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Press Release

Subgroup Analysis of ENGAGE AF-TIMI 48 Explores the Relationship Between Edoxaban Dose, Concentration, Anti-Factor Xa Activity and Outcomes

Results presented during ESC Congress 2014 Clinical Trial Update Hot Line session

Barcelona, Spain, September 2, 2014 – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced data from a subgroup analysis of the phase 3 ENGAGE AF-TIMI 48 study, that explores the relationship between edoxaban dose, concentration and anti-factor Xa activity in patients with non-valvular atrial fibrillation (NVAF). The analysis also compared rates of major bleeding and efficacy outcomes [stroke and systemic embolic events (SEE)] of edoxaban versus warfarin, stratified by dose reduction status.

The ENGAGE AF-TIMI 48 study compared two once-daily edoxaban treatment strategies, a high-dose regimen (60 mg or 30 mg dose-reduced) and a low-dose regimen (30 mg or 15 mg dose-reduced), with warfarin for a median of 2.8 years. Of patients randomized to edoxaban, 25.4% were dose reduced based on pre-specified clinical factors known to potentially increase the risk of bleeding due to higher drug exposure [creatinine clearance 30-50 mL/min, body weight $\leq$ 60 kg, or concomitant use of certain P-glycoprotein inhibitors (verapamil, quinidine)]. Regardless of treatment received (edoxaban or warfarin), patients who met pre-specified clinical criteria for dose reduction had higher rates of stroke or SEE and major bleeding.[1]

In patients who were eligible for inclusion in this subgroup analysis, trough edoxaban concentration was measured in 6,780 patients and anti-factor Xa activity was measured in 2,865 patients. A 4-fold edoxaban dose range (15 mg-60 mg) was associated with a 3-fold gradient of the mean edoxaban trough concentration and a 2.4-fold gradient of mean anti-factor Xa activity.[1]

Edoxaban 50% dose reduction in selected patients with NVAF resulted in a decrease in mean edoxaban trough concentration by 29% and 35%, and a decrease in mean anti-factor Xa activity by 25% and 20% in the high-dose and low-dose regimens, respectively.[1]

The pre-specified analysis found that in the high-dose regimen of edoxaban, compared with warfarin, the relative risk reduction of stroke or SEE observed in patients receiving 60 mg (hazard ratio [HR],

0.78; 95% confidence interval [CI], 0.61 to 0.99) was consistent with that seen in patients receiving dose-reduction to 30 mg (HR, 0.81; CI, 0.58 to 1.13) (edoxaban p-interaction=0.85). A numerically lower incidence of major bleeding was observed in patients receiving edoxaban 60 mg compared to warfarin (HR 0.88; 95% CI, 0.76 to1.03) and in patients receiving dose reduced edoxaban 30 mg compared to warfarin (HR 0.63; 95% CI, 0.50 to 0.81), with a greater relative reduction seen in the dose reduced 30 mg arm (edoxaban p-interaction=0.02).[1]

In the low-dose regimen of edoxaban, compared to warfarin, the relative risk of stroke or SEE observed in patients receiving 30 mg (HR, 1.07; 95% CI, 0.86 to 1.34) was consistent with that seen in patients receiving dose-reduction to 15 mg (HR, 1.07; 95% CI, 0.79 to 1.46) (edoxaban p-interaction=0.99). A lower incidence of major bleeding was observed in patients receiving edoxaban 30 mg compared to warfarin (HR, 0.55; 95% CI, 0.46 to 0.65) and in patients receiving dose reduced edoxaban 15 mg compared to warfarin (HR, 0.31; 95% CI, 0.23 to 0.42), with a greater relative reduction seen in the dose reduced 15 mg arm (edoxaban p-interaction=0.002).[1]

“This is the first analysis of a novel oral anticoagulant that evaluates edoxaban dose, concentration, anti-factor Xa activity and the relationship with efficacy and bleeding outcomes,” said Christian Ruff, MD, MPH, Investigator, TIMI Study Group, Associate Physician, Brigham and Women’s Hospital, Assistant Professor of Medicine, Harvard Medical School, Boston, MA. “As part of the ENGAGE AF-TIMI 48 trial, we administered a reduced edoxaban dose to patients with pre-specified clinical factors known to increase the risk of bleeding due to higher drug exposure. This analysis showed that while edoxaban concentrations and anti-factor Xa activity were decreased in these patients, the rates of stroke or SEE were consistent with those who did not receive a dose reduction, with greater relative reductions in bleeding compared to warfarin.”

“The findings from this exploratory analysis are interesting, as they provide additional insights on how edoxaban dose reduction impacted treatment concentration, anti-factor Xa activity and outcomes in patients in the ENGAGE AF-TIMI 48 study,” said Mahmoud Ghazzi, MD, PhD, Executive Vice President and Global Head of Development for Daiichi Sankyo.

These analyses were performed using paired measurements of edoxaban concentration and anti-factor Xa activity at a single point in time (one month post-randomization) in a subset of patients from the

ENGAGE AF-TIMI 48 trial. As this was an exploratory analysis, there are limitations to correlating the finding of the sub-study with the overall clinical outcomes of ENGAGE AF-TIMI 48 and the results may not be representative of the entire population.

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. This represents the largest and longest trial with a novel anticoagulant in patients with AF performed to date.[2]

The full results, which were presented at the American Heart Association Scientific Sessions 2013 in Dallas and published in the *New England Journal of Medicine*, demonstrated that edoxaban met the primary efficacy endpoint of non-inferiority compared to warfarin for the prevention of stroke or SEE in patients with NVAF. The data from ENGAGE AF-TIMI 48 provided the basis for regulatory filings in the EU, Japan and the U.S.[2]

The edoxaban high-dose regimen 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 regimen 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, ischemic stroke was evaluated as a component of the primary endpoint, overall incidence of stroke or SEE. The annualized ischemic stroke event rate for the warfarin treatment arm was 1.25% (235 total events) compared with 1.25% for the edoxaban high-dose treatment arm (236 total events) (HR, 1.00; 95% CI, 0.83 to 1.19; $p=0.97$) and 1.77% for the edoxaban low-dose treatment arm (333 total events) (HR, 1.41; 95% CI, 1.19 to 1.67; $p<0.001$).[2]

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.[3] AF affects approximately 6 million people in the EU,[4] approximately 6.1 million people in the U.S.,[5] approximately 1.5 million people in Brazil,[6] and more than 800,000 people in Japan.[7] Stroke due to all causes is the second most common cause of death worldwide, responsible for approximately 6.2 million deaths each year.[8] 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 at 30 days[9] and have poorer prognosis than non-AF related strokes, with a 50% increased risk of remaining disabled at three months.[10]

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.[11] 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 included nearly 30,000 patients combined. The results from these trials form the basis of regulatory filings for edoxaban for symptomatic venous thromboembolism (VTE) in patients with deep vein thrombosis and/or pulmonary embolism, and for the prevention of stroke in NVAF, respectively.[2,12] 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 has not been approved in any indication.[13]

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, dyslipidemia and bacterial infections used by patients around the world, the Group has also launched treatments for thrombotic disorders and is building new product franchises. Furthermore, Daiichi Sankyo research and development is focused on bringing forth novel therapies in oncology and cardiovascular-metabolic diseases,

including biologics. The Daiichi Sankyo Group has created a "Hybrid Business Model," to 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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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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