

Press Release

Once-Daily Edoxaban Evaluated in Two Subgroup Analyses of East Asian Patients from the Largest Comparative Phase 3 Trials of a Novel Oral Anticoagulant

- *Subgroup analyses of East Asian populations from two phase 3 studies, ENGAGE AF-TIMI 48 and Hokusai-VTE, showed consistent results compared to the global study populations from these trials^{1,2,3,4}*
- *The results were presented during a late-breaking session at the Japanese Circulation Society 2014 Annual Scientific Meeting*
- *Daiichi Sankyo has filed for approval of once-daily edoxaban in Japan, the U.S. and the EU for non-valvular atrial fibrillation and symptomatic venous thromboembolism*

Tokyo, Japan, March 24, 2014 – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced late-breaking data from two pre-specified subgroup analyses of East Asian patients with non-valvular atrial fibrillation (NVAf) or venous thromboembolism (VTE) enrolled in two phase 3 edoxaban studies. The findings of the two subgroup analyses of 1,943 East Asian patients (Japan, China, Korea and Taiwan) enrolled in the ENGAGE AF-TIMI 48 study and 1,101 East Asian patients enrolled in the Hokusai-VTE study were consistent with the results from the global study populations, which demonstrated investigational edoxaban was comparable to warfarin for the prevention of stroke or systemic embolic events (SEE) in NVAf patients and for the treatment and prevention of VTE, respectively. The subgroup analyses also demonstrated findings consistent with the full study populations for the principal safety outcomes in both studies. The data were presented at the Japanese Circulation Society 2014 Annual Scientific Meeting in Tokyo, Japan.^{1,2,3,4}

In the subgroup analysis from the ENGAGE AF-TIMI 48 study, once-daily edoxaban was evaluated in two treatment strategies, a high-dose arm (60 mg or 30 mg dose reduced) and a low-dose arm (30 mg or 15 mg dose reduced), compared to warfarin in 1,943 East Asian patients with NVAf.¹ In both edoxaban treatment arms, the edoxaban dose was reduced by half for patients with clinical factors that were known to increase the risk of bleeding (renal impairment, low body weight or concomitant use of certain P-glycoprotein inhibitors).³ The edoxaban high-dose treatment arm had an annual incidence of stroke or SEE of 1.34% versus 2.62% for warfarin (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.31 to

0.90; p=0.02), and resulted in fewer major bleeding events (2.86% vs. 4.80% per year, respectively) (HR, 0.61; 95% CI, 0.41 to 0.89; p=0.011). The edoxaban low-dose treatment arm had an annual incidence of stroke or SEE of 2.52% versus 2.62% for warfarin (HR, 0.98; 95% CI, 0.63 to 1.54; p=0.93), and resulted in fewer major bleeding events (1.59% vs. 4.80% per year, respectively) (HR, 0.34; 95% CI, 0.21 to 0.54; p<0.001).¹

In the subgroup analysis from Hokusai-VTE, which evaluated once-daily edoxaban in patients with either acute symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), or both, 1,101 East Asian patients treated with edoxaban 60 mg (or a patient specific dose of edoxaban 30 mg for patients with renal impairment or low body weight or p-glycoprotein inhibitor use) had a numerically lower incidence of recurrent symptomatic VTE compared to warfarin (2.8% vs. 4.5%, respectively) (HR, 0.64; 95% CI, 0.34 to 1.19; p=0.1601). Once-daily edoxaban also had a lower incidence of clinically relevant bleeding (major or non-major) compared to warfarin (9.9% vs. 17.3%, respectively) (HR, 0.56; 95% CI, 0.40 to 0.78; p<0.001).² The Hokusai-VTE study was designed to reflect clinical practice using a flexible treatment duration of three to 12 months, including initial heparin treatment.^{2,4}

“The ENGAGE AF-TIMI 48 and Hokusai-VTE trials enrolled large numbers of patients from all regions of the world to advance the understanding of how edoxaban works in a heterogeneous group of patients,” said Glenn Gormley, MD, PhD, Senior Executive Officer and Global Head of Research and Development, Daiichi Sankyo Co., Ltd. and President and CEO of Daiichi Sankyo, Inc. in the United States. “The findings from these subgroup analyses further our understanding of edoxaban in East Asian populations, and were consistent with the global patient populations studied.”

About ENGAGE AF-TIMI 48

ENGAGE AF-TIMI 48 (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation) was a three-arm, randomized, double-blind, double-dummy, global phase 3 clinical trial comparing once-daily edoxaban with warfarin in 21,105 patients with NVAF at moderate-to-high risk of thromboembolic events at 1,393 centers in 46 countries. ENGAGE AF-TIMI 48 compared two edoxaban treatment strategies, a high-dose arm (60 mg or 30 mg dose reduced) once-daily and a low-dose arm (30 mg or 15 mg dose reduced) once-daily, with warfarin in patients with NVAF, including 1,943 East Asian patients, for a median of 2.8 years. Both treatment strategies prospectively evaluated a patient specific dose reduction of 50% for patients with known factors to increase the risk of bleeding (renal impairment, low body weight or concomitant use of certain P-glycoprotein inhibitors). This represents the largest and longest trial with a novel anticoagulant in patients with AF performed to date.³

The full results were presented at the AHA Scientific Sessions 2013 in Dallas and published in the *New England Journal of Medicine*, demonstrating that edoxaban met the primary efficacy endpoint of non-inferiority compared to warfarin for the prevention of stroke or SEE in patients with NVAF. Once-daily edoxaban also demonstrated significant reductions in major bleeding compared to warfarin, achieving superiority for the principal safety endpoint.³

The edoxaban high-dose treatment arm had an annual incidence of stroke or SEE of 1.18% versus 1.50% for warfarin (HR, 0.79; 97.5% CI, 0.63 to 0.99, $p < 0.001$ for non-inferiority), and significantly reduced major bleeding by 20% (2.75% vs. 3.43% per year, respectively) (HR, 0.80; 95% CI, 0.71 to 0.91; $p < 0.001$ for superiority). The edoxaban low-dose treatment arm had an annual incidence of stroke or SEE of 1.61% versus 1.50% for warfarin (HR, 1.07; 97.5% CI, 0.87 to 1.31; $p = 0.005$ for non-inferiority), and significantly reduced major bleeding by 53% (1.61% vs. 3.43% per year, respectively) (HR, 0.47; 95% CI, 0.41 to 0.55; $p < 0.001$ for superiority).³

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 either acute symptomatic DVT, PE or both. The Hokusai-VTE study was designed to reflect clinical practice using a flexible treatment duration of three to 12 months, including initial use of heparin, the proven global standard of care, in both arms, in a broad spectrum of VTE patients, including 1,101 East Asian patients. Following treatment with open-label enoxaparin or unfractionated heparin for at least five days, and either warfarin or placebo (administered to edoxaban group), patients were randomized to receive either edoxaban 60 mg (patients with renal impairment or low body weight or p-glycoprotein inhibitor use were administered a patient specific dose of 30 mg) or warfarin 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).⁴

The full results were presented at the ESC Congress 2013 in Amsterdam and published in the *New England Journal of Medicine*, demonstrating that edoxaban met the primary efficacy endpoint of non-inferiority, with a numerically lower incidence of recurrent symptomatic VTE compared to warfarin (3.2% vs. 3.5%, respectively) (HR, 0.89; 95% CI, 0.70 to 1.13; $p < 0.001$ for non-inferiority) following initial use of heparin in both arms. Recurrent symptomatic VTE was defined as the composite of recurrent symptomatic DVT, non-fatal symptomatic PE and fatal PE in patients during the 12-month study period.

Once-daily 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) occurring during or within three days of interrupting or stopping study treatment.⁴

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

About Atrial Fibrillation

AF is a condition in which the heartbeat is rapid and irregular, and can potentially lead to a stroke. AF is a common condition, affecting approximately 2.3-3.4% of people in developed nations.⁵ Stroke is the second most common cause of death worldwide, responsible for approximately 6.2 million deaths each year.⁶ Compared to those without AF, people with the arrhythmia have a 3-5 times higher risk of stroke.⁵ Strokes due to AF are nearly twice as likely to be fatal than strokes in patients without AF at 30 days⁷ and have poorer prognosis than non-AF related strokes, with a 50% increased risk of remaining disabled at three months.⁸ AF is a major cause of mortality in several East Asian countries, with a relative risk of all-cause mortality of approximately 1.88-fold in Japan⁹ and 2.23-fold in Taiwan.¹⁰ The overall prevalence of stroke among Chinese and Japanese patients with AF generally ranges from 13-14%.^{11,12} The incidence of AF among the Asian population is increasing.¹³ For example, the number of people in Japan with AF was estimated to be more than 800,000 in 2010, and by 2050 that number is projected to increase to an estimated 1 million.¹⁴

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.¹⁵ In the Asian population, VTE is a major cause of inpatient mortality with estimated rates of 7.3% and 23.8% for DVT and PE respectively.¹⁶ In Japan, the calculated number of new patients with PE per year doubled from 1996 to 2006.¹⁷ In Taiwan, the incidence of VTE is 15.9 per 100,000 and its recurrence rate is 5.1% per year.¹⁸ In China, the overall incidence of DVT and PE was 17.1 and 3.9 per 100,000 between 2000-2001.¹⁹ The incidence of VTE among the Asian population is increasing.²⁰ For example, in Korea, annual incidences of VTE, DVT and PE per 100,000 has increased significantly from 8.83, 3.91 and 3.74 in 2004 to 13.8, 5.31 and 7.01 in 2008.²¹

About Edoxaban

Edoxaban is an investigational, oral, once-daily anticoagulant that specifically inhibits factor Xa, which is an important factor in the coagulation system that leads to blood clotting.²² The global edoxaban clinical trial program includes two phase 3 clinical studies, Hokusai-VTE and ENGAGE AF-TIMI 48 (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation). The results from these trials form the basis of regulatory filings for edoxaban for symptomatic VTE in patients with DVT and/or PE, and for non-valvular atrial fibrillation, respectively.^{4,3} Edoxaban is currently under regulatory review in Japan, the U.S. and EU for these indications.

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.²³

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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