These Clinical Trial Results are provided for informational purposes only.

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2. SYNOPSIS

Name of Sponsor/Company: Daiichi Sankyo Pharma Development	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: DU-176b		
Name of Active Ingredient: Edoxaban		

Title of Study:
A Phase 3, Randomized, Double-blind, Double-dummy, Parallel-group, Multi-center, Multi-national Study for Evaluation of Efficacy and Safety of DU-176b (Edoxaban) Versus Warfarin in Subjects with Atrial Fibrillation, Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE AF-TIMI 48)

Phase of Development: Phase 3

Study Period: First subject randomized: 19 Nov 2008
Last subject completed: 24 May 2013

Investigators: A total of 1420 sites screened at least 1 subject and 1393 sites randomized at least 1 subject in this study. [redacted] was the Global Principal Investigator.

Study Centers: Multicenter study in six regions (North America, Latin America, Western Europe, Eastern Europe, Asia Pacific and South Africa, and Japan) including 46 countries.

Publication (reference): Not applicable

Study Objectives/Hypothesis:
The primary objective was to compare each of the two dose regimens of DU-176b (edoxaban) (High Exposure Regimen and Low Exposure Regimen) to warfarin with regard to the composite primary endpoint of stroke and systemic embolic event (SEE). Each edoxaban regimen was to be compared with warfarin for non-inferiority. If non-inferiority was established for the Edoxaban High Exposure regimen, the Edoxaban High Exposure regimen was to be compared with warfarin for superiority.

The secondary objectives were to compare:

- Edoxaban to warfarin with regard to the composite clinical outcome of stroke, SEE, and cardiovascular (CV) mortality, as well as each component separately.
- Edoxaban to warfarin with regard to major adverse cardiovascular event (MACE), defined for this Phase 3 study as a composite of non-fatal myocardial infarction (MI), non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding, as well as each component separately.
- Edoxaban to warfarin with regard to the composite clinical outcome of stroke, SEE, and all-cause mortality, as well as each component separately.
- Edoxaban to warfarin with regard to Major bleeding as well as major plus clinically relevant non-major (CRNM) bleeding.

Study Hypothesis: The study hypothesis was that at least one edoxaban dosage regimen will be non-inferior to warfarin in reducing the risk of the composite primary endpoint of stroke and SEE in subjects with AF.

Study Design/Methodology:
This was an event-driven, Phase 3, multi-national, multi-center, randomized, double-blind, double-dummy, parallel-group study in subjects with documented AF within the preceding 12 months and in whom anticoagulation therapy was indicated and planned for the duration of the study.

Eligible subjects were stratified by $CHADS_2$ risk score at randomization.

- Stratum 1: $CHADS_2$ risk score 2 and 3

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- Stratum 2: $CHADS_2$ risk score 4, 5, and 6

Within each $CHADS_2$ stratum, subjects were further stratified based on whether or not a subject required edoxaban dose reduction for factors such as low creatinine clearance, low body weight, or a need for concomitant treatment with P-glycoprotein (P-gp) inhibitors such as quinidine and/or verapamil.

After this second stratification, subjects were randomly assigned to 1 of the following 3 treatment groups (1:1:1 ratio):

- Edoxaban Low Exposure group (30 mg QD with dosage reduction to 15 mg QD for moderate renal impairment, low body weight, or specified concomitant medications), referred to as edoxaban 30 mg group hereafter.
- Edoxaban High Exposure group (60 mg QD with dosage reduction to 30 mg QD for moderate renal impairment, low body weight, or specified concomitant medications), referred to as edoxaban 60 mg group hereafter;
- Warfarin group (warfarin once daily (QD) with dose adjusted to maintain INR between 2.0 and 3.0).

In both edoxaban treatment groups, the regimen was halved for subjects with moderate renal impairment (creatinine clearance [CrCL] ≥ 30 and ≤ 50 mL/min as calculated using the Cockcroft-Gault formula or low body weight (≤ 60 kg) or for subjects on specified concomitant medications (eg, verapamil, quinidine). Dynamic dose adjustments were allowed during the study for subjects who developed 1 of the factors requiring dose adjustment. Dronedarone was added to the list of concomitant medications requiring dose adjustment after study randomization was complete.

This was an event-driven study. The statistical considerations and plan for the study required approximately 672 primary endpoint events for the on-treatment period (defined as events occurring during study drug treatment and up to and including 3 days after the last dose).

Based on the projected primary endpoint event accrual, the plan was to randomize approximately 20,500 subjects. There was no pre-specified duration of treatment for subjects enrolled in the study. All subjects were to be treated and followed until approximately 672 targeted primary endpoint events were collected. A “stop randomization” letter was sent to Investigators on 22 Nov 2010. A total of 21,105 subjects were randomized by the time all sites could comply with the letter.

Based on the actual accrual of primary endpoint events, study close-out procedures commenced via a numbered memo sent on 22 January 2013, announcing to the sites that the Common Study End Date (CSED) phase was to start. The sites were informed to schedule and complete the mandatory CSED Visit for all subjects within a 90 day period after the CSED. Subjects were to continue to take study drug beyond the CSED announcement until the day of the CSED Visit. All randomized subjects, including those with premature permanent discontinuation of study drug, were required to complete the CSED Visit. Those subjects who were receiving study drug on the day of the CSED Visit had their final dose at this visit.

An independent Data Management Committee (DMC) comprised of a panel of external experts reviewed and monitored the study data in an unblinded manner, as defined in 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 needed in the study conduct.

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An independent study specific Clinical Events Committee (CEC) reviewed and adjudicated pre-specified efficacy and safety endpoint events (all deaths, suspected strokes/TIAs, suspected SEEs, suspected MIs, overt bleeding events that required medical attention, and cases of pre-defined hepatic dysfunction, etc) in a blinded manner.

Duration of Treatment and Follow-Up:
In this event driven study, the median duration of exposure to study drug was 2.5 years and the overall median subject-year follow-up was 2.8 years. In the edoxaban 30 mg, edoxaban 60 mg, and warfarin groups, the median subject-year exposure on study drug was 15,840, 15,471, and 15,569 years, respectively, and the median subject-year follow-up during the study was 19,216, 19,191, and 19,080 years, respectively.

Number of Subjects: Planned: 20,500
Screened: 25,497
Randomized: 21,105
Completed CSED Visit: 18,635

Diagnosis and Main Criteria for Study Entry:
Male or female subjects ≥ 21 years of age with documented AF within the preceding 12 months and in whom anticoagulation therapy was indicated and planned for the duration of the study. Subjects who were receiving or had received prior anticoagulant and/or antiplatelet therapies were eligible, as well as subjects who were naive to anticoagulant and/or antiplatelet therapy. Subjects must have had a $CHADS_2$ index score ≥ 2.

Investigational Product:

Treatment Description	Bulk Lot Numbers
Edoxaban 60mg	[redacted]
Edoxaban 30mg	[redacted]
Edoxaban 15mg	[redacted]
Edoxaban Placebo	[redacted]
Warfarin 0.5mg (Japan only)	[redacted]
Warfarin 0.5mg Placebo (Japan only)	[redacted]
Warfarin 1mg	[redacted]
Warfarin 1mg Placebo	[redacted]

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Warfarin 2.5mg	[redacted]
Warfarin 2.5mg Placebo	[redacted]
Warfarin 5mg	[redacted]
Warfarin 5mg Placebo	[redacted]
Warfarin Combo Unit	[redacted]
Warfarin Combo Unit Placebo	[redacted]
Warfarin 1 mg Transition Supply	[redacted]
Warfarin 1 mg Placebo Transition Supply	[redacted]
Edoxaban 30mg Transition Wallet	[redacted]
Edoxaban 15mg Transition Wallet	[redacted]
Edoxaban Placebo Transition Wallet	[redacted]

Study Variables and Criteria for Evaluation:
An independent CEC adjudicated key primary and secondary efficacy and safety endpoints in a blinded manner.

Efficacy: The primary efficacy endpoint was the composite of stroke and SEE.
Secondary efficacy endpoints included:

- Composite of stroke, SEE, and CV mortality;
- Major adverse cardiovascular 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: The primary safety endpoint was Major bleeding. Secondary safety endpoints included Major bleeding or CRNM bleeding. Other safety assessments included, but were not limited to, all bleeding or non-bleeding AEs (including malignancies, bone fractures, hepatic, and all other AEs), and laboratory assessments. Liver enzymes and bilirubin abnormalities were evaluated as safety events of special interest.

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Statistical Methods:
The planned analysis sets for the efficacy and safety analyses are specified in the following table:

Analysis Set	Overall Study Period	On-Treatment Period
mITT (treated subjects as per randomization)	Non-inferiority (Primary Efficacy Endpoint)	Non-inferiority (Primary Efficacy Endpoint)
Per Protocol (treated subjects excluding subjects with critical violations directly affecting evaluation of primary endpoint)	Non-inferiority (Primary Efficacy Endpoint)	Non-inferiority (Primary Efficacy Endpoint)
ITT (all randomized subjects)	Superiority (Primary Efficacy Endpoint)	Not applicable
Safety (treated subjects as per actual treatment received)	Safety	Safety

The analyses included all events from the day of randomization up to and including the day of CSED Visit. For each subject, the actual day of the CSED Visit was the formal study end date for primary statistical analyses.

Primary Efficacy Endpoint: Non-inferiority Testing
Two edoxaban treatment groups were compared with warfarin:

- Edoxaban 60 mg group versus warfarin
- Edoxaban 30 mg group versus warfarin

The primary analysis was designed to demonstrate that at least one edoxaban treatment group was non-inferior to warfarin at a non-inferiority margin of 1.38, using a pairwise comparison significance level of $\alpha=0.05/2$ (where 2 is the number of comparisons for non-inferiority).

For the primary efficacy variable, the time to first event was analyzed using the Cox proportional hazards model including treatment groups and the stratification factors as covariates:
The mITT analysis set (randomized subjects who received 1 or more dose of study drug) for the on-treatment period was used for the primary analysis for non-inferiority testing.

The two-sided 97.5% (from 100[1-0.05/2]%) CI for the hazard ratios (each edoxaban treatment regimen versus warfarin) was estimated using the proportional hazards model. If the upper limit of the CI of the hazard ratio was below 1.38, then non-inferiority to warfarin was considered established for the edoxaban treatment regimen.

Additional sensitivity analyses for non-inferiority testing included:

- Per Protocol analysis set with the "on-treatment" approach.
- mITT analysis set with inclusion of all events (strokes/SEEs) that occurred during the overall study period.
- Per Protocol analysis set with inclusion of all events (strokes/SEEs) that occurred during the overall study period.

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Primary Efficacy Endpoint: Superiority Testing

Superiority of the edoxaban 60 mg group versus warfarin was tested only if non-inferiority was first established for that regimen. The superiority analysis compared treatment efficacy for the first occurrence of a primary efficacy endpoint event (stroke or SEE) for all subjects in the Intent-to-Treat (ITT) Analysis Set (all randomized subjects regardless of whether they actually received study drug). In this analysis, all strokes and SEEs that occurred during the overall study period were counted as events, including those that occurred during study drug interruptions and those that occurred after the study drug discontinuation but prior to the CSED visit. The time to first event is defined as the time (years) from the day of randomization to the first event experienced by a subject. For subjects who did not experience an event (stroke/SEE), the time to first event was censored at the CSED Visit, the subject's last assessment, or death, whichever came first.

The time to first event was estimated by a Kaplan-Meier estimate and was compared between the edoxaban treatment regimen and warfarin using a log-rank test, at a pairwise comparison significance level of α=0.01. In addition, data were examined for significance of 0.05.

Secondary Efficacy Endpoints

Secondary efficacy endpoints were analyzed based on the ITT Analysis Set with inclusion of all overall study period events (counting first events only). For the edoxaban 60 mg group, the test for superiority for the first secondary efficacy endpoint was performed only if superiority of the edoxaban group for the primary efficacy endpoint (ITT Analysis Set) was shown. A test for superiority of the second secondary efficacy endpoint was done only if superiority was shown for the first secondary efficacy endpoint and a similar method was used for the third secondary endpoint. The time to first event is defined as the time (years) from the day of randomization to the first event experienced by a subject. The time to first event was estimated by a Kaplan-Meier estimate and was compared between the edoxaban 60 mg group and warfarin using a log-rank test at a pairwise comparison significance level of α=0.01.

Other efficacy endpoints and variables were analyzed with no correction for multiplicity.

Safety Assessments

The Safety analysis set included all randomized subjects who received at least one dose of randomized study drug. Analyses were based on the randomized treatment, unless a subject inadvertently received the incorrect drug or dosage during the entire study, in which case, the subject was grouped according to the treatment actually received.

The event rates of adjudicated Major, Clinically Relevant Non-major, Minor, and any bleeding were analyzed for the Safety Analysis Set using the on-treatment approach. Subjects were considered "at risk" while on study drug (date of any "first" dose up to and including 3 days following the date of the corresponding "last" dose). The hazard ratios (edoxaban [60 mg and 30 mg groups] versus warfarin) were estimated with 95% CIs.

The number and percentage of subjects with concurrent (within 37 days) elevation of alanine transaminase (ALT) or aspartate transaminase (AST) $\geq$3 x upper limit of normal (ULN) and total bilirubin (TBL) $\geq$2 x ULN were summarized by treatment group. In addition, these cases were further assessed by independent CEC hepatic specialists in a blinded manner to further evaluate the type and severity of liver injury and relationship to the study drug.

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Subgroup Analyses

Subgroup analyses included, but were not be limited to, demographic and baseline characteristics (such as age, gender, geographic region, type of AF [paroxysmal versus persistent/permanent], baseline $CHADS_2$ score, and history of prior use of VKA (VKA-naïve versus VKA-experienced), concomitant medications (for example, aspirin), and subgroups based on INR-TTR observed in warfarin subjects during the study.

Results:

Disposition and Demographic Results:

A total of 25,497 subjects were screened and 21,105 subjects (83% of screened) were randomized and assigned to the edoxaban 30 mg, edoxaban 60 mg, or warfarin treatment groups (7034, 7035, and 7036, respectively) and comprised the ITT analysis set. Of these subjects, 79 never received treatment with study drug. Therefore, a total of 21,026 subjects were treated with study drug (7002, 7012, and 7012 in the edoxaban 30 mg, edoxaban 60 mg, and warfarin treatment groups, respectively), and comprised the mITT and Safety analysis set. The mITT and Safety analysis sets were identical. In addition to the 79 subjects who never received study drug, 56 subjects had critical protocol deviations and were excluded from PP analysis set, which included 6982, 6995, and 6993 subjects in the edoxaban 30 mg, edoxaban 60 mg, and warfarin treatment groups, respectively.

A similar percentage of subjects in the edoxaban 30 mg, edoxaban 60 mg, and the warfarin treatment groups completed the CSED Visit (88.9%, 88.5%, and 87.5%, respectively).

All demographic and baseline characteristics were comparable among the 3 treatment groups, as was the use of baseline and concomitant medications.

Efficacy Results:

For the primary efficacy endpoint (stroke or SEE), both the edoxaban 60 mg and edoxaban 30 mg dose groups were non-inferior to well-managed warfarin therapy (median TTR 68.4%), with the upper boundary of the 97.5% CI below the pre-specified non-inferiority margin of 1.38. In the mITT on-treatment period, the HR in the edoxaban 60 mg group was 0.79 (97.5% CI: 0.632, 0.985, $p<0.0001$ for non-inferiority) and in the edoxaban 30 mg group was 1.07 (97.5% CI: 0.874, 1.314, $p=0.0055$ for non-inferiority) compared to warfarin-treated subjects. Results were consistent for the mITT and PP analysis sets and for both the on-treatment and overall study periods.

Superiority testing for the comparison of the edoxaban 60 mg group with the warfarin group for the ITT analysis set overall study period resulted in an HR of 0.87 (log rank $p=0.0807$). Superiority testing for the mITT analysis set on-treatment period resulted in an HR of 0.79 (Cox proportional hazard $p=0.0167$).

Results of superiority testing for the secondary efficacy endpoints demonstrated that subjects in the edoxaban 60 mg group had a reduced risk of experiencing the 3 secondary efficacy endpoints of stroke, SEE, or CV mortality (HR 0.87, 95% CI: 0.786, 0.959), MACE (HR 0.89, 95% CI: 0.806, 0.972), and stroke, SEE, or all-cause mortality (HR 0.90, 95% CI: 0.823, 0.981) compared with subjects in the warfarin group. The HR for the comparison of the edoxaban 30 mg group and the warfarin group for the 3 secondary efficacy endpoints was between 0.94 and 0.98.

The event rate for ischemic strokes was the same in both the edoxaban 60 mg group and the warfarin group (1.25% per year), with an HR of 1.00. More subjects in the edoxaban 30 mg group experienced

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ischemic stroke compared with the warfarin group (1.77 and 1.25% per year, respectively), with an HR of 1.41. Fewer subjects in the edoxaban 60 mg group and the edoxaban 30 mg group experienced hemorrhagic strokes than the warfarin group (0.26%, 0.16%, and 0.47% per year, respectively), with an HR of 0.54 and 0.33, respectively.

Edoxaban-treated subjects had a lower CV and all-cause mortality than those treated with warfarin. Fewer subjects in the edoxaban 60 mg and edoxaban 30 mg groups experienced CV mortality than the warfarin group (2.74%, 2.71%, and 3.17% per year, respectively), with an HR of 0.86 and 0.85, respectively. Fewer subjects in the edoxaban 60 mg and edoxaban 30 mg groups experienced all-cause mortality than the warfarin group (3.99%, 3.80%, and 4.35% per year, respectively), with an HR of 0.92 and 0.87, respectively. Fatal bleeds were included in the category of CV deaths, and edoxaban-treated subjects experienced fewer deaths due to bleed events.

The primary efficacy analysis by treatment regimen (does reduced versus full dose subjects) for the mITT analysis set on-treatment and overall study periods showed that the edoxaban 60 mg group experienced fewer events and the edoxaban 30 mg group experienced more events than the matching warfarin group in both subsets (subjects with dose reduction and subjects who received the full dose). Subjects who received edoxaban 15 mg (dose reduced subjects for the edoxaban 30 mg group) had a higher event rate than the matching dose reduced subjects in the edoxaban 60 mg group or the warfarin group.

The primary efficacy findings for subgroups based on demographic and baseline characteristics (such as age, gender, race, body weight, creatinine clearance, CHADS2 score, dose reduced or not, warfarin naïve or not, geographic regions, etc.) were generally consistent with the overall study results. For most subgroups, the primary efficacy endpoint event rate was lower in the edoxaban 60 mg group than in the warfarin group, with the HR for the comparison of the edoxaban 60 mg group versus the warfarin group 1.0 or less. The p-value for the interaction was < 0.05 for subgroups based on CrCL and geographic regions, with an HR of more than 1.0 between the edoxaban 60 mg and warfarin groups for subjects with CrCL > 80 mL/min and subjects in Western Europe. However, in these 2 subgroups, the edoxaban 60 mg group event rates for the mITT analysis set on-treatment period were still low (1.06% per year for subjects with CrCL $\geq$ 80 mL/min; 1.67% per year for subjects in Western Europe.

For most subgroups, the primary efficacy endpoint event rate was larger in the edoxaban 30 mg group than in the warfarin group, with the HR for the comparison of the edoxaban 30 mg group versus the warfarin group more than 1.0.

Overall, both edoxaban dose groups were non-inferior to warfarin in reducing the risk of stroke or systemic embolism in patients with non-valvular atrial fibrillation, while providing the added benefit of reduction in mortality and hemorrhagic strokes.

Safety Results:
Edoxaban-treated subjects experienced significantly lower rates of Major, ICH, Fatal, and CRNM bleeding events than those treated with warfarin. The annualized rates of Major bleeding (primary safety endpoint) in the edoxaban 60 mg and warfarin groups were 2.75% and 3.43% per year, respectively (HR 0.80, 95% CI: 0.71, 0.91; p=0.0009) and 1.61% per year with edoxaban 30 mg (HR 0.47; 95% CI: 0.41, 0.55; p<0.0001). Annualized event rates for Major plus CRNM bleeding in the edoxaban 60 mg, edoxaban 30 mg, and warfarin groups were 11.1%, 8.0% 13.0%, respectively. Rates of ICH or Fatal bleeding were also higher in the warfarin group (0.85% and 0.38% respectively) than in either the

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edoxaban 60 mg (0.39% and 0.21 %, respectively) or edoxaban 30 mg (0.26% and 0.13 %, respectively) groups.

The lower rates of bleeding in edoxaban-treated subjects were also observed in various subgroups based on demographic and baseline characteristics such as age, gender, body weight, renal function, $CHADS_2$ score (risk stratification scheme for stroke), or past history of stroke or TIA. A similar advantage for lower bleeding with the edoxaban groups than the warfarin group was also observed in subjects receiving concomitant medications such as aspirin, antiplatelet agents, and NSAIDs, although the bleeding event rates were higher in these groups.

While in general the bleeding rate was lower for edoxaban for most locations, this was not observed for GI bleeds. The annualized rate of Major GI bleeding was higher in the edoxaban 60 mg group than in the warfarin group (1.51% and 1.23% per year, respectively), but lower in the edoxaban 30 mg group (0.82% per year).

Edoxaban-treated subjects experienced a significantly lower rate of CV mortality than those treated with warfarin (ITT analysis set overall study period). Overall, fewer edoxaban-treated subjects died compared with warfarin-treated subjects. The annualized event rate for CV mortality was significantly lower in both the edoxaban 60 mg (2.74%) and edoxaban 30 mg (2.71%) groups than in the warfarin group (3.17%). The corresponding rates for all-cause mortality in the edoxaban 60 mg, edoxaban 30 mg, or warfarin groups were 3.99%, 3.80%, and 4.35% per year, respectively. As expected for the study population (median age 72 years, average $CHADS_2$ score 2.8), approximately 70% of deaths were due to CV illnesses. Fatal bleeds were included in the category of CV deaths, and edoxaban treated subjects experienced fewer deaths due to bleed events.

The non-bleeding TEAEs and TESAEs were generally similar for both edoxaban and warfarin-treated subjects. Overall, non-bleeding TEAEs leading to study drug interruptions or discontinuations were also similar in both edoxaban and warfarin-treated subjects. The edoxaban 60 mg group had more reports of anemia than the warfarin group, which could possibly be due to the higher GI bleeding events in this group.

Review of the laboratory data for liver enzyme and bilirubin abnormalities, as well as cases that were adjudicated by 2 independent hepatic specialists in a blinded manner, did not indicate any clinically concerning signal for drug induced hepatic injury. Two subjects in the edoxaban 60 mg group and 1 subject in the edoxaban 30 mg group were adjudicated as having met Hy's rule. In each case, there were additional factors potentially contributing to the liver enzyme elevation.

Overall, the results of this study demonstrate that edoxaban is a well-tolerated novel anticoagulant agent with a significantly lower risk of bleeding events and CV mortality than those treated with warfarin.

Net Clinical Outcome Results:

Net clinical outcome was evaluated by comparing each edoxaban group with the warfarin group for composite efficacy and safety events (such as the composite of stroke, SEE, major bleed or all-cause mortality), and focused on events (either efficacy or safety) which may lead to significant morbidity or CV mortality. Both edoxaban groups were superior to the warfarin group for net clinical outcome, with the upper boundary of the 95% CI less than 1 for all comparisons. Overall, edoxaban provides a more favorable risk-benefit profile compared with warfarin.

<table>
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<tr><td colspan="3"><u>Transition Period Results:</u>
At the end of the study after the final dose of study drug, subjects were transitioned to open-label anticoagulant therapies in accordance with a pre-specified transition scheme. This scheme was designed to maintain adequate anticoagulation protection during the transition, and thus avoid an undue risk of stroke or SEE during the transition. This study supplied a transition kit for edoxaban-treated subjects who were transitioning from edoxaban to open-label VKA therapy at the end of the study to use as a bridging therapy until the INR reached ≥ 2.0. The transition scheme was effective, as there were few events during the transition period, and no increase in the risk of stroke/SEE, all-cause mortality, or Major bleeding when subjects in the edoxaban groups transitioned to open-label anticoagulant at the end of the study.</td></tr>
<tr><td colspan="3">Conclusions:
• Both edoxaban dose groups were non-inferior to well-managed warfarin for the prevention of stroke or SEE, with lower event rates in the edoxaban 60 mg group.
• Both edoxaban groups significantly reduced hemorrhagic stroke. The rates of ischemic stroke were similar in the edoxaban 60 mg and warfarin groups, but the rate was higher in the edoxaban 30 mg group.
• The dose reduction scheme was safe and effective. Subjects in the dose reduced group benefited from equal efficacy and protection as did the full dose group, without any compromise in safety or bleeding profiles.
• Both edoxaban groups had fewer MACE, fewer CV deaths, and fewer all-cause deaths. CV mortality was significantly reduced in both edoxaban groups compared to the warfarin group. All-cause mortality was significantly reduced in the edoxaban 30 mg group compared to the warfarin group, with a similar trend (p=0.0816) observed for the edoxaban 60 mg group.
• Compared with warfarin, edoxaban was associated with a consistent and dose related reduction in all types of bleeding, including Major and ICH bleeding. The single exception was GI bleeding, which occurred more frequently in the edoxaban 60 mg group.
• Net clinical outcomes combining all-cause mortality, CV events, and bleeding were significantly reduced in both edoxaban groups.
• In this study, edoxaban provided a more favorable risk-benefit profile than warfarin, with a flexible dosing scheme based on the individual subject's health profile.</td></tr>
<tr><td colspan="3">Version and Date of the Report: Version 2.0, 15 November 2013</td></tr>
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