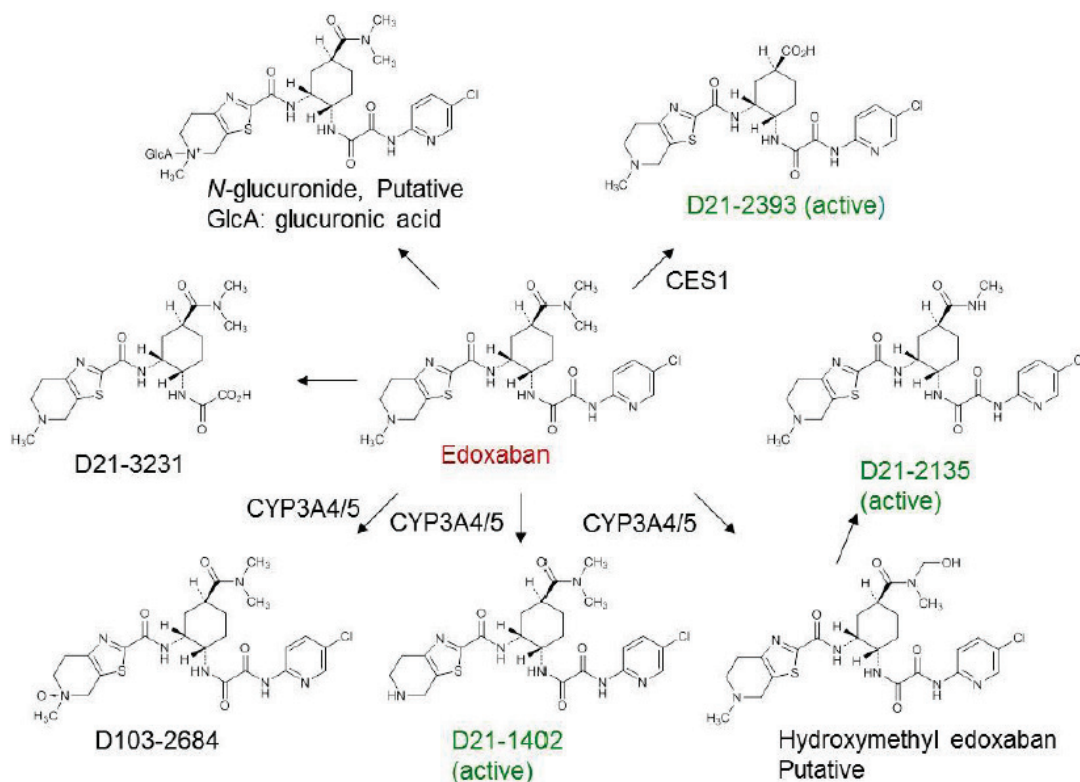


Figure 4-1 Postulated Metabolic Pathway in Humans

Edoxaban is cleared both through metabolism and as unchanged drug in urine and feces. Renal clearance (CL_r) of unchanged drug contributes approximately 50% to total clearance, with the remaining 50% of nonrenal clearance (CL_{nr}/F) occurring through metabolism and biliary secretion. The human-specific metabolite, D21-2393, has been detected in small amounts in both urine and feces, but not quantified.

4.1.2 Healthy Subject Pharmacokinetics

Oral administration of a 60 mg dose results in peak plasma concentrations of 309 ± 97 ng/mL within 1 to 2 hours. The total clearance (arithmetic mean \pm standard deviation [SD]) of edoxaban is 21.8 ± 3.03 L/h with a steady-state volume of distribution of 107 ± 19.9 L. The absolute bioavailability of edoxaban is approximately 62%. While the intravenous (IV) half-life is approximately 7 hours, the oral half-life is approximately 10 to 14 hours, suggesting a higher terminal-phase volume. Inter- and intrasubject variability for edoxaban clearance and volume of distribution is low (< 30%).

The PK profile of edoxaban is similar for single and multiple dosing (**Figure 4-2**). Steady-state is achieved within 3 days of QD dosing, with minimal accumulation (< 2-fold). At steady-state, a 60 mg dose QD results in peak concentrations of 303 ± 88 ng/mL at median (range) time to maximum observed concentration (T_{max}) values of 1.5 hours (0.5, 4.00 hours). The steady-state exposure (AUC_{tau}) is 1990 ± 403 ng·h/mL. With increasing doses, the increase in exposure is slightly less than dose proportional above the 30 mg dose. PopPK modeling suggests that for

every 30 mg increase in dose, there is a 6.7% decrease in bioavailability, presumably due to decreased dissolution rate.

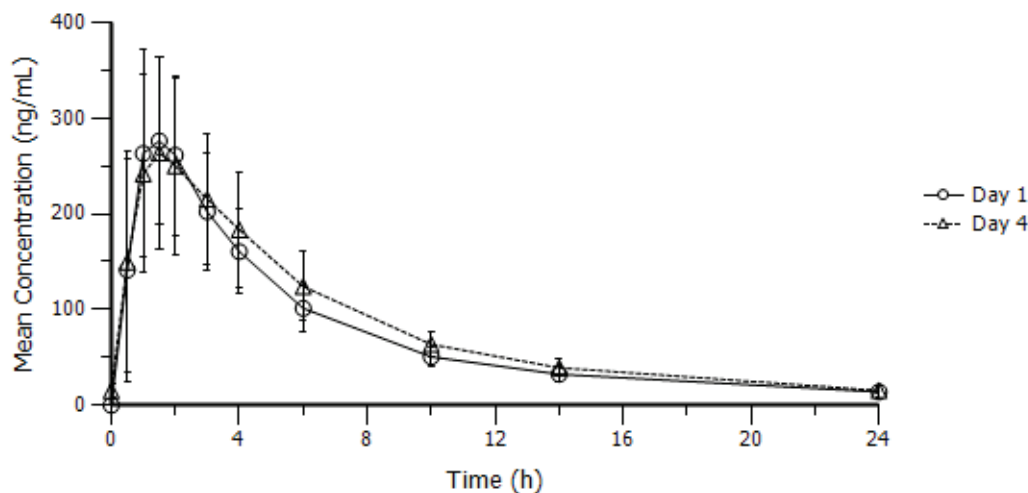


Figure 4-2 Mean (± SD) Plasma Concentration-Time Profile of Edoxaban on Days 1 and 4 Following Once-Daily Oral Administration of 60 mg Edoxaban for 4 Days

Abbreviations: h, hour; SD, standard deviation.

4.1.3 Effect of Intrinsic Factors on Edoxaban Pharmacokinetics

4.1.3.1 Renal Impairment

The total exposure of edoxaban increases with increasing degree of renal impairment, with 32%, 74%, and 72% higher exposure in subjects with mild renal impairment (MiRI), moderate renal impairment, and severe renal impairment (SRI), respectively, compared to subjects with normal renal function (defined in these studies as CrCL \geq 80 mL/min). In end-stage renal disease (ESRD) subjects undergoing peritoneal dialysis, the total exposure is 93% higher. A decrease in CL_r results in higher exposure, but as CL_r contributes only 50% to total clearance, there is a plateauing of effect of renal impairment on total clearance (**Table 4-1**). Subjects with moderate renal impairment and SRI have approximately similar total clearance values, despite the difference in CL_r.

Table 4-1 Summary of Renal Clearance and Total Edoxaban Clearance in Subjects With Renal Impairment

Parameter	Healthy CrCL \geq 80 mL/min	Renal Impairment		
		Mild > 50 to < 80 mL/min	Moderate 30 to 50 mL/min	Severe < 30 mL/min
CL _r (L/h)	11.9 \pm 1.88	7.68 \pm 2.57	4.30 \pm 1.72	2.12 \pm 0.876
CL/F (L/h)	34.6 \pm 7.32	24.8 \pm 6.00	19.4 \pm 4.69	18.5 \pm 4.87

Abbreviations: CL_r, renal clearance; CL/F, oral clearance; CrCL, creatinine clearance; h, hour; min, minute.

In subjects with renal impairment, the total exposure of metabolites (D21-2393, D21-1402 and D21-3231) increases with the extent of renal impairment (**Table 4-2**). However, the total exposure to these metabolites is still low and unlikely to contribute significantly to overall anticoagulant effect of edoxaban.

Table 4-2 Relative Exposure (Percent) of Active Metabolites in Renal Impairment Study (U120)

Metabolite	Activity Relative to Edoxaban (IC ₅₀ ratio)	Relative Exposure of Metabolite (metabolite to parent drug exposure ratio expressed as %)			
		Normal Renal Function	Renal Impairment		
			Mild	Moderate	Severe
D21-2393	1.67	5.70	9.02	11.2	12.4
D21-1402	0.43	2.75	3.69	5.09	4.63
D21-2135	1.11	Not quantifiable at most time points			

Abbreviations: FXa, factor Xa; IC₅₀ = 50% inhibitory concentration.

Note: Edoxaban anti-FXa IC₅₀ = 3 nM; D21-2393 anti-FXa IC₅₀ = 1.8 nM; D21-1402 anti-FXa IC₅₀ = 6.9 nM; D21-2135 anti-FXa IC₅₀ = 2.7 nM.

Hemodialysis has minimal effect on the clearance of edoxaban in subjects with ESRD. Apparent oral clearances (CL/F) with and without dialysis is 24 and 23 L/h, respectively. Total hemodialysis clearance is 6 L/h, indicating that hemodialysis is inefficient in clearing edoxaban from systemic circulation. Thus, hemodialysis is not an effective means to remove edoxaban.

A PopPK analysis of 13 Phase 1 studies shows the apparent CL_r decreases with decreasing CrCL in a nonlinear fashion (**Figure 4-3**). Thus, for a subject weighing 70 kg and having CrCL of 20, 40, 65, or 100 mL/min, the typical values of total apparent clearance are predicted to be 20.2, 23.3, 27.2, and 31.6 L/h, respectively. PopPK analysis of eight Phase 1, one Phase 2, and two Phase 3 studies in AF and deep vein thrombosis (DVT) subjects with severe renal impairment (studies conducted in Japan) suggests that a 30 mg dose in severe renal impairment provides approximately comparable exposure to that observed in normal/mild subjects receiving a 60 mg dose (**Table 4-3**).

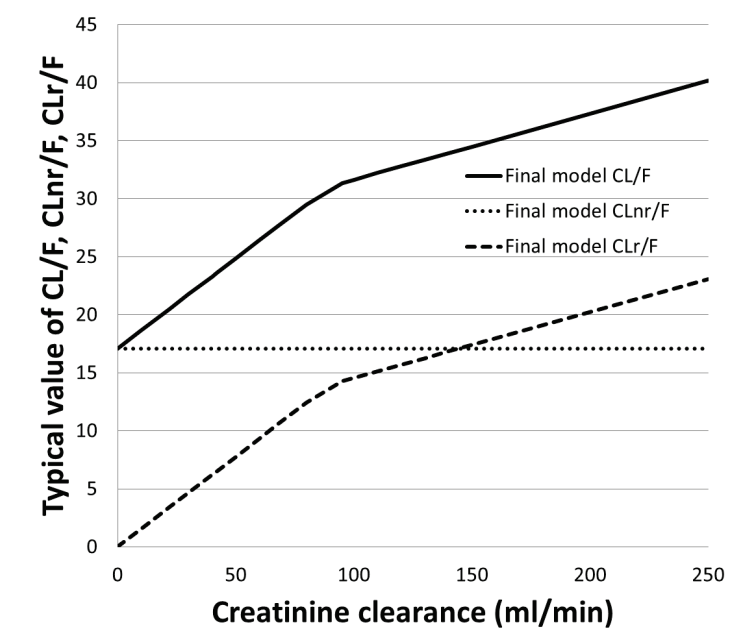


Figure 4-3 Effect of Renal Function on Typical Oral Clearance, Typical Non-Renal Clearance, and Typical Oral Renal Clearance in the Final PopPK Model

Abbreviations: CL/F, oral clearance; CLnr/F, non-renal clearance; CLr/F, oral renal clearance; min, minute; PopPK, population pharmacokinetics.

Table 4-3 Summary of Post-Hoc Bayesian Predicted Steady-State Exposure

Renal Group	Dose Received	AUC _{ss} (ng·h/mL)	C _{max} (ng/mL)	C _{min,ss} (ng/mL)
SRI (N = 49)	30 mg (n = 49) ^a	1742 (982, 2996)	134 (70.8, 276)	27.4 (9.88, 47.5)
Normal/miRI (N = 21)	60 mg (n = 13)	2143 (1388, 3155)	210 (128, 326)	23.5 (9.46, 40.2)

Abbreviations: AUC_{ss}, area under the concentration-time curve at steady-state; C_{max}, maximum observed concentration; C_{min,ss}, minimum observed concentration at steady-state; MiRI, mild renal impairment; PK, pharmacokinetics; QD, once daily; SRI, severe renal impairment.

^a Simulated PK profiles assuming subjects in SRI group received edoxaban 30 mg QD.

Notes: Values of PK measures are presented as median (min, max).

Based on the totality of the data (exposures as well as Phase 2 and Phase 3 safety and efficacy results), subjects with normal and MiRI are recommended to receive edoxaban doses of 60 mg QD for optimum efficacy and safety. For subjects with moderate or SRI, a 50% dose reduction (to 30 mg) is recommended to provide exposure overlapping that of subjects with normal and MiRI receiving a full dose of 60 mg, but also takes into consideration a potential for greater bleeding in patients with more severe renal impairment.

4.1.3.2 Hepatic Impairment

Mild or moderate hepatic impairment had a minimal effect on total edoxaban exposures (area under the concentration-time curve from time zero to infinity [AUC_{0-∞}]), with only a 6% and 5% decrease, respectively, in total exposures versus those observed in healthy controls. The apparent mean total clearance was comparable across subjects with varying mild (32.9 ± 9.09

L/h) and moderate (33.8 ± 9.53 L/h) hepatic impairment, versus results from matched healthy controls (31.2 ± 8.01 and 31.8 ± 7.15 L/h, respectively). The small difference in mean clearance values does not warrant a dose reduction for mild and moderate hepatic impairment subjects, as nonrenal elimination only contributes approximately 50% to total clearance. Edoxaban has not been studied in subjects with severe hepatic impairment. No dose reduction is recommended in subjects with mild to moderate hepatic impairment, and edoxaban use is not recommended in subjects with intrinsic coagulopathies.

4.1.3.3 Body Weight, Age, Gender, and Race

Body Weight: In healthy subjects, body weight is a significant covariate for both clearance and disposition, with respective increases in allometrically scaled parameters based on increasing weight. In AF subjects, peak and total exposure appear to be 40% and 13% higher, respectively, for subjects with lower body weight (e.g., 55 kg) compared with subjects with higher body weight (e.g., 84 kg). Therefore, a dose reduction by 50% is recommended in subjects with low body weight (≤ 60 kg/132 lbs).

Age: Pooled PopPK analysis of data from healthy, and AF or DVT subjects with SRI suggests a decrease in clearance (both CL_r and CL_{nr}/F) and a decrease in the rate of absorption with increasing age. However, in subjects with AF, after taking renal function and body weight into account, age did not have an additional clinically significant effect on edoxaban PK. Therefore, a dose reduction is not deemed necessary.

Gender: PopPK analysis of healthy subject data indicates that gender is a significant covariate, with 13% lower clearance values for females. This is only partially explained by the lower body weight of female subjects. However, in subjects with AF, after accounting for body weight, gender had no additional clinically significant effect on edoxaban PK. Therefore, the same dose is recommended in both genders.

Race: PopPK modeling of 9 pooled Phase 1 studies and studies in AF and DVT subjects with severe renal impairment indicates that after accounting for body weight, there are no obvious differences between races, including between Japanese and non-Japanese populations. However, a PopPK analysis of Phase 3 data from AF subjects indicates that Asian subjects have 74% higher apparent volume of central compartment, 42% higher bioavailability, and 48% higher apparent clearance compared to non-Asian subjects. As these changes are correlated, there is minimal change in exposure. The amount of data from African-American subjects is limited; however, no important differences were observed. No dose reduction is recommended based on race.

4.1.4 Effect of Extrinsic Factors on Edoxaban Pharmacokinetics

Because edoxaban is a substrate of the efflux transporter P-gp, numerous DDI studies were conducted with P-gp inhibitors; many of these drugs are also inhibitors of CYP3A4. Although it is a substrate of CYP3A4, P-gp represents a minor pathway in the total clearance of edoxaban.

4.1.4.1 P-glycoprotein Inhibitors

The effect of P-gp inhibitors on edoxaban PK was evaluated in individual healthy volunteer studies. Each P-gp inhibitor, some of which are also CYP inducers/inhibitors, had a different

effect on the PK parameters. In general, P-gp inhibitors increased the exposure (C_{max} and AUC) to edoxaban, but the increase was less than 2-fold.

The studied effect of P-gp inhibitors and inducers on the exposure of edoxaban is presented in Figure 4-4.

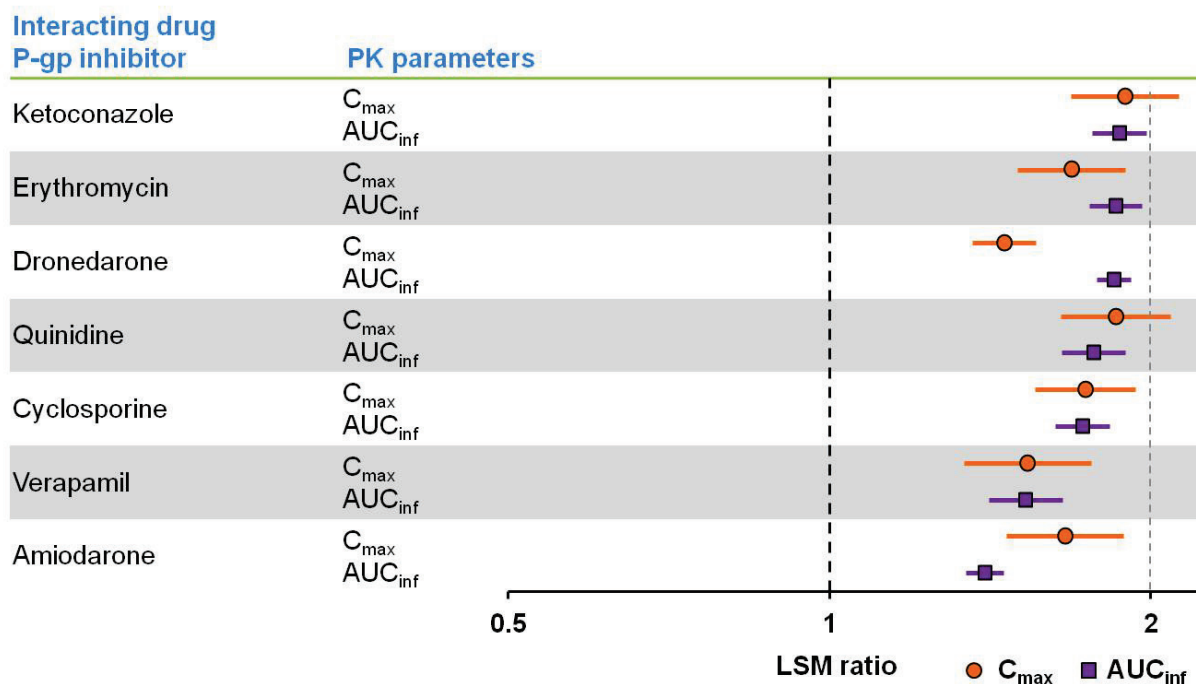


Figure 4-4 Forest Plot of LSM Edoxaban Exposure Ratios From Drug-Drug Interaction Studies With P-gp Inhibitors (With Co-Administered Drug:Without)

Abbreviations: AUC_{inf} , area under the concentration-time curve from time zero to infinity; CI, confidence interval; C_{max} , maximum observed concentration; LSM, least-squares mean; P-gp, P-glycoprotein; PK, pharmacokinetics.
Note: The error bars represent the 95% CI of the LSM.

4.1.4.2 P-glycoprotein Inducer

Rifampin is an inducer of P-gp; a moderate inducer of CYP2B6, 2C8, 2C9, and 2C19; and a strong inducer of CYP3A4. It is also an inhibitor of OATP1B1 and OATP1B3. Rifampin dosing for 7 days, with co-administration of edoxaban and rifampin on Day 7, did not affect the peak exposure of edoxaban but decreased total exposure by approximately 34%. However, the PD results showed approximately 10% or less change with rifampin, presumably due to increased contribution from active metabolites. Thus, no change in dosing is recommended with rifampin.

4.1.4.3 Commonly Used Concomitant Medications

Individual studies were conducted in healthy subjects to evaluate potential interactions with other drugs that might be commonly prescribed with edoxaban (e.g., digoxin, atorvastatin, esomeprazole, naproxen, and aspirin). Some of these drugs share a common pathway for

metabolism and transport, while such pathways are not clearly elucidated for others. A summary of exposure changes for edoxaban (from corresponding DDI studies) is provided in **Figure 4-5**. In general, changes in exposure were less than 2-fold; thus, no dose reduction is recommended on the basis of PK, with the exception of high-dose (325 mg) aspirin, which causes an increase in exposure but also an increase in anticoagulant effects. The concomitant usage of high doses of aspirin is not recommended. Similarly, due to an increased risk of bleeding, chronic use of naproxen (for ≥ 4 days) with edoxaban is not recommended.

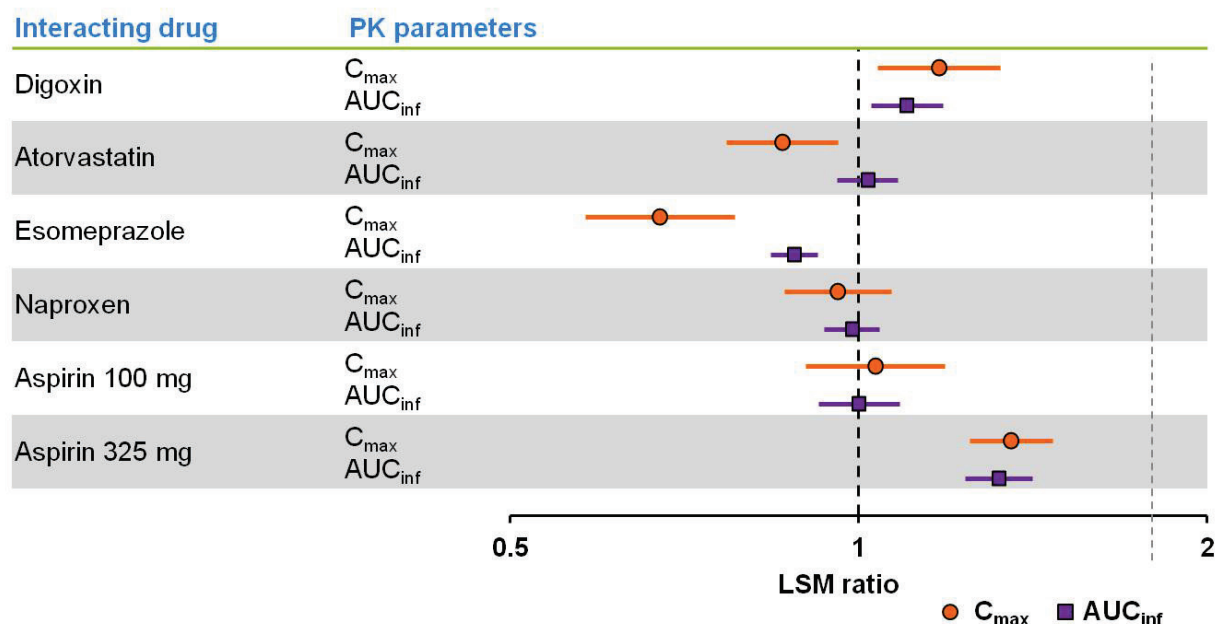


Figure 4-5 Forest Plot of LSM Edoxaban Exposure Ratios From Drug-Drug Interaction Studies With Likely Coadministered Medications (With Co-Administered Drug:Without)

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max} , maximum observed concentration; LSM, least-squares mean; PK, pharmacokinetics.

Note: The error bars represent the 95% CI of the LSM.

4.2 Pharmacodynamics

In vitro edoxaban inhibited FXa, with inhibition constant (K_i) values of 0.561 nM for free FXa, and exhibited $> 10,000$ -fold selectivity for FXa over other coagulation factors.

Following single- or multiple-dose administration, the effect-time profiles for PD parameters paralleled the plasma concentration-time profiles. The plasma-concentration-time profile of edoxaban, on single- and multiple-dosing, parallels anti-FXa activity (**Figure 4-6**), with peak concentrations achieved within 1 to 3 hours, and decreasing to baseline levels by 24 hours.

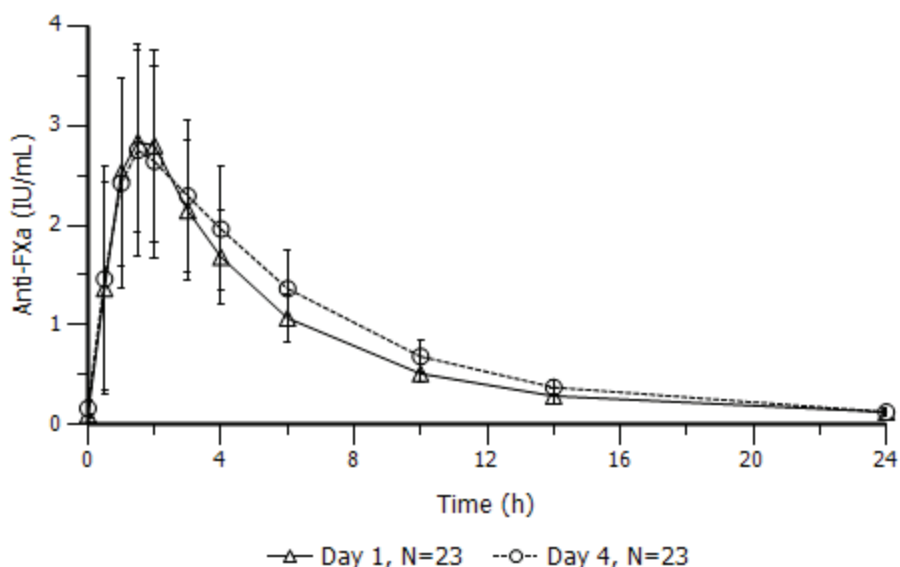


Figure 4-6 Mean (± SD) Anti-FXa Profile Over 24 Hours Following Single and Steady-State (Day 4) Administration of 60 mg QD Edoxaban

Abbreviations: FXa, factor Xa; h, hour; IU, international unit; QD, once daily; SD, standard deviation.
Note: Mean presented as arithmetic mean.

Single oral doses of edoxaban from 10 to 150 mg resulted in a rapid increase in anti-FXa activity and rapid prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT). For all dose levels, the maximum activity was observed between 1 to 3 hours post-dose. Recovery to pre-dose dose values was dose-dependent, with return to baseline by 24 to 36 hours post-dose in all subjects. For QD dosing, multiple-dose administration of edoxaban resulted in similar peak PT, aPTT, and anti-FXa activity on Day 10 as on Day 1. A direct linear correlation was observed between plasma concentrations and PT, aPTT, and anti-FXa activity, suggesting that single doses up to 150 mg did not achieve maximum response using these specific assays. In addition to prolongation of PT and aPTT, a rapid increase in anti-FXa activity was observed along with an inhibition of TG. Repeat-dose administration of edoxaban showed a rapid and sustained inhibition of thrombus-formation and turnover biomarkers (thrombin anti-thrombin complexes, prothrombin fragment 1 + 2 [F1+2], and D-dimer). However, biomarkers correlating best with clinical anticoagulation status and bleeding events on edoxaban remain to be defined. No rebound effect was observed after cessation of edoxaban in a clinical pharmacology study (PRT009) based on biomarkers of thrombus formation.

4.2.1 Switching From Another Anticoagulant to Edoxaban

Switching from various anticoagulants to edoxaban was examined in healthy subject studies through effects on PD markers of coagulation. Studies with warfarin, rivaroxaban, and apixaban evaluated the effect on PT prolongation of pretreatment with each anticoagulant before edoxaban initiation; with dabigatran, aPTT was the primary biomarker; and with enoxaparin, TG was the primary biomarker.

Warfarin: Administering edoxaban 60 mg 24 hours after cessation of therapeutic warfarin (INR 2.0-3.0) was associated with a statistically significant increase in INR and PT compared with placebo for the first 12 hours, but the mean values were similar to placebo within 24 hours of dosing.

Enoxaparin: Edoxaban administered 12 hours after the last enoxaparin dose did not potentiate anti-factor IIa (FIIa) activity, and the inhibitory effect on TG was similar or lower to that of an enoxaparin dose alone (A-U136). The anti-FXa activity of edoxaban dosed 12 hours after enoxaparin 1 mg/kg, administered subcutaneously (SC) was only slightly higher than that for edoxaban dosed alone. Therefore, switching from enoxaparin to edoxaban is recommended at the next scheduled dosing time for enoxaparin.

Rivaroxaban: A single oral dose of edoxaban 60 mg administered on Day 4, following multiple-dose administration of 20 mg rivaroxaban QD for 3 days, produced anticoagulant effects, as assessed by PT and other biomarkers such as anti-FXa, aPTT, and TG, similar to dosing of edoxaban, 60 mg once daily for 4 days (A-U151). The peak values for PT on Day 4 for edoxaban dosed alone (21.75 ± 2.46 seconds) were similar to edoxaban dosed after switching from rivaroxaban (21.83 ± 2.88 seconds). Therefore, switching from rivaroxaban to edoxaban is recommended at the next scheduled dosing time of rivaroxaban.

Dabigatran: Switching from multiple-dose administration of dabigatran 150 mg BID for 3 days to an edoxaban 60 mg single dose produced anticoagulant effects that were consistent with the PD effects of multiple-dose administration of dabigatran (A-U151). The peak values for aPTT on Day 4 for edoxaban dosed alone (35.87 ± 3.15 seconds) were lower than for edoxaban dosed after switching from dabigatran (50.83 ± 8.92 seconds). The higher aPTT values upon switching from dabigatran represent residual effects of dabigatran and are within the reported range for median aPTT values (of $1.5 \times$) for the majority of subjects at 12 hours after cessation of dabigatran 150 mg BID therapy. Therefore, switching from dabigatran to edoxaban is recommended at the next scheduled dosing time of dabigatran (12 hours after last dose).

Apixaban: The anticoagulant effects of edoxaban 60 mg once daily for 4 days, versus when switching from multiple-dose administration of apixaban 5 mg BID for 3 days to edoxaban 60 mg single dose were similar, as assessed by PT and other biomarkers such as anti-FXa, aPTT, TG assay, and bleeding time (A-E152). The peak values for PT on Day 4 for edoxaban dosed alone (23.05 ± 2.46 seconds) were similar to edoxaban dosed after switching from apixaban (22.65 ± 1.92 seconds). Therefore, switching from apixaban to edoxaban is recommended at the next scheduled dosing time of apixaban.

Based on these studies, edoxaban can be initiated at the next scheduled dosing time for all other anticoagulant drugs.

4.2.2 Reversal of Anticoagulant Effects of Edoxaban

As with all NOACs, no specific reversal agent for edoxaban is currently available. Nonclinical and clinical data suggest that prothrombin complex concentrate (PCC), activated PCC (aPCC), or activated recombinant factor VII (rVIIa) can be considered as potential reversal agents for edoxaban; however, this premise is based on reversal of biomarker responses to edoxaban. There are currently no data on the effect of PCC, aPCC or rVIIa on bleeding in edoxaban-treated patients. A clinical study showed differential effects of a 3-factor PCC on PT and endogenous thrombin potential (ETP). Findings were consistent with a recently published abstract that

indicated in healthy volunteers ETP was more sensitive to a 3-factor PCC while PT was more sensitive to a 4-factor PCC.⁴³ Thus, potential reversal agents may differentially affect biomarkers of FXa inhibitor activity, and, unlike the situation for warfarin, it is not yet clear which biomarkers correlate best with clinical anticoagulation status and bleeding events. Although no clinical studies have been conducted to validate the use of PCC, aPCC, or rVIIa (as reversal agents for edoxaban), consistent with edoxaban's mode of action, these are logical choices in urgent situations requiring immediate reversal of edoxaban activity. Based on biomarker data, a PCC dose of 25 to 50 international units (IU)/kg is predicted to be sufficient to reverse the anticoagulation effects of a therapeutic dose of edoxaban.

4.3 Cardiac Polarization

In an active and placebo-controlled, healthy subject "thorough QT/QTc study", edoxaban doses of 90 and 180 mg did not have a threshold pharmacologic effect on cardiac repolarization. The upper bounds of the 95% 1-sided confidence intervals (CIs) for the least-squares mean (LSM) of the placebo-corrected QTc interval based on an individual correction (QTcI) change from time-matched baseline did not exceed 4 milliseconds at any time point after administration of either dose. The absolute value of the QTcI interval did not exceed 450 milliseconds for any subject (on either dose of edoxaban), and all except 1 subject had changes in QTcI that were below 30 milliseconds (at all time points). One subject in the 90 mg edoxaban dose group had a change in QTcI value of 32 milliseconds at 10 hours post-dose. No clinically relevant changes in electrocardiogram (ECG) waveforms were noted on edoxaban treatment. A positive correlation between plasma concentrations and change in QTcI was not observed at edoxaban concentrations up to 857 ng/mL.

4.4 Overall Summary and Conclusions

The clinical pharmacology of edoxaban has been well characterized. Clinically relevant effects of intrinsic factors (body weight and renal function) and extrinsic factors (P-gp inhibitors) on edoxaban exposure were identified and helped inform development of the dose-adjustment strategy employed in the Phase 3 trial.

5.0 CLINICAL DEVELOPMENT PROGRAM IN ATRIAL FIBRILLATION

5.1 Overview

The clinical development program of edoxaban in AF is composed of five Phase 2 studies and one large Phase 3 trial involving > 23,000 subjects in total (**Table 5-1**). The Phase 2 controlled studies conducted in subjects with AF were primarily designed to evaluate the safety (bleeding events) of 3 months' therapy at different dose levels and regimens of edoxaban compared with warfarin. The efficacy and safety data supporting the AF indication are derived from the pivotal Phase 3 trial, ENGAGE AF-TIMI 48.⁴⁴ Supportive data are available from studies in other indications, including a Phase 3 trial (Hokusai VTE) that evaluated edoxaban for the treatment of VTE and prevention of recurrent VTE,⁴⁵ Phase 2/3 VTE prophylaxis studies in subjects undergoing orthopedic surgeries, Phase 1 PK/PD/DDI studies, and ongoing studies. This briefing document will focus primarily on the data from ENGAGE AF-TIMI 48.

Table 5-1 Summary of Edoxaban Clinical Studies

Study Type	Planned Duration of Treatment	Number of Subjects Treated		
		Edoxaban	Control Group	Total
Studies in Atrial Fibrillation				
Phase 3 (ENGAGE AF-TIMI 48)	2.5 years	14,069	7036 (warfarin)	21,026
Phase 2 studies				
J03—open label, testing edoxaban 30, 45, and 60 mg BID	10 weeks	32	0	32
J05—open label, testing edoxaban 5, 15, and 30 mg QD	6 weeks	24	0	24
PRT018—randomized, testing edoxaban 30 mg QD & BID, and 60 mg QD & BID	12 weeks	893	250 (warfarin)	1143
C-J225—randomized, testing edoxaban 30, 45, and 60 mg QD	12 weeks	394	125 (warfarin)	519
C-J226—randomized, testing edoxaban 30 and 60 mg QD	12 weeks	159	75 (warfarin)	234
Supportive Studies in Other Indications				
Phase 3 (Hokusai VTE): VTE treatment and secondary prevention	3-12 months	4118	4122 (warfarin)	8240
Phase 2/3: VTE prophylaxis in subjects undergoing orthopedic surgeries (J-STARS)	7-14 days (postoperative; in hospital)	2638	1040 (enoxaparin, dalteparin, placebo)	3678
Phase 1 PK/PD/DDI studies (integrated): healthy volunteers or special populations	Single or multiple dose	1468 ^{a,c}	159 ^b	1627 ^c
Phase 3 severe renal impairment studies in Japanese subjects	2 or 12 weeks	152	20 (fondaparinux)	172
Other ongoing studies: eTRIS (subjects with DVT) and ePAD (peripheral arterial disease)	12 weeks	157	130 (LMWH/warfarin or clopidogrel)	287

Abbreviations: AF, atrial fibrillation; BID, twice daily; DDI, drug-drug interaction; DVT, deep vein thrombosis; ePAD, Edoxaban in Peripheral Arterial Disease; eTRIS, Edoxaban Thrombus Reduction Imaging Study; LMWH, low molecular weight heparin; NA, not applicable; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; VTE, venous thromboembolism.

^a Includes subjects with renal or hepatic impairment in the integrated Phase 1 studies.

^b Excludes concomitant treatment groups in DDI studies.

^c Includes non-integrated data from healthy volunteers or subjects with end-stage renal disease undergoing hemodialysis.

5.2 Selection of Edoxaban Dosing Regimens for the Phase 3 Trial in Atrial Fibrillation (ENGAGE AF-TIMI 48)

The edoxaban dosing regimens for the Phase 3 ENGAGE AF-TIMI 48 trial were selected based on data from Phase 1 PK/PD and DDI studies, Phase 2 studies in subjects undergoing lower extremity orthopedic surgeries (approximately 10 days of treatment) and subjects with AF (approximately 12 weeks of treatment), and modeling and simulation.

The safety data on bleeding events observed in Phase 2 studies in subjects with AF played the primary role in selecting the edoxaban dosing regimens for the Phase 3 trial. The Phase 1/2 PK/PD evaluations including population PK and modeling and simulation data were important in

recommending dose reductions for subjects with renal impairment, concomitant use of P-gp inhibitors or low body weight.

Phase 2 studies in AF subjects showed that subjects treated with BID regimens had higher bleeding rates than those treated with QD regimens. Consequently, the Phase 3 trial included only QD regimens. Phase 2 studies in AF also showed that the subjects with body weight ≤ 60 kg had higher bleeding than those with > 60 kg; consequently the Phase 3 trial included dose reduction for subjects with body weight ≤ 60 kg. The Phase 1/2 PK/PD evaluations including PopPK and modeling and simulation data also support the QD regimen.

Phase 2 AF studies were primarily designed to evaluate safety of treatment for 3 months with the goal to identify the highest tolerated dose regimen of edoxaban (with bleeding similar or lower than warfarin). That dose regimen would then be used in Phase 3 to maximize the chances for a better or similar efficacy profile compared with warfarin.

Evaluation of the effects of intrinsic factors (CrCL and body weight) on PK indicated dose reductions for subjects with low CrCL (≤ 50 mL/min) and low body weight (≤ 60 kg), and evaluations of the DDI studies indicated dose reductions for subjects requiring P-gp inhibitors.

In the Phase 2 study of subjects with nonvalvular AF (PRT 018), 1146 subjects were randomized to receive either edoxaban at a dose of 30 mg QD, 30 mg BID, 60 mg QD, or 60 mg BID, or warfarin (INR 2.0-3.0) for 3 months. Of the 4 edoxaban dosage regimens tested in this study, the 30 mg BID and 60 mg BID groups demonstrated higher incidence rates of bleeding (all categories combined) than the warfarin control group. The Data Monitoring Committee (DMC) discontinued the 60 mg BID regimen before the end of the study by due to increased bleeding. The 60 mg QD and 30 mg QD groups demonstrated similar and lower bleeding rates (all categories combined), respectively, than the warfarin group. Similarly, results of a Japanese study (J-225) in subjects with AF also showed that the edoxaban 60 mg QD and 30 mg QD groups had overall bleeding incidences similar to that of the warfarin control group. However, edoxaban-treated Japanese subjects with body weight ≤ 60 kg had a significantly higher incidence of bleeding than those with body weight > 60 kg.

For the total daily dose, edoxaban 30 mg BID (1.49%) demonstrated greater bleeding (all bleeds) than 60 mg QD (0.92%). The 60 mg BID dose regimen was discontinued early due to unacceptable bleeding. A logistic regression model showed that steady-state trough concentrations ($C_{\min,ss}$) were a better predictor of bleeding than peak concentrations ($C_{\max,ss}$) or total exposure (AUC_{ss} ; **Figure 5-1**). Relative to the observed warfarin bleeding, only the 30 and 60 mg QD dose regimens demonstrated acceptable bleeding profiles. Both the 30 and 60 mg BID dose regimens resulted in plasma concentrations that remained above the $C_{\min,ss}$ corresponding to warfarin bleeding rate, while the 30 and 60 mg QD dose regimens had concentrations elevated at this level for approximately 12 and 20 hours, respectively.

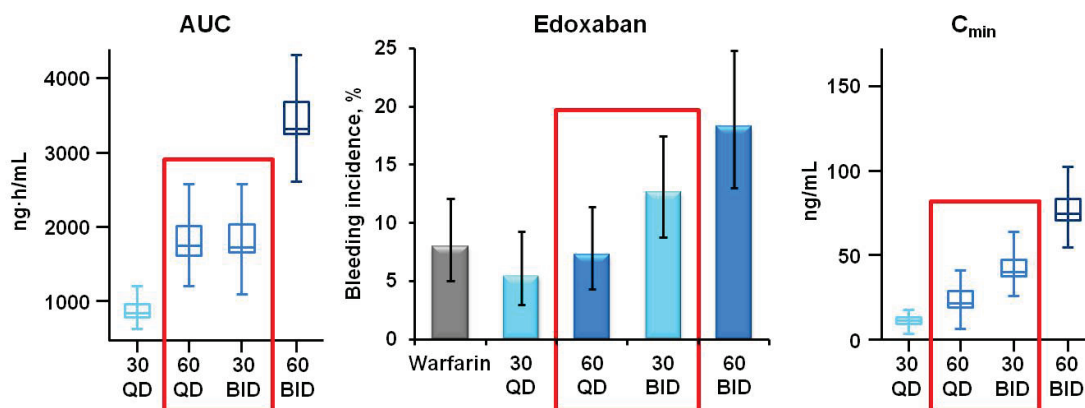


Figure 5-1 Edoxaban in AF: Exposure and Bleeding

Abbreviations: AF, atrial fibrillation; AUC_{ss}, steady-state area under the concentration-time curve; BID, twice daily; C_{max,ss}, maximum steady-state plasma concentration; C_{min,ss}, minimum steady-state plasma concentration; QD, once daily.

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Effects of edoxaban on anti-FXa activity were also evaluated in Phase 2 study (PRT 018). The results showed an anti-FXa activity level of 2.5 IU/L at 1 to 3 hours post-dose (~peak effect) and 0.625 IU/L just prior to the next dose (~trough effect), indicating a trough/peak ratio of 0.25 or approximately 25% of the peak effect at trough.

In the Phase 2 studies conducted for VTE prophylaxis in subjects undergoing orthopedic surgery (7 to 14 days post-surgery treatment), both edoxaban 30 mg and 60 mg QD showed efficacy. Edoxaban 60 mg QD showed greater efficacy (preventing DVT/pulmonary embolism [PE]) compared to edoxaban 30 mg QD.

Based on the above described overall results of Phase 1/2 clinical studies, DDI studies, and extrapolated PK/PD evaluations, it was concluded that edoxaban 60 mg QD can be considered the best tolerated higher-dose regimen compared with warfarin. The 30 mg QD dose (1/2 of the highest tolerated regimen from a safety perspective) was included to evaluate 2 regimens in a large Phase 3 trial to maximize the chances of finding the optimal regimen of edoxaban compared to warfarin from both a safety and efficacy perspective. Edoxaban 60 mg QD and 30 mg QD were selected as the 2 dosing regimens that would likely provide non-inferior efficacy to warfarin and a bleeding safety benefit. Edoxaban dose reductions by 50% were recommended for moderate renal impairment (CrCL 30 to 50 mL/min), concomitant use of specific P-gp inhibitors (verapamil, quinidine, or dronedarone), and low body weight (≤ 60 kg).

5.3 ENGAGE AF-TIMI 48

ENGAGE AF-TIMI 48 was an event-driven, Phase 3, multinational, multicenter, double-blind, double-dummy, randomized trial conducted to determine whether edoxaban was noninferior to warfarin (INR 2.0-3.0) with respect to the composite primary efficacy endpoint of stroke (ischemic or hemorrhagic) or SEE in subjects with nonvalvular AF. This study investigated 2 edoxaban dosing regimens: a higher-dose regimen (60 mg QD with possible dose reduction to 30 mg QD), and a lower-dose regimen (30 mg QD with possible dose reduction to 15 mg QD). ENGAGE AF-TIMI 48 was the largest, most geographically diverse, adequately controlled

clinical trial of a NOAC conducted in subjects with AF, and it was the only double-blind study to evaluate 2 dosing regimens with a prespecified dose-reduction strategy to mitigate bleeding risk. In addition, the study design included a prespecified and comprehensive procedure to allow subjects to safely transition at the end of the clinical trial to an approved anticoagulant therapy.

5.3.1 Study Design and Methods

5.3.1.1 Study Design

Eligible subjects were stratified by CHADS₂ risk score at randomization: Stratum 1–CHADS₂ risk score 2 and 3; and Stratum 2–CHADS₂ risk score 4, 5, and 6 (**Figure 5-2**). Within each CHADS₂ stratum, subjects were further stratified based on whether they required edoxaban dose reduction for factors such as moderate renal impairment (CrCL 30 to 50 mL/min, as calculated using the Cockcroft-Gault formula), low body weight (≤ 60 kg), or a need for concomitant treatment with P-gp inhibitors (quinidine, verapamil, dronedarone).

After the second stratification, subjects were randomly assigned in a 1:1:1 ratio to the following 3 treatment groups:

- Edoxaban 60/30 mg (60 mg QD with dose reductions to 30 mg QD for moderate renal impairment, low body weight, or specific concomitant P-gp inhibitors; hereafter referred to as the edoxaban 60/30 mg regimen or group)
- Edoxaban 30/15 mg (30 mg QD with dose reductions to 15 mg QD for moderate renal impairment, low body weight, or specific concomitant P-gp inhibitors; hereafter referred to as the edoxaban 30/15 mg regimen or group)
- Warfarin (QD with dose adjusted to maintain INR 2.0-3.0)

During the study, dynamic dose modifications (decrease or increase) were allowed for subjects who met 1 of the above-mentioned dose modification criteria. A subject with multiple factors requiring edoxaban dosage reduction were to get the halved edoxaban dosage regimen, similar to a subject with only 1 factor requiring edoxaban dosage reduction (i.e., subjects could only be dose-reduced once).

All subjects were to be treated and followed until approximately 672 targeted primary efficacy endpoint events were collected. Based on the accrual of primary endpoint (stroke or SEE) events, study close-out procedure commenced via a common study end date (CSED).

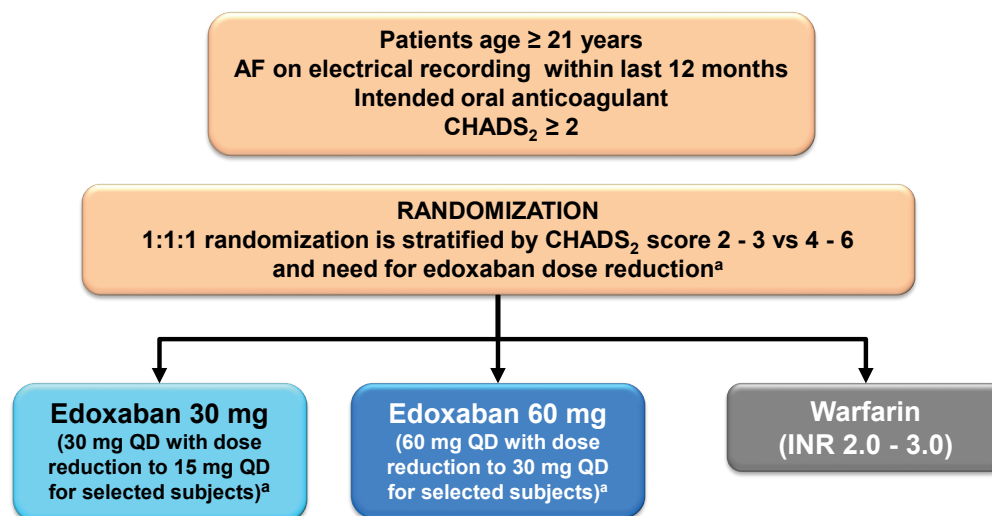


Figure 5-2 ENGAGE AF-TIMI 48 Study Design

Abbreviations: AF, atrial fibrillation; INR, international normalized ratio; min, minute; QD, once daily.

^a Dose reduced by 50% if creatinine clearance 30-50 mL/min, body weight ≤ 60 kg or subject receiving verapamil, quinidine or dronedarone.

5.3.1.2 Target Study Population

This study enrolled subjects with documented AF within the preceding 12 months and in whom anticoagulant therapy was indicated for the duration of the study. Subjects must have been at a medium to high risk for stroke and SEE (CHADS₂ score ≥ 2).

Inclusion Criteria

Subjects were included if they met the following inclusion criteria:

- History of AF documented by an electrical tracing (routine 12-lead ECG, Holter monitor [continuous ECG recording], rhythm strip, intracardiac electrogram, or pacemaker or implantable cardiac defibrillator interrogation) within the prior 12 months and for which anticoagulation therapy was indicated and planned for the study duration
 - Including paroxysmal, persistent, or permanent AF
 - Including subjects with or without previous VKA experience
- CHADS₂ index score ≥ 2

Key Exclusion Criteria

Subjects were excluded if they met any of the following key criteria:

- Transient AF secondary to other reversible disorders (e.g., thyrotoxicosis, cardiac or thoracic surgery, pneumonia, severe anemia)
- Severe renal insufficiency (calculated CrCL < 30 mL/min)
- High bleeding risk (i.e., past history of intracranial hemorrhage [ICH] or contraindications to anticoagulant therapy)

- Dual antiplatelet therapy (e.g., aspirin plus thienopyridine) or anticipated need to receive such therapy
- Moderate or severe mitral stenosis, unresected atrial myxoma, or mechanical heart valve
- Acute myocardial infarction (MI), stroke, acute coronary syndrome, or percutaneous coronary intervention within the previous 30 days

5.3.1.3 Study Treatments

Subjects were randomly assigned to receive the edoxaban 60/30 mg regimen, the edoxaban 30/15 mg regimen, or warfarin. To maintain the blind, subjects randomized to an edoxaban regimen were dispensed active edoxaban plus placebo-to-match warfarin and subjects randomized to the warfarin treatment group were dispensed active warfarin plus placebo-to-match edoxaban.

Edoxaban (Experimental) Treatments

In both edoxaban groups (60/30 or 30/15 mg QD), the edoxaban dosage regimen was to be reduced by 50% as described above for subjects with 1 or more of the following factors:

- Moderate renal impairment (calculated CrCL 30 to 50 mL/min),
- Low body weight (≤ 60 kg),
- Concomitant treatment with specific P-gp inhibitors (verapamil, quinidine, dronedarone)

For low body weight and/or moderate renal impairment present at randomization, the edoxaban dose was to be reduced permanently.

After randomization, if the subject's CrCL became 30 to 50 mL/min (confirmed by repeat measurement at least 1 week apart) and the CrCL change was $> 20\%$ of the subject's baseline CrCL, then the edoxaban dose was to be reduced permanently. Even if the subject subsequently experienced improved CrCL, the edoxaban dose was to remain halved.

For specified concomitant medications (verapamil, quinidine, dronedarone), dosage adjustment (decrease or increase) of edoxaban could have occurred at any time during the study. The edoxaban dose was to be reduced (60 to 30 mg QD or 30 to 15 mg QD) at any time the subject was taking 1 or more of these concomitant medications. Conversely, the edoxaban dose was to be returned to the regular dose of 60 mg QD (edoxaban 60/30 mg regimen) or 30 mg QD (edoxaban 30/15 mg regimen) any time the subject was not taking the concomitant medication, unless another criterion for dose reduction was met.

Warfarin (Control) Treatment

Warfarin was the active blinded control. Warfarin doses were to be adjusted to maintain INR 2.0-3.0. A Japan-specific amendment was created to allow investigators in Japan to comply with Japanese guidelines for warfarin management in subjects ≥ 70 years of age. In those subjects, the dose of warfarin was to be adjusted to maintain an INR between 2.0 and 2.5 (INR 2.0-2.5).

INR Measurements Before Randomization

Before randomization, for study qualification purposes, the INR was assessed. The INR result requirements prior to randomization included the following:

- All subjects must have had an INR value ≤ 2.5 before randomization.
- For subjects receiving open-label VKA at the time of randomization, INR must have been ≤ 2.5 within 48 hours prior to randomization, provided that the VKA dose had not been increased within those 48 hours.
- If the subject's INR was ≤ 2.5 , the subject could have been randomized into the study.
- If the subject's INR was > 2.5 , the subject's VKA should have been adjusted and the INR monitored until it was ≤ 2.5 .
- For subjects who had not received any VKA during the 60 days prior to randomization, the INR must have been ≤ 2.5 within 60 days before randomization.
- At the investigator's discretion, during study qualification, the subject may have been given a parenteral (IV or SC) anticoagulant as approved for use in the local country. This anticoagulant use was meant as a "bridge" so that the subject remained protected after discontinuing prior VKA to get the INR ≤ 2.5 before randomization.

Initiating Treatment with Blinded Study Drug

For subjects who were VKA-experienced before the initial dose of double-blind study drug, the starting dosage (mg/day) of warfarin (or placebo-to-match warfarin) was to be determined by the investigator based on the subject's history (previous VKA maintenance regimen) and overall clinical profile including concomitant therapies.

For subjects who were not VKA-experienced before the initial dose of double-blind study drug, the starting dosage (mg/day) of warfarin (or placebo-to-match) was to be determined by the investigator based on the clinical profile (age, body weight, CrCL, other clinical condition[s], and concomitant therapies) of the subject.

Adjusting Warfarin (Placebo-to-Match) Dosage to Maintain INR 2.0-3.0

Dose adjustment of warfarin (or placebo-to-match) based on INR was performed according to local/regional guidelines of warfarin therapy or the representative dosing algorithm provided in the study protocol. However, in managing warfarin therapy and dose adjustment based on INR, the investigator used discretion/good clinical judgment and considered the subject's overall clinical condition, recent rate of change in INR, concomitant medications, concurrent illnesses, diet changes, alcohol intake, and other clinical factors to do what was best for the subject. The goal was to maintain the INR 2.0-3.0 throughout the study.

5.3.1.4 Transition Strategy

At the end of the study, all subjects were required to transition to an approved open-label anticoagulant therapy, unless a medical contraindication to anticoagulation existed. To maintain appropriate anticoagulation and blinding during the transition to the open-label anticoagulant at the end of study, double-blind edoxaban/placebo transition kits (TKs) were provided to be used for subjects who received their final dose of double-blind study drug at the CSED visit.

At the CSED visit, investigators measured trough INR (at least 8 hours after the last dose of study drug). Subjects were instructed not to take their study drug before they came to the site on the day of the CSED visit, as the dose was to be administered at the study site after the INR measurement.

Each TK allowed for up to 14 days of treatment. The double-blind TK contained either edoxaban (active drug) or matching placebo. The TK for subjects transitioning from edoxaban to VKA therapy contained edoxaban (active drug). The TK for subjects transitioning from warfarin study drug to VKA therapy contained placebo (edoxaban matching placebo).

Subjects who transitioned from edoxaban to an open-label VKA received both active lower-dose edoxaban and an open-label VKA until the INR reached 2.0 or for 2 weeks (whichever came first). At least 3 INR measurements were mandated between Days 4 and 14 of the transition period; the use of an approved dosing algorithm for the VKA was required to maintain INR 2.0-3.0.

Subjects transitioning to FIIa or FXa inhibitor therapy were not assigned a TK. These subjects were asked at the CSED visit to take the first dose of FIIa or FXa inhibitor 24 hours after the last dose of double-blind study drug, as long as the INR was < 2.0 . If the blinded INR on the CSED visit was ≥ 2.0 , treatment with a FIIa or FXa inhibitor was not initiated. The open INR was repeated on Day 4 (window, 4 to 7 days) and then thereafter if necessary until the INR was < 2.0 . If the INR continued to be ≥ 2.0 , the INR was repeated every 1 to 2 days until it fell to < 2.0 . Once the INR was < 2.0 , FIIa or FXa inhibitor therapy was started.

5.3.1.5 Study Endpoints and Assessments

Efficacy Outcomes

The primary efficacy endpoint was time to first stroke (ischemic or hemorrhagic) or SEE.

Secondary efficacy endpoints included:

- Composite of stroke, SEE, and cardiovascular (CV) mortality (including fatal bleed)
- Major adverse cardiac event (MACE), which is the 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

Safety Outcomes

The principal safety endpoint was adjudicated major bleeding. In addition, hepatic events were independently adjudicated by external hepatic specialists blinded to study drug treatment allocation. Safety outcomes are further described in **Section 8.0**.

Other Assessments

Net clinical outcomes—composite endpoints included:

- Stroke, SEE, major bleeding and death
- Disabling stroke, life-threatening bleeding and death
- Stroke, SEE, life-threatening bleed, and all-cause mortality

Net clinical outcomes will be discussed in **Section 12.0** as part of the benefit-risk assessment.

5.3.1.6 Statistical Methods

Statistical Considerations

Four analysis populations were defined in ENGAGE AF-TIMI 48:

- **Intent-to-treat (ITT) analysis set** included all randomized subjects.
- **Modified intent-to-treat (mITT) analysis set** included all randomized subjects who received at least 1 dose of study drug; analyses were based on randomized treatment.
- **Per Protocol (PP) analysis set** included all randomized subjects who received at least 1 dose of study drug and had no major protocol violations. Analyses were based on randomized treatment even if a subject inadvertently received the incorrect drug or dosage or had their edoxaban dose adjusted (decreased/increased) 1 or more times during the study.
- **Safety analysis set** included randomized subjects who received at least 1 dose of study drug; analyses were based on actual treatment received.

Two treatment periods were investigated:

- **Overall treatment period:** time from the reference date (randomization date or initial dose of study drug date, depending on analysis set) to the CSED visit.
- **On-treatment period:** 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.

Analysis of the Primary Efficacy Endpoint

The study protocol specified that noninferiority of edoxaban for the primary efficacy endpoint would be analyzed using 4 datasets, as shown in **Table 5-2**. The primary noninferiority analysis used the mITT analysis set for the on-treatment period.

If noninferiority was established, superiority testing was performed for the edoxaban 60/30 mg group versus warfarin for the overall study period using the ITT population.

Table 5-2 Primary Efficacy Endpoint Analyses

Analysis Set	Analysis by Study Period	
	Overall Study Period	On-Treatment Period
mITT	Noninferiority	Noninferiority (Primary Efficacy)
PP	Noninferiority	Noninferiority
ITT	Superiority	Not applicable

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat; PP, per protocol.

Primary Efficacy Endpoint Noninferiority Testing

The 2 edoxaban regimens were compared with warfarin for noninferiority (**Figure 5-3**). The time to first on-treatment event (defined as the time at risk, from the initial dose of study drug to the first event experienced by a subject while at risk) was analyzed using the Cox proportional-hazards regression model (counting process method) including treatment groups and the 2 stratification variables dichotomized CHADS₂ score and dichotomized dose-reduction factor as covariates. The 2-sided 97.5% CI ($\alpha = 0.05/2$; 2 is the number of comparisons) for the hazard ratio (HR) was estimated using the Cox regression model. If the upper limit of this CI of the HR was below 1.38, then noninferiority to warfarin was considered established for that edoxaban regimen.

Primary Efficacy Endpoint Superiority Testing

If noninferiority was confirmed for the edoxaban 60/30 mg regimen versus warfarin, the edoxaban 60/30 mg regimen would be tested for superiority (**Figure 5-3**). The time to first event was estimated by a Kaplan-Meier (KM) estimate and was compared between the edoxaban regimens and warfarin using a log-rank test, at a pairwise comparison significance level of $\alpha = 0.01$. In addition, data were examined for significance of 0.05.

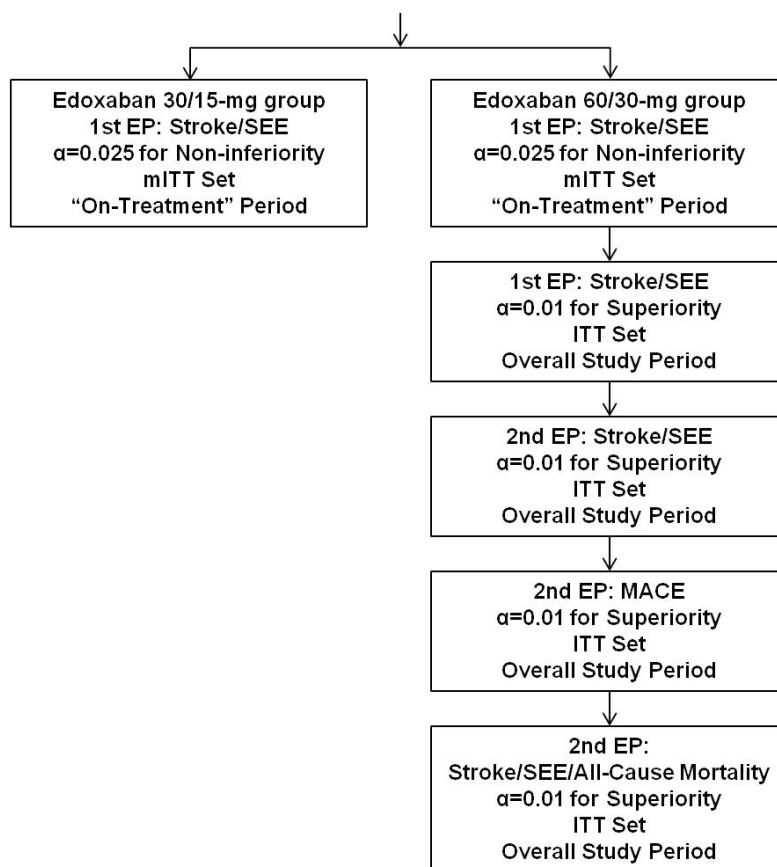


Figure 5-3 Overall Multiplicity Adjustment Testing Procedure

Abbreviations: CV, cardiovascular; EP, endpoint; ITT, intent-to-treat; MACE, major adverse cardiovascular event; mITT, modified intent-to-treat; SEE, systemic embolic event.

Analyses of Secondary Efficacy Endpoints

If superiority of the edoxaban 60/30 mg regimen versus the warfarin group was established for the primary efficacy endpoint, then superiority was tested for the secondary efficacy endpoints in a hierarchical sequence using the ITT overall analysis set and following the testing procedure as outlined for the primary analysis with each test performed at $\alpha = 0.01$:

1. Stroke/SEE/CV mortality
2. MACE
3. Stroke/SEE/all-cause mortality

For all 3 of the secondary efficacy endpoints, the time to first event was estimated by a KM estimate and was compared between the edoxaban 60/30 mg regimen and warfarin using a log-rank test at a pairwise comparison significance level of $\alpha = 0.01$. The time to first event was defined as the time from the day of randomization to the first event experienced by a subject. As the superiority of the edoxaban 60/30 mg regimen versus warfarin for the primary endpoint was not demonstrated, results of the secondary endpoints are provided with HR and 95% CI only.

Analyses of Other Efficacy Endpoints

Other efficacy endpoints were analyzed for exploratory purposes based on the ITT, mITT, and PP analysis sets with no multiplicity adjustment.

Subgroup Analyses

Subgroup analyses of the adjudicated primary endpoint were performed on the mITT on-treatment dataset based on baseline characteristics, INR time in therapeutic range (TTR) for warfarin subjects, and concomitant medications using descriptive summaries and the 2-sided 95% CIs for the HRs (each randomized edoxaban group versus warfarin). Where applicable, each subgroup was analyzed using a Cox proportional-hazards regression model including treatment group, and the 2 stratification variables (i.e., dichotomized CHADS₂ score and dichotomized dose-reduction factor) as covariates. The results were summarized using forest plots.

Subgroup data for relevant baseline characteristics included but were not limited to:

- Age (≥ 75 versus < 75 years)
- Gender (male versus female)
- CHADS₂ scores, (≤ 3 versus ≥ 4); 2, ≥ 3
- Dose-reduction factor, (dose adjusted: yes/no) and also by:
 - Body weight ≤ 60 versus > 60 kg
 - Calculated CrCL 30 to 50 mL/min, > 50 to < 80 mL/min, and ≥ 80 mL/min
 - Concomitant use of verapamil/quinidine at randomization
- VKA naive versus VKA experienced
- Geographic region/country
- Type of AF: paroxysmal, persistent, or permanent

Subgroup data by concomitant medications included aspirin, anti-platelet drugs other than aspirin, statins, angiotensin-converting enzyme (ACE) or angiotensin II receptor blocker (ARB) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), and amiodarone or dronedarone.

Subgroup data by INR TTR in warfarin subjects included center-level INR percent TTR for warfarin subjects (e.g., < 60% versus \geq 60%, < median versus \geq median, and by quartiles).

5.3.1.7 Data Monitoring and Adjudication

An independent, blinded to treatment assignment, and central study-specific Clinical Events Committee (CEC) reviewed and adjudicated prespecified key efficacy and safety endpoint events (e.g., all deaths, suspected strokes/TIAs, suspected SEEs, suspected MIs, overt bleeding events that required medical attention, and cases of predefined hepatic dysfunction).

A Sponsor-independent and study specific DMC of external experts reviewed and monitored the study data in a treatment-unblinded manner, as per the DMC charter, while the study was ongoing. The purpose of the DMC was to protect the safety of the subjects and to alert the chairman of the Study Oversight Committee if there were any concerns requiring protocol modifications or any other changes in the study. No protocol modifications were recommended by the DMC after any of their data reviews.

6.0 ENGAGE AF-TIMI 48 STUDY POPULATION

The population enrolled in ENGAGE AF-TIMI 48 was reflective of the nonvalvular AF population requiring anticoagulant therapy seen in clinical practice. Subjects had a median age of 72 years with a mean CHADS₂ score of 2.8, and approximately 53% of subjects had a CHADS₂ score ≥ 3 . Of the 21,105 subjects randomized, only 1 subject had unknown vital status at end of study, and there was a low percentage of missing data due to withdrawal of consent ($< 1.3\%$), indicating that the study was well conducted. Compliance with study treatment was high ($\sim 98\%$) and consistent across the edoxaban groups. Furthermore, double-blind warfarin therapy was administered and closely monitored to maintain INR 2.0-3.0. The median TTR of 68%, which exceeds that achieved in other NOAC trials, indicates excellent clinical management of warfarin.

6.1 Subject Disposition

Overall, 21,105 subjects were randomly assigned to the edoxaban 60/30 mg regimen ($n = 7035$), edoxaban 30/15 mg regimen ($n = 7034$), or warfarin ($n = 7036$) (ITT analysis set; **Figure 6-1**). Of these subjects, 21,026 received at least 1 dose of edoxaban 60/30 mg ($n = 7012$), edoxaban 30/15 mg ($n = 7002$), or warfarin ($n = 7012$). These 21,026 treated subjects constituted the mITT analysis set (identical to the Safety analysis set).

A similar percentage of subjects in the edoxaban 60/30 mg, edoxaban 30/15 mg, and the warfarin treatment groups completed the CSED visit (88.5%, 88.9%, and 87.5%, respectively). Reasons for not completing this study visit were death prior to CSED announcement (10.5% overall) and withdrawal of consent (1.2% overall). One subject in the edoxaban 30/15 mg group had unknown vital status at end of study. One hundred and four subjects (37 in edoxaban 60/30 mg group, 36 in edoxaban 30/15 mg group, and 31 in warfarin group) had no information on the primary endpoint data at the end of the study.

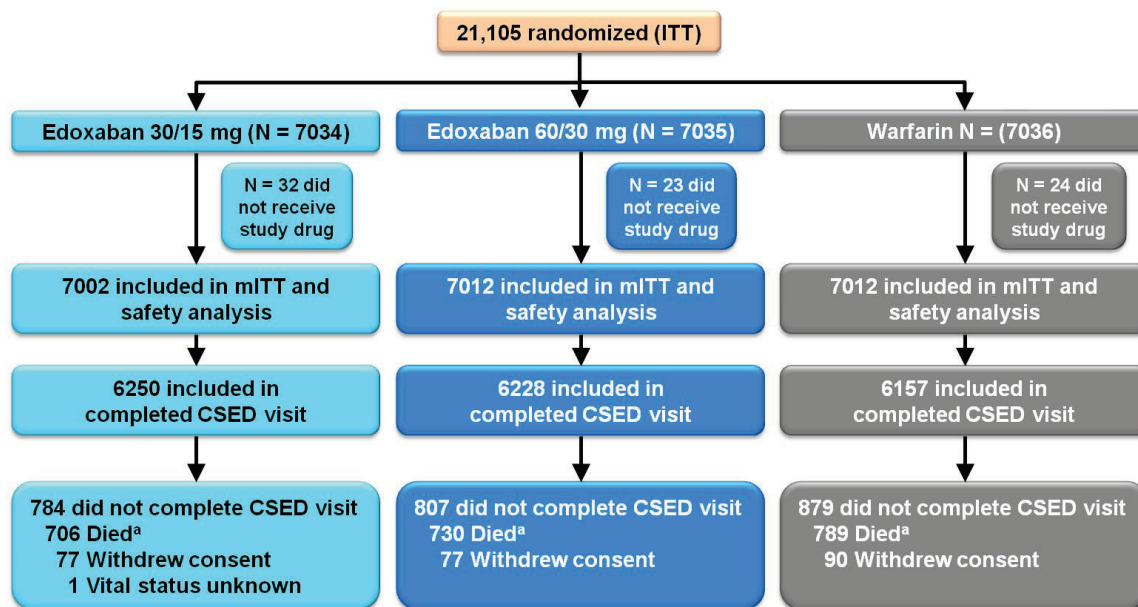


Figure 6-1 Disposition of Subjects in ENGAGE AF-TIMI 48

Abbreviations: CSED, common study end date; ITT, intent-to-treat; mITT, modified intent-to-treat.

^a Deaths before the study end date.

6.2 Dose Modifications

Approximately 25% of subjects in all 3 treatment groups had their edoxaban (or placebo in the warfarin group) dose modified (i.e., reduced) at randomization (**Table 6-1**). The most common reason for dose reduction in all 3 treatment groups was CrCL ≤ 50 mL/min (approximately 18%), either alone or in combination with other reasons. In the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin treatment groups, < 5% of subjects had their dose reduced because of low body weight only (4.2%, 4.2%, and 3.7%, respectively).

Table 6-1 Dose Reductions at Randomization: Safety Analysis Set

	Edoxaban 30/15 mg (N = 7002) n (%)	Edoxaban 60/30 mg (N = 7012) n (%)	Warfarin (N = 7012) n (%)
Subjects dose adjusted 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 body weight	381 (5.4)	364 (5.2)	414 (5.9)
Low CrCL and quinidine and/or verapamil use	28 (0.4)	31 (0.4)	31 (0.4)
Low CrCL, low body weight, and quinidine and/or verapamil use	16 (0.2)	17 (0.2)	15 (0.2)
Low body weight only	294 (4.2)	291 (4.2)	259 (3.7)
Quinidine and/or verapamil use only	169 (2.4)	167 (2.4)	156 (2.2)
Low body weight and quinidine and/or verapamil use	15 (0.2)	12 (0.2)	13 (0.2)

Abbreviations: CrCL, creatinine clearance.

The percentage of subjects in the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin treatment groups that had their edoxaban or edoxaban-placebo dose modified after randomization was low and comparable among the treatment groups (7.6%, 7.8%, and 6.7%, respectively), with very few subjects having their dose modified on more than 1 occasion (0.9%, 0.8%, and 0.9%, respectively). The most common reasons for dose modification after randomization were low CrCL, followed by concomitant use of verapamil, dronedarone or quinidine.

6.3 Demographic and Baseline Characteristics

Overall, demographic and baseline characteristics were comparable among the 3 treatment groups (**Table 6-2**). The population had a median age of 72 years with a mean CHADS₂ score of 2.8, and approximately 53% of subjects had a CHADS₂ score \geq 3. In all 3 treatment groups, CrCL was 30 to 50 mL/min in approximately 18% of subjects, and 41% of subjects were VKA naive. Approximately 25% of subjects had their dose reduced at randomization.

The percentage of subjects from each region was comparable among the treatment groups. Approximately half of the subjects were from Europe, 22% from North America, 13% from Latin America, 11% from Asia/Pacific and South Africa (excluding Japan), and 5% from Japan.

Table 6-2 Demographic and Baseline Characteristics: mITT Analysis Set

Characteristic	Edoxaban 30/15 mg (N = 7002)	Edoxaban 60/30 mg (N = 7012)	Warfarin (N = 7012)
Age (years), n	7002	7012	7012
Median	72.0	72.0	72.0
Min - max	27 - 95	25 - 96	27 - 95
Gender, n (%)	7002	7012	7012
Male	4284 (61.2)	4353 (62.1)	4383 (62.5)
Female	2718 (38.8)	2659 (37.9)	2629 (37.5)
Race, n (%) ^a	7001	7012	7012
Caucasian	5650 (80.7)	5679 (81.0)	5679 (81.0)
Black	94 (1.3)	96 (1.4)	88 (1.3)
Asian	975 (13.9)	956 (13.6)	963 (13.7)
Other	282 (4.0)	281 (4.0)	282 (4.0)
Edoxaban/placebo dose adjusted at randomization, n (%)	7002	7012	7012
Yes	1774 (25.3)	1776 (25.3)	1780 (25.4)
No	5228 (74.7)	5236 (74.7)	5232 (74.6)
CrCL (mL/min), n (%) ^b	6961	6954	6973
< 30	42 (0.6)	70 (1.0)	51 (0.7)
30 to 50	1274 (18.2)	1287 (18.4)	1297 (18.5)
> 50	5645 (80.6)	5597 (79.8)	5625 (80.2)
> 50 to < 80	3034 (43.3)	2985 (42.6)	3030 (43.2)
\geq 80	2611 (37.3)	2612 (37.3)	2595 (37.0)
Weight (kg), n (%) ^c	6996	7007	7007
\leq 50	148 (2.1)	158 (2.3)	172 (2.5)
\leq 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)

Table 6-2 Demographic and Baseline Characteristics: mITT Analysis Set

Characteristic	Edoxaban 30/15 mg (N = 7002)	Edoxaban 60/30 mg (N = 7012)	Warfarin (N = 7012)
BMI, n (%) ^c	6976	6985	6984
≤ 30	4160 (59.4)	4116 (58.7)	4238 (60.4)
> 30	2816 (40.2)	2869 (40.9)	2746 (39.2)
Mean (SD)	29.5 (5.93)	29.6 (6.05)	29.3 (5.89)
Verapamil or quinidine use at randomization, n (%) ^d	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 (%) ^e	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)
VKA use, n (%) ^f	7001	7012	7012
Naïve	2857 (40.8)	2879 (41.1)	2888 (41.2)
Experienced	4144 (59.2)	4133 (58.9)	4124 (58.8)
Type of atrial fibrillation, n (%)	7001	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)

Abbreviations: BMI, body mass index; CHADS₂, Index score for stroke prediction based on the scoring system for Congestive heart failure, High blood pressure, Age, Diabetes, previous Stroke/Transient Ischemic Attack; CrCL, creatinine clearance; DosAdj, dose adjustment; mITT, modified intent-to-treat; SD, standard deviation; USA, United States of America; VKA, vitamin-K antagonist.

^a Subjects could only select 1 race. "Other" was chosen if none of the other prespecified categories applied, or if the subject was multiracial.

^b CrCL was derived from information recorded in central lab or local lab results.

^c Weight and BMI were derived from information recorded in the electronic case report form (eCRF).

^d Verapamil/quinidine use at randomization was derived from information recorded in both the Interactive Voice and Web Response System (IXRS) and the eCRF. If at least 1 source indicated verapamil/quinidine use, then the subject was counted as "Yes," else "No."

^e CHADS₂ = derived index score for stroke prediction per information recorded in the eCRF.

^f VKA Experienced is defined as "Current Users" as well as "Former Users" who took VKA for more than 2 months. VKA Naïve is defined by the complement of VKA experienced for those subjects with eCRF data present.

6.3.1 Demographic and Baseline Characteristics by Dose Reduction at Randomization

Demographic and baseline characteristics by treatment administered are presented in **Table 6-3**. There were differences in the demographic and baseline characteristics between subjects who had their dose reduced compared with subjects who received the full dose. In all 3 treatment

groups in subjects who had their dose reduced, the median age was higher (77 years) compared with subjects who received the full dose (70 years), there were more females (approximately 55% vs 32%), the median CrCL was lower (approximately 46 vs 79 mL/min), the median weight was lower (approximately 65 vs 86 kg), more subjects had a CHADS₂ scores ≥ 3 (approximately 62% vs 50%), and more subjects had a prior stroke or TIA (approximately 32% vs 27%).

Overall, the subset of subjects who received the reduced dose was a higher risk population (older subjects, higher CHADS₂ score, and past history of stroke or TIA) for the primary efficacy and safety endpoints.

Table 6-3 Demographic and Baseline Characteristics by Treatment Administered: mITT Analysis Set

Regimen Treatment Received	Subjects With Dose Reduction ^a			Subjects Who Received the Full Dose		
	Edoxaban 30/15 mg 15 mg (N = 1774)	Edoxaban 60/30 mg 30 mg (N = 1776)	Warfarin PBO-Edoxaban (N = 1780)	Edoxaban 30/15 mg 30 mg (N = 5228)	Edoxaban 60/30 mg 60 mg (N = 5236)	Warfarin PBO-Edoxaban (N = 5232)
Age (years)	1774	1776	1780	5228	5236	5232
Median	77	77	77	70	70	70
≥ 75, n (%)	1137 (64.1)	1160 (65.3)	1171 (65.8)	1652 (31.6)	1678 (32.0)	1634 (31.2)
≥ 80, n (%)	622 (35.1)	617 (34.7)	640 (36.0)	575 (11.0)	560 (10.7)	555 (10.6)
Gender, n (%)	1774	1776	1780	5228	5236	5232
Male	806 (45.4)	802 (45.2)	811 (45.6)	3478 (66.5)	3551 (67.8)	3572 (68.3)
Female	968 (54.6)	974 (54.8)	969 (54.4)	1750 (33.5)	1685 (32.2)	1660 (31.7)
CrCL (mL/min) ^b	1765	1760	1769	5196	5194	5204
Median	46.7	46.2	45.7	78.7	78.7	78.6
≤ 50, n (%)	1081 (60.9)	1123 (63.2)	1151 (64.7)	235 (4.5)	234 (4.5)	197 (3.8)
Weight (kg) ^c	1774	1775	1778	5222	5232	5229
Median	65.3	65	65	86	86.2	86
≤ 50, n (%)	148 (8.3)	158 (8.9)	172 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)
≤ 60, n (%)	690 (38.9)	675 (38.0)	693 (38.9)	2 (< 0.1)	6 (0.1)	4 (< 0.1)
CHADS₂ score	1774	1776	1780	5228	5236	5232
Mean (SD)	3 (1.03)	3 (1.04)	3 (1.05)	2.8 (0.93)	2.8 (0.93)	2.8 (0.95)
≥ 3, n (%)	1081 (60.9)	1110 (62.5)	1091 (61.3)	2624 (50.2)	2674 (51.1)	2595 (49.6)
4-6, n (%)	505 (28.5)	529 (29.8)	517 (29.0)	1054 (20.2)	1077 (20.6)	1068 (20.4)
Prior stroke or TIA ^d	1774	1776	1780	5228	5236	5232
Yes, n (%)	600 (33.8)	566 (31.9)	562 (31.6)	1399 (26.8)	1402 (26.8)	1421 (27.2)

Abbreviations: CHADS₂, Index score for stroke prediction based on the scoring system for Congestive heart failure, High blood pressure, Age, Diabetes, previous Stroke/Transient Ischemic Attack; CrCL, creatinine clearance; eCRF, electronic case report; mITT, modified intent-to-treat; PBO, placebo; TIA, transient ischemic attack; SD, standard deviation.

^a At randomization, there were dosage adjustments for moderate renal impairment, low body weight, or specified concomitant medications.

^b CrCL was derived from central or local lab results.

^c Weight was derived from information recorded in the electronic case report form (eCRF).

^d Medical history of prior stroke or TIA was based on the cardiovascular page of the eCRF.

Note: Percentages are based on N, the total number of subjects.

6.3.2 Cardiovascular History and Disease Characteristics at Baseline

The baseline CV history was comparable among the edoxaban 60/30 mg, edoxaban 30/15 mg, and the warfarin treatment groups. Overall, approximately 94% of subjects had prior hypertension, 58% had CHF, and 28% had prior stroke or TIA.

6.4 Concomitant Medications

6.4.1 Concomitant Medications Used at Baseline (Study Entry)

The use of medications of interest (predefined CV and other medications) at baseline was comparable among the treatment groups. The percentage of VKA-experienced subjects was 59%. More than 65% of subjects were receiving ACE inhibitors or ARBs, or beta blockers, and approximately 60% were taking diuretic agents. Other more frequent medications used included lipid-lowering agents (approximately 48%), aspirin (approximately 29%), calcium-channel blockers (approximately 31%), and amiodarone (approximately 12%).

6.4.2 Concomitant Medications Used During the Study

The use of concomitant medications of interest during the study in the mITT analysis set overall study period was generally comparable among the 3 treatment groups (**Table 6-4**). The most commonly used concomitant medications were ACE inhibitors or ARBs, beta blockers, diuretics, lipid-lowering agents, calcium-channel blockers, and aspirin.

Table 6-4 Concomitant Medications of Interest Used During Study: mITT Analysis Set, Overall Study Period (ENGAGE AF-TIMI 48)

Concomitant Medication of Interest	Edoxaban 30/15 mg (N = 7002)	Edoxaban 60/30 mg (N = 7012)	Warfarin (N = 7012)
ACE inhibitors or ARBs	5758 (82.2)	5744 (81.9)	5731 (81.7)
Beta blockers	5342 (76.3)	5332 (76.0)	5402 (77.0)
Diuretics	5134 (73.3)	5142 (73.3)	5163 (73.6)
Lipid-lowering agents (statins, others)	4302 (61.4)	4185 (59.7)	4279 (61.0)
Calcium-channel blocker ^a	3118 (44.5)	3018 (43.0)	3085 (44.0)
Aspirin	2628 (37.5)	2636 (37.6)	2626 (37.5)
Amiodarone	1213 (17.3)	1202 (17.1)	1220 (17.4)
NSAIDs	1071 (15.3)	1089 (15.5)	1208 (17.2)
Anti-platelet drug excluding aspirin	554 (7.9)	500 (7.1)	518 (7.4)
Thienopyridines	418 (6.0)	383 (5.5)	388 (5.5)
Verapamil	346 (4.9)	325 (4.6)	332 (4.7)
Dronedarone	119 (1.7)	136 (1.9)	126 (1.8)
Quinidine	9 (0.1)	12 (0.2)	8 (0.1)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; mITT, modified intent-to-treat; NSAID, nonsteroidal anti-inflammatory drug.

^a Calcium-channel blocker includes verapamil.

6.5 Treatment Compliance

Compliance with edoxaban (or matching edoxaban placebo for the warfarin group) was assessed by percentage of doses taken ($\geq 80\%$ vs $< 80\%$) at visits every 3 months. In the edoxaban

60/30 mg group and 30/15 mg group, at least 98% of subjects were considered compliant at all 3-monthly visits, with the exception of Month 45 where the 30/15 mg group had a lower compliance rate (93%).

Compliance with warfarin was assessed by monitoring the TTR (i.e., the percentage of time subjects' INR was within the range of 2.0-3.0). The median TTR was 68.4% (mean, 64.9%) and the median time for INR 1.8–3.2 was 83.1% (mean, 78.4%; **Table 6-5**). The overall median time for INR < 2 was 17.7% (mean, 22.8%) and > 3 was 10.8% (mean, 12.4%). The median TTR in ENGAGE AF-TIMI 48 was high compared with other NOAC studies in AF and indicates that warfarin was well managed in this study.

Table 6-5 Time in Various INR Ranges for Subjects Randomized to Warfarin: Safety Analysis Set, On-Treatment Period, Excluding Initial 7 Days

Overall (N = 6897)	Percent Time in INR Range ^a								
	< 1.5	1.5 - 2.0	< 2	2 - 3 (TTR)	> 3	≥ 4	> 5	≥ 8	1.8 - 3.2
Mean (SD)	6.1 (13.8)	22.7 (13.3)	22.8 (18.9)	64.9 (18.7)	12.4 (10.3)	1.8 (4.5)	0.3 (2.3)	0.0 (0.8)	78.4 (18.1)
Median	1.9	21.0	17.7	68.4	10.8	0.4	0.0	0.0	83.1

Abbreviations: INR, international normalized ratio; SD, standard deviation; TTR, time in therapeutic range.

^a Percent time in INR range was defined by the percentage of days the subjects had been within the specified range. Percent TTR was 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 used a liner interpolation method to impute INR for study days that did not have an actual INR value.

7.0 CLINICAL EFFICACY

ENGAGE AF-TIMI 48 met its primary efficacy endpoint, demonstrating noninferiority of once-daily edoxaban to warfarin for the prevention of stroke or SEE. The edoxaban 60/30 mg regimen reduced the risk of stroke or SEE by approximately 20% compared with well-managed warfarin, and it was as effective as warfarin at reducing the risk of ischemic stroke. Consistent clinical benefit was observed across primary and secondary efficacy endpoints and most of the subgroups, including MACE, CV, and all-cause mortality. Overall, the efficacy results are clinically meaningful.

7.1 Primary Efficacy Outcome: Stroke or SEE

7.1.1 Noninferiority Analysis

The prespecified noninferiority efficacy criteria were met for both edoxaban 60/30 mg and 30/15 mg regimens versus warfarin (**Figure 7-1**). The upper bound of the 97.5% CI of the HR for both the edoxaban 60/30 mg and 30/15 mg regimens was below the prespecified noninferiority margin of 1.38 for the primary efficacy endpoint of stroke or SEE.

In the mITT analysis set on-treatment period, the edoxaban 60/30 mg regimen demonstrated a lower event rate of stroke or SEE than warfarin (1.18% vs 1.50% per year, respectively), with a clinically meaningful treatment effect, as demonstrated by a relative risk reduction of 21% (HR = 0.79; 97.5% CI: 0.63, 0.99; $P < 0.001$ for noninferiority). In contrast, the edoxaban 30/15 mg regimen demonstrated a numerically higher annual incidence of events (1.61%) than the edoxaban 60/30 mg group, and comparable treatment effects to warfarin with a relative risk increase of 7%, which satisfied the condition for noninferiority (HR = 1.07; 97.5% CI: 0.87, 1.31; $P = 0.006$ for noninferiority).

The robustness of the primary efficacy endpoint analysis was confirmed by all prespecified sensitivity analyses, including various subject cohort sets (mITT or PP analysis sets) and treatment sets (on-treatment or overall study periods).

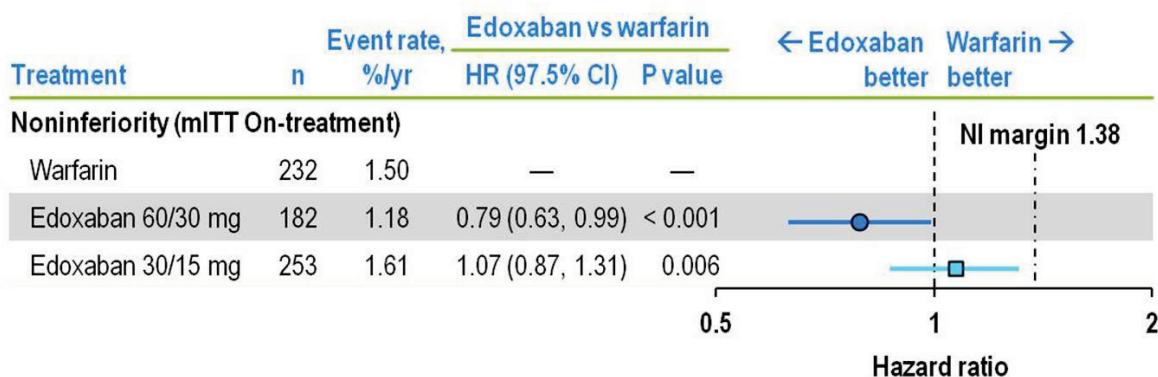


Figure 7-1 Forest Plot of the Primary Efficacy Analysis: mITT Analysis Set, On-Treatment and Overall Study Period (Noninferiority)

Abbreviations: CI, confidence interval; HR, hazard ratio; mITT, modified intent-to-treat; NI, noninferiority; QD, once daily.

7.1.2 Superiority Analysis

In the prespecified superiority analysis for efficacy that was performed in the ITT analysis set with data from the overall study period, there was a trend favoring the edoxaban 60/30 mg regimen versus warfarin (HR = 0.87; 99% CI: 0.71, 1.07; $P = 0.081$; **Figure 7-2**).

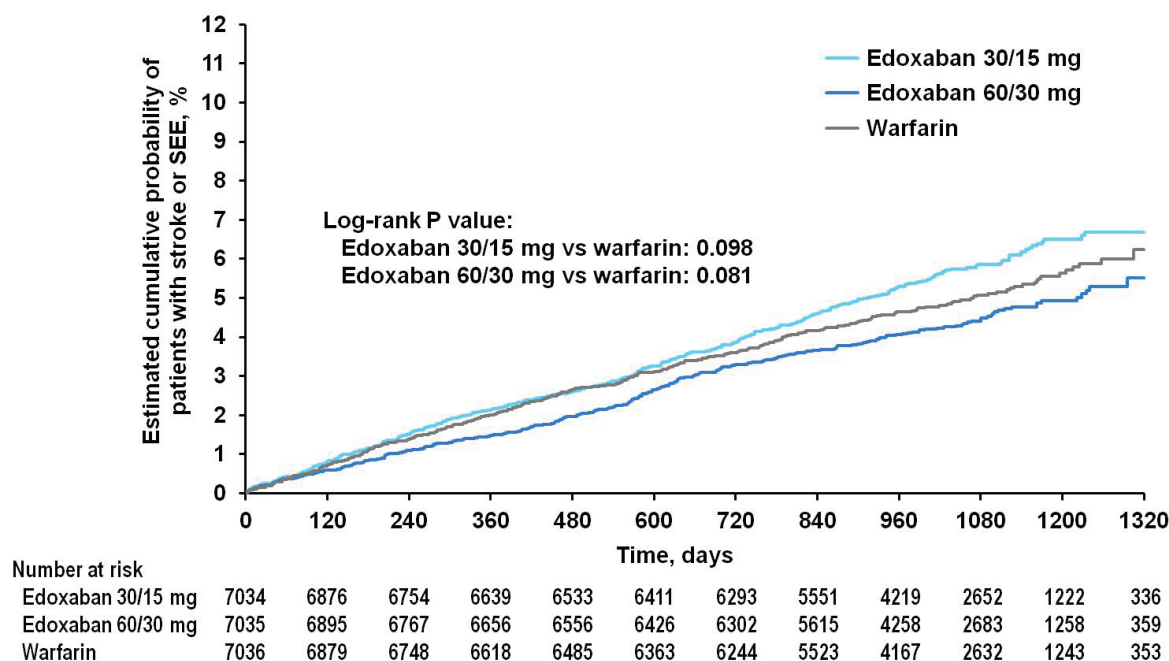


Figure 7-2 Cumulative Incidence Estimate of Time to First Occurrence of Stroke or SEE: ITT Analysis Set, Overall Study Period (Superiority)

Abbreviations: ITT, intent-to-treat; SEE, systemic embolic event.

Overall, there was consistent and clinically meaningful risk reduction for the primary efficacy endpoint for all on-treatment and overall study period analyses, comparing the edoxaban 60/30 mg and warfarin groups.

7.2 Secondary Efficacy Endpoints

The analysis of the 3 composite secondary efficacy endpoints are summarized in **Figure 7-3** for the ITT analysis set overall study period. The secondary endpoints were a composite of 1) stroke, SEE, and CV mortality; 2) MACE; and 3) stroke, SEE, and all-cause mortality.

The edoxaban 60/30 mg regimen was associated with a clinically significantly reduced risk for all 3 composite secondary efficacy endpoints compared with warfarin. The edoxaban 30/15 mg regimen also demonstrated a clinically significant risk reduction for all 3 composite secondary efficacy endpoints compared with warfarin, but the risk reduction was numerically smaller than that of the edoxaban 60/30 mg regimen. The edoxaban 30/15 mg regimen was associated with a numerically lower incidence of all-cause mortality and CV mortality compared to warfarin, despite an increase in ischemic events.

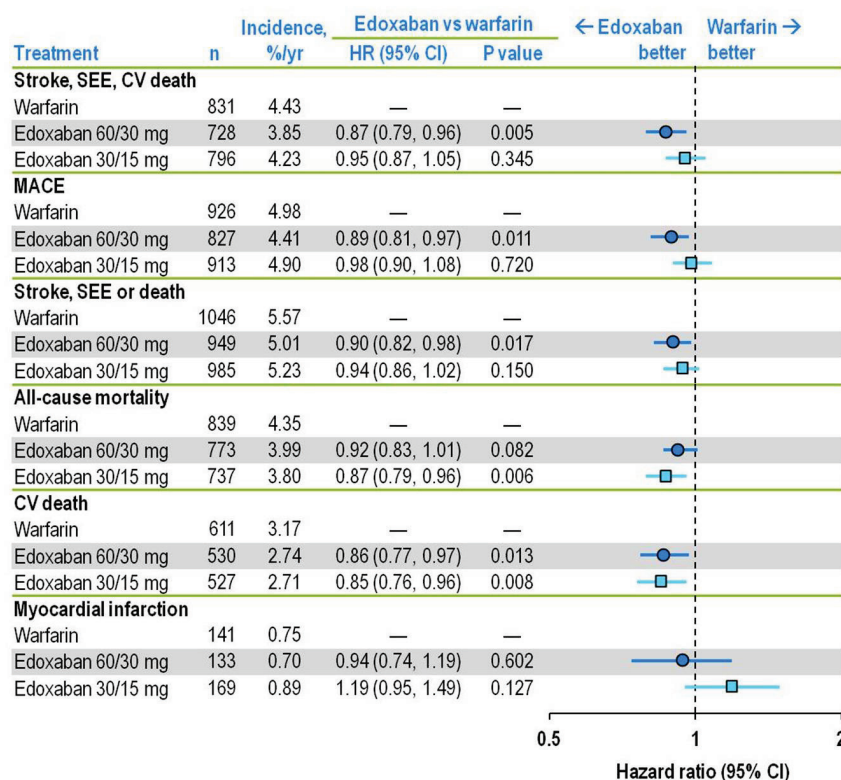


Figure 7-3 Secondary Efficacy Endpoints: ITT Analysis Set, Overall Study Period

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intent-to-treat; MACE, major adverse cardiac event; SEE, systemic embolic event.

^a Nominal *P* values for all edoxaban versus warfarin comparisons.

7.3 Individual Components and Subcomponents of the Primary and Secondary Endpoints

7.3.1 Primary Endpoint Components

Results for the components of the primary efficacy endpoint (stroke or SEE), as well as subcomponents of stroke (ischemic, hemorrhagic, fatal, and disabling), are summarized in **Table 7-1** for the mITT analysis on-treatment period. The CEC adjudicated primary ischemic, hemorrhagic, and fatal strokes, as per the CEC charter. Disabling stroke was based on the modified Rankin score, as assessed by the investigator.

Ischemic Stroke

The annualized ischemic stroke rate was similar in the edoxaban 60/30 mg and warfarin groups. Conversely, significantly more subjects in the edoxaban 30/15 mg group experienced ischemic strokes during the study when compared to warfarin.

Hemorrhagic Stroke

The annualized rates of hemorrhagic strokes for both edoxaban 60/30 mg and 30/15 mg regimens were statistically significantly reduced compared with the rate observed in warfarin-treated subjects.

Fatal Stroke

The annualized fatal stroke rate was similar in all 3 treatment groups (edoxaban 30/15 mg, edoxaban 60/30 mg, and warfarin).

Table 7-1 Components of Primary Efficacy Endpoint (Stroke or SEE): mITT Analysis Set, On-Treatment Period

Outcome	Edoxaban 30/15 mg (N = 7002)		Edoxaban 60/30 mg (N = 7012)		Warfarin (N = 7012)		Edoxaban 30/15 mg vs warfarin		Edoxaban 60/30 mg vs warfarin	
	n	%/yr	n	%/yr	n	%/yr	HR (95% CI)	P	HR (95% CI)	P
Stroke	244	1.55	174	1.13	219	1.41	1.10 (0.91, 1.32)	0.325	0.80 (0.66, 0.98)	0.027
Ischemic	226	1.43	135	0.87	144	0.93	1.54 (1.25, 1.90)	<0.001 ^a	0.94 (0.75, 1.19)	0.626
Hemorrhagic	18	0.11	40	0.26	76	0.49	0.23 (0.14, 0.39)	<0.001	0.53 (0.36, 0.78)	0.001
Disabling ^b	57	0.36	35	0.23	41	0.26	1.36 (0.91, 2.03)	0.132	0.86 (0.55, 1.35)	0.511
Fatal	40	0.25	45	0.29	43	0.28	0.91 (0.59, 1.40)	0.670	1.05 (0.69, 1.60)	0.804
SEE	11	0.07	8	0.05	13	0.08	0.83 (0.37, 1.85)	0.645	0.62 (0.26, 1.50)	0.288

Abbreviations: CEC, Clinical Events Committee; CI, confidence interval; HR, hazard ratio; mITT, modified intent-to-treat; SEE, systemic embolic event; yr, year.

^a Significantly higher increase in ischemic stroke with edoxaban 30 mg compared with warfarin.

^b The CEC adjudicated primary ischemic strokes, primary hemorrhagic strokes, and fatal strokes, as per the CEC charter. Disabling stroke was based on modified Rankin score, as assessed by the investigator, and did not include fatal strokes.

7.3.2 Secondary Endpoint Components

Key components of the secondary composite efficacy endpoints are summarized in **Table 7-2** for the ITT analysis set overall study period.

Myocardial Infarction

Significantly fewer subjects in the edoxaban 60/30 mg group experienced MI than in the warfarin group (0.70% vs 0.75% per year, respectively; HR = 0.94; 95% CI: 0.74, 1.19). Numerically more subjects in the edoxaban 30/15 mg group had MIs than the warfarin group, with an event rate for MI of 0.89% vs 0.75% per year, respectively (HR = 1.19; 95% CI: 0.95, 1.49).

CV Mortality

Significantly fewer subjects in the edoxaban 60/30 mg group experienced CV mortality than in the warfarin group (2.74% vs 3.17% per year, respectively; HR = 0.86; 95% CI: 0.77, 0.97). Significantly fewer subjects in the edoxaban 30/15 mg group than warfarin group experienced CV mortality (2.71% vs 3.17% per year, respectively; HR = 0.85; 95% CI: 0.76, 0.96).

The lower CV mortality in the edoxaban groups was driven by lower bleeding events (ICH and non-ICH), lower sudden/unwitnessed death, and lower CHF/cardiogenic shock.

All-Cause Mortality

Numerically fewer subjects in the edoxaban 60/30 mg group than in the warfarin group died of any cause (3.99% vs 4.35% per year, respectively; HR = 0.92; 95% CI: 0.83, 1.01). Significantly fewer subjects in the edoxaban 30/15 mg group than in the warfarin group died of any cause (3.80% and 4.35% per year, respectively; HR = 0.87; 95% CI: 0.79, 0.96).

As expected for the study population (elderly subjects with AF and underlying CV diseases), approximately 70% of deaths were due to CV illnesses. Both the edoxaban 60/30 mg and 30/15 mg regimens had a significantly lower incidence of CV deaths than the warfarin group. Fatal bleeds were included in the category of CV deaths. Edoxaban-treated subjects experienced numerically fewer deaths due to bleeding events. Death was considered to be related to bleeding in fewer subjects in the edoxaban 60/30 mg and edoxaban 30/15 mg groups than in the warfarin group (0.8%, 0.8%, and 1.4%, respectively). Death was due to fatal bleeding in 0.5%, 0.3%, and 0.9% of subjects in the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin groups, respectively. The remaining deaths were in the categories of malignancy or non-CV/non-malignancy death. The percentage of subjects with malignancies was comparable among the 3 treatment groups. Non-CV/non-malignancy deaths were slightly fewer in the edoxaban 30/15 mg than in the edoxaban 60/30 mg or warfarin groups (1.7%, 2.1%, and 2.1%, respectively).

Table 7-2 Components of Secondary Efficacy Endpoints: ITT Analysis Set, Overall Study Period

Outcome	Edoxaban 30/15 mg (N = 7034)		Edoxaban 60/30 mg (N = 7035)		Warfarin (N = 7036)		Edoxaban 30/15 mg vs warfarin		Edoxaban 60/30 mg vs warfarin	
	n	%/yr	n	%/yr	n	%/yr	HR (95% CI)	P	HR (95% CI)	P
Myocardial infarction	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)	0.008	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)	0.006	0.92 (0.83, 1.01)	0.082

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intent-to-treat; yr, year.

Note: A subject can appear in multiple rows of this table (e.g., myocardial infarction and death).

7.4 Subgroup Analyses

The primary efficacy endpoint (stroke or SEE) was analyzed by level of INR TTR, demographic and baseline characteristics, and concomitant medications. Results from these prespecified analyses are presented.

7.4.1 Primary Efficacy Endpoint by INR TTR Level

The subgroup analyses for the primary endpoint by the level of INR control (INR TTR) in warfarin-treated subjects are presented for the mITT analysis set on-treatment period by centers with TTR above or below the median (66.4%) and above or below 60%, and by quartiles in **Table 7-3**.

The edoxaban 60/30 mg group had numerically fewer events than the warfarin group in the subgroup of centers with TTR above or below the median. The HRs for the primary endpoint in the subgroup of centers with TTR above or below the median were 0.85 and 0.77, respectively, in the edoxaban 60/30 mg group and 1.24 and 0.93 respectively, in the edoxaban 30/15 mg group compared with the warfarin group. The HRs for the primary endpoint in the subgroup of centers with TTR above or below 60% were 0.84 and 0.71, respectively, in the edoxaban 60/30 mg group and 1.19 and 0.81 respectively, in the edoxaban 30/15 mg group compared with warfarin.

When the TTR data were examined by quartiles for the edoxaban 60/30 mg group compared to warfarin, the HRs for the primary endpoint in the 1st, 2nd, and 3rd quartile were 0.80, 0.73, and 0.74, respectively, and for the 4th quartile was 1.07. For the edoxaban 30/15 mg group compared to warfarin, the HRs for 1st, 2nd, 3rd, and 4th quartiles were 0.82, 1.02, 1.22, and 1.30, respectively.

Table 7-3 Primary Endpoint (Stroke or SEE) by INR TTR (Center Level and Quartiles): mITT Analysis Set, On-Treatment Period

	Edoxaban 30/15 mg (N = 7002)		Edoxaban 60/30 mg (N = 7012)		Warfarin (N = 7012)		Edoxaban 30/15 mg vs Warfarin	Edoxaban 60/30 mg vs Warfarin
	n/M ^a	Event Rate (%/yr) ^b	n/M ^a	Event Rate (%/yr) ^b	n/M ^a	Event Rate (%/yr) ^b	HR (95% CI)	HR (95% CI)
First Stroke or SEE								
Center Level INR TTR								
Centers with TTR > 66.4% (median)	110/3273	1.46	73/3277	1.00	94/3402	1.19	1.24 (0.94, 1.64)	0.85 (0.62, 1.15)
Center with TTR ≤ 66.4% (median)	134/3509	1.72	107/3517	1.39	138/3602	1.82	0.93 (0.74, 1.19)	0.77 (0.60, 0.99)
<i>P</i> value for the interaction							0.124	0.627
Centers with TTR ≥ 60%	175/4990	1.54	120/4960	1.09	155/5191	1.30	1.19 (0.96, 1.47)	0.84 (0.66, 1.07)
Centers with TTR < 60%	69/1792	1.77	60/1834	1.51	77/1813	2.14	0.81 (0.58, 1.12)	0.71 (0.50, 0.99)
<i>P</i> value for the interaction							0.056	0.411
Quartiles of INR TTR								
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, 1.39)	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)
<i>P</i> value for the interaction							0.338	0.637

Abbreviations: CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; SEE, systemic embolic event; TTR, time in therapeutic range; yr, year.

^a n is the number of events, M is the total number of subjects on whom the information is available for that subgroup.

^b The event rate (%/yr) is calculated as number of events/subject-year of exposure.

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

7.4.2 Primary Efficacy Endpoint by Demographic and Baseline Characteristics

For most subgroups, the primary efficacy endpoint event rate was lower in the edoxaban 60/30 mg group than in the warfarin group, with a HR < 1.0 for the comparison of the edoxaban 60/30 mg group versus the warfarin group (**Figure 7-4**).

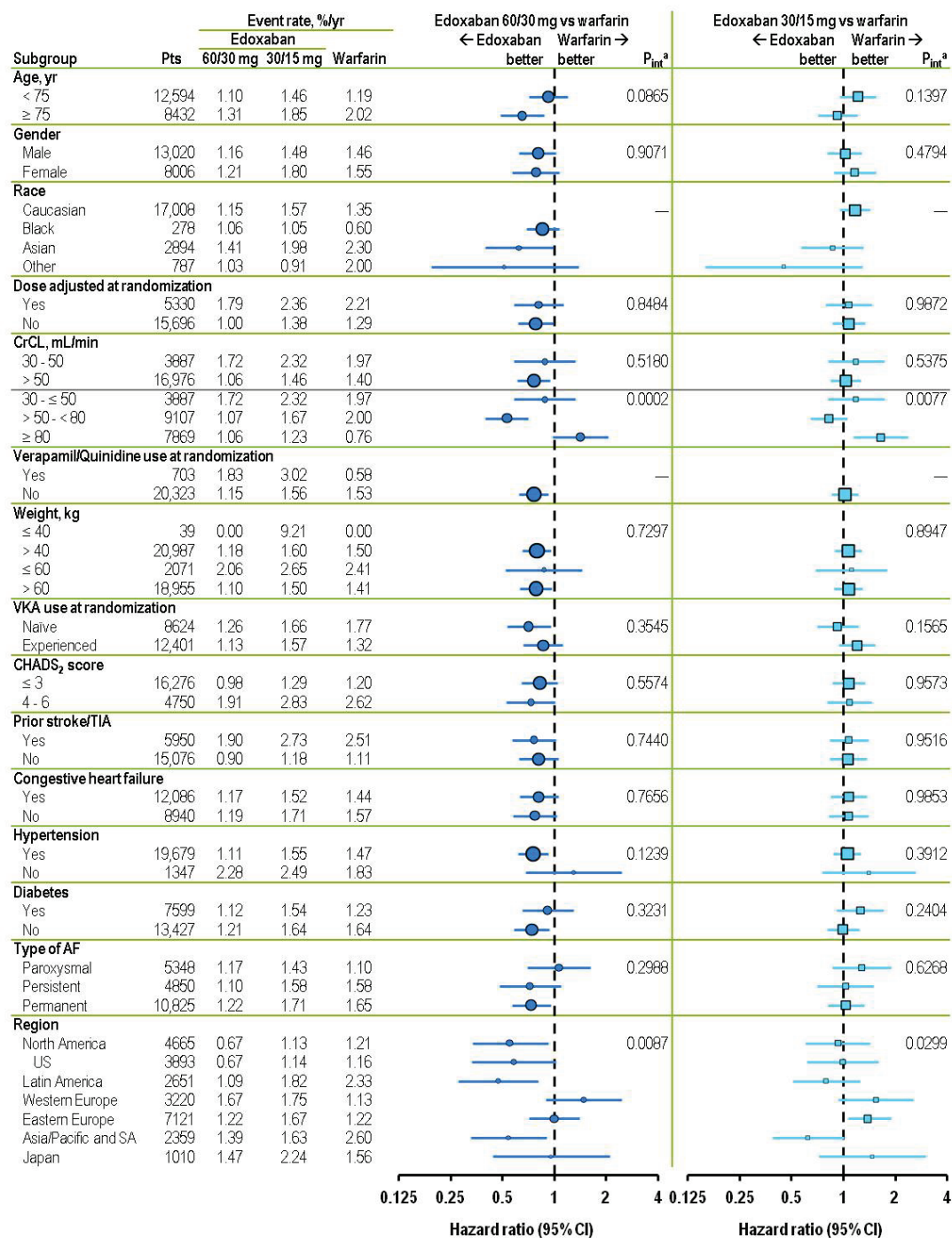


Figure 7-4 Primary Efficacy Endpoint by Demographic and Baseline Characteristics: mITT Analysis Set, On-Treatment Period

^a P value for the interaction.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CrCL, creatinine clearance; mITT, modified intent-to-treat; Pts, patients; TIA, transient ischemic attack; US, United States; VKA, vitamin K antagonist.

7.4.3 Primary Efficacy Endpoint by Concomitant Medications

For most subgroups, the primary efficacy endpoint event rate was lower in the edoxaban 60/30 mg group than in the warfarin group, with HR < 1.0 for the comparison of the edoxaban 60/30 mg group and the warfarin group (**Table 7-4**). Numerically fewer subjects experienced the primary endpoint in the edoxaban 60/30 mg group than in the warfarin group in the subgroup that took concomitant aspirin (1.67% and 2.25% per year, respectively; HR = 0.74), or did not take concomitant aspirin (0.91% and 1.08% per year, respectively; HR = 0.84). Similar findings were observed in the edoxaban 30/15 mg group.

Numerically fewer subjects in the subgroup that took concomitant amiodarone experienced the primary endpoint in the edoxaban 60/30 mg group than in the warfarin group (1.31% and 1.74% per year, respectively; HR = 0.75), compared with the subgroup that did not take concomitant amiodarone (1.60% and 1.82% per year, respectively; HR = 0.88).

Table 7-4 Adjudicated Stroke or SEE Subgroup Analysis for Concomitant Medications: mITT Analysis Set, On-Treatment Study Period

Subgroup	Edoxaban 30/15 mg (N = 7002)		Edoxaban 60/30 mg (N = 7012)		Warfarin (N = 7012)
	Event Rate (%/yr)	HR (95% CI)	Event Rate (%/yr)	HR (95% CI)	Event Rate (%/yr)
Aspirin					
Yes	2.23	0.98 (0.77, 1.25)	1.67	0.74 (0.57, 0.97)	2.25
No	1.25	1.17 (0.90, 1.51)	0.91	0.84 (0.64, 1.12)	1.08
Thienopyridines					
Yes	3.35	1.15 (0.66, 2.01)	2.45	0.86 (0.46, 1.61)	2.89
No	1.50	1.06 (0.88, 1.28)	1.12	0.78 (0.64, 0.96)	1.42
Lipid-Lowering Agents (Statins, Others)					
Yes	1.64	1.07 (0.86, 1.33)	1.13	0.74 (0.57, 0.94)	1.53
No	1.54	1.08 (0.80, 1.46)	1.26	0.88 (0.64, 1.20)	1.44
NSAIDs					
Yes	1.40	1.28 (0.80, 2.03)	0.98	0.88 (0.53, 1.45)	1.13
No	1.65	1.04 (0.86, 1.26)	1.22	0.77 (0.63, 0.95)	1.58
Verapamil					
Yes	2.55	--	1.91	--	0.51
No	1.56	1.01 (0.84, 1.21)	1.14	0.74 (0.61, 0.90)	1.55
Quinidine					
Yes	0.00	--	0.00	--	0.00
No	1.61	1.07 (0.90, 1.28)	1.18	0.79 (0.65, 0.96)	1.50
Amiodarone					
Yes	1.02	0.67 (0.42, 1.09)	1.03	0.67 (0.41, 1.10)	1.53
No	1.73	1.16 (0.95, 1.40)	1.21	0.81 (0.66, 1.01)	1.49
ACE Inhibitors or ARBs					
Yes	1.50	0.99 (0.81, 1.20)	1.17	0.77 (0.62, 0.95)	1.53
No	2.13	1.57 (1.03, 2.39)	1.23	0.91 (0.56, 1.46)	1.34

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; HR, hazard ratio; mITT, modified intent-to-treat; NSAID, nonsteroidal anti-inflammatory drug; SEE, systemic embolic event.

7.5 Other Efficacy Analyses

7.5.1 Primary Efficacy Endpoint by Treatment Regimen (Dose Reduced and Full Dose)

At randomization, approximately 25% of subjects received a reduced dose of edoxaban or a reduced edoxaban placebo if allocated to receive the control treatment of warfarin. Approximately two thirds of those subjects (~19%) had moderate renal impairment with or without other qualifying conditions. Less than 3% received a reduced dose of edoxaban because of the concomitant need for quinidine and/or verapamil. Subjects receiving a reduced dose of edoxaban were older, at higher CHADS₂ risk, with a higher incidence of past history of stroke or TIA, and a lower CrCL and body weight.

For the edoxaban 60/30 mg regimen, the dose reduction scheme was effective. For the mITT on-treatment period, subjects in the edoxaban 60/30 mg group (both those receiving the edoxaban dose reduced to 30/15 mg and the edoxaban full dose of 60/30 mg) had a reduced risk of stroke or SEE compared with the matching subjects in the warfarin group (HR = 0.81 and 0.78, respectively; **Table 7-5**), indicating a similar risk reduction (19% and 22%, respectively) in both dose-reduced and full-dose subjects.

In contrast, subjects in the edoxaban 30/15 mg group who received either a reduced dose of 15 mg or full dose of 30 mg both had a numerically higher risk of stroke or SEE compared with matching subjects in the warfarin group (HR = 1.07 for both; **Table 7-5**).

Table 7-5 Adjudicated Primary Endpoint (Stroke or SEE) by Treatment Administered: mITT Analysis Set, On-Treatment Period

Regimen	Subjects With Dose Reduction ^a			Subjects Who Received the Full Dose		
	Edoxaban 30/15 mg	Edoxaban 60/30 mg	Warfarin	Edoxaban 30/15 mg	Edoxaban 60/30 mg	Warfarin
Treatment Received	15 mg (1) (N = 1774)	30 mg (2) (N = 1776)	PBO-Edoxaban (3) (N = 1780)	30 mg (4) (N = 5228)	60 mg (5) (N = 5236)	PBO-Edoxaban (6) (N = 5232)
First stroke or SEE (primary endpoint)						
Number of events	85	62	77	168	120	155
Event rate (%/yr) ^b	2.36	1.79	2.21	1.38	1.00	1.29
HR (95% CI) ^c	1.07 (0.79, 1.46)	0.81 (0.58, 1.13)	--	1.07 (0.86, 1.34)	0.78 (0.61, 0.99)	--

Abbreviations: CI, confidence interval; HR, hazard ratio; mITT, modified intent-to-treat; PBO, placebo; SEE, systemic embolic event; yr, year.

^a At randomization, there were dosage adjustments for moderate renal impairment, low body weight, or specified concomitant medications. Subjects with adjustment in the 30 mg group received edoxaban 15 mg and subjects in the 60 mg group received edoxaban 30 mg. The warfarin group shows the dose-adjusted group for edoxaban placebo component.

^b The event rate (%/yr) was calculated as number of events/subject-year exposure.

^c The pairwise comparisons include column (1) versus (3), (2) versus (3), (4) versus (6), and (5) versus (6).

7.6 Efficacy Conclusions

ENGAGE AF-TIMI 48 met its primary noninferiority efficacy endpoint of noninferiority to warfarin, with consistent findings across multiple prespecified subgroup analyses. Both edoxaban 60/30 mg and 30/15 mg regimens were noninferior to well-managed warfarin (as demonstrated by a TTR of 68%) for prevention of stroke or SEE, with lower rates reported with the edoxaban 60/30 mg regimen. In addition, the edoxaban 60/30 mg regimen was as effective as warfarin at reducing the risk of ischemic stroke (HR = 1.0), whereas the edoxaban 30/15 mg regimen was associated with a higher risk of ischemic stroke than warfarin. The study confirmed that there was a favorable reduction in hemorrhagic stroke with both edoxaban doses.

Consistent clinical benefit was observed across a variety of other efficacy endpoints and subgroups. Subjects randomized to the edoxaban 60/30 mg regimen had a significantly reduced risk of experiencing the 3 composite secondary efficacy endpoints (stroke, SEE, and CV mortality; MACE; and stroke, SEE, and all-cause mortality) compared with subjects in the warfarin group. The primary efficacy subgroup findings were consistent with the overall study results. Importantly, the primary efficacy outcome results did not appear to be driven by any of the multiple prespecified subgroups.

Overall, the dose-modification scheme was effective for subjects in the edoxaban 60/30 mg and 30/15 mg groups. Both dose-reduced and full-dose subjects in the 60/30 mg group had a reduced risk of stroke or SEE compared with matching subjects in the warfarin group.

8.0 CLINICAL SAFETY

Overall, more than 23,500 subjects in the clinical studies and an estimated 155,000 patients during postmarketing surveillance have been treated with edoxaban. The safety profile of edoxaban is well characterized based on more than 34,100 subject-years of exposure to edoxaban in the global clinical development program across multiple indications. ENGAGE AF-TIMI 48 safety data, with 14,014 edoxaban subjects with total 31,311 subject-years of exposure, comprise the largest portion of the total edoxaban clinical experience.

8.1 ENGAGE AF-TIMI 48

8.1.1 Safety Endpoints and Definitions

The principal safety endpoint of ENGAGE AF-TIMI 48 was major bleeding adjudicated by the CEC. Secondary safety endpoints included the composite of major bleeding and clinically relevant non-major (CRNM) bleeding.

Definitions for major bleeding were based on the International Society on Thrombosis and Haemostasis (ISTH) guidance with minor modifications for hemoglobin decrease and blood transfusion requirements.⁴⁷

A CRNM bleeding event was defined as clinically overt bleeding visualized by examination or radiologic imaging and requiring medical attention.

Other safety assessments included, but were not limited to, hepatic safety, and treatment-emergent adverse events (TEAEs).

8.1.2 Extent of Exposure

Both exposure to study drug and median follow-up during the study were comparable across treatment groups (**Table 8-1**). Among the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin groups, 80.7%, 83.1%, and 81.2% of subjects, respectively, received study drug for more than 360 days, and total subject-years of exposure was 15,471, 15,840, and 15,569, respectively. Median study drug exposure was approximately 2.5 years, and median follow-up was approximately 2.8 years.

Table 8-1 Study Drug Exposure and Duration of Study Period: Safety Analysis Set (ENGAGE AF-TIMI 48)

Characteristic	Edoxaban 30/15 mg (N = 7002)	Edoxaban 60/30 mg (N = 7012)	Warfarin (N = 7012)
Study drug exposure			
Mean (SD), days	826.3 (374.24)	805.9 (390.82)	811.0 (383.14)
Median, days	916.0	904.0	904.0
Total subject-years exposure	15,839.85	15,470.96	15,569.23
Number of days exposed to study drug, n (%) ^a			
≥ 1	7002 (100.0)	7012 (100.0)	7012 (100.0)
≥ 30	6741 (96.3)	6679 (95.3)	6747 (96.2)
≥ 60	6608 (94.4)	6523 (93.0)	6590 (94.0)
≥ 90	6489 (92.7)	6383 (91.0)	6468 (92.2)
≥ 180	6234 (89.0)	6074 (86.6)	6168 (88.0)
≥ 270	6015 (85.9)	5855 (83.5)	5908 (84.3)
≥ 360	5820 (83.1)	5659 (80.7)	5696 (81.2)
≥ 450	5634 (80.5)	5493 (78.3)	5519 (78.7)
≥ 540	5471 (78.1)	5312 (75.8)	5366 (76.5)
≥ 630	5293 (75.6)	5147 (73.4)	5198 (74.1)
≥ 720	5094 (72.8)	4981 (71.0)	5021 (71.6)
≥ 810	4696 (67.1)	4621 (65.9)	4630 (66.0)
≥ 900	3769 (53.8)	3673 (52.4)	3618 (51.6)
Overall study period^b			
Mean (SD), days	1002.4 (243.66)	999.6 (249.94)	993.9 (254.15)
Median, days	1023.0	1023.0	1021.0
Subject-years follow-up	19,216.12	19,190.99	19,080.37
Percentage of exposed days			
Mean (SD)	82.2 (30.56)	80.3 (32.51)	81.4 (31.27)

Abbreviations: CSED, common study end date; SD, standard deviation.

^a Number of days exposed to study drug is defined as the total number of days the subject takes study drug during the study period, with interruptions not included in the interval of time. This is actual exposure and does not include 3 days after the last dose in subjects who interrupted. A subject may have multiple periods of drug use if they temporarily interrupt and resume study drug during the study.

^b Study period includes all study days from initial dose of study drug until common study end date (CSED) visit, date of death, or CSED announcement + 90 days, whichever is earliest. For subjects without CSED visit, the end of the study period is derived using CSED announcement + 90 days, date of death, date of withdrawal of consent, and last contact date.

8.1.3 Bleeding Events

8.1.3.1 Principal Safety Endpoint: Adjudicated Major Bleeding

Subjects in both the edoxaban 60/30 mg and 30/15 mg groups experienced significantly lower rates of major, bleeding, including fatal, life-threatening (LT), and fatal or LT bleeding than those treated with warfarin (**Figure 8-1**). The annualized rates of major bleeding in the edoxaban 60/30 mg and 30/15 mg groups were 2.75% (HR = 0.80; 95% CI: 0.71, 0.91) and 1.61% (HR = 0.47; 95% CI: 0.41, 0.55), respectively, compared with 3.43% in the warfarin group. Similar benefits were observed for subjects in the edoxaban 60/30 mg and 30/15 mg

groups who experienced fatal bleeds (HR = 0.55 and 0.35, respectively) and LT bleeds (HR = 0.51 and 0.32, respectively).

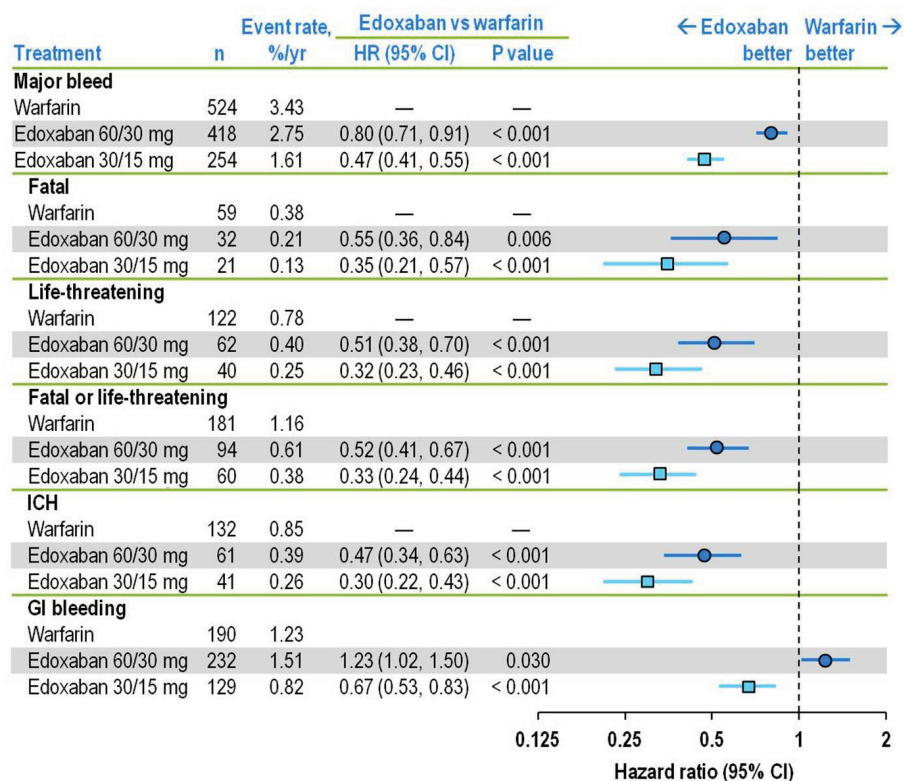


Figure 8-1 Adjudicated Major Bleeding Events: Safety Analysis Set, On-Treatment Period (ENGAGE AF-TIMI 48)

Abbreviations: CI, confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage; yr, year.

^a The event rate (%/yr) was calculated as number of events/subjects-year exposure.

^b ICH includes primary hemorrhagic stroke, subarachnoid hemorrhage, epi/subdural hemorrhage, and ischemic stroke with major hemorrhagic conversion. All ICHs reported on the Adjudicated Cerebrovascular and Non-Intracranial Bleed electronic case report forms confirmed by the adjudicators are included in the ICH counts.

^c Life-threatening bleeds are defined as all non-fatal ICH and non-fatal non-intracranial major bleeds with hemodynamic compromise requiring intervention.

^d Any confirmed bleed includes those that the adjudicator defined as clinically overt.

Note: A subject can be included in multiple subcategories if he/she had an event for those categories. The first event of each category is included in the analysis.

The KM estimate of time to first adjudicated major bleeding for the Safety analysis set overall study period is shown in **Figure 8-2**. That analysis shows that both the edoxaban 60/30 mg and 30/15 mg regimens reduced the cumulative incidence of major bleeding compared with warfarin.

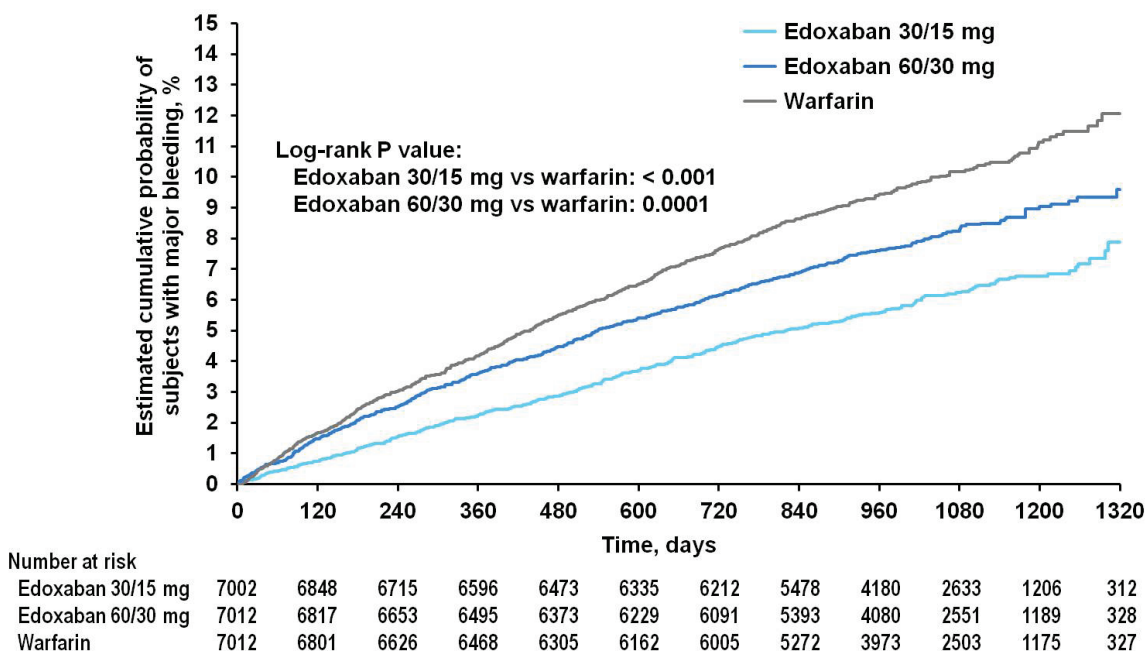


Figure 8-2 Kaplan-Meier Estimate of Time to First Adjudicated Major Bleeding Event: Safety Analysis Set, Overall Study Period (ENGAGE AF-TIMI 48)

Note: After 1320 days, in the edoxaban 60-mg, edoxaban 30-mg, and warfarin groups, respectively, there were 359, 336, and 353 subjects at risk, and 0, 2, and 2 events.

8.1.3.2 Other Adjudicated Bleeding Events

Consistent with the results for major bleeding, subjects in both the edoxaban 60/30 mg and 30/15 mg groups also experienced significantly lower rates of CRNM bleeding, major or CRNM bleeding, and any confirmed bleeding than those treated with warfarin (Table 8-2).

Table 8-2 Adjudicated Major Bleeding Events: Safety Analysis Set, On-Treatment Period (ENGAGE AF-TIMI 48)

Bleeding Category: First Event	Edoxaban 30/15 mg (N = 7002)		Edoxaban 60/30 mg (N = 7012)		Warfarin (N = 7012)		Edoxaban 30/15 mg vs warfarin	Edoxaban 60/30 mg vs warfarin
	# of Events	%/yr^a	# of Events	%/yr^a	# of Events	%/yr^a	HR (95% CI)	HR (95% CI)
Major or clinically relevant non-major	1161	7.97	1528	11.10	1761	13.02	0.62 (0.57, 0.67)	0.86 (0.80, 0.92)
<i>P</i> value							< 0.001	< 0.001
Clinically relevant non-major	969	6.60	1214	8.67	1396	10.15	0.66 (0.60, 0.71)	0.86 (0.79, 0.93)
<i>P</i> value							< 0.001	< 0.001
Any confirmed bleed ^b	1499	10.68	1865	14.15	2114	16.40	0.66 (0.62, 0.71)	0.87 (0.82, 0.92)
<i>P</i> value							< 0.001	< 0.001

Abbreviations: CI, confidence interval; HR, hazard ratio versus warfarin; yr, year.

^a The event rate (%/yr) is calculated as number of events/subject-year exposure.

^b Any confirmed bleed includes those that the adjudicator defined as clinically overt.

Note: A subject can be included in multiple subcategories if he/she had an event for those categories. The first event of each category is included in the analysis.

8.1.3.3 Additional Analyses of Bleeding Events

Adjudicated Bleeding by Anatomic Location

Adjudicated major bleeding by treatment group and anatomic location is summarized in **Table 8-3**. The adjudicated major bleeding rate was lower in most anatomic locations, including ICH, for the edoxaban 60/30 mg group and in all locations for the edoxaban 30/15 mg group compared with the warfarin group. However, there were more major GI bleeds in the edoxaban 60/30 mg group and fewer major GI bleeds in the edoxaban 30/15 mg group compared with the warfarin group (1.51%, 0.82%, and 1.23% per year, respectively).

Table 8-3 Adjudicated Major Bleeding by Treatment Group and Anatomic Location: Safety Analysis Set, On-Treatment Period (ENGAGE AF-TIMI 48)

First Event	Edoxaban 30/15 mg (N = 7002)		Edoxaban 60/30 mg (N = 7012)		Warfarin (N = 7012)	
	# of Events	Event Rate (%/yr) ^a	# of Events	Event Rate (%/yr) ^a	# of Events	Event Rate (%/yr) ^a
Any major bleed	254	1.61	418	2.75	524	3.43
Gastrointestinal	129	0.82	232	1.51	190	1.23
Upper gastrointestinal	88	0.56	140	0.91	111	0.71
Lower gastrointestinal	44	0.28	96	0.62	81	0.52
ICH	41	0.26	61	0.39	132	0.85
Intraocular	16	0.10	30	0.19	37	0.24
Macroscopic hematuria/urethral	11	0.07	28	0.18	26	0.17
Cutaneous soft tissue	15	0.09	19	0.12	57	0.37
Surgical site	6	0.04	15	0.10	12	0.08
Intra-articular	7	0.04	8	0.05	25	0.16
Epistaxis	10	0.06	7	0.05	15	0.10
Other	4	0.03	6	0.04	9	0.06
Retroperitoneal	6	0.04	6	0.04	8	0.05
Pericardial	0	0.0	4	0.03	1	0.01
Intramuscular, no compartment syndrome	5	0.03	3	0.02	8	0.05
Puncture site	2	0.01	3	0.02	6	0.04
Vaginal ^b	2	0.03	3	0.05	2	0.03
Hemoptysis	3	0.02	1	0.01	5	0.03
Oral/pharyngeal	0	0.0	1	0.01	1	0.01
Intramuscular with compartment syndrome	0	0.0	0	0.0	3	0.02
Intraspinal	0	0.0	0	0.0	4	0.03

Abbreviations: ICH, intracranial hemorrhage.

^a The event rate (%/yr) is calculated as number of events/subject-year exposure. The subject-year exposure is the sum, across subjects, of the number of at-risk years up to the event or censoring.

^b For gender-specific category (vaginal bleeding), the event rate is based on the gender-specific subject numbers.

Note: A subject may be counted in multiple subcategories when multiple events occurred.

Note: Events are sorted in descending order of frequency in the edoxaban 60-mg group.

The adjudicated CRNM bleeding rate was numerically lower in most anatomic locations in the edoxaban 60/30 mg and 30/15 mg groups compared with the warfarin group; however, there

were numerically more CRNM GI bleeds (2.17%, 1.49%, and 1.31% per year, respectively) and vaginal bleeds (0.58%, 0.58%, and 0.44% per year, respectively; **Table 8-4**).

Table 8-4 Adjudicated Clinically Relevant Non-Major Bleeding by Treatment Group and Anatomic Location: Safety Analysis Set, On-Treatment Period (ENGAGE AF-TIMI 48)

First Event	Edoxaban 30/15 mg (N = 7002)		Edoxaban 60/30 mg (N = 7012)		Warfarin (N = 7012)	
	# of Events	Event Rate (%/yr) ^a	# of Events	Event Rate (%/yr) ^a	# of Events	Event Rate (%/yr) ^a
Any clinically relevant non-major bleed	969	6.60	1214	8.67	1396	10.15
Gastrointestinal	232	1.49	328	2.17	201	1.31
Upper gastrointestinal	46	0.29	52	0.34	34	0.22
Lower gastrointestinal	187	1.19	282	1.86	169	1.10
Cutaneous soft tissue	299	1.93	309	2.04	613	4.13
Macroscopic hematuria/urethral	178	1.14	262	1.73	219	1.43
Epistaxis	174	1.11	248	1.63	242	1.58
Other	57	0.36	68	0.44	121	0.78
Oral/pharyngeal	33	0.21	57	0.37	93	0.60
Hemoptysis	48	0.30	56	0.36	70	0.45
Surgical site	23	0.15	36	0.23	44	0.28
Vaginal ^b	35	0.58	32	0.58	25	0.44
Intramuscular, no compartment syndrome	2	0.01	8	0.05	8	0.05
Puncture site	11	0.07	3	0.02	15	0.10
Intraocular	0	0.00	2	0.01	0	0.00

^a The event rate (%/yr) is calculated as number of events/subject-year exposure. The subject-year exposure is the sum, across subjects, of the number of at-risk years up to the event or censoring.

^b For gender-specific category (vaginal bleeding), the event rate is based on the gender-specific subject numbers.

Note: A subject may be counted in multiple subcategories when multiple events occurred.

Note: Events are sorted in descending order of frequency in the edoxaban 60-mg group.

Adjudicated Major Bleeding Events by Level of INR TTR

The bleeding profile of edoxaban was also demonstrated in various subsets based on center-level INR TTR for warfarin-treated subjects. Fewer subjects experienced major bleeding in both the edoxaban 60/30 mg and 30/15 mg groups than the warfarin group when evaluated for the subset of warfarin subjects at centers with INR TTR either above the median (HR = 0.90 and 0.47, respectively) or below the median (HR = 0.70 and 0.44, respectively), or either above 60% (HR = 0.85 and 0.49, respectively) or below 60% (HR = 0.64 and 0.37, respectively; **Table 8-5**).

When the TTR data were examined by quartiles for the edoxaban 60/30 mg group compared to warfarin, the HRs for major bleeding in the 1st, 2nd, and 3rd quartile were 0.69, 0.70, and 0.80, respectively, and for the 4th quartile was 1.05 (**Table 8-5**). For the edoxaban 30/15 mg group compared to warfarin, the HRs for 1st, 2nd, 3rd, and 4th quartiles was 0.42, 0.46, 0.45, and 0.50, respectively.

**Table 8-5 Adjudicated Major Bleeds by Center Level and Quartiles: Safety Analysis Set, On-Treatment Period
(ENGAGE AF-TIMI 48)**

Outcome	Edoxaban 30/15 mg (N = 7002)		Edoxaban 60/30 mg (N = 7012)		Warfarin (N = 7012)		Edoxaban 30/15 mg vs warfarin	Edoxaban 60/30 mg vs warfarin
	n/M ^c	%/yr ^a	n/M ^c	%/yr ^a	n/M ^c	%/yr ^a	HR (95% CI) ^b	HR (95% CI) ^b
Adjudicated Major Bleeds by Center INR Control								
Centers with TTR > 66.4% (median)	122/3273	1.62	225/3277	3.15	273/3402	3.51	0.47 (0.38, 0.578)	0.90 (0.75, 1.07)
Center with TTR ≤ 66.4% (median)	116/3509	1.49	177/3517	2.33	251/3602	3.35	0.44 (0.36, 0.554)	0.70 (0.58, 0.85)
P value for interaction ^d							0.756	0.061
Centers with TTR ≥ 60%	184/4990	1.62	308/4960	2.85	391/5191	3.33	0.49 (0.41, 0.58)	0.85 (0.74, 0.99)
Centers with TTR < 60%	54/1792	1.38	94/1834	2.39	133/1813	3.76	0.37 (0.27, 0.51)	0.64 (0.49, 0.84)
P value for interaction ^d							0.131	0.068
Adjudicated Major Bleeds by Quartiles of INR TTR								
1st quartile (≤ 57.7%)	48/1406	1.59	78/1413	2.60	102/1406	3.77	0.42 (0.29, 0.59)	0.69 (0.52, 0.93)
2nd quartile (> 57.7% to ≤ 66.4%)	68/2103	1.43	99/2104	2.15	149/2196	3.12	0.46 (0.35, 0.62)	0.70 (0.54, 0.90)
3rd quartile (> 66.4% to ≤ 73.9%)	69/1906	1.59	119/1908	2.84	165/2038	3.59	0.45 (0.34, 0.59)	0.80 (0.63, 1.01)
4th quartile (> 73.9%)	53/1367	1.67	106/1369	3.58	108/1364	3.39	0.50 (0.36, 0.69)	1.05 (0.80, 1.37)
P value for interaction ^d							0.894	0.110

Abbreviations: CHADS₂, Index score for stroke prediction based on the scoring system for Congestive heart failure, High blood pressure, Age, Diabetes, previous Stroke/Transient Ischemic Attack; CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; TTR, time in therapeutic range; yr, year.

^a The event rate (%/yr) is calculated as number of events/subject-year exposure. The subject-year exposure is the sum, across subjects, the number of at-risk years up to the event or censoring.

^b The HR and 2-sided CI for pairwise comparison versus warfarin are based on the Cox regression model with counting process approach for on-treatment period including treatment and the 2 stratification factors as covariates: the dichotomized CHADS₂ score and the dichotomized dose-adjustment factor.

^c M is the total number of subjects on whom the information is available for that subgroup.

^d The *P* value for interaction is based on the Cox regression model with counting process approach for on-treatment period including treatment, the 2 stratification factors: dichotomized CHADS₂ score and dichotomized dose-adjustment factor, subgroup, treatment and subgroup interaction.

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

Adjudicated Major Bleeding by Subgroups

Major bleeding was analyzed for subgroups based on demographic and baseline characteristics, as well as concomitant therapies.

Subgroup Analyses Based on Demographic and Baseline Characteristics

For all subgroups, both the edoxaban 60/30 mg and 30/15 mg groups had a lower event rate and an HR < 1.0 for major bleeding compared to the warfarin group (**Figure 8-3**).

In the subgroup of subjects with a high risk of bleeding, such as age ≥ 75 years, CrCL 30 to 50 mL/min and > 50 to < 80 mL/min, or CHADS₂ score 4 to 6, edoxaban reduced the risk of major bleeding compared with warfarin. Renal subgroups are further described in **Section 9.4.3**.

There was a significant interaction ($P < 0.05$) for subgroups based on subjects who had their dose reduced compared with those that received the full dose. However, in both subgroups, fewer subjects in both the edoxaban 60/30 mg and 30/15 mg groups experienced major bleeds than in the warfarin group; the results were consistent with the overall results for major bleeds.

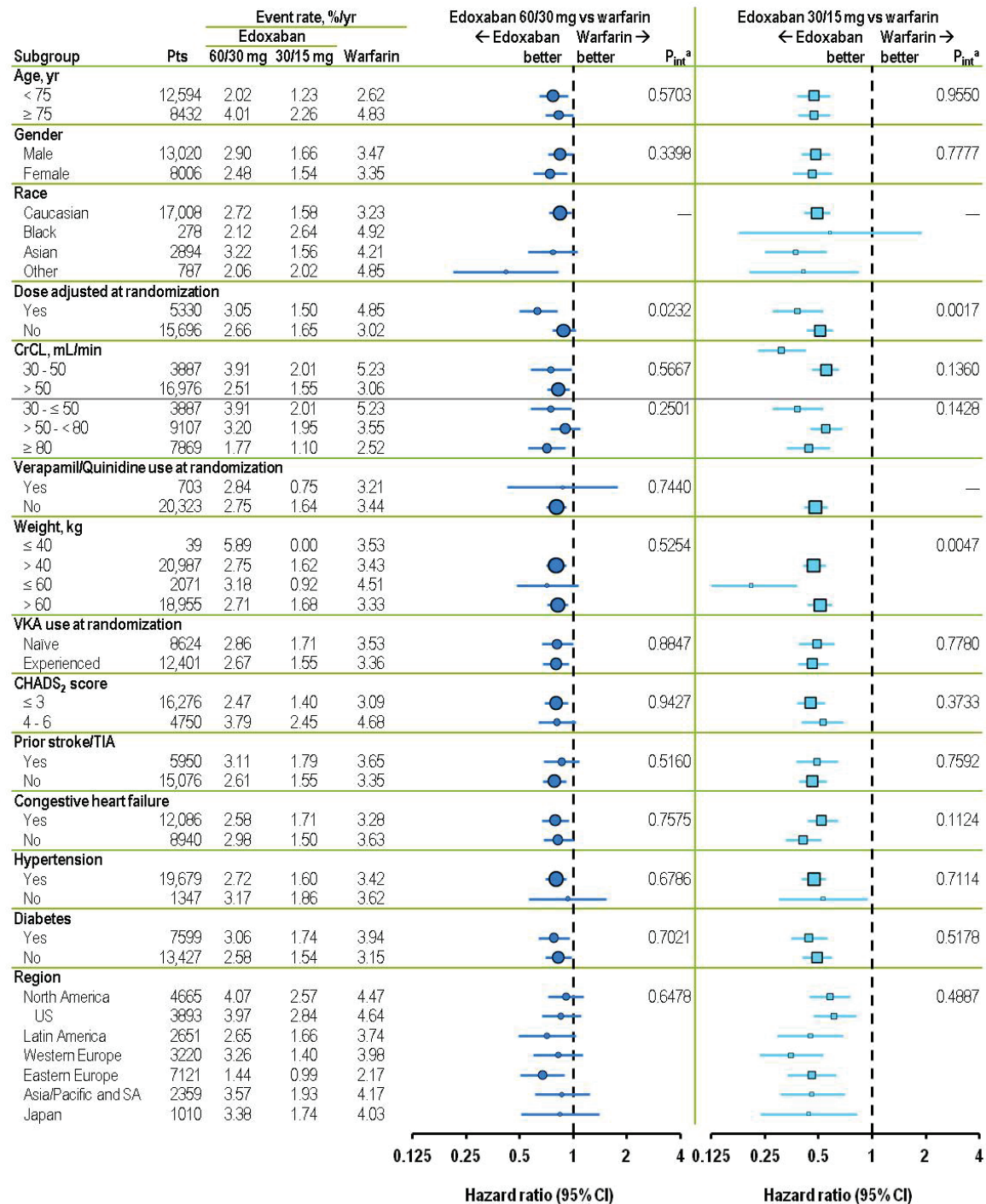


Figure 8-3 Adjudicated Major Bleeding Events by Demographic and Baseline Characteristics

^a P value for the interaction.

Abbreviations: CHADS₂, index score for stroke prediction based on the scoring system for Congestive heart failure, High blood pressure, Age, Diabetes, previous Stroke/transient ischemic attack; CI, confidence interval; CrCL, creatinine clearance; P_{int} , P value for the interaction; TIA, transient ischemic attack; VKA, vitamin K antagonist; US, United States, yr, year.

Subgroup Analyses Based on Concomitant Medications of Interest

Subjects in all 3 treatment groups receiving concomitant aspirin, other antiplatelets, or thienopyridines had a higher annual event rate for major bleeding than those who did not receive these medications (**Table 8-6**). In these subgroups, there was a reduced risk of major bleeding with edoxaban compared with warfarin. Subjects receiving concomitant NSAIDs also had a higher annual event rate of major bleeding in all 3 treatment groups compared to no NSAID use, but both edoxaban groups had less bleeding than the corresponding warfarin group.

Both edoxaban groups had less major bleeding than the warfarin group regardless of the use of concomitant medication, with the exception of subjects in the edoxaban 60/30 mg group who received concomitant amiodarone and subjects who did not receive concomitant ACE inhibitors/ARBs. Among subjects who received amiodarone, the event rate for major bleeding in the edoxaban 60/30 mg group was 2.98% (HR = 1.04; 95% CI: 0.76, 1.43). For those who did not receive ACE inhibitors/ARBs, the event rate for major bleeding in the edoxaban 60/30 mg group was 3.12% (HR = 1.12; 95% CI: 0.81, 1.54).

Table 8-6 Adjudicated Major Bleeding Events Subgroup Analysis for Concomitant Medications: Safety Analysis Set, On-Treatment Period

Subgroup	Edoxaban 30/15 mg (N = 7002)		Edoxaban 60/30 mg (N = 7012)		Warfarin (N = 7012)
	Event Rate (%/yr)	HR (95% CI)	Event Rate (%/yr)	HR (95% CI)	Event Rate (%/yr)
Aspirin					
Yes	2.27	0.46 (0.37, 0.57)	3.87	0.78 (0.65, 0.94)	4.95
No	1.24	0.48 (0.39, 0.59)	2.13	0.82 (0.68, 0.99)	2.60
Thienopyridines					
Yes	2.41	0.46 (0.27, 0.78)	4.72	0.91 (0.58, 1.44)	5.23
No	1.57	0.47 (0.40, 0.55)	2.65	0.80 (0.70, 0.91)	3.34
Lipid-Lowering Agents (Statins, Others)					
Yes	1.58	0.47 (0.39, 0.56)	2.78	0.82 (0.70, 0.97)	3.38
No	1.67	0.48 (0.38, 0.61)	2.71	0.77 (0.63, 0.95)	3.51
NSAIDs					
Yes	2.12	0.56 (0.40, 0.77)	3.71	0.97 (0.74, 1.27)	3.87
No	1.51	0.45 (0.38, 0.54)	2.55	0.77 (0.66, 0.89)	3.33
Verapamil					
Yes	1.54	0.50 (0.25, 1.02)	2.81	0.95 (0.52, 1.72)	2.91
No	1.62	0.47 (0.40, 0.55)	2.75	0.80 (0.70, 0.91)	3.46
Quinidine					
Yes	0.00	--	4.23	--	0.00
No	1.62	0.47 (0.41, 0.55)	2.75	0.80 (0.70, 0.91)	3.44
Amiodarone					
Yes	1.24	0.44 (0.29, 0.66)	2.98	1.04 (0.76, 1.43)	2.85
No	1.69	0.48 (0.41, 0.56)	2.70	0.76 (0.66, 0.88)	3.55
ACE Inhibitors or ARBs					
Yes	1.57	0.44 (0.38, 0.52)	2.67	0.75 (0.65, 0.87)	3.56
No	1.83	0.66 (0.45, 0.95)	3.12	1.12 (0.81, 1.54)	2.79

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.

Adjudicated Bleeding Events by Treatment Regimen (by Dose Reduced and Full Dose)

In subjects who had their dose reduced, both the edoxaban 60/30 mg and 30/15 mg groups had significantly fewer major bleeding events compared with the warfarin group (HR = 0.63 and 0.31, respectively; **Table 8-7**). Comparable results were seen for subjects who received the full dose (HR = 0.88 and 0.55, respectively).

Similar trends were observed for other types of bleeding events.

Table 8-7 Adjudicated Bleeding Events by Treatment Regimen: Safety Analysis Set, On-Treatment Period

	Subjects With Dose Reduction ^b			Subjects Who Received the Full Dose		
Regimen	Edoxaban 30/15 mg	Edoxaban 60/30 mg	Warfarin	Edoxaban 30/15 mg	Edoxaban 60/30 mg	Warfarin
Treatment received	15 mg (1) (N = 1774)	30 mg (2) (N = 1776)	PBO-Edoxaban (3) (N = 1780)	30 mg (4) (N = 5228)	60 mg (5) (N = 5236)	PBO-Edoxaban (6) (N = 5232)
Major						
n (event rate, %/yr) ^a	54 (1.50)	104 (3.05)	166 (4.85)	200 (1.65)	314 (2.66)	358 (3.02)
HR (95% CI) ^c	0.31 (0.23, 0.42)	0.63 (0.49, 0.81)	--	0.55 (0.46, 0.65)	0.88 (0.76, 1.03)	--
ICH ^d						
n (event rate, %/yr) ^a	5 (0.14)	20 (0.57)	44 (1.26)	36 (0.29)	41 (0.34)	88 (0.73)
HR (95% CI) ^c	0.11 (0.04, 0.28)	0.46 (0.27, 0.78)	--	0.40 (0.27, 0.60)	0.47 (0.32, 0.68)	--
Non-ICH						
n (event rate, %/yr) ^a	49 (1.36)	85 (2.49)	125 (3.65)	165 (1.36)	274 (2.32)	273 (2.30)
HR (95% CI) ^c	0.38 (0.27, 0.52)	0.69 (0.52, 0.90)	--	0.59 (0.49, 0.72)	1.01 (0.85, 1.19)	--
Total life-threatening ^e						
n (event rate, %/yr) ^a	7 (0.19)	15 (0.43)	33 (0.94)	33 (0.27)	47 (0.39)	89 (0.74)
HR (95% CI) ^c	0.20 (0.09, 0.46)	0.46 (0.25, 0.84)	--	0.37 (0.25, 0.55)	0.53 (0.37, 0.76)	--
Total fatal						
n (event rate, %/yr) ^a	4 (0.11)	12 (0.34)	26 (0.74)	17 (0.14)	20 (0.17)	33 (0.27)
HR (95% CI) ^c	--	0.46 (0.23, 0.92)	--	0.51 (0.28, 0.91)	0.61 (0.35, 1.06)	--
CRNM						
n (event rate, %/yr) ^a	248 (7.42)	292 (9.30)	422 (14.01)	721 (6.36)	922 (8.49)	974 (9.07)
HR (95% CI) ^c	0.54 (0.46, 0.63)	0.67 (0.58, 0.78)	--	0.71 (0.64, 0.79)	0.94 (0.89, 1.03)	--
Major or CRNM						
n (event rate, %/yr) ^a	289 (8.72)	378 (12.27)	537 (18.13)	872 (7.75)	1150 (10.77)	1224 (11.58)
HR (95% CI) ^c	0.49 (0.43, 0.57)	0.69 (0.60, 0.78)	--	0.68 (0.62, 0.74)	0.93 (0.86, 1.01)	--
Any confirmed bleed ^f						
n (event rate, %/yr) ^a	381 (11.96)	459 (15.54)	625 (22.15)	1118 (10.31)	1406 (13.75)	1489 (14.79)
HR (95% CI) ^c	0.56 (0.49, 0.63)	0.71 (0.63, 0.80)	--	0.71 (0.65, 0.76)	0.93 (0.87, 1.00)	--

Table 8-7 Adjudicated Bleeding Events by Treatment Regimen: Safety Analysis Set, On-Treatment Period

	Subjects With Dose Reduction ^b			Subjects Who Received the Full Dose		
Regimen	Edoxaban 30/15 mg	Edoxaban 60/30 mg	Warfarin	Edoxaban 30/15 mg	Edoxaban 60/30 mg	Warfarin
Treatment received	15 mg (1) (N = 1774)	30 mg (2) (N = 1776)	PBO-Edoxaban (3) (N = 1780)	30 mg (4) (N = 5228)	60 mg (5) (N = 5236)	PBO-Edoxaban (6) (N = 5232)

Abbreviations: CI, confidence interval; CRNM, clinically relevant non-major; HR, hazard ratio; ICH, intracranial hemorrhage; PBO, placebo.

^a The event rate (%/yr) is calculated as number of events/subject-year exposure. The subject-year exposure is the sum, across subjects, the number of at-risk years up to the event or censoring.

^b At randomization, there were dosage adjustments for moderate renal impairment, low body weight, or specified concomitant medications. Subjects with dosage adjustment in the edoxaban 30 mg group received edoxaban 15 mg and subjects in the edoxaban 60 mg group received edoxaban 30 mg. The warfarin group shows the dose-adjusted group for edoxaban placebo component.

^c The HR, 2-sided CI, and *P* value for pairwise comparison versus the appropriate warfarin/placebo group are based on the Cox regression model with counting process approach for on-treatment period including treatment and the 2 stratification factors as covariates: the dichotomized CHADS2 score and the dichotomized dose-adjustment factor. The pairwise comparisons include column (1) versus (3), (2) versus (3), (4) versus (6), and (5) versus (6).

^d ICH includes primary hemorrhagic stroke, subarachnoid hemorrhage, epi/subdural hemorrhage, and ischemic stroke with major hemorrhagic conversion. All ICHs reported on the adjudicated cerebrovascular and non-intracranial bleed eCRF confirmed by the adjudicators are included in ICH counts.

^e Life-threatening bleeds are defined as all non-fatal ICH and non-fatal non-intracranial major bleeds with hemodynamic compromise requiring intervention.

^f "Any confirmed bleed" includes those that the adjudicator defined as clinically overt.

Note: A subject can be included in multiple subcategories if he/she had an event for those categories. The first event of each category is included in the analysis.

8.1.4 Non-Bleeding Adverse Events

The incidence of non-bleeding TEAEs during the on-treatment period was generally similar for the edoxaban 30/15 mg, edoxaban 60/30 mg, and warfarin groups (**Table 8-8**). The incidence of non-bleeding TEAEs leading to study drug interruptions/discontinuations (32.4%, 31.9%, and 35.4%, respectively) or discontinuations (10.1%, 11.2%, and 11.0%, respectively) were similar across the edoxaban 30/15 mg, edoxaban 60/30 mg, and warfarin groups. The incidence of non-bleeding TEAEs considered by the investigator to be related to study drug was also generally comparable among the 3 treatment groups (10.0%, 11.0%, and 12.2%, respectively).

Table 8-8 Summary of Non-Bleeding Adverse Events: Safety Analysis Set, On-Treatment Study Period (ENGAGE AF-TIMI 48)

Type of Event	Edoxaban 30/15 mg (N = 7002) n (%)	Edoxaban 60/30 mg (N = 7012) n (%)	Warfarin (N = 7012) n (%)
TEAE, %	5868 (83.8)	5866 (83.7)	5867 (83.7)
Drug-related TEAE	703 (10.0)	773 (11.0)	856 (12.2)
TESAE	2418 (34.5)	2315 (33.0)	2516 (35.9)
TEAE leading to temporary study drug interruption/discontinuation	2271 (32.4)	2235 (31.9)	2480 (35.4)
TEAE leading to permanent study drug discontinuation	709 (10.1)	784 (11.2)	768 (11.0)
TEAE leading to fatal outcome	274 (3.9)	284 (4.1)	316 (4.5)

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

8.1.4.1 Frequency of Non-Bleeding Adverse Events

Across the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin groups, TEAEs were most frequently reported in the system organ class (SOC) of infections and infestations (44.6%, 44.7%, and 44.8%, respectively; **Table 8-9**). The 5 most frequent TEAEs (regardless of causality) reported among the treatment groups were urinary tract infections, nasopharyngitis, bronchitis, dizziness, and peripheral edema. Anemia was the only non-bleeding TEAE occurring more frequently ($\geq 1\%$ difference) in an edoxaban group (60/30 mg or 30/15 mg) compared to warfarin (5.2% or 3.7% vs 3.5%, respectively). Anemia events reported as severe were low (31 [0.4%] for edoxaban 60/30 mg, 21 [0.3%] for edoxaban 30/15 mg, and 19 [0.3%] for warfarin).

Table 8-9 Treatment-Emergent Non-Bleeding Adverse Events Reported by at Least 5% of Subjects by System Organ Class and Preferred Term: Safety Analysis Set, On-Treatment Study Period (ENGAGE AF-TIMI 48)

System Organ Class Preferred Term	Edoxaban 30/15 mg (N = 7002) n (%)	Edoxaban 60/30 mg (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)

Note: Treatment-emergence is defined as events which start on or after initial dose of study drug or started prior to but then worsened after initial dose of study drug. All events are based on investigator report.

Note: This summary includes all preferred terms with at least 5% of incidence in any of the treatment groups in international order of system organ class (SOC) counts, and within SOC, in descending order of frequency of preferred term in edoxaban 60 mg (30 mg dose adjusted).

Note: Adverse events above are based on entries from the AE and SAE electronic case report form, as well as the investigator-reported hepatic, bone fracture, and malignancy event pages.

Note: Bleeding events and efficacy endpoint events are summarized separately.

8.1.4.2 Deaths and Other Serious and Significant Adverse Events

Deaths

All deaths were adjudicated and categorized as CV or non-CV by the CEC and defined in this study as an efficacy endpoint, and thus were included in the analysis of efficacy (see **Section 7.3**). Death due to bleeding was included as part of CV death (**Section 7.3**).

Fewer subjects in the edoxaban 60/30 mg and 30/15 mg groups died of any cause compared to the warfarin group (11.0%, 10.4%, and 11.9%, respectively; **Table 8-10**). As expected for the study population (median age, 72 years; average CHADS₂ score, 2.8; **Section 6.3**), approximately 70% of deaths were due to CV diseases. Both the edoxaban 60/30 mg and 30/15 mg groups had a lower incidence of CV deaths than the warfarin group (7.5%, 7.5%, and 8.7%, respectively). The remaining deaths were in the categories of malignancy or non-CV/non-malignancy death. The percentage of subjects with deaths due to malignancies was comparable among the 3 treatment groups (1.3%, 1.3%, and 1.2%, respectively).

Table 8-10 Adjudicated Death: mITT Analysis Set, Overall Study Period (ENGAGE AF-TIMI 48)

	Edoxaban 30/15 mg (N = 7002) n (%)	Edoxaban 6/300 mg (N = 7012) n (%)	Warfarin (N = 7012) n (%)
Total	731 (10.4)	769 (11.0)	836 (11.9)
Primary cause			
Cardiovascular	522 (7.5)	527 (7.5)	608 (8.7)
Malignancies	93 (1.3)	94 (1.3)	84 (1.2)
Non-cardiovascular/non-malignancies	116 (1.7)	148 (2.1)	144 (2.1)

Abbreviation: mITT, modified intent-to-treat.

Serious Non-Bleeding Adverse Events

The percentage of subjects in the edoxaban 30/15 mg, 60/30 mg, and warfarin groups with non-bleeding treatment-emergent serious adverse events (TESAEs) was comparable for events during the on-treatment period (34.5%, 33.0%, and 35.9%, respectively; **Table 8-8**). As expected for this study population, the most common non-bleeding TESAEs were reported in the SOC of cardiac disorders (13.0%, 12.3%, and 13.9% for the edoxaban 30/15 mg, edoxaban 60/30 mg, and warfarin groups, respectively; **Table 8-11**). Other common TESAEs were related to infectious diseases (7.7%, 7.5%, and 8.2%, respectively) or respiratory conditions (2.8%, 2.8%, and 2.5%, respectively). The incidence of these TESAEs was generally comparable among the treatment groups. Overall, there were no clinically meaningful differences in TESAEs between the edoxaban and warfarin groups for the Safety analysis set on-treatment period.

Table 8-11 Treatment-Emergent Serious Non-Bleeding Adverse Events Reported by ≥1% of Subjects (at Preferred Term Level): Safety Analysis Set, On-Treatment Period (ENGAGE AF-TIMI 48)

System Organ Class Preferred Term	Edoxaban 30/15 mg (N = 7002) n (%)	Edoxaban 60/30 mg (N = 7012) n (%)	Warfarin (N = 7012) n (%)
Infections and Infestations	536 (7.7)	529 (7.5)	577 (8.2)
Pneumonia	151 (2.2)	164 (2.3)	172 (2.5)
Cardiac Disorders	908 (13.0)	865 (12.3)	975 (13.9)
Atrial fibrillation	286 (4.1)	242 (3.5)	283 (4.0)
Cardiac failure	227 (3.2)	240 (3.4)	279 (4.0)
Cardiac failure congestive	197 (2.8)	187 (2.7)	200 (2.9)
Respiratory, Thoracic and Mediastinal Disorders	197 (2.8)	199 (2.8)	175 (2.5)
Chronic obstructive pulmonary disease	84 (1.2)	73 (1.0)	64 (0.9)

Abbreviation: SAE, serious adverse event.

Note: Treatment-emergence is defined as events that start on or after initial dose of study drug or started prior to but then worsened after initial dose of study drug. All events are based on investigator report.

Note: This summary includes all preferred terms with at least 1% of incidence in any of the treatment groups by system organ class (SOC) and preferred term in international order of SOC counts, and within SOC, in descending order of frequency of preferred term counts in edoxaban 60 mg.

Note: SAEs above are based on entries from the SAE electronic case report form, as well as the investigator reported hepatic, bone fracture, and malignancy event pages.

Interruptions/Discontinuations due to Non-Bleeding Adverse Events

The incidence of non-bleeding TEAEs that caused study drug interruptions/discontinuations were generally comparable among the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin groups (31.9%, 32.4%, and 35.4%, respectively). Non-bleeding TEAEs reported to have caused study drug interruption/discontinuation were comparable between treatment groups except for anemia, which led to interruption/discontinuation more frequently in the edoxaban 60/30 mg group (1.1%) than in both the edoxaban 30/15 mg and warfarin groups (0.7% each). The events leading to study drug interruption/discontinuation by at least 1% of subjects are presented in Table 8-12.

Table 8-12 Study Drug Interruption/Discontinuation Due to Non-Bleeding Adverse Events Reported by $\geq 1\%$ of Subjects (at Preferred Term Level): Safety Analysis Set (ENGAGE AF-TIMI 48)

System Organ Class Preferred Term	Edoxaban 30/15 mg (N = 7002) n (%)	Edoxaban 60/30 mg (N = 7012) n (%)	Warfarin (N = 7012) n (%)
Cardiac Disorders	404 (5.8)	386 (5.5)	436 (6.2)
Cardiac failure	73 (1.0)	85 (1.2)	105 (1.5)
Atrial fibrillation	89 (1.3)	79 (1.1)	83 (1.2)
Cardiac failure congestive	80 (1.1)	75 (1.1)	87 (1.2)
Infections and Infestations	380 (5.4)	336 (4.8)	407 (5.8)
Pneumonia	66 (0.9)	67 (1.0)	80 (1.1)
Investigations	202 (2.9)	211 (3.0)	367 (5.2)
Creatinine renal clearance decreased	84 (1.2)	96 (1.4)	91 (1.3)
International normalized ratio increased	9 (0.1)	8 (0.1)	151 (2.2)
Blood and Lymphatic System Disorders	75 (1.1)	130 (1.9)	88 (1.3)
Anaemia	48 (0.7)	77 (1.1)	49 (0.7)

Note: Treatment-emergence is defined as events which start on or after initial dose of study drug or started prior to but then worsened after initial dose of study drug. All events are based on investigator report.

Note: This summary includes all preferred terms with at least 0.5% of incidence in any of the treatment groups in descending order of system organ class (SOC) count, and within SOC, in descending order of frequency of preferred term in edoxaban 60 mg group.

Note: Subjects are considered to have interrupted study drug due to an adverse event if action taken on study drug is interrupted as reported on the associated event electronic case report form (eCRF) page.

Note: Adverse events (AEs) above are based on entries from the AE and serious adverse event (SAE) eCRF pages, as well as the investigator-reported hepatic, bone fracture, and malignancy event pages.

Note: Bleeding events and efficacy endpoint events are summarized separately.

Non-bleeding TEAEs from the overall study period were consistent with the on-treatment study period and did not reveal any safety concerns.

8.1.5 Adverse Events of Special Interest

Protocol-specified hepatic, malignancy, and bone fracture events were considered events of interest. There was no preclinical evidence or early clinical data suggestive of a direct edoxaban effect. However, systematic data collection of these events of special interest was undertaken for the following reasons:

- **Hepatic:** Drug-induced liver injury is an event of interest for any new investigational product.
- **Malignancy:** Although there is no evidence that anticoagulant therapy may increase risk of cancer, bleeding evaluation may lead to a diagnosis of a malignancy that would otherwise have been undetected.
- **Bone fracture:** There is some evidence that chronic therapy with warfarin may increase the risk of bone fracture, especially in men.⁴⁸

8.1.5.1 Hepatic Events

Hepatic Monitoring and Adjudication

Routine liver enzyme testing was performed at baseline, once monthly for the first 12 months, and every 3 months beyond 1 year. Two independent hepatic specialists performed blinded adjudication of all hepatic events meeting any 1 of the following criteria:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 8 x upper limit of normal (ULN)
- ALT or AST ≥ 3 x ULN with total bilirubin (TBL) ≥ 2 x ULN
- Elevation in ALT or AST (2 to 8 x ULN) with the clinical symptoms and signs suggestive of hepatitis
- Clinical jaundice
- Hepatic abnormalities or cases reported as serious adverse events (SAEs)
- Hepatic abnormalities requiring discontinuation of the study drug

Hepatic specialists adjudicated for the nature and severity of liver injury and the causal relationship to study drug. To satisfy Hy's law, alternative causes must have been excluded in a case with combination laboratory abnormality ALT or AST ≥ 3 x ULN with simultaneous TBL ≥ 2 x ULN elevation).

Hepatic Laboratory Data

Table 8-13 summarizes liver enzyme and bilirubin abnormalities for the Safety analysis set on-treatment period. The percentage of subjects in the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin groups with ALT or AST ≥ 3 x ULN was comparable (2.5%, 2.3%, and 2.4%, respectively). The percentage of subjects with concurrent ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN and alkaline phosphatase (ALP) < 2 x ULN was 0.2%, 0.1%, and 0.1%, respectively.

Table 8-13 Liver Enzyme and Bilirubin Abnormalities: Safety Analysis Set, On-Treatment Period (ENGAGE AF-TIMI 48)

	Edoxaban 30/15 mg (N = 7002) n (%)	Edoxaban 60/30 mg (N = 7012) n (%)	Warfarin (N = 7012) n (%)
ALT or AST, n (%)			
≥ 3 x ULN	161 (2.3)	170 (2.5)	163 (2.4)
≥ 8 x ULN	21 (0.3)	35 (0.5)	25 (0.4)
≥ 10 x ULN	13 (0.2)	23 (0.3)	16 (0.2)
≥ 20 x ULN	7 (0.1)	6 (<0.1)	1 (<0.1)
Concurrent ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN and ALP < 2 x ULN	9 (0.1)	12 (0.2)	10 (0.1)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBL, total bilirubin; ULN, upper limit of normal.

Note: Summaries evaluating concurrent data include any TBL value ≥ 2 x ULN within 37 (30 + 7 day window) days on or after the maximum ALT or maximum AST value ≥ 3 x ULN.

Events Evaluated and Adjudicated by Hepatic Specialists

Across the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin groups, the number of events sent for adjudication were comparable (146 [2.1%] for edoxaban 30/15 mg, 145 [2.1%] for edoxaban 60/30 mg, and 144 [2.1%] for warfarin). Of these events, 3 (1 in the edoxaban 30/15 mg group and 2 in the edoxaban 60/30 mg group) were assessed as meeting Hy's law criteria. These Hy's law cases were assessed as possibly/probably related to the study drug. No events were assessed as definitely related to the study drug.

Description of CEC Adjudicated Hy's Law Cases

In ENGAGE AF-TIMI 48, 3 subjects (2 in the edoxaban 60/30 mg group and 1 in the edoxaban 30/15 mg group) were adjudicated as having met Hy's law criteria (possibly/probably related to study drug). Brief narratives for these 3 subjects are provided below.

- Subject 44130008 (72-year-old male; India; randomized to edoxaban 60/30 mg regimen) with history of diabetes, hypertension, and stroke with baseline transaminase elevations (AST 74 IU/L [ULN 45 IU/L], ALT 76 IU/L [ULN 48 IU/L]). Onset of asymptomatic liver function test (LFT) elevations (ALT 705 IU/L [ULN 48 IU/L], AST 558 IU/L [ULN 45 IU/L], TBL 1.9 mg/dL [ULN 1.2 mg/dL], gamma-glutamyltransferase (GGT) 105 IU/L, ALP 159 IU/L [ULN 145 IU/L]) appeared at Month 8. Bilirubin peaked at 2.9 x ULN 10 days later. Evaluation for this event consisted of negative hepatitis B serology and normal abdominal ultrasound. On hepatic adjudication, this Month 8 event was hepatocellular, severe, probably/possibly related, and considered Hy's rule satisfied. Study drug was resumed after a 3-week interruption for the event. At this time, ALT/AST were within normal limits and TBL remained elevated at 1.9 mg/dL. Approximately 3 months later during work-up of MI and GI bleeding, subject was diagnosed with esophageal varices and cirrhosis of the liver on another abdominal ultrasound. Liver enzymes showed peak TBL 2.0 mg/dL [ULN 1.0 mg/dL], direct bilirubin 0.9 mg/dL [ULN 0.3 mg/dL], and normal ALT, AST, ALP. Serologies were negative for hepatitis A/B/C/E, antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), cytomegalovirus (CMV) immunoglobulin M (IgM), and Epstein-Barr virus (EBV) IgM. Hepatic adjudication categorized this second event as long-standing liver cirrhosis, moderate, and unlikely/unrelated. Liver biopsy was not performed. Edoxaban was permanently discontinued at Month 15 due to a continued decrease in CrCL. The subject experienced GI bleed and MI approximately 2.5 months after the last edoxaban dose, and sudden death occurred 1 month later.
- Subject 70350002 (66-year-old male; United Kingdom; randomized to edoxaban 60/30 mg regimen), with a history of alcohol use (1 to 2 drinks/day) and baseline TBL elevation of 1.4 mg/dL (ULN 1.2 mg/dL), which remained elevated during the first month of the study with normal ALT/AST (Day 29 TBL 1.7 mg/dL, ALT 37 [ULN 48] and AST 32 [ULN 45]). Asymptomatic LFT elevations (ALT 519 IU/L [ULN 48], AST 455 IU/L [ULN 45], total bilirubin was 2.6 mg/dL [ULN 1.2] – direct bilirubin 0.4 [ULN: 0.3], ALP 151 IU/L [ULN 145 IU/L], GGT not available) occurred at Month 2. Edoxaban was discontinued and transaminases normalized 2 weeks later (ALT 35 IU/L, AST 30 IU/L, TBL 1.1 mg/dL). Liver biopsy was not performed. Serologies showed ASMA 40 titer and were negative for ANA, hepatitis B/C/E, EBV IgM, and CMV IgM. Hepatic

adjudication categorized this event as hepatocellular, severe, probable/possible, and Hy's rule satisfied.

- Subject 71110020 (72-year-old male; US; randomized to edoxaban 30/15 mg regimen) with a known history of CHF. The subject was hospitalized on Day 199 for CHF exacerbation and elevated LFTs (ALT 426 U/L [ULN 63 U/L], AST 802 U/L [ULN 41 U/L], ALP 162 U/L [ULN 91 U/L], TBL 2.6 mg/dL [ULN 1.2 mg/dL]). Peak values were reported the following day (ALT 1382 U/L, AST 1713 U/L, ALP 174 U/L, TBL 3.2 mg/dL). Edoxaban was permanently discontinued and the subject was treated with diuretic/nitrates. Transaminases normalized approximately 2 weeks after hospital discharge (ALT 48 U/L, AST 27 U/L). Liver biopsy was not performed. Serologies were negative for hepatitis A/B/C. Hepatic adjudication categorized this event as hepatocellular, severe, probable/possible, and Hy's rule satisfied.

The overall evaluation of hepatic events and laboratory abnormalities reported as well as the results of adjudication did not suggest a clinically concerning signal of drug-induced liver injury associated with edoxaban. The incidence of liver enzyme elevations (AST/ALT $\geq 3 \times$ ULN) were comparable across the edoxaban and warfarin treatment groups; 3 cases adjudicated as meeting Hy's law criteria revealed potential confounding factors(s) or a plausible explanation for the liver enzyme elevations in each case.

Results of the adjudicated hepatic abnormalities observed in the Hokusai VTE Phase 3 study are summarized in **Section 8.2.1**. In that study, although no edoxaban subject's liver abnormalities were adjudicated as meeting Hy's law criteria. However, 2 warfarin subjects with liver abnormalities were adjudicated as meeting Hy's law criteria.

In the global Phase 3 program including the Hokusai VTE study, the number of cases adjudicated as meeting Hy's law were balanced (3/18,010 subjects encompassing 34,048 subject-years of exposure on edoxaban, and 2/11,010 subjects encompassing 18,352 subject-years of exposure on warfarin; see **Section 8.2.1**). There were no Hy's law cases from any other edoxaban studies.

8.1.5.2 Malignancy

The annualized event rate for clinically evident postrandomization malignancies was comparable among the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin groups (2.68, 2.50, and 2.64%, respectively).

8.1.5.3 Bone Fractures

The percentage of subjects with new bone fractures was comparable among the edoxaban 60/30 mg, edoxaban 30/15 mg, and warfarin groups (5.7%, 6.3%, and 6.4%, respectively). The most common bone fracture was hip/pelvis/proximal femur.

8.2 Supportive Clinical Studies

Supportive safety data for the AF indication were derived from the pivotal Phase 3 VTE trial (Hokusai VTE), Phase 2 AF studies, Phase 2/3 VTE prophylaxis studies in subjects undergoing orthopedic surgeries, Phase 1 PK/PD/DDI studies, and ongoing studies (Edoxaban Thrombus Reduction Imaging Study [eTRIS] and Edoxaban in Peripheral Arterial Disease [ePAD]; data

cutoff date, 31 Dec 2013; **Table 5-1**). Approximately 10,000 subjects have been treated with edoxaban in these studies. Safety data from these studies are summarized in this section.

8.2.1 Hokusai VTE

Hokusai VTE was a large pivotal, double-blind, Phase 3 safety and efficacy trial of low molecular weight heparin (LMWH)/edoxaban versus LMWH/warfarin in subjects with symptomatic DVT and/or PE. A total of 8240 subjects were treated with edoxaban 60/30 mg QD (n = 4118) or warfarin (INR 2.0-3.0; n = 4122). The median treatment duration was 267 days for edoxaban-treated subjects and 266 days for warfarin-treated subjects. In the edoxaban and warfarin groups, 62.1% and 60.9% of subjects, respectively, received > 6 months of treatment, and 40.3% and 40.2% of subjects, respectively, received the full 12 months of treatment.

Demographic and Baseline Characteristics

Demographic and baseline characteristics were comparable between the treatment groups including age, gender, race, presenting diagnosis, and risk factors. The mean age was 55.8 years, and the majority of subjects were male (57.2%) and Caucasian (69.9%). Of the 8240 subjects, 1452 (17.6%) required dose reduction to 30 mg edoxaban/edoxaban placebo.

Bleeding Events

For the primary safety endpoint of adjudicated major bleeding/CRNM bleeding, the edoxaban regimen was superior to warfarin (HR = 0.81; 95% CI: 0.70, 0.94; **Table 8-14**). For major bleeding, the observed difference was 16% (HR = 0.84; 95% CI: 0.59, 1.20). Across all bleeding categories, lower bleeding rates were consistently shown for edoxaban versus warfarin. Notably, fewer edoxaban-treated than warfarin-treated subjects had any fatal bleeding (2 vs 10 subjects), fatal ICH bleeding (0 vs 6 subjects), and any ICH bleeding (5 vs 18 subjects).

Table 8-14 Adjudicated Bleeding Events: Safety Analysis Set, On-Treatment Period (Hokusai VTE)

Adjudicated Bleeding	Edoxaban (N = 4118)	Warfarin (N = 4122)
Major/CRNM bleeding, n (%)	349 (8.5)	423 (10.3)
HR edoxaban vs warfarin (95% CI) ^a	0.81 (0.71, 0.94)	
<i>P</i> value ^a	0.004	
Major bleeding, n (%)	56 (1.4)	66 (1.6)
HR edoxaban vs warfarin (95% CI) ^a	0.84 (0.59, 1.20)	
<i>P</i> value ^a	0.352	
Fatal bleeding, n (%) ^b	2 (<0.1)	10 (0.2)
CRNM bleeding, n (%)	298 (7.2)	368 (8.9)
Nuisance bleeding, n (%)	663 (16.1)	787 (19.1)
All bleeding, n (%)	895 (21.7)	1056 (25.6)

Abbreviations: CI, confidence interval; CRNM, clinically relevant non-major; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

Note: Events are included in the On-treatment study period if they occurred on or after the date of first dose of any study drug. Events that start after the third day following the calendar date of any “last dose” and before the date of the next “first dose” are not considered for the On-treatment study period.

^a The HR and 2-sided CI are based on the Cox-proportional hazards regression model including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo dose at randomization (yes, no), *P* value $\alpha = 0.01$ (2-sided).

^b Of the 2 fatal bleeding events that occurred in the subjects on the edoxaban group, neither had yet received edoxaban study drug (i.e., event occurred during the initial [low molecular weight] heparin treatment).

The incidence of major/CRNM GI bleeding was higher in the edoxaban group compared to warfarin (98 [2.4%] edoxaban, 94 [2.3%] warfarin). The incidence of major/CRNM vaginal bleeding was higher in the edoxaban group than the warfarin group (81 subjects [4.6%] vs 56 subjects [3.2%], respectively). Upon individual case review, vaginal bleeding appeared to occur more frequently related to the menstrual cycle but with few subjects (10 edoxaban, 1 warfarin) discontinuing study drug due to the events.

The composite endpoint of MACE (MI, stroke, SEE, and CV death) was observed in 1.2% of subjects in the edoxaban group and 1.0% of subjects in the warfarin group (**Table 8-15**). Similar to ENGAGE AF-TIMI 48, all deaths were adjudicated for cause of death.

Table 8-15 Summary of Adjudicated MACE: Safety Analysis Set, On-Treatment Period (Hokusai VTE)

Adjudicated MACE	Edoxaban (N = 4118) n (%)	Warfarin (N = 4122) n (%)	Edoxaban vs Warfarin
Subjects with MACE events	49 (1.2)	40 (1.0)	1.22 (0.80, 1.85)
<i>P</i> value ^a			0.349
Subjects with events ^b			
MI	20 (0.5)	13 (0.3)	1.54 (0.76, 3.08)
Stroke	26 (0.6)	26 (0.6)	1.00 (0.58, 1.72)
SEE	4 (<0.1)	0 (0.0)	NC
Cardiovascular death ^c	6 (0.1)	3 (<0.1)	NC

Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event (composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and cardiovascular death); MI, myocardial infarction; NC, not calculated when number of observed events were below 5 in either treatment group; SEE, systemic embolic event; VTE, venous thromboembolism.

Note: Events are included in the On-treatment study period if they occurred on or after the date of first dose of any study drug. Events that start after the third day following the calendar date of any “last dose” and before the date of the next “first dose” are not considered for the On-treatment study period.

^a The HR and 2-sided CI are based on the Cox-proportional hazards regression model including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo dose at randomization (yes, no).

^b The total number of MI, stroke, SEE, and cardiovascular death separately do not equal the total number of MACE because subjects may be counted in more than 1 MACE category but are only counted in the overall row.

^c Includes total of fatal MI, ischemic stroke, SEE and other cardiac deaths. Other cardiac deaths were postoperative tamponade, heart failure, ruptured aortic aneurysm (edoxaban group) and arrhythmia (warfarin group).

Non-Bleeding Events

Non-bleeding TEAEs, including TESAEs, were comparable between treatment groups (Table 8-16).

Table 8-16 Overview of Treatment-Emergent Adverse Events: Safety Analysis Set, On-Treatment Period (Hokusai VTE)

Treatment-Emergent Adverse Event	Edoxaban (N = 4118) n (%)	Warfarin (N = 4122) n (%)
All TEAEs	2821 (68.5)	2928 (71.0)
All TESAEs	503 (12.2)	544 (13.2)
TESAEs with fatal outcome	68 (1.7)	61 (1.5)
TEAEs leading to study drug interruption	295 (7.2)	467 (11.3)
TEAEs leading to permanent study drug discontinuation	195 (4.7)	185 (4.5)

Abbreviations: TEAE, treatment-emergent adverse event; TESA, treatment-emergent serious adverse event.

Adverse events (AEs) reported as serious for the edoxaban and warfarin groups were comparable with the exception of more investigations events (INR increased reported as serious for the warfarin group). Anemia was reported more frequently in the edoxaban group (72 [1.7%]) compared to the warfarin group (55 (1.3%), with few reported as serious (3 [<0.1%] and 10 [0.2%] for edoxaban and warfarin groups respectively) and few leading to study drug discontinuation (2 [<0.1%] and 3 [<0.1%] for edoxaban and warfarin groups respectively).

Adverse Events of Interest

Because transaminase elevations with LMWH are well known, liver enzyme and bilirubin abnormalities reported from the initial LMWH treatment period were excluded from the main analysis. The number of subjects with ALT or AST $\geq 3 \times$ ULN were comparable: 106 (2.7%) and 100 (2.6%) subjects in the edoxaban and warfarin treatment groups, respectively. The numbers of subjects with concurrent ALT or AST $\geq 3 \times$ and TBL $\geq 2 \times$ elevations with ALP $< 2 \times$ ULN were 3 ($< 0.1\%$) for edoxaban and 1 ($< 0.1\%$) for warfarin (Table 8-17).

Table 8-17 Overview of Treatment-Emergent Adverse Events: Safety Analysis Set, On-Treatment Period (Hokusai VTE)

Lab Test/Abnormality ^a	Edoxaban (N = 4118) n (%)	Warfarin (N = 4122) n (%)
Subjects with ALT or AST	3901	3903
$\geq 3 \times$ ULN	106 (2.7)	100 (2.6)
$\geq 8 \times$ ULN	14 (0.4)	15 (0.4)
$\geq 10 \times$ ULN	9 (0.2)	5 (0.1)
$\geq 20 \times$ ULN	1 (< 0.1)	0 (0.0)
Concurrent ALT or AST $\geq 3 \times$ ULN and TBL $\geq 2 \times$ ULN and ALP $< 2 \times$ ULN ^c	3 (< 0.1)	1 (< 0.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBL, total bilirubin; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; ULN, upper limit of normal.

^a Includes liver enzyme and bilirubin abnormalities that occurred at least 1 day after the first dose of edoxaban or edoxaban placebo, and excludes abnormalities during the open-label heparin treatment period.

^b A case of “ALT or AST $\geq 3 \times$ ULN and TBL $\geq 2 \times$ ULN” is considered a concurrent combination case if the TBL $\geq 2 \times$ ULN occurs within 37 days after the maximum ALT or AST $\geq 3 \times$ ULN elevation.

^c An event of concurrent combination is considered a concurrent ALP $< 2 \times$ ULN case if all ALP values are $< 2 \times$ ULN within 37 days of the maximum ALT or AST $\geq 3 \times$ ULN elevation.

Adjudicated hepatic abnormalities are summarized in Table 8-18. No edoxaban subject’s liver abnormalities were adjudicated as meeting Hy’s law criteria. Two warfarin subjects with liver abnormalities were adjudicated as meeting Hy’s law criteria.

Table 8-18 Adjudicated Hepatic Abnormalities: Safety Analysis Set, On-Treatment Period (Hokusai VTE)

Hepatic Abnormalities	Edoxaban (N = 4118) n (%)	Warfarin (N = 4122) n (%)
Subjects with suspected hepatic events meeting criteria for adjudication	103 (2.5)	90 (2.2)
Subjects with events confirmed as liver injury	59 (1.4)	48 (1.2)
Subjects with events satisfying Hy’s law criteria	0 (0.0)	2 (< 0.1)

Abbreviation: VTE, venous thromboembolism.

Events satisfying Hy’s law criteria from the warfarin group (randomized to warfarin and received warfarin) are described as follows:

- Fulminant hepatitis with fatal outcome (Subject ID: 29145612): This warfarin subject was a 60-year-old female with a history of diclofenac use who developed liver enzyme elevations starting at Month 6 (AST-1.9xULN, ALT-2.5xULN). Subject progressed to

fulminant hepatitis while off study drug (AST 43.6xULN, ALT 23.7xULN), subsequently required liver transplant with postoperative fatality. Pathology report showed severe hepatitis with confluent (submassive) hepatic necrosis and impaired regeneration. This event was adjudicated as severe hepatocellular liver injury probably related to study drug.

- Biliary obstruction (Subject ID: 61333247): This warfarin subject was a 61-year-old male with history of lung cancer and alcohol use (1-2 drinks per day) who developed nausea, abdominal pain, and diarrhea after eating greasy food at Month 11. Abdominal ultrasound was consistent with gallbladder polyp without stone or obstruction. Labs at the time of the event: AST 10xULN, ALT 4xULN, TBL 2.7xULN, GGT and ALP-not available. This event was adjudicated as moderate hepatocellular liver injury possibly related to study drug.

8.2.2 Other Phase 2/3 Studies in AF and Other Indications

The safety findings from completed Phase 2 studies in subjects with nonvalvular AF, completed Phase 2/3 studies of VTE prophylaxis in subjects undergoing orthopedic surgeries, and ongoing studies were consistent with those in the ENGAGE AF-TIMI 48 and Hokusai VTE trials, and did not reveal any clinical safety concerns.

8.3 Postmarketing Data

Edoxaban was approved in Japan on 22 Apr 2011 for the prevention of VTE following total knee replacement, total hip replacement, and hip fracture surgery.

As of the 31 December 2013 cut-off date for the edoxaban New Drug Application (NDA), there has been a total estimated exposure of approximately 155,000 patients excluding clinical and postmarketing studies. There were an additional 2419 patients enrolled in the postmarketing Drug Use Survey (LIX-011-011) study.

As of the cut-off date (31 December 2013), there were a total of 871 postmarketing cases (including spontaneous report and reports from the Drug Use Survey) with 1,151 AEs, of which 104 were serious adverse events (SAEs). Bleeding (e.g., subcutaneous hemorrhage) was the most common event. Overall, the safety profile of edoxaban from these postmarketing surveillance data appears consistent with that in the clinical studies.

8.4 Overall Safety Conclusions

Results of ENGAGE AF-TIMI 48 demonstrated that edoxaban was superior to warfarin in reducing the risk of major bleeding (principal safety endpoint). The edoxaban 60/30 mg regimen yielded a clinically relevant 20% reduction in the risk of major bleeding. The benefit of edoxaban compared with warfarin was also demonstrated across other bleeding categories, including ICH, fatal bleeds, life-threatening, CRNM bleeds, and any confirmed bleed. In addition, the lower bleeding rates in edoxaban-treated subjects were observed in various subgroups based on demographic and baseline characteristics (e.g., age, gender, body weight, renal function, CHADS₂ score, or past history of stroke or TIA). A similar advantage favoring the edoxaban groups was demonstrated in subjects receiving concomitant medications (e.g., aspirin, antiplatelets, and NSAIDs), although the overall bleeding event rates were higher in these groups compared to subjects who did not receive these concomitant medications. While in general the major bleeding rate was lower with edoxaban in most anatomic locations, this was

not observed for GI bleeds, which occurred at a numerically higher rate in the edoxaban 60/30 mg group than in the warfarin group.

Non-bleeding TEAEs were generally similar in the edoxaban and warfarin treatment groups. The edoxaban 60/30 mg group had more reports of anemia than the warfarin group. Most of the anemia in the edoxaban 60/30 mg group was not severe, with only approximately 1% leading to study drug interruption or permanent study drug discontinuation. Overall, non-bleeding TEAEs leading to study drug interruptions or discontinuations were also similar in both edoxaban and warfarin-treated subjects.

Review of the hepatic laboratory data (liver enzyme and bilirubin abnormalities), as well as cases adjudicated by 2 independent, blinded hepatic specialists, did not indicate any clinically concerning signal for drug-induced liver injury. The incidence of ALT/AST elevations $\geq 3 \times$ ULN was comparable between the edoxaban and warfarin treatment groups. Two subjects in the edoxaban 60/30 mg group and 1 subject in the edoxaban 30/15 mg group were adjudicated as having met Hy's law criteria. In each case, additional factors potentially contributed to the liver enzyme elevation. In the global Phase 3 edoxaban program, there were 5 cases adjudicated as Hy's law (3/18,010 subjects treated with edoxaban encompassing 34,048 subject-years of exposure and 2/11,010 subjects treated with warfarin encompassing 18,352 subject-years of exposure). There were no Hy's law cases in any other edoxaban studies.

Overall, results of ENGAGE AF-TIMI 48 demonstrated that edoxaban is a well-tolerated NOAC with a significantly lower risk of bleeding events across all bleeding categories. The safety profile of edoxaban is consistent with that expected in AF patients with a medium to high risk of stroke treated with anticoagulants.

9.0 SPECIAL POPULATIONS

The incidence of bleeding events and stroke or SEE events was examined in post-hoc analyses in subjects with severe renal impairment (subjects with at least 1 CrCL value of ≤ 30 mL/min at either study entry or during the study). While the numbers are small, at approximately 400 subjects per treatment group, and the results should be interpreted with caution, these data provide valuable additional information on efficacy and safety for subjects with severe renal impairment (CrCL < 30 mL/min), since the experience for NOACs (FIIa or FXa inhibitors) in subjects with severe renal impairment is very limited.

Subjects with CrCL < 30 mL/min were to be excluded from the study; however, some investigators included at their discretion subjects who had borderline CrCL values from the central laboratory (around 30 mL/min) or whose local lab value was above 30 mL/min. In addition, some subjects developed renal impairment with a decreased CrCL < 30 mL/min during the study and continued to receive drug while awaiting the results of the protocol-mandated confirmatory re-test.

Bleeding events and stroke or SEE were counted for the on-treatment period from the reference date (the date on which the first time CrCL ≤ 30 mL/min was observed and documented) to the CSED visit, regardless of the CrCL values between the reference date and the CSED visit. In some cases, the CrCL values may have fluctuated above and below 30 mL/min after the reference date. The primary focus was to compare the incidence of bleeding events and stroke or SEE events between subjects who had their dose reduced and were treated with edoxaban 30 mg (60/30 mg group dose reduced) or edoxaban 15 mg (30/15 mg group dose reduced), and in subjects with at least 1 CrCL value of ≤ 30 mL/min at either study entry or during the study.

9.1 Stroke or SEE in Subjects With Severe Renal Impairment

Data for stroke or SEE events in subjects with CrCL < 30 mL/min at baseline or post-baseline are summarized in **Table 9-1**. In more than 90% of these cases the CrCL values were between 15 and 30 mL/min, with some fluctuations above and below 30 mL/min. In these subjects with SRI, there were more stroke or SEE events in subjects treated with edoxaban 15 mg than in those treated with edoxaban 30 mg or warfarin. Overall, the incidence of stroke or SEE was similar between subjects treated with edoxaban 30 mg and warfarin.

Table 9-1 Adjudicated Stroke or SEE in Subjects with CrCL ≤ 30 mL/min at Baseline or Post-Baseline: mITT Analysis Set, On-Treatment Period

Regimen Treatment Received	Edoxaban 30/15 mg	Edoxaban 60/30 mg	Warfarin (Placebo Dose Reduced) (N = 407)
	Edoxaban 15 mg (N = 395)	Edoxaban 30 mg (N = 400)	
Stroke or SEE			
Number of events	11	6	5
Subject year exposure	250.26	254.18	263.98
Event rate (%/yr)	4.40	2.36	1.89

Abbreviations: CrCL, creatinine clearance; mITT, modified intent-to-treat; SEE, systemic embolic event; yr, year.

9.2 Adjudicated Bleeding Events in Subjects With Severe Renal Impairment

In subjects with SRI (CrCL < 30 mL/min), the rate for major bleeds was lowest in those treated with edoxaban 15 mg (3.56%) and comparable between edoxaban 30 mg and warfarin-treated subjects (6.83% and 6.49%, respectively) (**Table 9-2**). There were no fatal bleeds in subjects receiving edoxaban 30 mg, while the rate for subjects receiving edoxaban 15 mg was similar to that in subjects receiving warfarin (1.19% and 1.13%, respectively). The rate of LT bleeds was similar between subjects receiving edoxaban 15 mg and warfarin (0.79% and 0.76, respectively), with the edoxaban 15 mg dose resulting in a slighter lower rate compared to the edoxaban 30 mg dose (0.79% vs 1.17%). Overall, the incidence of major or CRNM bleeds as well any confirmed bleeding was similar between the edoxaban 30 mg and 15 mg dose levels and higher in the warfarin group (14.73%, 15.24%, and 19.61%, respectively for major or CRNM bleeding, and 19.05%, 19.42%, and 27.69% respectively, for any confirmed bleeding).

Table 9-2 Adjudicated Bleeding Events in Subjects with CrCL ≤ 30 mL/min at Baseline or Post-Baseline: Safety Analysis Set, On-Treatment Period (ENGAGE AF-TIMI 48)

Regimen Treatment Received		Edoxaban 30/15 mg	Edoxaban 60/30 mg	Warfarin (Placebo Dose Reduced)
		Edoxaban 15 mg (N = 395)	Edoxaban 30 mg (N = 400)	(N = 407)
Major	# of Events	9	17	17
	Subj Yr Expo	252.58	248.92	262.01
	Event Rate (%/yr)	3.56	6.83	6.49
Fatal	# of Events	3	0	3
	Subj Yr Expo	252.69	256.90	264.37
	Event Rate (%/yr)	1.19	0.00	1.13
Life-threatening	# of Events	2	3	2
	Subj Yr Expo	252.56	256.87	264.37
	Event Rate (%/yr)	0.79	1.17	0.76
Clinically relevant non-major	# of Events	28	19	34
	Subj Yr Expo	236.10	245.51	240.70
	Event Rate (%/yr)	11.86	7.74	14.13
Major or clinically relevant non-major	# of Events	36	35	47
	Subj Yr Expo	236.21	237.64	239.67
	Event Rate (%/yr)	15.24	14.73	19.61
Any confirmed	# of Events	44	44	64
	Subj Yr Expo	226.63	231.01	231.11
	Event Rate (%/yr)	19.42	19.05	27.69

Abbreviations: CrCL, creatinine clearance; Subj Yr Expo, subject year exposure.

Note: This table includes subjects with first CrCL ≤ 30 mL/min at baseline or post-baseline.

Note: For subjects who had CrCL ≤ 30 mL/min at baseline, the reference date is the date of initial study drug. For other subjects, the reference date is the date of first post-baseline ≤ 30 mL/min.

Note: Dose regimen is determined by the dose adjustment status on the reference date.

Note: Any confirmed bleed includes those that the adjudicator defined as clinically overt.

Note: The event rate (%/yr) is calculated as # of event/subject year exposure. The subject year exposure is the sum across subjects, of the number of at risk years from reference date up to the event or censoring. At risk is started from the reference date. Only at risk event and subject year exposure are included.

9.3 Summary and Conclusion (Special Populations)

Results from these post-hoc analyses showed that the edoxaban 30 mg dose is safe and effective in patients with severe renal impairment. The edoxaban 15 mg dose, although showing reduced bleeding rates, did not provide adequate protection from ischemic stroke. The PK data showed that the 30 mg dose provides comparable exposure in subjects with moderate renal impairment and SRI. Therefore, a dose of 30 mg QD is recommended for patients with SRI.

9.4 Additional Analyses and Subpopulations

The Statistical Analysis Plan (SAP) prospectively defined numerous analyses to be conducted on multiple analysis datasets. These included both individual and composite endpoints as well as co-variables identifying potential risk factors for either efficacy and/or safety. With regard to baseline characteristics, a test for heterogeneity was used to evaluate whether observed treatment effects are different in various subgroup categories. Prespecified subgroup analyses were conducted for multiple baseline characteristics and various endpoints including, but not limited to age, gender, race, weight, VKA use at baseline, CHADS₂ score, and CrCL. The results of these subgroup analyses were largely consistent with the overall study results and were supportive of the key study outcomes. Although these subgroup analyses are important to assess consistency of the main results across subgroups, caution is recommended against over-interpretation of the results due to well-known issues with subgroup analyses.

9.4.1 Primary Efficacy Endpoint (Stroke or SEE) by Subgroups

The primary efficacy findings for subgroups based on demographic and baseline characteristics were largely consistent with the overall study results. For most subgroups, the event rate for stroke or SEE was lower in the edoxaban 60/30 mg group than in the warfarin group ($HR \leq 1.0$). See also **Figure 7-4**.

9.4.2 Principal Safety Endpoint (Major Bleeding Subgroups)

Edoxaban-treated subjects had lower bleeding rates compared with the warfarin group across all prespecified subgroups based on demographic and baseline characteristics. A similar advantage for lower bleeding rates with edoxaban over warfarin was also observed in subjects receiving concomitant medications such as aspirin, antiplatelet agents, and NSAIDs, although the bleeding event rates were higher in these subgroups compared to those not taking these concomitant medications. See also **Figure 8-1**.

9.4.3 Subgroup Analyses by Renal Function

The SAP stated that 1 of the subgroup analyses was to be performed using the original stratification criteria for dose reduction, (i.e., $CrCL \leq 50$ mL/min vs > 50 mL/min). Using these categories for renal function, there was no interaction for heterogeneity for either edoxaban dose comparisons versus warfarin ($P = 0.5$ in both). Another prespecified subset analysis by renal function across 4 categories of CrCL (as proxies for renal function: normal renal function [≥ 80 mL/min]; mild renal impairment [> 50 to < 80 mL/min]; moderate renal impairment [30 to 50 mL/min]; and SRI [< 30 mL/min]) indicated a significant interaction for heterogeneity for both the edoxaban 60/30 mg ($P < 0.001$) and 30/15 mg ($P = 0.008$) regimens (**Table 9-3**).

Table 9-3 Adjudicated Endpoint of Stroke or SEE Subgroup Analysis for Baseline Characteristics: mITT Analysis Set, On-Treatment Period (ENGAGE AF-TIMI 48)

CrCL (mL/min)	Statistic	Edoxaban 30/15 mg (N = 7002)	Edoxaban 60/30 mg (N = 7012)	Warfarin (N = 7012)
< 30	# of Events	2	2	1
	Subj Yr Expo	38.51	60.43	54.54
	Event Rate (%/yr)	5.19	3.31	1.83
	HR (95% CI)	--	--	--
30 to 50	# of Events	58	43	49
	Subj Yr Expo	2501.80	2506.22	2493.38
	Event Rate (%/yr)	2.23	1.72	1.97
	HR (95% CI)	1.18 (0.81, 1.73)	0.88 (0.58, 1.32)	--
> 50 to < 80	# of Events	116	71	135
	Subj Yr Expo	6954.89	6655.92	6762.32
	Event Rate (%/yr)	1.67	1.07	2.00
	HR (95% CI)	0.82 (0.64, 1.06)	0.53 (0.40, 0.70)	--
≥ 80	# of Events	77	66	47
	Subj Yr Expo	6260.38	6215.69	6202.08
	Event Rate (%/yr)	1.23	1.06	0.76
	HR (95% CI)	1.64 (1.14, 2.36)	1.41 (0.97, 2.06)	--
<i>P</i> value for interaction		0.008	< 0.001	--

Abbreviations: CI, confidence interval; CrCL, creatinine clearance; HR, hazard ratio; mITT, modified intent-to-treat; SEE, systemic embolic event; Subj Yr Expo, subject year exposure.

A less favorable HR for the edoxaban 60/30 mg regimen versus warfarin was observed in subjects with normal renal function (HR = 1.41, 95% CI: 0.97, 2.06), while a more favorable HR was observed for edoxaban 60/30 mg versus warfarin in the mild renal insufficiency group (HR = 0.53, 95% CI: 0.40, 0.70). When the principal safety endpoint of major bleeding was analyzed in the same manner, no interaction was found and consistently favorable HRs for the edoxaban 60/30 mg regimen versus warfarin were observed (**Table 9-4**).

Table 9-4 Adjudicated Major Bleeding Events Subgroup Analysis for Baseline Characteristics: Safety Analysis Set, On-Treatment Period (ENGAGE AF-TIMI 48)

CrCL (mL/min)	Statistic	Edoxaban 30/15 mg (N = 7002)	Edoxaban 60/30 mg (N = 7012)	Warfarin (N = 7012)
< 30	# of Events	0	4	5
	Subj Yr Expo	39.63	59.16	53.83
	Event Rate (%/yr)	0.00	6.76	9.29
	HR (95% CI)	--	--	--
30 to 50	# of Events	50	96	128
	Subj Yr Expo	2491.21	2457.43	2448.96
	Event Rate (%/yr)	2.01	3.91	5.23
	HR (95% CI)	0.38 (0.28, 0.53)	0.75 (0.58, 0.98)	--
> 50 to < 80	# of Events	135	209	237
	Subj Yr Expo	6932.22	6538.11	6674.28
	Event Rate (%/yr)	1.95	3.20	3.55
	HR (95% CI)	0.55 (0.45, 0.68)	0.90 (0.75, 1.08)	--
≥ 80	# of Events	69	109	154
	Subj Yr Expo	6270.11	6146.74	6101.03
	Event Rate (%/yr)	1.10	1.77	2.52
	HR (95% CI)	0.44 (0.33, 0.58)	0.71 (0.55, 0.90)	--
P value for interaction		0.143	0.250	--

Abbreviations: CI, confidence interval; CrCL, creatinine clearance; HR, hazard ratio; Subj Yr Expo, subject year exposure.

These findings prompted additional analyses to further understand what may have contributed to the observed HR in the subgroup of subjects with normal renal function. The results of those analyses are described below.

Exposure analysis: A PK analysis showed that exposure to edoxaban varied by renal function, as described in **Section 11.0**. Subjects with normal renal function (CrCL ≥ 80 mL/min) had a lower exposure compared to subjects with mild renal impairment (CrCL > 50 to < 80 mL/min), and slightly higher than subjects with moderate renal impairment (CrCL 30 to 50 mL/min) (median C_{av} = 74, 98, 62 ng/mL for normal, mild, and moderate, respectively). On the other hand, the observed HR was 0.88 in the moderate renal impairment subgroup compared with a HR of 1.41 for normal renal function.

Event rate analysis: A comparison of the annualized event rates for stroke or SEE in the edoxaban 60/30 mg group demonstrated that the event rates were very similar in the subgroups with normal renal function and mild renal impairment (1.06% per year and 1.07% per year, respectively) (**Table 9-5; Figure 9-1**). In contrast, the event rates in the warfarin group were different (0.76% per year and 2.0% per year, respectively). This represents a 62% reduction in the event rate between the mild renal impairment and the normal renal function subgroups treated with warfarin. This has not been seen in other similar studies. Moreover, the striking similarity of event rates in the 60/30 mg edoxaban group was not anticipated considering that these 2 subgroups differed with respect to their median CHADS₂ score at baseline (2.6 in the normal renal function subgroup and 2.9 in the mild renal impairment subgroup) (**Table 9-5; Figure 9-1**).

In the edoxaban 30/15 mg group, the observed rates of stroke or SEE increased in a near linear manner across the defined renal subgroups (1.23% per year for normal renal function, 1.67% per year for mild renal impairment, and 2.32% per year, for moderate renal impairment). This is consistent with the near linear increase in baseline CHADS₂ score across the renal subgroups (2.6, 2.9, and 3.1, respectively).

Table 9-5 Events and Annualized Event Rate by CrCL Subgroup (ENGAGE AF-TIMI 48)

Renal Function (CrCL)	Subjects, n	Events, n	Point Estimate, %/yr (95% CI)
Moderate (30 to 50 mL/min)			
Edoxaban 30/15 mg	1280	58	2.46 (1.80, 2.99)
Edoxaban 60/30 mg	1302	43	1.75 (1.28, 2.30)
Warfarin	1305	49	1.96 (1.45, 2.54)
Mild (> 50 to < 80 mL/min)			
Edoxaban 30/15 mg	3052	116	1.67 (1.38, 1.99)
Edoxaban 60/30 mg	3007	71	1.07 (0.83, 1.33)
Warfarin	3048	135	2.00 (1.67, 2.35)
Normal (≥ 80 mL/min)			
Edoxaban 30/15 mg	2628	77	1.23 (0.97, 1.52)
Edoxaban 60/30 mg	2633	66	1.06 (0.82, 1.33)
Warfarin	2608	47	0.76 (0.56, 0.99)

Abbreviations: CI, confidence interval; yr, year.

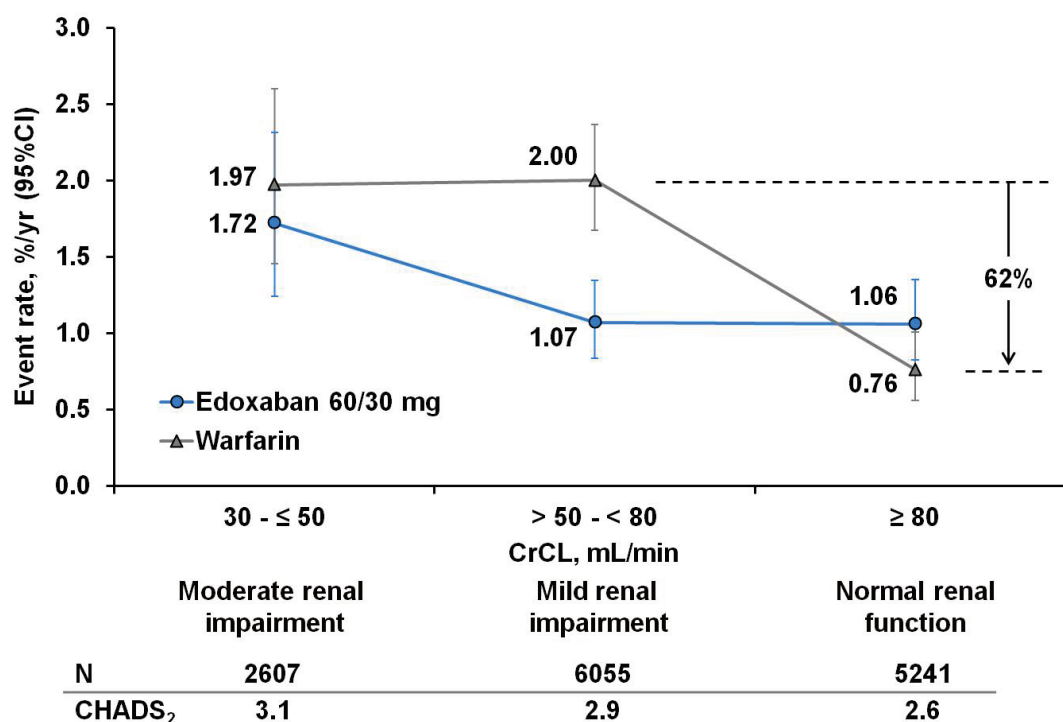


Figure 9-1 Annualized Event Rate for Stroke or SEE by Renal Subgroup

Abbreviations: CI, confidence interval; CrCL, creatinine clearance; SEE, systemic embolic event.

Myocardial infarction analysis: We sought other possible corroborating findings in the ENGAGE AF-TIMI 48 database looking for evidence of consistency. For instance, among subjects with normal renal function, the rates for MI, another prespecified ischemic endpoint reflecting a mechanism-mediated outcome, showed an event rate of 0.4%/year for edoxaban 60/30 mg and 0.5%/year for warfarin-treated subjects (**Figure 9-2**). This latter outcome is consistent with the overall trial results establishing noninferiority of edoxaban compared with warfarin and suggests a lack of biologic plausibility of the observed interaction.

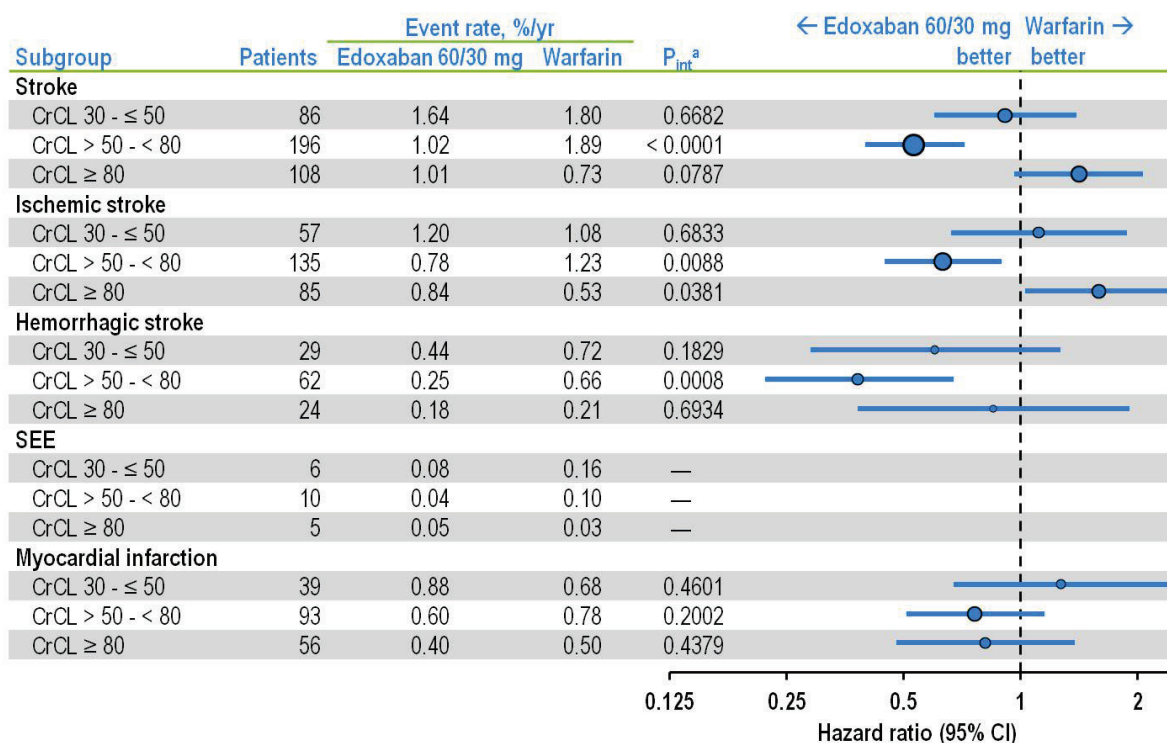


Figure 9-2 Efficacy Endpoint Subcategories by Creatinine Clearance: mITT Analysis Set, On-Treatment Period

^a P value for the interaction.

Abbreviations: CI, confidence interval; CrCL, creatinine clearance; mITT, modified intent-to-treat SEE; systemic embolic event.

Analysis of the Hokusai VTE Study: In addition, a similar subset analysis of the primary efficacy endpoint (prevention of recurrence of VTE) by CrCL was conducted in the Hokusai VTE study (described in **Section 8.2.1**), and that analysis did not corroborate the interaction noted in the CrCL ≥ 80 mL/min subgroup in ENGAGE AF-TIMI 48. In the Hokusai VTE study, the observed HR in the subgroup of subjects with CrCL ≥ 80 mL/min was 1.05 for edoxaban 60/30 mg compared to warfarin (**Table 9-6**).

**Table 9-6 Primary Efficacy Endpoint by Creatinine Clearance Subgroup:
Hokusai VTE Study**

CrCL (mL/min)	Edoxaban 60/30 mg (N = 4118)		Warfarin (N = 4122)		Edoxaban 60/30 mg vs Warfarin
	N	n (%)	N	n (%)	HR (95% CI)
Recurrent VTE					
CrCL ≥ 30 to ≤ 50	219	6 (2.7)	218	15 (6.9)	0.38 (0.147, 0.977)
CrCL > 50 to ≤ 80	885	24 (2.7)	901	38 (4.2)	0.66 (0.393, 1.091)
CrCL > 80	2792	93 (3.3)	2769	88 (3.2)	1.05 (0.782, 1.401)
PE with or without DVT					
CrCL ≥ 30 to ≤ 50	96	2 (2.1)	96	7 (7.3)	--
CrCL > 50 to ≤ 80	377	11 (2.9)	412	22 (5.3)	0.55 (0.264, 1.133)
CrCL > 80	1072	33 (3.1)	1061	33 (3.1)	0.99 (0.610, 1.594)
DVT only					
CrCL ≥ 30 to ≤ 50	123	4 (3.3)	122	8 (6.6)	--
CrCL > 50 to ≤ 80	508	13 (2.6)	489	16 (3.3)	0.80 (0.379, 1.676)
CrCL > 80	1720	60 (3.5)	1708	55 (3.2)	1.09 (0.753, 1.565)

Abbreviations: CI, confidence interval; CrCL, creatinine clearance; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

9.4.3.1 Summary of the Subgroup Population Profile

Due to the lack of stratification by renal function, there may have been some unidentifiable sources of bias across treatment groups within the renal subgroups in terms of baseline characteristics, demographics, concomitant medication, and geographic recruitment that could have contributed to differences in event rates for stroke or SEE. Compared to the other renal function subgroups, subjects with CrCL ≥ 80 mL/min were more likely to be male, from Eastern Europe, overweight or obese, and diabetic. While the overall CHADS₂ scores ranged from 2.6 to 3.1 there were some marked changes in the components of CHADS₂ that went in opposite directions. Among subjects with CrCL ≥ 80 mL/min there were notably fewer subjects over 75 years of age but more subjects with diabetes.

9.4.4 Overall Summary (Additional Analyses and Subpopulations)

In summary, a variety of factors including exposure to edoxaban, an unusually low event rate in the warfarin group, and potential imbalances between treatment groups due to randomization not being performed within renal function subgroups could have contributed to the observed HR for stroke or SEE compared with warfarin in the subgroup of subjects with normal renal function (defined as CrCL ≥ 80 mL/min). Combined with the fact that edoxaban exposure differences do not account for the HR difference and the lack of similar results in the Hokusai VTE study, this finding should be interpreted in the context of a rather low absolute event rate for stroke or SEE and the small between-treatment group differences driving this observation, which are of questionable clinical significance.

10.0 EFFICACY AND SAFETY OF THE POST-STUDY TRANSITION STRATEGY

As described in **Section 5.3.1.4**, after the final dose of study drug was administered at the end of ENGAGE AF-TIMI 48, subjects were transitioned to open-label anticoagulant therapies in accordance with a prespecified transition scheme carefully designed to maintain the blinded study design, to maintain adequate anticoagulation protection during the transition, and to avoid an undue risk of stroke or SEE during the transition. The transition period began the day after the CSED visit and ended 30 days later. There was an end of study transition plan available for subjects who were transitioning to open-label VKA therapy, which included the use of a transition kit (TK) and the requirement for frequent INR testing. For subjects in the edoxaban group transitioning to a VKA, the TK contained either edoxaban 30 mg QD (for full-dose subjects) or edoxaban 15 mg QD (for dose-reduced subjects) to be used as a bridging therapy until the INR reached ≥ 2.0 . For subjects in the warfarin group transitioning to a VKA, the TK contained only placebo. Subjects transitioning to a FIIa inhibitor or FXa inhibitor did not receive a TK. Investigators started these subjects on open-label FIIa or FXa inhibitor 24 hours after the last dose of study drug as long as their last INR was < 2.0 . A FIIa or FXa inhibitor was not to be started until the INR was < 2 . All events collected during the transition were adjudicated as per the CEC charter.

A total of 13,651 subjects completed the CSED visit and were on study drug within 3 days of the CSED visit.⁴⁹ Of these subjects, 9282 (68.0%) received a TK and were transitioned to a VKA, 4258 (31.2%) transitioned to an open-label FIIa/FXa inhibitor (2140 [15.7%] transitioned to open-label FIIa inhibitor therapy and 2118 [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%).

Adjudicated events occurring during the transition period at the end of the study by type of therapy are presented in **Table 10-1**. The percentage of subjects with adjudicated events (stroke or SEE, all-cause mortality) was similar for subjects using a TK and being transitioned to VKA, and for subjects who received an open-label FIIa or FXa inhibitor. There were more bleeding events in the edoxaban 30 mg group; however, the majority of these occurred after Day 15, after the TK scheme was completed. Two additional subjects in the edoxaban 30 mg group had a primary ischemic stroke on Days 34 and 35, respectively, after the CSED visit and are not included in the table below.

Table 10-1 Adjudicated Events Occurring During the End-of-Study Transition Period, Subjects Who Completed the CSED Visit and Were On Study Drug Within 3 Days of the CSED Visit (ENGAGE AF-TIMI 48)

Subjects With Adjudicated Events During Transition Period ^a	Edoxaban 30 mg (N = 4616) n (%)	Edoxaban 60/30 mg (N = 4529) n (%)	Warfarin (N = 4506) n (%)
Stroke or SEE	7 (0.2)	7 (0.2)	7 (0.2)
All-cause mortality	10 (0.2)	8 (0.2)	7 (0.2)
Adjudicated major bleeding	18 (0.4)	10 (0.2)	11 (0.2)
Transitioned to VKA Using Transition Kit	3103	3041	3138
Stroke or SEE	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 FIIa or FXa Inhibitor	1485	1445	1328
Stroke or SEE	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
Stroke or SEE	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)

Abbreviations: CSED, common study end date; eCRF, electronic case report form; FIIa, factor IIa; FXa, factor Xa; SEE, systemic embolic event; VKA, vitamin K antagonist.

^a The transition period is defined as the time from CSED visit + 1 day to CSED visit + 30 days.

Note: Percentages in the first row are based on N, the total number of subject who completed CSED visit and were on study drug within 3 days of the CSED visit. All other percentages are based on M, the total number of subjects in the given transition category.

Note: Categories are based on information reported on the Transition Kit eCRF page. Subjects may be counted in multiple categories.

Taken together, results obtained during the 30-day end of study transition period of ENGAGE AF-TIMI 48 indicate that the prospectively designed transition plan was effective in protecting against the risk of excess stroke or SEE, death or major bleeding for edoxaban-treated subjects transitioning to VKA or NOACs. This supports the following prescribing guidance for physicians to ensure a safe and effective transition from edoxaban to other anticoagulant therapies (**Table 10-2**).

Table 10-2 Transition Guidance for Physicians

From	To	Recommendation
Edoxaban	VKA	<u>Oral option:</u> For patients taking 60/30 mg of edoxaban, reduce the dose to 30 mg and begin warfarin concomitantly. For patients receiving 30 mg of edoxaban for one or more clinical factors, reduce the dose to 15 mg and begin VKA concomitantly. INR must be measured at least weekly and just prior to the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR ≥ 2.0 is achieved, edoxaban should be discontinued.
Edoxaban	VKA	<u>Parenteral option:</u> Discontinue edoxaban and administer a parenteral anticoagulant and VKA at the time of the next scheduled edoxaban dose. Once a stable INR ≥ 2.0 is achieved the parenteral anticoagulant should be discontinued and the VKA continued.
Edoxaban	Oral anticoagulants other than warfarin	Discontinue edoxaban and start the other oral anticoagulant at the time of the next dose of edoxaban.
Edoxaban	Parenteral anticoagulants	Discontinue edoxaban and start the parenteral anticoagulant at the time of the next dose of edoxaban.
Abbreviations: INR, international normalized ratio; VKA, vitamin K antagonist.		

11.0 POPULATION PHARMACOKINETICS AND EXPOSURE RESPONSE

11.1 Population Pharmacokinetics in AF Subjects (ENGAGE AF-TIMI 48)

In ENGAGE AF-TIMI 48, subjects were assigned to 1 of 2 edoxaban regimens, based on 60/30 mg or 30/15 mg QD, or warfarin. For those on edoxaban, the dose was halved if any 1 of the following applied: body weight \leq 60 kg, moderate renal impairment (calculated CrCL 50 to 30 mL/min), and/or subject was taking concomitant verapamil, quinidine, or dronedarone (P-gp inhibitors). Pharmacokinetic samples were collected at random in a sample of the population pre-dose, post-dose (1 to 3 hours) on Day 29, and at Months 3 and 12 visits.

The plasma concentration-time course of edoxaban in ENGAGE AF-TIMI 48 was characterized by a 2-compartment disposition model, with first-order absorption and an absorption lag time. To obtain post-hoc Bayesian estimates of exposure, the following covariates were significant and included in the final model: body weight, CrCL, disease status (healthy subject [Phase 1] vs patients), race (Asian vs non-Asian), and P-gp inhibitors. The modeling demonstrated that the applied dose reductions yielded lower systemic exposure in dose-reduced subjects than in their non-dose-reduced counterparts, both in the 60/30 mg and 30/15 mg edoxaban treatment groups.

Renal function was an important determinant of overall exposure. As CL_r contributes approximately 50% to total clearance, lower renal function (as evidenced by lower CrCL) resulted in higher systemic exposure. For the same dose, subjects with mild, moderate, or severe renal impairment achieved, on average, 25%, 57%, or 97%, respectively, higher exposures for C_{av} and AUC_{tau} (versus those with normal renal function). In ENGAGE AF-TIMI 48, when subjects with mild (treated with 60 mg), moderate (treated with 30 mg), or severe (treated with 30 mg) renal impairment received their respective daily doses, the observed mean change in estimated C_{av} was +25%, -22%, or -1.4%, respectively, compared to subjects with normal renal function receiving 60 mg QD. The post-hoc Bayesian estimates of systemic edoxaban exposure by renal function are presented in **Table 11-1**.

Table 11-1 Summary of Post-Hoc Bayesian Estimates of Exposure for AF Patients in ENGAGE AF-TIMI 48
(N = number of PK samples included in the analysis)

Regimen, dose received	All	Normal (≥ 80 mL/min)	Renal Impairment (CrCL, mL/min)		
			Mild (> 50 to < 80)	Moderate (30 to 50)	Severe (< 30)
C _{av} (ng/mL)					
Higher dose, 60 mg	85.6 (39.4, 161) N = 10272	73.0 (39.4, 101) N = 5056	96.3 (69.1, 155) N = 4807	116 (87.4, 161) N = 409	--
Higher dose, 30 mg	59.7 (22.5, 97.6) N = 2960	42.9 (22.5, 56.1) N = 224	55.8 (42.0, 72.7) N = 1038	64.2 (45.5, 97.6) N = 1685	75.7 (61.6, 91.9) N = 13
Lower dose, 30 mg	43.2 (15.0, 77.5) N = 10472	36.7 (15.0, 49.6) N = 5073	48.6 (34.4, 65.3) N = 4961	58.9 (46.1, 77.5) N = 436	67.5 (61.8, 73.3) N = 2
Lower dose, 15 mg	29.6 (11.6, 48.8) N = 2972	21.1 (11.6, 28.0) N = 254	27.8 (19.5, 37.5) N = 1098	32.1 (23.3, 48.8) N = 1613	40.6 (36.8, 43.3) N = 7
C _{min} (ng/mL)					
Higher dose, 60 mg	28.1 (5.67, 67.6) N = 10272	22.1 (5.67, 38.2) N = 5056	33.1 (14.1, 91.9) N = 4807	44.0 (20.7, 67.6) N = 409	--
Higher dose, 30 mg	20.8 (3.51, 39.8) N = 2960	12.2 (3.51, 21.6) N = 224	17.6 (7.87, 29.8) N = 1038	23.9 (9.15, 39.4) N = 1685	32.2 (25.9, 39.8) N = 13
Lower dose, 30 mg	14.2 (3.98, 35.4) N = 10472	11.1 (3.98, 18.8) N = 5073	16.6 (4.38, 26.9) N = 4961	22.3 (14.53, 35.4) N = 436	33.3 (32.7, 33.8) N = 2
Lower dose, 15 mg	10.2 (1.81, 19.3) N = 2972	5.94 (1.81, 10.7) N = 254	8.70 (3.43, 14.3) N = 1098	11.9 (4.80, 19.3) N = 1613	16.0 (15.5, 17.2) N = 7
AUC _{0-24,ss} (ng.hr/mL)					
Higher dose, 60 mg	2055 (946, 3862) N = 10272	1753 (946, 2417) N = 5056	2311 (1659, 3713) N = 4807	2784 (2097, 3862) N = 409	--
Higher dose, 30 mg	1433 (539, 2342) N = 2960	1029 (539, 1345) N = 224	1340 (1009, 1745) N = 1038	1540 (1093, 2342) N = 1685	1816 (1478, 2207) N = 13
Lower dose, 30 mg	1037 (360, 1860) N = 10472	880 (360, 1189) N = 5073	1165 (826, 1566) N = 4961	1414 (1105, 1860) N = 436	1621 (1484, 1758) N = 2
Lower dose, 15 mg	710 (278, 1171) N = 2972	506 (278, 672) N = 254	667 (468, 900) N = 1098	770 (559, 1171) N = 1613	974 (884, 1039) N = 7

Abbreviations: AUC_{0-24,ss}, area under the concentration-time curve from time zero to 24 hours at steady-state; CrCL, creatinine clearance; C_{min}, minimum observed concentration; C_{av}, average concentration.

Note: Mean (min, max) values are presented.

11.2 Exposure-Response Modeling and Benefit-Risk Analysis

Exposure-response analyses of systemic edoxaban exposure and efficacy (time to first occurrence of stroke or SEE, ischemic stroke or SEE and hemorrhagic stroke) and safety endpoints (time to first occurrence of major bleeding) demonstrated statistically significant exposure-response relationships for stroke or SEE (C_{av}), ischemic stroke or SEE (C_{av}), and major bleeding (minimum observed concentration [C_{min}]), but not for hemorrhagic stroke. For stroke or SEE and ischemic stroke or SEE, the final exposure-response models included a non-linear maximum effect relationship with C_{av} .

The predicted probability of a stroke or SEE within 1 year in a typical edoxaban subject with median age of 72 years, no other risk factors, and a constant C_{av} of 54 ng/mL (median in total C_{av} distribution) was 1.01% (**Figure 11-1**). Over the same time period, the predicted probability for subjects with a previous stroke or TIA (identified as an important risk factor in the model) was 2.51% (not shown in figure).

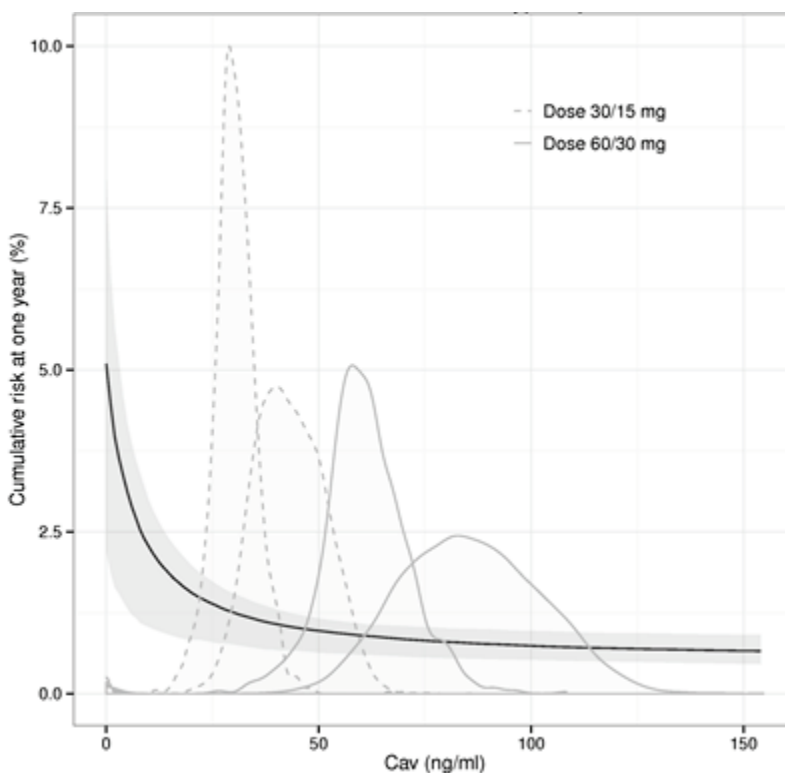


Figure 11-1 Probability of a Stroke or SEE Within 1 Year in an Edoxaban Subject Versus Average Exposure (C_{av}) of Edoxaban

Abbreviations: C_{av} , average concentration; PopPK, population pharmacokinetics; SEE, systemic embolic event. The solid line represents the median model prediction for a typical edoxaban subject (age 72 years and no other risk factors). The gray shaded area shows the 90% predictive probability interval. The 4 distributions represent the predicted (from the full PopPK model) distributions of C_{av} (as a proxy for exposure) in the higher, or 60-mg based (solid lines), and lower, 30-mg based (dashed lines), exposure groups. For each exposure group, the distribution to the right represents observations from non-dose-reduced subjects and the distribution to the left, observations from dose-reduced subjects.

For major bleeding (**Figure 11-2**), age and aspirin use increased the risk of experiencing an event (i.e., age and aspirin use were identified as risk factors in the model). The predicted probability of a major bleeding event within 1 year in a typical edoxaban subject with median age of 72 years, no other risk factors, and a C_{av} of 54 ng/mL was 1.79%.

Analyses failed to identify an exposure-response relationship for hemorrhagic stroke, probably due to the low incidence of hemorrhagic stroke in the analysis dataset. Race (Asian/non-Asian) was identified as a risk factor for hemorrhagic stroke. The exposure-response relationship for hemorrhagic stroke (not shown) has a constant probability of an event (0.15%), independent of PK exposure. After 1 year, the predicted probability in an Asian subject was 0.36% compared to 0.15% in a non-Asian subject.

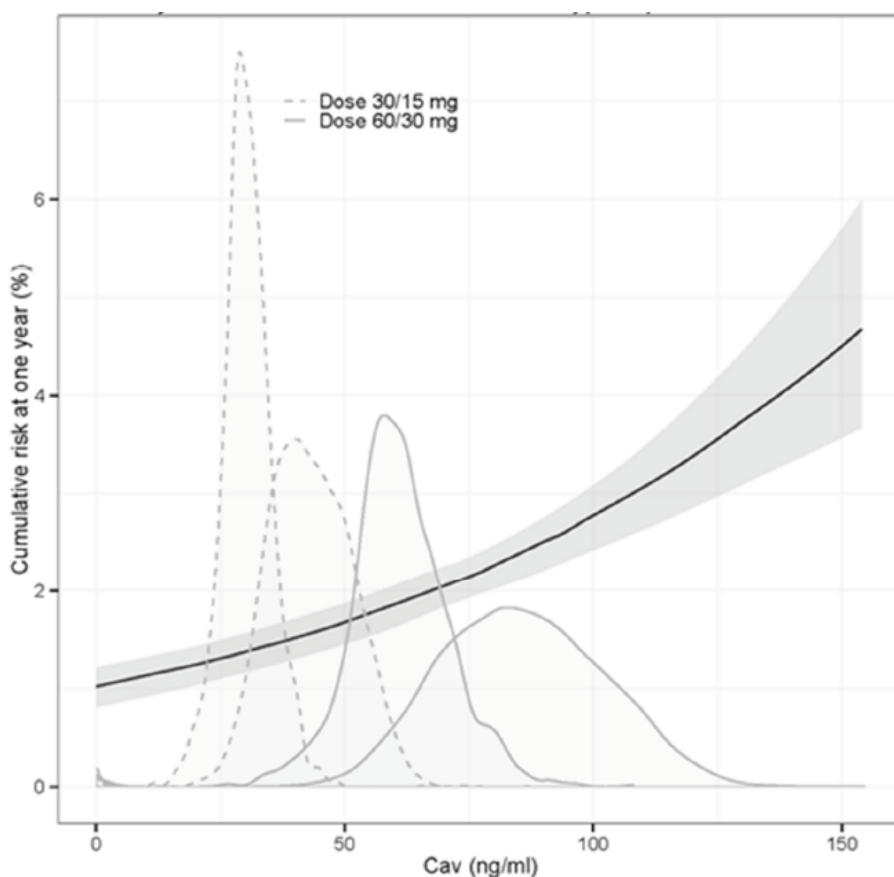


Figure 11-2 Probability of Major Bleeding Event Within 1 Year in an Edoxaban Subject Versus Average Exposure (C_{av}) of Edoxaban

Abbreviations: C_{av} , average concentration.

The solid line represents the median model prediction for a typical edoxaban subject (age 72 years and no other risk factors) given the model parameters. The gray shaded area shows the 90% predictive probability interval given the uncertainty in the model parameters. The 4 distributions represent the predicted (from the full PopPK model) distributions of C_{av} (as a proxy for exposure) in the higher, or 60-mg based (solid lines), and lower, or 30-mg based (dashed lines), exposure groups. For each exposure group, the distribution to the right represents observations from non-dose-adjusted subjects, and the distribution to the left, observations from dose-adjusted subjects. For illustrative purposes the distributions (densities) have been adjusted to fit the graph.

The clinical utility index (CUI) can be graphed as the summed probability of incurring both efficacy-related (e.g., stroke or SEE) and safety-related (e.g., major bleeding events) outcomes versus systemic edoxaban exposure (**Figure 11-3**). Event probability to the left of the nadir represents predominantly strokes and SEEs; event probability to the right represents mostly major bleeding. The edoxaban exposure (C_{av}) associated with the lowest event probability corresponds to the nadir (of the plotted curves) and changes little among different risk factors, with an exception for subjects with a prior TIA or stroke history (whose CUI curve favors higher exposure than those for subjects with other risk factors; not shown). This suggests that the need for dose adjustment based on risk factors is limited. Within the predicted exposure range, from the full PopPK model (for the edoxaban 60/30 mg regimen), the CUI curves are relatively flat towards increasing exposure (i.e., a less steep slope to the right of the nadir) indicating a marginally increased risk (with increasing exposure). The lowest CUI values (i.e., the region around the nadir) are at the low end of (or slightly below) the predicted exposure range; however, the CUI curves are steeper with lower exposures to the left of the nadir (i.e., higher incremental risk with too low [vs too high] exposure). The proposed edoxaban dosing regimen will avoid this area.

Evaluation of the CUIs should take into consideration the relative weightings attributed to the probability of efficacy outcomes (stroke or SEE) and the safety outcome (major bleeding episodes). If the emphasis is on safety, the optimal CUI in terms of benefit-risk will tend to predict lower exposures as optimal. If the emphasis is on efficacy, the optimal CUI in terms of benefit-risk will tend to predict higher levels of exposure. The depicted weightings of efficacy to safety of 1:1, 2:1, 1:2 (**Figure 11-3**) are subjective and intended to provide scenarios that require clinical judgment. The weightings represent a multiplier for efficacy- or safety-based probabilities, prior to adding to give the final value plotted on the vertical axis. Across the scenarios shown, exposure of the edoxaban 60/30 mg regimen provides a balance between safety and efficacy that is slightly more weighted to efficacy in subjects with AF, based on minimizing strokes and SEEs (events to the left of the nadir) and containing major bleeding (just to the right of the nadir where the probability slope is relatively flat).

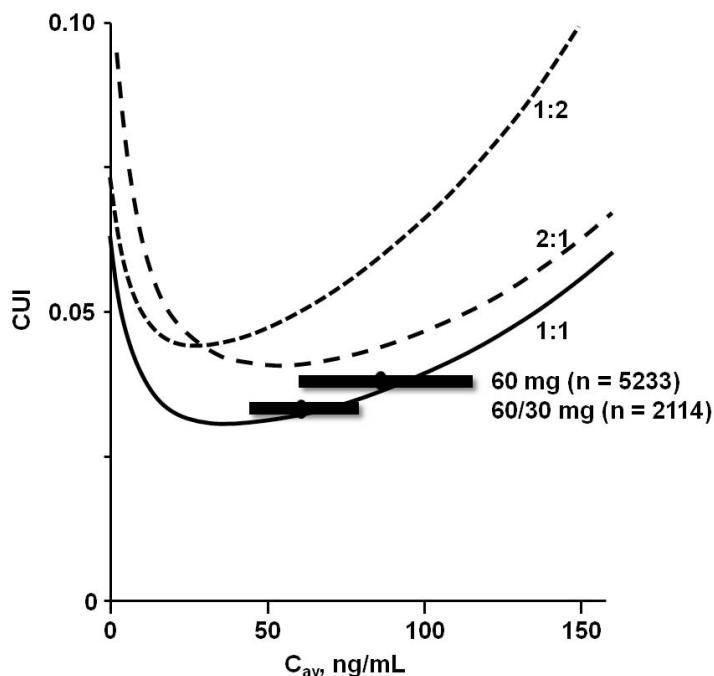


Figure 11-3 Typical Clinical Utility Index (CUI) Based on Cumulative Risk of Stroke or SEE and Major Bleeding at 1 Year for Clinical Weights of 1:1, 2:1, 1:2 Versus Average Concentrations (C_{av})

Abbreviations: C_{av} , average concentration; CUI, clinical utility index; PopPK, population pharmacokinetics; SEE, systemic embolic event.

The CUI curves (thin black lines) represent the CUI probability prediction for a typical edoxaban subject (no risk factors) given the models and no parameter uncertainty. The horizontal bars represent the 90% predictive probability interval of C_{av} PK exposure (dot represents median) for specific doses of 60 mg, and a reduction to 30 mg (labeled 60/30 mg) based on the PopPK model. The number of individuals in each subgroup is displayed in the subgroup label.

11.3 Exposure-Response Modeling Based on Renal Function

Output from the exposure-response model for the efficacy endpoints, stroke or SEE, was stratified by renal function (i.e., normal, mildly impaired, or moderately impaired). Additionally, simulated exposure levels resulting from several different edoxaban doses were modeled to predict the clinical benefit (change in probability of event within 1 year) resulting from increasing exposure in the normal renal function subgroup to a level similar to that in the mild renal impairment subgroup. A parametric time-to-event analysis was conducted, based on separate modeling of edoxaban subjects. Average concentration (C_{av}) was used as a proxy for exposure.

The results of the exposure-response modeling are shown on **Figure 11-4** for the total population stratified by CrCL subgroups. The exposure range for each CrCL subgroup is noted in green, orange, or blue for moderately impaired, mildly impaired, or normal kidney function, respectively.

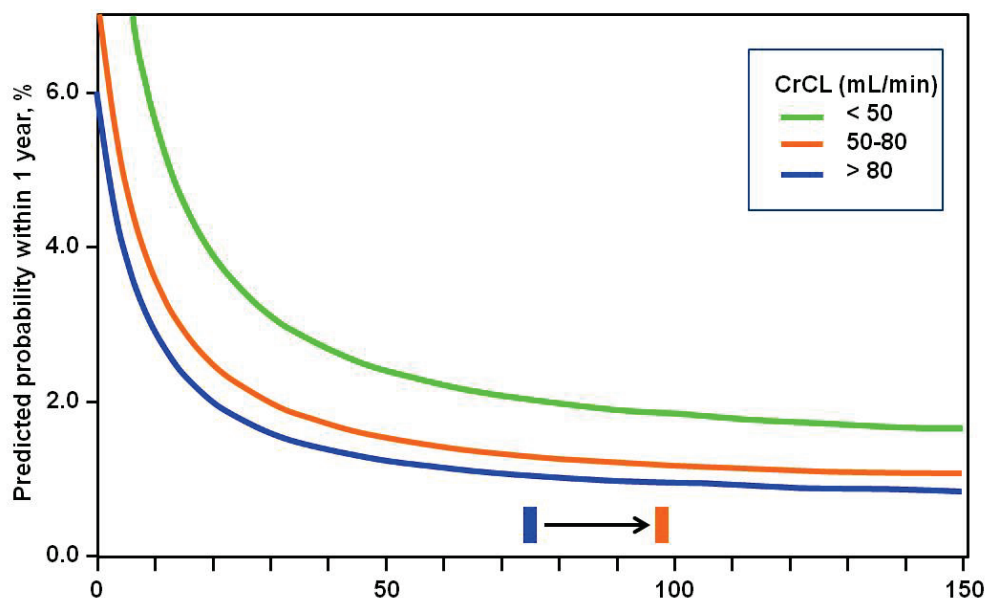


Figure 11-4 Predicted Probability of Stroke or SEE Versus Exposure Stratified by Renal Function for All Subjects (ENGAGE AF-TIMI 48)

Abbreviations: CrCL, creatinine clearance; SEE, systemic embolic event; TIA, transient ischemic attack. The colored lines represent the average (expected) probability of a stroke or SEE event given an average ENGAGE AF-TIMI 48 subject stratified by renal function category (blue: normal; red: mildly impaired; green: moderately impaired). The lines utilize the average age and proportion of history of stroke or TIA/no history of stroke or TIA in each renal function subgroup.

Using C_{av} as a proxy for exposure, increasing mean exposure from 73 ng/mL in the normal kidney function group on 60 mg edoxaban to 96 ng/mL, corresponding to the mild renal impairment subgroup administered 60 mg can be accomplished by a 75-mg dose of edoxaban. The predicted stroke or SEE event rates for the targeted increase in exposure is given on **Table 11-2**. As shown, the enhanced exposure in subjects with normal kidney function is predicted to reduce annual event rate by a modest 0.08%, translating into a reduction of 8 strokes or SEEs per 10,000 patients treated for a year. On the other hand, such an increase in exposure leads to a 0.32% increase in the risk of major bleeding, or 32 major bleeds for every 10,000 patients treated for a year (not shown).

Table 11-2 Observed and Predicted Stroke or SEE and Major Bleeding Event Rates, Normal Renal Function Subgroup (C_{av} Model)

Treatment	Observed		Predicted
	n/N	Rate	Rate
Stroke or SEE			
Warfarin	33/2588	0.76	--
60 mg	49/2499	1.07	1.10
75 mg	--	--	1.02
Change	--	--	-0.08
Major Bleeding			
Warfarin	106/2588	2.3	--
60 mg	77/2499	1.69	1.98
75 mg	--	--	2.30
Change	--	--	+0.32

Abbreviations: C_{av}, average concentration; SEE, systemic embolic event.

In summary, the efficacy model for stroke or SEE predicts that increasing exposure in the normal renal function subgroup (CrCL \geq 80 mL/min) to a level equal to that in the mildly impaired subgroup (CrCL $>$ 50 to $<$ 80 mL/min) would result in only a modest reduction in yearly event rates (0.08%). This magnitude of benefit would not materially change the observed HR in the normal renal function subgroup (HR = 1.4) compared to warfarin. Additionally, results indicate that while subjects with CrCL \geq 80 mL/min who received edoxaban 60/30 mg had lower exposure compared to subjects with mild renal impairment also receiving 60/30 mg, exposure ranges for both subgroups correspond to a relatively flat part of the efficacy-response curve. Thus, increasing the dose may be of limited value.

12.0 BENEFIT-RISK SUMMARY

The results of ENGAGE AF-TIMI 48 demonstrated that the edoxaban 60/30 mg regimen is a safe and effective alternative to the current standard of care, warfarin, to prevent stroke and SEE in subjects with AF. The study met all of its endpoints prespecified in the SPA. ENGAGE AF-TIMI 48 was the largest, geographically diverse, adequately controlled, clinical trial of a NOAC conducted in AF subjects. It was the only double-blind study to test 2 QD dosing regimens (60/30 mg and 30/15 mg) with a prespecified dose-reduction strategy to mitigate bleeding risk. Additionally, ENGAGE AF-TIMI 48 included a prespecified and comprehensive algorithm to allow subjects to safely transition at the end of the clinical trial to an approved anticoagulant therapy. Approximately 89% of subjects completed the study, with very few subjects lost to follow-up. The median TTR of 68% observed in ENGAGE AF-TIMI 48 is the highest rate reported to date in a NOAC trial and indicated good clinical management of warfarin. The prespecified transition plan resulted in therapeutic anticoagulation in > 80% of subjects after 2 weeks. Moreover, because the study included sampling to support PopPK analyses and exposure-response modeling, extensive data exist to inform dose selection.

12.1 Overall Benefit-Risk of Edoxaban

12.1.1 Benefits of Edoxaban

ENGAGE AF-TIMI 48 met its primary efficacy endpoint, demonstrating that both edoxaban regimens were noninferior to well-managed warfarin for prevention of stroke or SEE. Compared with warfarin, the edoxaban 60/30 mg regimen reduced the relative risk of stroke by 21% (HR = 0.79; 97.5% CI: 0.632, 0.985). The rate of ischemic stroke was similar with edoxaban 60/30 mg and warfarin (HR = 0.94). In addition, the frequency of hemorrhagic stroke and the rate of all-cause mortality and CV mortality were significantly lower compared with warfarin.

Three clinically important secondary endpoints support the primary endpoint and provide additional evidence of the efficacy of edoxaban in AF. The edoxaban 60/30 mg group showed a significant reduction in the composite endpoints of stroke, SEE, and CV mortality (HR = 0.87), MACE (HR = 0.89), and the composite of stroke, SEE, and all-cause mortality (HR = 0.90) compared with warfarin.

The benefit of edoxaban 60/30 mg with respect to the primary efficacy endpoint was consistent across most major clinical subgroups, including those based on demographic and baseline characteristics, concomitant medications, and stroke risk (defined by CHADS₂ score).

12.1.2 Risks of Edoxaban

Edoxaban has been marketed as LIXIANA® in Japan since 2011 for prevention of VTE in patients undergoing any of the following orthopedic procedures on the lower limb: total knee replacement, total hip replacement, and hip fracture surgery. Based on exposure in > 23,500 subjects in the global clinical development program across multiple indications and an estimated 155,000 patients during postmarketing surveillance since 2011 in Japan, the postmarketing safety profile of edoxaban has been well characterized and is consistent with that demonstrated in the large clinical development program that included ENGAGE AF-TIMI 48.

Edoxaban was well tolerated in ENGAGE AF-TIMI 48. Compared with warfarin, edoxaban was associated with consistently lower rates of all types of bleeding, including major bleeding (primary safety endpoint), ICH, and LT bleeding. The only exception was GI bleeding, which occurred more frequently with edoxaban 60/30 mg, but less frequently with edoxaban 30/15 mg than with warfarin. In addition, both dose regimens of edoxaban were associated with significantly reduced CV mortality compared with warfarin. Moreover, the primary safety findings were consistent across major subgroups, including those based on demographic characteristics, risk of stroke (by CHADS₂ score), and geographic region.

The incidence of non-bleeding AEs was generally similar for the edoxaban and warfarin groups, except for anemia that occurred at a higher rate in the edoxaban 60/30 mg group than the warfarin group. The risk for drug-induced liver injury was low, with no signal of concern. The large body of evidence from ENGAGE AF-TIMI 48 supports the conclusion that any numerical imbalance in AEs, SAEs, or SAEs resulting in permanent discontinuation of edoxaban or fatal outcome was more likely a reflection of variability in a large population and not a reflection of any clinically relevant safety concerns.

Overall, edoxaban appeared to be safe, had no unexpected toxicities, and had fewer AEs than warfarin (as managed with a median TTR of 68.4%). The safety profile of edoxaban in AF is consistent with the well-characterized safety profile of edoxaban (LIXIANA[®]) for prevention of VTE and consistent with the known risks of anticoagulants. Most of the risks occur infrequently and are known to physicians.

12.2 Benefit-Risk Based on Net Clinical Outcomes

Anticoagulant therapy requires an understanding of the important balance between its therapeutic benefits (prevention of stroke or SEE) and risks (major bleeding, fatal bleeding, LT bleeding, and mortality). Both edoxaban regimens were superior to warfarin with regard to improving clinically important net clinical outcomes. The annualized rate of the composite of death from any cause, stroke, SEE, or major bleeding was lower with both edoxaban regimens than with warfarin: 8.11% with warfarin compared with 7.24% with edoxaban 60/30 mg (HR = 0.89; 95% CI: 0.83, 0.96) and 6.77% with edoxaban 30/15 mg (HR = 0.83; 95% CI: 0.77, 0.90; **Figure 12-1**). Similarly, as compared with warfarin, both edoxaban regimens were associated with significantly lower rates of the composite of death from any cause, disabling stroke, or LT bleeding, and the composite of stroke, SEE, LT bleeding, or death from any cause. Overall, the edoxaban 60/30 mg regimen was associated with fewer events than warfarin across all composites of clinically important efficacy and safety net clinical outcomes. Edoxaban provides a favorable benefit-risk profile compared with warfarin.

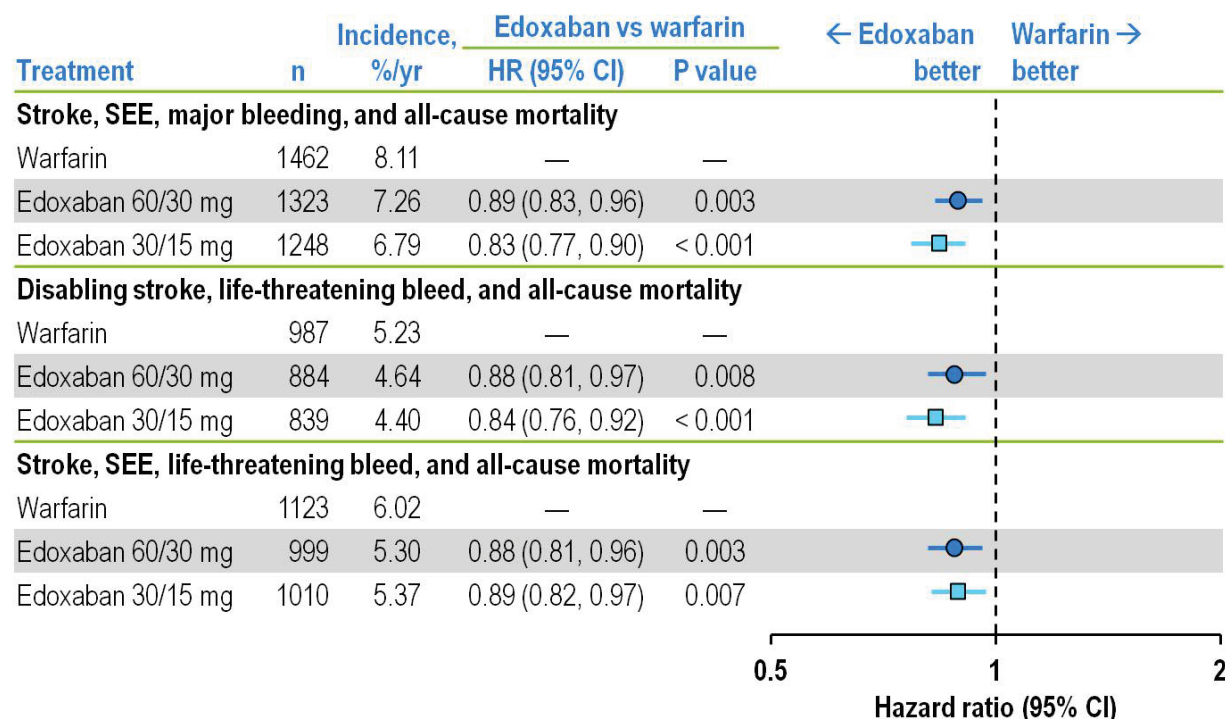


Figure 12-1 Net Clinical Outcomes (ENGAGE AF-TIMI 48)

Abbreviations: CI, confidence interval; HR, hazard ratio; QD, once daily; SEE, systemic embolic event.

^a Nominal *P* values for all edoxaban versus warfarin comparisons.

The primary net clinical outcome is a composite of stroke, SEE, major bleeding, and all-cause mortality.

Subgroup analyses support the benefit of edoxaban in several important clinical subgroups. Notably, stroke or SEE rates were lower with edoxaban than warfarin among subjects ≥ 75 years of age, those requiring dose reduction at randomization, subjects with CHADS₂ ≥ 3 , subjects with prior stroke or TIA, subjects with a history of CHF or hypertension, and subjects with persistent or permanent AF. In addition, lower rates of major bleeding in edoxaban-treated subjects were observed in various subgroups based on demographic and baseline characteristics such as age, gender, body weight, renal function, CHADS₂ score, or past history of stroke or TIA. A similar advantage for lower bleeding rates in the edoxaban groups than the warfarin group was also observed in subjects receiving concomitant medications such as aspirin, antiplatelet agents, and NSAIDs. Although the overall bleeding event rates were higher in these groups with concomitant use of aspirin, antiplatelet agents, and NSAIDs compared to those not taking these medications, the observed bleeding rates were lower in the edoxaban group compared with the warfarin group.

12.3 Overall Conclusions

A significant need remains for an alternative OAC that safely and effectively reduces the risk of stroke and SEE and improves upon the bleeding risk with warfarin in patients with AF while addressing the limitations of currently available anticoagulants. Results from ENGAGE AF-TIMI 48 demonstrate that edoxaban reduced the risk of stroke or SEE similar to warfarin while significantly reducing the risk of major bleeding, including ICH and LT bleeding,

compared with warfarin. Clinical outcomes in ENGAGE AF-TIMI 48 with respect to risk of stroke and major bleeding, as well as CV and all-cause mortality, were favorable both in absolute terms and relative to warfarin. The totality of the data from ENGAGE AF-TIMI 48 supports edoxaban 60 mg QD (with dose reduction to 30 mg in select patients) as a safe and effective regimen, which provides a favorable benefit-risk balance for the proposed AF indication.

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