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SYNOPSIS

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

Title of Study:	A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multi-Center, Multi-National Study for the Evaluation of Efficacy and Safety of (LMW) Heparin/Edoxaban Versus (LMW) Heparin/Warfarin in Subjects With Symptomatic Deep-Vein Thrombosis and/or Pulmonary Embolism
Phase of Development:	Phase 3
Study Period:	First subject first visit date: 28 Jan 2010 Last subject last follow-up date: 12 Jun 2013
Investigator(s):	A total of 439 investigative sites randomized subjects in this study. [redacted] was the Principal Investigator.
Study Center(s):	A total of 533 investigative sites in 38 countries were initiated for the study and 439 sites in 37 countries randomized subjects.
Publication (reference):	Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism The Hokusai-VTE Investigators NEJM: 01 September 2013 DOI: 10.1056/NEJMoa1306638
Study Objectives/Hypothesis:	The primary objective was to evaluate whether initial low molecular weight (LMW) heparin followed by edoxaban only ([LMW] heparin/edoxaban) is non-inferior to initial (LMW) heparin overlapping with warfarin, followed by warfarin only ([LMW] heparin/warfarin) in the treatment of subjects with acute symptomatic VTE for the prevention of symptomatic recurrent VTE during the 12-month study period.

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Secondary objectives included:

- Compare (LMW) heparin/edoxaban to (LMW) heparin/warfarin with regard to clinically relevant bleeding (i.e., Major or Clinically Relevant Non-major [CRNM] bleeding) occurring during treatment or within 3 days of interrupting or stopping study drug.
- Compare (LMW) heparin/edoxaban to (LMW) heparin/warfarin with regard to the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period.

Other objectives included:

1. Compare (LMW) heparin/edoxaban to (LMW) heparin/warfarin with regard to Major bleeding occurring during treatment or within 3 days of interrupting or stopping study drug.
2. Compare (LMW) heparin/edoxaban to (LMW) heparin/warfarin with regard to net clinical outcome defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, Major bleeding, and all-cause mortality.
3. Evaluate the safety of (LMW) heparin/edoxaban vs. (LMW) heparin/warfarin for:
    a. Any bleeding (Major, CRNM, and nuisance bleeding
    b. All other clinical and laboratory safety assessments including major adverse cardiovascular event (MACE, defined as a composite of non-fatal myocardial infarction [MI], non-fatal stroke, non-fatal systemic embolic events [SEE], and cardiovascular death) as well as liver enzyme and bilirubin abnormalities.

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	4. Evaluate the time in therapeutic range (TTR) based on international normalized ratio (INR) ranges (< 2.0; ≥ 2.0 to ≤ 3.0; and > 3.0) for warfarin-treated subjects during the warfarin-only period. 5. Evaluate the population pharmacokinetics (PK) and pharmacodynamics (PD) of edoxaban in relation to efficacy and safety endpoints. The **study hypothesis** was that (LMW) heparin/edoxaban will be non-inferior to (LMW) heparin/warfarin in preventing recurrence of acute, symptomatic VTE following an initial index event. (LMW) heparin/edoxaban was considered non-inferior to the standard therapy ([LMW] heparin/warfarin) if the upper limit of the two-sided 95% confidence interval (CI) for the Hazard Ratio ([LMW] heparin/edoxaban to standard therapy) was less than 1.5.
Study Design/Methodology:	This was an event-driven, Phase 3, multi-national, multi-center, randomized, double-blind, matching placebo, parallel-group, non-inferiority study to evaluate the benefits and risks of edoxaban in reducing the risk of recurrent venous thromboembolism (VTE) complications in subjects with documented acute symptomatic DVT and/or PE. Eligible subjects were stratified by: • Presenting diagnosis – PE with or without DVT and – DVT only, • Baseline risk factors

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Temporary risk factors only (such as trauma, surgery, immobilization, estrogen therapy, etc.)

versus

- All others,

- Need for dose edoxaban/edoxaban placebo 30 mg allocation
  - Body weight ≤ 60 kg;
  - Creatinine clearance (CrCL) between 30 and 50 mL/min; and
  - Concomitant use of the P-glycoprotein (P-gp) inhibitors verapamil or quinidine.

The edoxaban 60 mg QD (or matching placebo) dose was halved for subjects requiring 30 mg QD dose allocation.

After stratification and confirmation of eligibility, subjects were assigned randomly via interactive voice/web response system (IXRS) in a 1:1 ratio to one of two treatment groups:

(LMW) heparin/edoxaban group: Initial (LMW) heparin plus placebo warfarin for at least 5 days until the sham INR was ≥ 2.0 on two separate measurements at least one calendar day apart or a single supratherapeutic sham INR measurement > 3.0 was achieved (with the reasonable assumption that a therapeutic INR, i.e., ≥ 2.0, had been achieved for at least 24 hours). Then (LMW) heparin was to be stopped, and the subject started edoxaban (60 mg QD) and continued placebo warfarin (adjusted to maintain INR between 2.0 and 3.0.

(LMW) heparin/warfarin group: Initial (LMW) heparin plus warfarin for at least 5 days until the INR was ≥ 2.0 on two separate measurements at least one calendar day apart or after a single supratherapeutic INR measurement > 3.0 was achieved (with the reasonable assumption that a therapeutic INR, i.e., ≥ 2 had been achieved for at least

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24 hours). Then (LMW) heparin was to be stopped, and the subject started placebo edoxaban (60 mg QD) and continued warfarin (adjusted to maintain INR between 2.0 and 3.0).

Anticoagulation treatment, including up to a single dose of a Vitamin K antagonist (VKA) was allowed for a maximum of 48 hours prior to randomization.

This was an event-driven study. The study continued until approximately 220 Overall primary efficacy endpoint events (i.e., recurrent VTE) were recorded for the mITT Analysis Set (subjects who received at least one dose of randomized study drug) across both treatment groups.

The maximum possible treatment period for any individual subject after randomization was 12 months. While 12 months of treatment was planned, mitigating factors related to the subject's clinical status could influence the total duration of treatment a given subject actually received. Nevertheless, all subjects were to receive a minimum of three months treatment consistent with current American College of Chest Physicians (ACCP) Guidelines.

Throughout the study, the number of events was closely monitored and further randomization to treatment was stopped when the required number of events was projected to be reached (End of Randomization [EOR] date). Based on the EOR date a global End of Treatment (EOT) date was established that allowed up to 6 months of treatment for the last subject(s) randomized to study. A global Final Study Visit (FSV) date was set one month following the EOT date. All subjects were to complete their follow-up safety visit on or before the FSV date.

Regardless of the total duration of treatment actually received, efficacy and safety data were to be collected on all subjects, including those who temporarily interrupted or permanently discontinued study drug during the entire 12 month period following randomization, except for the subjects who had their duration of treatment and end of

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	study visit truncated based on the 6 month period between EOR and EOT. All other subjects were expected to have a Month 12 visit and a safety follow-up visit approximately 1 month after the last dose of study drug. For all subjects, contacts (visits or phone calls) were scheduled at regular time points. Subjects with suspected efficacy or safety endpoints had confirmatory testing. An independent Data Monitoring Committee (DMC) of external experts monitored the study data in an unblinded manner while the study was ongoing. The purpose of the DMC was to protect the safety of the subjects and to advise the Study Management Coordination Committee (SMCC) in case of any signals of safety concern. The study had oversight in a blinded manner by a SMCC which included the sponsor's representatives. An independent Clinical Events Committee (CEC) verified the adequacy of the presenting index diagnosis, and adjudicates the recurrence of protocol specified VTE endpoints, MACEs, hepatic events and to classify bleeding events in a blinded manner.
Duration of Treatment for Individual Subject:	The median duration of exposure to study drug was 265 days for subjects who received edoxaban and 261 days for subjects who received warfarin.
Number of Subjects:	Planned: 7500 Randomized: 8292 Completed Study: 7892 (95.8% of mITT/Safety population, n =8240)
Diagnosis and Main Criteria for Study Entry:	This study enrolled male or female subjects older than the minimum legal adult age (country specific) presenting with acute, symptomatic proximal DVT involving the popliteal, femoral or iliac veins, and/or PE requiring anticoagulant therapy. Exclusions included thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT

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	and/or PE; indication for warfarin other than DVT and/or PE; more than 48 hours pretreatment with therapeutic dosages of anticoagulant treatment (LMW heparin, unfractionated heparin [UFH], and fondaparinux per local labeling) or more than a single dose of a VKA prior to randomization to treat the current episode, calculated CrCL < 30 mL/min, and significant liver disease.	
Investigational Product and Comparator Information:	Warfarin 1 mg tablet [redacted] Warfarin 2.5 mg tablet [redacted] Warfarin 5 mg tablet [redacted] Placebo to match warfarin 1 mg tablet [redacted] Placebo to match warfarin 2.5 mg tablet [redacted] Placebo to match warfarin 5 mg tablet 080156, [redacted] Edoxaban 30 mg tablet [redacted] Edoxaban 60 mg tablet [redacted] Placebo to match edoxaban 30 mg tablet [redacted] Placebo to match edoxaban 60 mg tablet [redacted]	

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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 symptomatic recurrent VTE (i.e., the composite of DVT, non-fatal PE, and fatal PE)

The secondary efficacy endpoint was the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period.

Safety: The primary safety outcome was clinically relevant bleeding (i.e., a composite of Major bleeding or CRNM bleeding) as adjudicated by the CEC. An additional endpoint included MACE (non-fatal MI, non-fatal stroke, non-fatal systemic embolic events, and cardiovascular death).

Other safety assessments included, but were not limited to, all bleeding, clinical laboratory assessments, vital signs, physical examinations with electrocardiograms (ECGs), AEs, serious adverse events (SAEs), deaths, and other cardiovascular events. Liver enzymes and bilirubin abnormalities were evaluated as safety events of special interest.

Pharmacokinetics/Pharmacodynamics: Blood samples were collected at Months 3 and 12 and in conjunction with an event for PK evaluation of edoxaban and its active metabolite, D21-2393. Blood samples were collected at baseline (Day 1), Months 3 and 12, at follow-up, and in conjunction with an event for the measurement of PD markers including D dimer and anti-Factor Xa activity (Anti-FXa).

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Statistical Methods:

The primary efficacy analysis was based on a modified Intent-to-Treat (mITT) Analysis Set (subjects who are randomized and received at least one dose of study drug) using all primary efficacy events that occurred in the 12-month study period (i.e., primary efficacy events occurring from randomization through the end of the 12-month study period (or to the day of global end of treatment), regardless of whether the subject was taking study drug). Also included are subjects whose full 12-month study period was truncated due to declaration of the end of study. In this analysis, the time to the first event of the composite primary efficacy outcome was analyzed using a Cox proportional hazards model including treatment and the stratification factors as covariates. The (LMW) heparin/edoxaban: comparator Hazard Ratio (HR) was computed with a 95% CI (two-sided testing) based on this model. (LMW) heparin/edoxaban was considered non-inferior to the comparator if the upper limit of the CI is less than 1.5.

Analysis of the Secondary Efficacy Endpoint:

If non-inferiority of (LMW) heparin/edoxaban was established for the primary efficacy endpoint, (LMW) heparin/edoxaban was compared with (LMW) heparin/warfarin for superiority (α=0.01 two-sided) with regard to the time to an event in the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period. This analysis was based on the mITT Analysis Set using the same proportional hazard model as for the primary efficacy analysis.

Analysis of the Primary Safety Endpoint:

The time to first Major or CRNM bleeding was compared between treatment groups for superiority (α=0.05 two-sided) for subjects in the Safety Analysis Set (subjects who received at least one dose of randomized study drug), using a similar Cox proportional hazards model as in the primary efficacy analysis. However, only bleeding events occurring while on-treatment or within 3 days after interrupting or stopping study drug were counted for the primary safety analysis. Time to Major bleeding was also tested at the same significance level.

Pharmacokinetics/Pharmacodynamics:

Individual plasma concentration and biomarker data are presented by visit and time point and depicted using descriptive statistics. Population pharmacokinetic (Pop PK) parameters and exposure-response relationships were evaluated separately and are presented in a separate report.

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Summary:

Baseline Characteristics and Enrollment:

The Hokusai VTE study randomized 8292 subjects on a 1:1 basis into 2 treatment groups: edoxaban or warfarin. Of the 8,240 subjects who comprised the mITT and Safety populations, very few subjects did not complete the study (4.2% overall) including those who were lost to follow-up (0.1% overall), withdrew consent (0.8% overall), and those who died (3.2%). A full 12 months of follow-up was reported for 74.4% of subjects. Overall, 61.5% of all subjects remained on-treatment for at least six months, with 40.3% of all subjects receiving a full 12 months of treatment. The 2 treatment groups that made up the mITT population were very well matched with respect to the key demographic factors of age (mean age 55.8 years), gender, race, baseline medical history including presenting diagnosis, risk factors, and the use of prior and concomitant medications. This study enrolled a high percentage of subjects with PE (~40% in each group) and the treatment groups were well matched with respect to extent of PE.

Subjects with low body weight (≤ 60kg), moderate renal impairment (CrCL 30 to 50 ml/min), or pre-specified concomitant medications (e.g. verapamil. quinidine) in the edoxaban group received active edoxaban 30 mg (and placebo warfarin) while subjects in the warfarin group with the same low body weight, moderate renal impairment, or pre-specified concomitant medications received placebo edoxaban 30 mg (and active warfarin). These subjects tended to be older and included more female subjects.

The study was designed to provide quality warfarin care in the comparator arm (i.e., a TTR of 60%). The observed mean overall Time in Therapeutic Range (TTR) was 63.5%.

Efficacy Results:

- Non-inferiority of the primary efficacy endpoint was achieved and corroborated by consistent findings across the multiple pre-specified sensitivity analyses.
- Subjects with extensive and more severe PE were enrolled and characterized; edoxaban demonstrated a benefit across all index PE subjects and in particular those with a more severe PE presentation.
- Subjects with DVT also demonstrated non-inferiority to warfarin.

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- The relative risk reduction seen in the edoxaban group was sustained to 12 months.
- Recurrent VTE rates with the edoxaban 30 mg dose were comparable to the edoxaban 60 mg dose.
- The relative risk reduction for efficacy with edoxaban was demonstrated against a high quality standard of warfarin care.
- The duration of initial heparin treatment did not influence the efficacy outcome.
- Subgroup analysis of fragile subjects, elderly subjects, and subjects with a history of cancer demonstrated a favorable outcome with edoxaban therapy.

Safety Results:

- Superiority of the primary safety endpoint was achieved, and corroborated by consistent risk reductions across all bleeding categories.
- The relative risk reduction in Major/CRNM bleeding seen with edoxaban therapy was sustained to 12 months.
- Major/CRNM bleeding rates with the edoxaban 30 mg dose were comparable to the edoxaban 60 mg dose.
- Numerical imbalances in GI tract and vaginal bleeding events were noted and occurred more frequently in the edoxaban group.
- The relative risk reduction for bleeding with edoxaban was demonstrated against a high quality standard of warfarin care.
- The duration of initial heparin treatment did not influence the primary safety outcome.
- A numerical imbalance of MACE and death events was seen in the edoxaban group.
- No hepatic Hy's rule events were observed in the edoxaban subjects
- TEAEs reported among the edoxaban and warfarin groups were comparable.
- Subgroup analysis of fragile subjects, elderly subjects, and subjects with a history of cancer demonstrated a favorable bleeding outcome with edoxaban therapy.

Pharmacokinetic/Pharmacodynamic Results:

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The mean pre- and post-dose edoxaban plasma edoxaban concentrations in the 30 mg edoxaban dose group were slightly lower than the 60 mg edoxaban dose but with considerable overlap in plasma concentrations. Plasma edoxaban concentration and Anti-Factor Xa demonstrated a linear relationship, with a high level of correlation.

Conclusions:

An estimated 1 million people present with VTE every year and it remains the third most common cardiovascular illness after acute coronary syndrome and stroke, with the annual prevalence now projected to double by 2050. Rapid diagnosis and treatment are necessary to prevent significant mortality and morbidity. Standard of care therapy with warfarin is challenged by the need for blood monitoring, numerous drug and food interactions, and low levels of initial acceptance and long term compliance by patients. In this randomized, double-blind study of subjects with acute VTE, initially given heparin, edoxaban was non-inferior to warfarin for efficacy and was superior to warfarin for bleeding safety. A total of 8292 subjects were randomized (n = 8240 for mITT/Safety populations) with 4921 subjects with DVT only and 3319 subjects with PE with or without DVT, the largest single VTE trial to date. Overall time in therapeutic range for warfarin subjects was 63.5%. Lost to follow-up was low (less than 0.2%), as was the rate of subjects withdrawing consent (less than 0.9%). Unique features of this trial included flexible treatment duration, follow-up to 12 months, dose reductions for subjects with low body weight, moderate renal impairment, and concomitant use of pre-specified P-gp inhibitors, enrollment and physiologic characterization of subjects with more severe PE, and identification of high risk subject subgroups including the elderly, fragile, and cancer subjects. Risk reductions with edoxaban therapy were seen in all these categories. The Hokusai VTE study results support that once daily edoxaban 60 mg after an initial heparin course was non-inferior for efficacy with significantly less bleeding compared to quality standard warfarin therapy in a broad spectrum of VTE subjects, including severe pulmonary embolism. The data also supports edoxaban 30 mg as a clinically useful and important alternative in select higher risk subjects.

Date of the Report: 17 Oct 2013