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	A Phase IIb, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging, Multi-center Study in Patients Undergoing Total Knee Replacement
Investigators	63 investigators
Study Centre(s)	63 sites
Publication (reference)	Journal of Thrombosis and Haemostasis, 8: 2458–2468
Studied Period	1 year and 3 months Initiation Date (first subject enrolled): 3 July 2006 Completion Date (last subject completed): 19 September 2007
Phase of Development	Phase II
Objectives	To assess the dose-response relationship of the efficacy of edoxaban for the prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing total knee replacement (TKR), as well as its safety, in a randomized, double-blind, placebo-controlled, dose-ranging study.
Methodology	Study design: Multicenter, randomized, double-blind, placebo-controlled, parallel 5-group, dose-ranging study of edoxaban at the 4 dose levels of 5 mg/day, 15 mg/day, 30 mg/day, and 60 mg/day Duration of treatment: Oral treatment for 11 to 14 days
Number of Patients (planned and analyzed)	Planned: 500 subjects (100 subjects per group) Treatment: 520 subjects (edoxaban 5 mg group: 103 subjects; 15 mg group: 106 subjects; 30 mg group: 103 subjects; 60 mg group: 106 subjects; Placebo group: 102 subjects) Analyzed: 445 subjects (edoxaban 5 mg group: 88 subjects; 15 mg group: 92 subjects; 30 mg group: 88 subjects; 60 mg group: 88 subjects; Placebo group: 89 subjects)
Diagnosis and Main	Patients who were scheduled for primary TKR (excluding

Criteria for Inclusion	bilateral TKR), Patients aged 20 to < 85 years
Test Product, Dose and Mode of Administration, Batch Number	Four tablets were orally administered once daily, treatment was started within 6 to 24 hr after surgery, and was given in the morning, in principle, from the following day onwards. Lot number : 5 mg tablet S05042-1 , 15 mg tablet S04045-5
Duration of Treatment	The duration of treatment was set at 11 to 14 days.
Reference Therapy, Dose and Mode of Administration, Batch Number	Four tablets were orally administered once daily, treatment was started within 6 to 24 hr after surgery, and was given in the morning, in principle, from the following day onwards. Lot number: S04045-6
Criteria for Evaluation	(Efficacy Primary Endpoint) The primary efficacy endpoint was the proportion of subjects who experienced at least one of the thromboembolic events listed below during the period from the start of treatment with the study drug to the venography at the end of the study treatment. (1) Lower extremity DVT confirmed by bilateral venography at the end of study treatment (2) Definite diagnosis of symptomatic PE (3) Symptomatic DVT confirmed before the venography at the end of study treatment (Safety Primary Endpoint) The primary safety endpoints were those listed below during the period from the start of study treatment to the day of the follow-up examination. (1) Incidence of major bleeding (2) Incidence of clinically relevant non-major bleeding
Statistical Method	(Analyses of the Primary Efficacy Endpoint) As the primary analysis, the dose-response relationship in the incidence ([Number of subjects with events / Number of subjects assessed] × 100, the same hereinafter) of thromboembolic event (at least one of either DVT,

	symptomatic PE, or symptomatic DVT) was verified using the Cochran-Armitage test, and the difference between the placebo group and each edoxaban group was verified using the Shirley-Williams multiple comparison. (Analyses of the Primary Safety Endpoint) For the incidence of major bleeding, the difference between the placebo group and each edoxaban group was calculated with the 95% CI, and paired comparisons between the placebo group and each edoxaban group were performed using the $\chi 2$ test. To examine the dose-response relationship, the incidence was analyzed using the Cochran-Armitage test. Paired comparisons among the edoxaban groups were also performed using the $\chi 2$ test. The incidence of major bleeding and the 95% CI were calculated by treatment group. These analyses were also performed for the incidence of clinically relevant non-major bleeding, and the total of major bleeding and clinically relevant non-major bleeding.
Summary - Conclusion	In the FAS, the incidence of thromboembolic events (at least one of either DVT, symptomatic PE, or symptomatic DVT) was 48.3% (43/89) in the placebo group, 29.5% (26/88) in the edoxaban 5 mg group, 26.1% (24/92) in the 15 mg group, 12.5% (11/88) in the 30 mg group, and 9.1% (8/88) in the 60 mg group. The incidence of thromboembolic events decreased with increasing edoxaban dose, and a dose-response relationship for the effect of edoxaban in VTE prevention was verified in patients undergoing TKR (Cochran-Armitage test; $P < 0.001$). The results also verified the superiority of each edoxaban regimen to placebo in he incidence of thromboembolic events, which was achieved even in the 5 mg group (Shirley-Williams multiple comparison; $P = 0.005$). The incidence of all-causality major bleeding was 1.0% (1/102) in the placebo group and 0.9% (1/106) in the edoxaban 60 mg group, with no major bleeding in the 5 mg, 15 mg, or 30 mg group. No dose-response relationship on the incidence was observed (Cochran-Armitage test, P =

	0.494). The incidence of all-causality clinically relevant non-major bleeding was 3.9% (4/102) in the placebo group, 2.9% (3/103) in the edoxaban 5 mg group, 4.7% (5/106) in the 15 mg group, 3.9% (4/103) in the 30 mg group, and 3.8% (4/106) in the 60 mg group. No dose-response relationship on the incidence was observed (Cochran-Armitage test, P = 0.456). Based on these results, it was concluded that the appropriate dosage regimen of edoxaban for VTE prevention in patients undergoing TKR was 30 mg once daily.
Date of Report	25 July, 2014