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Press Release

Daiichi Sankyo´s Once-Daily Edoxaban Meets Primary Efficacy Endpoint for Stroke Prevention and Superiority for the Principal Safety Endpoint Compared to Warfarin for Patients with Atrial Fibrillation in a Phase 3 Clinical Trial

- *Once-daily edoxaban, evaluated in two treatment arms (60 mg and 30 mg), achieved the primary endpoint of non-inferior efficacy versus warfarin in the prevention of stroke or systemic embolism*
- *Rates of major bleeding were significantly reduced with edoxaban compared to warfarin*
- *Efficacy and safety findings for patients who received a dose reduction for renal impairment or low body weight were consistent with the overall study results*
- *ENGAGE AF-TIMI 48, the largest and longest single comparative clinical trial of stroke prevention in atrial fibrillation, presented at a late-breaking clinical trials session at the American Heart Association Scientific Sessions 2013 and published in the New England Journal of Medicine*

Dallas, Texas (November 19, 2013) and Tokyo, Japan (November 20, 2013) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) announced results today from the phase 3 ENGAGE AF-TIMI 48 study.[1] This clinical trial found that the investigational, oral, once-daily direct factor Xa-inhibitor edoxaban met the primary efficacy endpoint of non-inferiority compared to warfarin for the prevention of stroke or systemic embolic events (SEE) in patients with non-valvular atrial fibrillation (NVAF). Once-daily edoxaban also demonstrated significant reductions in major bleeding compared to warfarin, achieving superiority for the principal safety endpoint. Results from ENGAGE AF-TIMI 48 were presented today as a late-breaking clinical trial at the American Heart Association (AHA) Scientific Sessions 2013 in Dallas and published online in the *New England Journal of Medicine*.[2]

ENGAGE AF-TIMI 48 compared two edoxaban treatment arms, 60 mg and 30 mg, with warfarin in 21,105 patients with NVAF for a median of 2.8 years. This represents the largest and longest trial with a novel anticoagulant in patients with atrial fibrillation performed to date. The edoxaban 60 mg treatment arm had an annual incidence of stroke or SEE of 1.18% versus 1.50% for warfarin (hazard ratio [HR], 0.79; 97.5% confidence interval [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 30 mg 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).[2]

In ENGAGE AF-TIMI 48, patient-specific dosing was applied according to the study protocol. In both edoxaban treatment arms, the edoxaban dose was halved 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).[1, 2] Patients receiving a reduced edoxaban dose in the 60 mg treatment arm had an annual incidence of stroke or SEE of 2.32% versus 2.68% for warfarin and a significantly reduced major bleeding incidence of 3.05% versus 4.85%. Patients receiving a reduced edoxaban dose in the 30 mg treatment arm had an annual incidence of stroke or SEE of 3.14% versus 2.68% for warfarin and a significantly reduced major bleeding incidence of 1.50% versus 4.85%.[2]

“The results from the ENGAGE AF-TIMI 48 trial showed that edoxaban may provide a new treatment option for the prevention of stroke or systemic embolic events that demonstrates comparable efficacy to warfarin, while significantly reducing the risk of major bleeding. In addition, we identified an appropriate dose regimen for patients with clinical factors such as renal impairment and low body weight,” said Robert Giugliano, MD, SM, FAHA, FACC, Senior Investigator with the TIMI Study Group, Physician Cardiovascular Medicine, Brigham and Women's Hospital, Associate Professor of Medicine, Harvard Medical School, and Co-Global Lead Investigator of the ENGAGE AF-TIMI 48 trial. “In conducting this landmark trial we sought to provide clinicians with robust data, evident by the trial size and follow-up, high percentage of time in therapeutic range for the warfarin treatment arm, and very low rate of missing data. In addition, we specifically designed a comprehensive transition plan to protect patients from the undue risk of stroke and bleeding when switching to open-label anticoagulation at the end of the trial.”

“The edoxaban clinical trial program, the largest in the history of Daiichi Sankyo, has now yielded positive data for edoxaban in two major diseases, stroke prevention in atrial fibrillation and treatment of acute venous thromboembolism,” said Glenn Gormley, MD, PhD, Global Head of Research and Development and Senior Executive Officer, Daiichi Sankyo Company, Ltd. and Executive Chairman of Daiichi Sankyo, Inc. in the United States (US). “Based on the findings from ENGAGE AF-TIMI 48 and Hokusai-VTE, we look forward to submitting New Drug Applications for edoxaban in both indications by the first quarter of 2014 in the US, Japan and Europe.”

The annual incidence of hemorrhagic stroke was 0.47% for warfarin compared to 0.26% for edoxaban 60 mg (HR, 0.54; 95% CI, 0.38 to 0.77; p<0.001) and 0.16% for edoxaban 30 mg (HR, 0.33; 95% CI, 0.22 to 0.50; p<0.001). The annual incidence of ischemic stroke was 1.25% for warfarin compared to 1.25% in the edoxaban 60 mg treatment arm (HR, 1.00; 95% CI, 0.83 to 1.19; p=0.97) and 1.77% per year for the edoxaban 30 mg treatment arm (HR, 1.41; 95% CI, 1.19 to 1.67; p<0.001).[2]

The annual incidence of intracranial hemorrhage was 0.39% for patients in the edoxaban 60 mg treatment arm (HR, 0.47; 95% CI, 0.34 to 0.63; p<0.001) and 0.26% for the edoxaban 30 mg treatment arm (HR, 0.30; 95% CI, 0.21 to 0.43; p<0.001) compared to 0.85% for warfarin. Fatal bleeds occurred at an annual rate of 0.21% in the edoxaban 60 mg treatment arm (HR, 0.55; 95% CI, 0.36 to 0.84; p=0.006) and 0.13% for the edoxaban 30 mg treatment arm (HR, 0.35; 95% CI, 0.21 to 0.57; p<0.001) compared to 0.38% for warfarin.[2]

Annualized rates for the key secondary composite endpoint of stroke, SEE and cardiovascular death were 4.43% with warfarin, 3.85% with edoxaban 60 mg (p=0.005) and 4.23% with edoxaban 30 mg (p=0.32). Edoxaban was also associated with reduced annualized cardiovascular mortality rates versus warfarin: the incidence was 3.17% for warfarin, 2.74% (p=0.013) for the edoxaban 60 mg treatment arm and 2.71% (p=0.008) for the edoxaban 30 mg treatment arm. The primary net clinical outcome (defined in the study protocol as the composite of death, stroke, SEE or major bleeding) was 8.11% per year for warfarin, 7.26% per year for the edoxaban 60 mg treatment arm (p=0.003) and 6.79% per year for the edoxaban 30 mg treatment arm (p<0.001).[2]

About ENGAGE AF-TIMI 48

ENGAGE AF-TIMI 48 (**E**ffective a**N**ticoa**G**ulation with factor x**A** next **GE**neration in **A**trial **F**ibrillation) 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.[2]

Patients were randomized (1:1:1) to receive warfarin (n=7,036), edoxaban 60 mg (n=7,035) or edoxaban 30 mg (n=7,034). Edoxaban dosage was reduced by half if any of the following was present at randomization or during the course of the study: creatinine clearance 30-50 mL/min, body-weight ≤ 60 kg, or concomitant verapamil, quinidine or dronedarone (standard dosing was resumed if the concomitant drug was discontinued and no other dose reduction factors were present). The primary efficacy outcome was the time to first adjudicated stroke or SEE. The principal safety outcome was adjudicated major

bleeding. Complete information on the primary endpoint was ascertained for 99.5% of the total 56,346 patient-years of potential follow-up, with only one patient lost to follow-up. Warfarin therapy was proactively monitored throughout the trial, resulting in a median time within therapeutic range (TTR) of 68.4%. Adverse event (excluding bleeding) and discontinuation rates were similar among the three treatment groups.[2]

ENGAGE AF-TIMI 48 implemented a unique, pre-specified plan to transition patients to open-label anticoagulation at the end of the trial, which resulted in a low and evenly distributed number of events post-discontinuation of study therapy. In the 30 days following the transition, the number of patients experiencing stroke or SEE was the same in all three treatment groups (n=7), while major bleeding occurred in 11 patients in the warfarin group compared to 10 and 18 patients in the edoxaban 60 mg and 30 mg treatment arms, respectively. These results demonstrate that the transition plan was effective in preventing undue risk of excessive stroke / SEE for edoxaban-treated subjects transitioning to a vitamin K antagonist (VKA) or a novel oral anticoagulant.[2]

About Atrial Fibrillation

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 1-2% of people in developed nations.[3] Stroke is the second most common cause of death worldwide, responsible for approximately 6.2 million deaths each year.[4] Compared to those without AF, people with the arrhythmia have a 3-5 times higher risk of stroke.[3] Strokes due to AF are nearly twice as likely to be fatal than strokes in patients without AF[5] and have poorer prognosis than non-AF related strokes with a 50% increased risk of remaining disabled at three months.[6]

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.[7] The global edoxaban clinical trial program includes two phase 3 clinical trials, Hokusai-VTE[8] and ENGAGE AF-TIMI 48 (**E**ffective a**N**ticoa**G**ulation with Factor X**A** Next **GE**neration in **A**trial **F**ibrillation)[1,2], 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.[1,2,8]

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 US, edoxaban is currently in phase 3 clinical development and has not been approved in any indication.[9] Results from the Hokusai-VTE clinical trial were presented at the European Society of Cardiology Congress on September 1, 2013 and published in the *New England Journal of Medicine*.[8,9]

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

References

1. Ruff et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J. 2010;160:635-41.
2. Giugliano, RP et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2013.
3. Ball, J et al. Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century. Int J Cardiol. 2013;167:1807–24.
4. World Health Organization. The top 10 causes of death. July 2013. Available at: who.int/mediacentre/factsheets/fs310/en/. [Last accessed: October 2013].
5. Lin, H et al. Stroke Severity in Atrial Fibrillation. Stroke. 1996;27:1760–1764.
6. Lamassa, M et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). Stroke. 2001;32:392–8.
7. Ogata, K et al. Clinical Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of the Novel Factor Xa Inhibitor Edoxaban in Healthy Volunteers. *J Clin Pharmacol*. 2010;50:743-753.
8. Büller, H et al. Edoxaban versus Warfarin for the treatment of Symptomatic Venous Thromboembolism. *N Engl J Med*. 2013;369:1406-15.
9. Daiichi Sankyo press release - Daiichi Sankyo Launches LIXIANA® (edoxaban), a Direct Oral Factor Xa Inhibitor, in Japan for the Prevention of Venous Thromboembolism after Major Orthopaedic Surgery. 19 July 2011. Available at: http://www.daiichisankyo.com/news/detail/004123.html. [Last accessed: October 2013].