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 3 clinical study of DU-176b (non-valvular atrial fibrillation) -A Japanese, multicenter, open-label study of DU-176b in patients with non-valvular atrial fibrillation and severe renal impairment-
Investigators	13 investigators.
Study Centre(s)	13 sites.
Publication (reference)	N.A.
Studied Period	
Phase of Development	Phase III
Objectives	The study objective was to compare the safety and pharmacokinetics of edoxaban in non-valvular atrial fibrillation (NVAF) patients with severe renal impairment (SRI, 15 mL/min ≤ creatinine clearance (CL_{CR}) < 30 mL/min [excluding patients on hemodialysis]) at a dose of 15 mg once daily for 12 weeks with those in NVAF patients with normal renal function or mild renal impairment (Normal/MiRI, 50 mL/min ≤ CL_{CR}) at a dose of 30 mg or 60 mg once daily for 12 weeks.
Methodology	This study was a Japanese, multicenter, open-label, 3-parallel-group study of edoxaban in NVAF patients with SRI or Normal/MiRI. Subjects with SRI (the SRI 15-mg group) received 15 mg of edoxaban once daily. Subjects with Normal/MiRI were randomized to low-dose (the Normal/MiRI low-dose group) or high-dose (the Normal/MiRI high-dose group) of edoxaban in equal numbers. Subjects in the Normal/MiRI low-dose group received 30 mg of edoxaban once daily; subjects who had any dose adjustment factor received 15 mg of edoxaban once daily. Subjects in the Normal/MiRI high-dose group received 60 mg of edoxaban once daily; subjects who had any dose adjustment factor received 30 mg of edoxaban once daily.

Number of Patients (planned and analyzed)	Planned: 90 subjects (the SRI 15 mg group: 50 subjects; the Normal/MiRI low-dose group: 20 subjects; the Normal/MiRI high-dose group: 20 subjects) Safety Analyzed: 93 subjects (the SRI 15 mg group: 50 subjects; the Normal/MiRI low-dose group: 22 subjects; the Normal/MiRI high-dose group: 21 subjects) Pharmacokinetic Analyzed: 90 subjects (the SRI 15 mg group: 48 subjects; the Normal/MiRI low-dose group: 21 subjects; the Normal/MiRI high-dose group: 21 subjects)
Diagnosis and Main Criteria for Inclusion	The study enrolled patients with NVAF and SRI (15 mL/min ≤ CL_{CR} < 30 mL/min; CL_{CR} calculated by the Cockcroft-Gault formula), and patients with NVAF and Normal/MiRI (50 mL/min ≤ CL_{CR}). All patients had at least one of the risk factors for stroke ($CHADS_2$ score of at least 1 point), Patients aged 20 years or older
Test Product, Dose and Mode of Administration, Batch Number	Once daily for 12 weeks. Lot number: 15 mg tablet DU176F1T08T01B, 30 mg tablet DU176F1T07T02B
Duration of Treatment	12 weeks
Reference Therapy, Dose and Mode of Administration, Batch Number	N.A.
Criteria for Evaluation	(Safety Endpoint) (1) Incidence of adjudicated major bleeding or clinically relevant non-major bleeding (2) Incidence of any adjudicated bleeding events (3) Incidence of adjudicated major bleeding (4) Incidence of adjudicated clinically relevant non-major bleeding (5) Incidence of adverse events (6) Incidence of adverse drug reactions (Pharmacokinetic Endpoints) (1) Plasma DU-176 concentration (2) Plasma D21-2393 concentration
Statistical Method	(Analyses of the Safety Endpoint) Incidences and 95% CIs were calculated by treatment

	group (Analysis of Plasma Drug Concentrations) Descriptive statistics of plasma drug (DU-176 or D21-2393) concentrations were calculated by treatment group at each time point. Descriptive statistics of the ratio of the plasma D21-2393 concentration to the plasma DU-176 concentration ratio were also calculated by treatment group at each time point. Scatter plots showing the plasma drug concentration-time profile were prepared.
Summary - Conclusion	This study demonstrated that the plasma concentrations in the subjects with SRI (15 mL/min ≤ CL_{CR} < 30 mL/min) receiving 15 mg of edoxaban overlapped considerably with those concentrations in the subjects with Normal/MiRI (50 mL/min ≤ CL_{CR}) receiving the low dose (30 mg, or 15 mg with dose adjustment) or high dose (60 mg, or 30 mg with dose adjustment) of edoxaban. It was also demonstrated that administration of 15 mg of edoxaban for 12 weeks in patients with SRI did not result in a marked increase in bleeding compared to the low dose or high dose of edoxaban in patients with Normal/MiRI.
Date of Report	25 July, 2014