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Daiichi-Sankyo

Press Release

Daiichi Sankyo's Once-Daily Edoxaban Shows Comparable Efficacy and Superiority for the Principal Safety Endpoint Compared to Warfarin in a Phase 3 Study for the Treatment of Symptomatic VTE and Prevention of its Recurrence

- *Hokusai-VTE, the first global phase 3 double-blind study for once-daily edoxaban and the largest single comparative study for this patient population, achieves these results in a broad spectrum of VTE patients, including those with severe pulmonary embolism*
- *Efficacy and safety findings were consistent with the overall results for patients administered edoxaban 30 mg for renal impairment or low body weight*
- *Results from Hokusai-VTE presented during ESC Congress 2013 Hot Line session and published in the New England Journal of Medicine*

Tokyo, Japan, September 1, 2013 – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced results from the global phase 3 Hokusai-VTE study of 8,292 patients with either acute symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), or both. The study found that the investigational, oral, once-daily direct factor Xa-inhibitor edoxaban met the primary efficacy endpoint of non-inferiority compared to warfarin, following initial use of heparin in both arms, for the treatment and prevention of recurrent symptomatic venous thromboembolism (VTE). Once-daily edoxaban also demonstrated superiority compared to warfarin for the principal safety outcome of clinically relevant bleeding (the composite of major or clinically relevant non-major bleeding).[1] Results from Hokusai-VTE were presented today at the ESC Congress 2013 in Amsterdam and published online in the *New England Journal of Medicine*.

The Hokusai-VTE study was designed to reflect clinical practice using a flexible treatment duration of three to 12 months, including initial heparin treatment, in a broad spectrum of VTE patients, including those with severe PE. For the primary efficacy outcome, edoxaban demonstrated non-inferiority with a numerically lower incidence of recurrent symptomatic VTE compared to warfarin (3.2% vs. 3.5%, respectively) (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.70 to1.13; P<0.001 for non-inferiority).[1] Edoxaban was also found to be superior to warfarin for the pre-specified principal safety outcome of clinically relevant bleeding (8.5% vs. 10.3%, respectively) (HR, 0.81; 95% CI, 0.71 to 0.94; P=0.004 for superiority).[1]

In the Hokusai-VTE study, patient specific dosing was applied according to the study protocol. Edoxaban was dosed at 60 mg once-daily, except for those patients with clinical factors that commonly impact response to oral anticoagulants (renal impairment, low body weight, or concomitant use of certain p-glycoprotein inhibitors) who received edoxaban 30 mg according to the study protocol. The reduced dose of edoxaban was found to have an efficacy profile consistent with the overall study cohort, with fewer recurrent VTE events in patients receiving 30 mg edoxaban (n=733) compared to warfarin (n=719) (VTE recurrence of 3.0% vs. 4.2%; HR, 0.73; 95% CI, 0.42 to 1.26). Clinically relevant bleeding in patients receiving edoxaban 30 mg was significantly lower compared to warfarin (7.9% vs. 12.8%, respectively) (HR, 0.62; 95% CI, 0.44 to 0.86).[1]

Among patients with DVT (n=4,921), VTE recurrence was similar in the edoxaban and warfarin groups (3.4% vs. 3.3%, respectively) (HR, 1.02; 95% CI, 0.75 to 1.38), while the incidence of recurrent VTE among patients with PE (n=3,319) was numerically lower for patients treated with once-daily edoxaban compared to warfarin (2.8% vs. 3.9%, respectively) (HR, 0.73; 95% CI, 0.50 to 1.06). Additionally, in a sub-group analysis, patients with severe PE and evidence of right ventricular dysfunction (defined as NT pro-BNP $\geq$ 500 pg/mL, n=938) treated with edoxaban had a 48% lower risk of recurrent symptomatic VTE compared to warfarin (3.3% vs. 6.2%, respectively) (HR, 0.52; 95% CI, 0.28 to 0.98).[1]

“Hokusai-VTE was designed to include a broad range of VTE patients, including those with severe pulmonary embolism, and we are therefore pleased that the study found that edoxaban administered once-daily is as efficacious as warfarin for the prevention of recurrent symptomatic VTE while significantly reducing the risk of bleeding,” said Harry Büller, MD, PhD, Professor of Internal Medicine, Chairman of the Department of Vascular Medicine at the Academic Medical Center in Amsterdam, The Netherlands and Chairman of the Hokusai-VTE steering committee. “A promising finding was the sizeable reduction in recurrent symptomatic VTE among patients with severe pulmonary embolism who were treated with edoxaban.”

“We are excited about the results from the Hokusai-VTE study demonstrating that once-daily edoxaban may provide a new treatment option for a broad range of VTE patients. Daiichi Sankyo plans to submit New Drug Applications for edoxaban for VTE by the first quarter of 2014 in the US, Japan and Europe,” said Glenn Gormley, MD, PhD, Global Head of Research and Development and Senior Executive Officer, Daiichi Sankyo. “Daiichi Sankyo is committed to continuing the global development of edoxaban and looks forward to the presentation of the results from the phase 3 ENGAGE AF-TIMI 48 study in patients with atrial fibrillation at the 2013 American Heart Association Scientific Sessions in November.”

About Hokusai-VTE

Hokusai-VTE was a global, event-driven, randomized, double-blind, parallel-group phase 3 clinical study involving 8,292 patients in 439 clinical sites across 37 countries to evaluate once-daily edoxaban in patients with symptomatic DVT and/or PE.[1]

Patients were randomized to one of two different treatment groups. Both groups received open-label enoxaparin or unfractionated heparin for at least five days, and either warfarin or placebo (administered to edoxaban group), followed by double-blind edoxaban 60 mg (n=4,118) (edoxaban 30 mg for patients with renal impairment or low body weight or p-glycoprotein inhibitor use) or warfarin (n=4,122) for at least three months and up to a maximum of one year (duration of study treatment was determined by the investigator based on the patient's clinical features). Patients were followed for 12 months regardless of treatment duration to provide investigators with a better understanding of outcomes in clinical practice relative to an on-treatment analysis only.[1]

The primary efficacy outcome was the recurrence of symptomatic VTE, defined as the composite of recurrent symptomatic DVT, non-fatal symptomatic PE and fatal PE in patients during the 12-month study period. The principal safety outcome was clinically relevant bleeding (major or non-major) occurring during or within three days of interrupting or stopping study treatment. Secondary efficacy outcomes included the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE and all-cause mortality.[1]

The study is named after the famous Japanese artist and painter Katsushika Hokusai.

About Venous Thromboembolism

VTE is an umbrella term for two conditions, DVT and PE. DVT is a blood clot found anywhere in the deep veins of the legs, while PE occurs when part of a clot detaches and lodges in the pulmonary arteries, causing a potentially fatal condition.[2]

VTE is a major cause of morbidity and mortality worldwide with an annual incidence of approximately one per 1,000 in developed countries, including an estimated 430,000 PE events, 680,000 DVT events and 540,000 deaths each year in the EU.[3,4] In the U.S., it is currently estimated that more than 950,000 VTE events and approximately 300,000 VTE related deaths occur each year.[5,6] Thirty percent of people with VTE die within one month of diagnosis and about 20% of those with PE experience sudden death.[7]

About Edoxaban

Edoxaban is an investigational, oral, once-daily anticoagulant that specifically and reversibly inhibits factor Xa, which is an important factor in the coagulation system that leads to blood clotting.[8] The global edoxaban clinical trial program includes two phase 3 clinical studies, Hokusai-VTE and ENGAGE AF-TIMI 48 (**E**ffective a**N**ticoa**G**ulation with Factor X**A** Next **GE**neration in **A**trial **F**ibrillation), which are evaluating edoxaban, administered once-daily, for treatment and prevention of recurrence of venous thromboembolism (VTE) in patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE), and for the prevention of stroke and systemic embolic events (SEE) in patients with non-valvular atrial fibrillation, respectively.[9]

Edoxaban is currently approved only in Japan, since April 2011, for the prevention of VTE after major orthopedic surgery, and was launched in July 2011 under the brand name Lixiana®. Elsewhere, including Europe and the U.S., edoxaban is currently in phase 3 clinical development and has not been approved in any indication.[10] Results from the ENGAGE AF-TIMI 48 study will be presented at the American Heart Association Scientific Sessions on November 19th, 2013.

About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address the diversified, unmet medical needs of patients in both mature and emerging markets. While maintaining its portfolio of marketed pharmaceuticals for hypertension, hyperlipidemia, and bacterial infections, the Group is engaged in the development of treatments for thrombotic disorders and focused on the discovery of novel oncology and cardiovascular-metabolic therapies. Furthermore, the Daiichi Sankyo Group has created a "Hybrid Business Model," which will respond to market and customer diversity and optimize growth opportunities across the value chain. For more information, please visit: www.daiichisankyo.com.

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Forward-looking statements

This press release contains forward-looking statements and information about future developments in the sector, and the legal and business conditions of DAIICHI SANKYO, Co. Ltd. Such forward-looking statements are uncertain and are subject at all times to the risks of change, particularly to the usual risks faced by a global pharmaceutical company, including the impact of the prices for products and raw materials, medication safety, changes in exchange rates, government regulations, employee relations, taxes, political instability and terrorism as well as the results of independent demands and governmental inquiries that affect the affairs of the company. All forward-looking statements contained in this release hold true as of the date of publication. They do not represent any guarantee of future performance. Actual events and developments could differ materially from the forward-looking statements that are explicitly expressed or implied in these statements. DAIICHI SANKYO, Co. Ltd assume no responsibility for the updating of such forward-looking statements about future developments of the sector, legal and business conditions and the company.

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