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	DU-176b Phase III Clinical Study(Venous Thromboembolism) -Randomized Double-Blind Study of DU-176b in Patients Undergoing Total Hip Arthroplasty with Enoxaparin as an Active Control -
Investigators	58 investigators
Study Centre(s)	58 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 hip 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 lower limbs were performed within 24 hours after the completion of administration.
Number of Patients (planned and analyzed)	Planned: 600 subjects (300 subjects per group) Treatment: 601 subjects (edoxaban group, 303 subjects; enoxaparin group, 301 subjects) Efficacy Analyzed: 503 subjects (edoxaban group, 255 subjects; enoxaparin group, 248 subjects)
Diagnosis and Main Criteria for Inclusion	Patients who were scheduled for primary THA (excluding bilateral THA), 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 efficacy outcome was the composite of symptomatic and asymptomatic DVT, and PE. (Safety Primary Endpoint) The primary safety outcome was the incidence of major or clinically relevant non-major bleeding.
Statistical Method	(Analyses of the Primary Efficacy Endpoint) The percentage of subjects with at least 1 thromboembolic event specified as the primary endpoint was analyzed using the Farrington and Manning method. (Analyses of the Primary Safety Endpoint) The incidence of major bleeding or clinically relevant non-major bleeding during the treatment period (from the start day of treatment until the day after the last dose) and its 95% CI was calculated for each group ; the difference in incidence between the edoxaban group and the enoxaparin group and its 95% CI were also calculated.
Summary - Conclusion	(Efficacy Primary Endpoint) The primary efficacy outcome occurred in 6 of 255 (2.4%) patients receiving edoxaban and 17 of 248 (6.9%) patients receiving enoxaparin. ($p < 0.001$ for non-inferiority; $p = 0.016$ for superiority).No symptomatic DVT or PE was observed in both treatment groups. (Safety Primary Endpoint) The incidence of major or clinically relevant non-major bleeding events was 2.6% (8/303) vs 3.7% (11/301) in the edoxaban and enoxaparin groups, respectively (p=0.475).

	Major bleeding occurred in 0.7% (2/303) of the edoxaban group and 2.0% (6/301) of the enoxaparin group (p=0.176). (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 THA with a similar incidence of bleeding events.
Date of Report	25 July, 2014