SYNOPSIS

Name of Sponsor/Company	Daiichi Sankyo Co., Ltd.
Name of Finished Product	LIXIANA TABLETS
Name of Active Ingredient	Edoxaban Tosilate Hydrate
Title of Study	Phase III Clinical Study of DU-176b (Venous Thromboembolism): Japan and Taiwan Multicenter Randomized Double-blind Study of DU-176b in Patients Undergoing Total Knee Arthroplasty with Enoxaparin as an Active Control
Investigators	71 investigators
Study Centre(s)	71 centers
Publication (reference)	N.A.
Studied Period	
Phase of Development	Phase III
Objectives	To verify the non-inferiority of edoxaban to enoxaparin with regard to prevention of venous thromboembolism (VTE) in patients undergoing total knee arthroplasty.
Methodology	Edoxaban administered at a dose of 30 mg once daily was assessed for efficacy and safety, compared with enoxaparin administered at a dose of 20 mg twice daily, under a double-blind, double-dummy design. The duration of treatment was set as 11 to 14 days, venography of the operated limb was performed within 24 hours after the completion of administration. The present study was performed as a Japan-Taiwan multicenter study.
Number of Patients (planned and analyzed)	Planned: 520 subjects (260 subjects per group) Treatment: 703 subjects (edoxaban group 354 subjects; enoxaparin group 349 subjects) Analyzed: 594 subjects (edoxaban group, 299 subjects; enoxaparin group, 295 subjects)
Diagnosis and Main Criteria for Inclusion	Patients who were scheduled for primary TKA (excluding bilateral TKA), Patients aged 20 to < 85 years
Test Product, Dose and Mode of Administration, Batch Number	Administration of 1 tablet was performed at 6 to 24 hours after surgery, and 1 tablet/day was administered orally in the morning from the next day (administration interval: Approximately 10 hours or longer).

	Lot number: edoxaban (30 mg tablets) (DU176F1T07T01) edoxaban placebo (DU176F1T07T06)
Duration of Treatment	The duration of treatment was set at 11 to 14 days.
Reference Therapy, Dose and Mode of Administration, Batch Number	Administration was started with 1 syringe at 24 to 36 hours after surgery, and 1 syringe was administered subcutaneously twice daily from the next day (administration interval: Approximately 12 hours). Lot number: Enoxaparin (2000 IU injection) (912004) Enoxaparin placebo (910918)
Criteria for Evaluation	(Efficacy Primary Endpoint) The primary endpoint was the proportion of subjects with one or more of the following thromboembolic events (incidence proportion of thromboembolic events) that occurred during the period from the start of administration of the study drug until the performance of venography at the completion of administration. ・Asymptomatic deep vein thrombosis (DVT) (DVT evaluated by venography performed on the operated lower limb after completing administration of the study drug.) ・Symptomatic and definitely diagnosed pulmonary embolism (PE). ・Symptomatic DVT that was confirmed before the performance of planned venography. (Safety Primary Endpoint) The occurrence of the following bleeding events, adverse events (AEs), and adverse drug reactions (ADRs) during the period from the start of administration of the study drug until the day of the follow-up examination was evaluated. 1) Incidence proportion of major bleeding. 2) Incidence proportion of major bleeding or clinically relevant non-major bleeding.
Statistical Method	(Analyses of the Primary Efficacy Endpoint) As primary analyses, the following hypothesis testing was carried out for the proportion of subjects with one or more thromboembolic events, defined as the primary endpoint,

	using Z test statistics. Null hypothesis H_{01}: The incidence proportion of thromboembolic events in the edoxaban group (P_{DU}) = The incidence proportion of thromboembolic events in the enoxaparin group (P_E) + Δ (5%) Alternative hypothesis H_{11}: $P_{DU} < P_E + \Delta$ (level of significance, 0.025; one-sided). If the null hypothesis H_{01} was rejected, the following analysis had to be sequentially performed using the χ^2 test statistic. Null hypothesis H_{02}: $P_{DU} = P_E$ Alternative hypothesis H_{12}: $P_{DU} \neq P_E$ (level of significance, 0.05; two-sided) (Analyses of the Primary Safety Endpoint) The incidence proportion of major bleeding that occurred during the treatment period (from the day of administration of the study drug to the next day of the completion of administration) and its 95% CI were calculated for each treatment group. The difference between the edoxaban and enoxaparin groups and its 95% CI were also calculated, and a paired comparison between the treatment groups was performed using the $\chi 2$ test. Concerning the breakdown of major bleeding events, the number of subjects with individual events and the incidence proportion were calculated for each treatment group. Similar analyses were performed for treatment-related major bleeding during the treatment period, as well as major bleeding and treatment-related major bleeding during the period from the start of administration of the study drug to the day of the follow-up examination. Similar analyses were also performed for clinically relevant non-major bleeding, major bleeding or clinically relevant non-major bleeding, and bleeding events (major bleeding, clinically relevant non-major bleeding, and minor bleeding).
Summary - Conclusion	(Efficacy Primary Endpoint)

	The primary efficacy outcome occurred in 22 of 299 (7.4%) patients receiving edoxaban and 41 of 295 (13.9%) patients receiving enoxaparin. ($p < 0.001$ for non-inferiority; $p = 0.010$ for superiority). (Safety Primary Endpoint) The incidence of major or clinically relevant non-major bleeding events was 6.2% (22/354) vs 3.7% (13/349) in the edoxaban and enoxaparin groups, respectively ($p=0.129$). Major bleeding occurred in 1.1% of the edoxaban group and 0.3% of the enoxaparin group ($p=0.373$). (Conclusions) This trial demonstrated that oral edoxaban 30 mg once daily has efficacy superior to enoxaparin in 2,000 IU twice daily in the prevention of thromboembolic events following TKA without a significant difference in incidence of bleeding events.
Date of Report	25 July, 2014