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 IIb clinical study (venous thromboembolism): Japan and Taiwan multicenter randomized double-blind dose-finding study using Enoxaparin as a reference in patients undergoing total hip replacement.
Investigators	34 investigators
Study Centre(s)	34 centers
Publication (reference)	Journal of Arthroplasty, DOI: 10.1016/j.arth.2014.05.029
Studied Period	6months Initiation Date (first subject enrolled): 19 Jun 2008 Completion Date (last subject completed): 11 December 2008
Phase of Development	Phase IIb
Objectives	The objectives are to compare the efficacy and safety of edoxaban at 15 mg and 30 mg once daily for 11 to 14 days in a double-blind manner, and to examine the appropriate dosage of edoxaban in patients undergoing total hip replacement. Enoxaparin was designated as a reference drug in order to understand the relationship between edoxaban and commercially supplied drugs for the efficacy and safety.
Methodology	Edoxaban 15 mg and 30 mg once daily are compared in double- blind manner and open- label enoxaparin is designated as a reference, in order to assess the efficacy and safety of edoxaban at 15 mg and 30 mg once daily and to examine the appropriate dosage of edoxaban. After being performed a total hip replacement, patients are randomly assigned to edoxaban 15 mg once daily group, edoxaban 30 mg once daily group, or enoxaparin group in a 1:1:1 ratio. After the administration for 11 to 14 days, bilateral venograms will be obtained.

Number of Patients (planned and analyzed)	Planned: 210 subjects (70 subjects per group) Treatment: 261 subjects (edoxaban 15 mg group, 89 subjects; edoxaban 30 mg group, 85 subjects; enoxaparin group, 87 subjects) Efficacy Analyzed: 224 subjects (edoxaban 15 mg group, 78 subjects; edoxaban 30 mg group, 72 subjects; enoxaparin group, 74 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 (15 mg tablets) (S06036-2) edoxaban placebo (S06036-3) Lot number:edoxaban (30 mg tablets) (S06036-5) edoxaban placebo (S06036-8)
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) (DU176b-B-J209-4) Enoxaparin placebo (DU176b-B-J209-4)
Criteria for Evaluation	(Efficacy Primary Endpoint) Proportion of subjects with one or more of the following thromboembolic events occur during the period from commencement of administration of the investigational product to venography implementation at the completion of administration of the investigational product is evaluated as a primary endpoint of efficacy ·Asymptomatic DVT (DVT evaluated by venography performed on both lower limbs at the completion of administration of the

	investigational product) · Symptomatic PE that was conclusively diagnosed · Symptomatic DVT confirmed before implementation of predetermined. (Safety Primary Endpoint) As a primary endpoint of safety, the following bleeding events observed during the period from commencement of administration of the investigational product to the follow-up visit date are evaluated. (1) Incidence rate of major bleeding (2) Incidence rate of clinically relevant non-major bleeding (3) Incidence rate of major bleeding or clinically relevant non-major bleeding
Statistical Method	(Analyses of the Primary Efficacy Endpoint) For the proportion of subjects with one or more of thromboembolic events (= incidence rate of thromboembolic events), the difference between edoxaban 15 mg group and edoxaban 30 mg group, and its 95% confidence interval thereof are calculated. In addition, the incidence rate of thromboembolic events by administration group and its 95% confidence interval thereof are also calculated. As reference, the difference between Enoxaparin group and each edoxaban group, and its 95% confidence interval thereof are also calculated. (Analyses of the Primary Safety Endpoint) The incidence rate of major bleeding are calculated by administration group. The incidence rate of clinically relevant non-major bleeding and its 95% confidence interval thereof are calculated by administration group. In addition, for the incidence rate of clinically relevant non-major bleeding, the difference between groups and its 95% confidence interval thereof are calculated. The incidence rate of major bleeding or clinically relevant non-major bleeding, and its 95% confidence interval thereof are calculated by administration group. In addition, for the incidence rate of major bleeding or

	clinically relevant non-major bleeding, the difference between groups and its 95% confidence interval thereof are calculated.
Summary - Conclusion	The incidence of thromboembolic events was 3.8% (3/78), 2.8% (2/72), and 4.1% (3/74) in 15 mg, 30 mg edoxaban, and enoxaparin groups, respectively. The thromboembolic events were all distal asymptomatic DVT. The incidence of major or clinically relevant non-major bleeding was 2.2% (2/89) in the 15 mg edoxaban group, 1.2% (1/85) in the 30 mg edoxaban group and 2.3% (2/87) in the enoxaparin group. There was one major bleeding event in the 30 mg edoxaban group. Of the biomarkers, D-dimer, F1+2, and soluble fibrin levels were most decreased in the edoxaban 30 mg group When both efficacy and safety are considered, the results suggest that edoxaban 30 mg once daily is the appropriate dosage regimen for prevention of thromboembolic events in patients undergoing THA.
Date of Report	25 July, 2014