

# Press Release

# ENSURE-AF Data Support the Efficacy and Safety Profile of Daiichi Sankyo's Once-Daily LIXIANA<sup>®</sup> in Patients with Atrial Fibrillation Undergoing Cardioversion

- ENSURE-AF is the largest clinical trial of a non-vitamin K antagonist oral anticoagulant in patients with non-valvular atrial fibrillation who undergo electrical cardioversion
- ENSURE-AF is a **P**rospective, **R**andomized, **O**pen-Label, **B**linded Endpoint evaluation (PROBE), parallel-group phase 3b study, evaluating the efficacy and safety of once-daily edoxaban versus enoxaparin/warfarin in patients undergoing electrical cardioversion
- The results demonstrate that LIXIANA<sup>®</sup> may be an effective and safe alternative to conventional treatment with enoxaparin and a VKA (vitamin K antagonist), and may allow prompt cardioversion to be performed with TEE (transoesophageal echocardiography)
- *Results from the ENSURE-AF study were presented during the ESC Congress 2016 Hot Line session and the full results are published in The Lancet*

Tokyo, Japan (August 30, 2016) – Daiichi Sankyo Company, Limited (hereafter "Daiichi Sankyo") today announced results from the global phase 3b ENSURE-AF study of 2,199 patients with non-valvular atrial fibrillation (NVAF) undergoing electrical cardioversion (low-energy shocks to trigger normal heart rhythm). The study demonstrated that oral, once-daily edoxaban (brand name; LIXIANA<sup>®</sup>) met the study's primary endpoints, demonstrating comparable efficacy and safety to well-managed enoxaparin/warfarin (mean time in therapeutic range on warfarin was 70.8%) for the prevention of stroke and other blood clot complications.<sup>1</sup> Results from ENSURE-AF were presented today during a Hot Line session and late-breaking oral presentation at the ESC Congress 2016 in Rome, and published online in *The Lancet*.

"The results of ENSURE-AF show that once-daily edoxaban may be a viable treatment option for NVAF patients undergoing cardioversion, as demonstrated by the largest prospective dataset for a non-vitamin K antagonist oral anticoagulant in this clinical setting to date," said Andreas Goette, MD, Chief Physician, St. Vincenz-Hospital Paderborn, Germany, Department of Cardiology and Intensive Care Medicine and

principal study investigator. "These results may have important clinical implications for newly diagnosed non-anticoagulated AF patients undergoing cardioversion. According to the study protocol, a newly diagnosed non-anticoagulated AF patient was started on edoxaban, and the cardioversion procedure was scheduled as early as two hours following the start of treatment when applying a TEE-guided approach."

ENSURE-AF is a PROBE parallel group study designed to evaluate the efficacy and safety of once-daily edoxaban versus enoxaparin/well-managed warfarin in patients with NVAF undergoing electrical cardioversion. For the primary efficacy outcome evaluating the composite of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality, edoxaban demonstrated a similar incidence compared to enoxaparin/warfarin (0.5% vs. 1.0%, respectively) (odds ratio [OR], 0.46; 95% confidence interval [CI], 0.12 to 1.43). The main difference between the treatment groups was driven by cardiovascular mortality, with one event in the edoxaban group and five events in the enoxaparin/warfarin group (0.1% vs. 0.5%, respectively).<sup>1,2</sup>

For the combined principal safety outcome of the incidence of major and clinically-relevant non-major (CRNM) bleeding, events occurred in 1.5% of patients in the edoxaban group and 1.0% in the enoxaparin/warfarin group (OR, 1.48; 95% CI, 0.64 to 3.55). The difference was statistically non-significant. The incidence of major bleeding was numerically lower in the edoxaban group compared to the warfarin group (0.3% vs. 0.5%, respectively) (OR: 0.61; 95% CI, 0.09 to 3.13). No intracranial bleedings were reported in the study in either of the treatment groups. No fatal bleeding was reported in the edoxaban group vs. one patient in the enoxaparin/warfarin group.<sup>1,2</sup>

The result for the net clinical outcome (composite of stroke, systemic embolic event, myocardial infarction, cardiovascular mortality, and major bleeding) was 0.7% in the edoxaban group and 1.4% in the enoxaparin/warfarin group (OR=0.50; 95% CI, 0.19–1.25) during the overall study period. Of note, the trial was not adequately powered to demonstrate statistical differences for efficacy or safety endpoints, but provides further insights on the use of edoxaban in the setting of electrical cardioversion of NVAF.<sup>1,2</sup>

In the ENSURE-AF study, patients were stratified according to cardioversion approach (TEE or non-TEE), a patient's prior experience taking anticoagulants at the time of randomization (i.e. anticoagulantexperienced or naïve), and edoxaban dose (60 mg once-daily or reduced 30 mg once-daily). Patients were randomized in a 1:1 ratio to two treatment groups within each stratum. Edoxaban was dosed at 60 mg once-daily. The dose was reduced to edoxaban 30 mg once-daily for those patients if one or more factors (renal impairment, low body weight, or concomitant use of certain P-glycoprotein inhibitors) were present. Patients in the enoxaparin/warfarin group received optimized standard of care such that those with International Normalized Ratio (INR) <2 began treatment with a minimum of one dose each of enoxaparin and warfarin before cardioversion and continued anticoagulation until therapeutic range (INR  $\geq$ 2) was achieved. Enoxaparin was discontinued after a therapeutic range was obtained. The efficacy and safety outcomes were consistent to the overall study cohort independent of TEE-guided strategies for cardioversion, prior anticoagulation naïve status.<sup>1</sup>

"We are pleased with the results from ENSURE-AF, which provide additional scientific information about the use of once-daily edoxaban for peri-cardioversion management of patients with atrial fibrillation," said Hans Lanz, MD, Executive Director, Global Medical Affairs, Edoxaban. "Daiichi Sankyo is committed to expanding the scientific knowledge about edoxaban. The results from ENSURE-AF represent an important step in further understanding the use of edoxaban in cardiovascular patients in critical need."

#### **About ENSURE-AF**

(EdoxabaN vs. warfarin in subjectS UndeRgoing cardiovErsion of AtrialFibrillation)

ENSURE-AF is a **P**rospective, **R**andomized, **O**pen-Label, **B**linded **E**ndpoint evaluation (PROBE), parallel-group phase 3b study, evaluating the efficacy and safety of once-daily edoxaban versus enoxaparin/warfarin in patients undergoing electrical cardioversion. The primary efficacy endpoint was the composite of stroke, systemic embolism, myocardial infarction and cardiovascular mortality. A total of 2,199 non-valvular atrial fibrillation patients undergoing electrical cardioversion were enrolled at 239 clinical sites across North America and Europe. Patients were randomized to receive edoxaban 60 mg (or a reduced dose of edoxaban 30 mg for specific patients with renal impairment or low body weight or P-glycoprotein inhibitor use) or enoxaparin/warfarin for 28-49 days.<sup>1</sup>

#### **About Atrial Fibrillation**

AF is a condition where the heart beats irregularly and rapidly. When this happens, blood can pool and thicken in the chambers of the heart causing an increased risk of blood clots. These blood clots can break off and travel through the blood stream to the brain (or sometimes to another part of the body), where they have the potential to cause a stroke.<sup>3</sup>

AF is the most common type of heart rhythm disorder, and is associated with substantial morbidity and mortality.<sup>4</sup> Compared to those without AF, people with the arrhythmia have a 3-5 times higher risk of stroke.<sup>5</sup> One in five of all strokes are as a result of AF.<sup>6</sup>

#### About Edoxaban

Edoxaban is an oral, once-daily, direct factor Xa (pronounced "Ten A") inhibitor. Factor Xa is one of the key components responsible for blood clotting, so inhibiting this makes the blood thin and less prone to clotting.

# About Extensive Clinical Research Program for Edoxaban

Daiichi Sankyo is committed to expanding scientific knowledge about edoxaban, as demonstrated through our research programs evaluating its use in a broad range of cardiovascular conditions, patient types and clinical settings in atrial fibrillation (AF) and venous thromboembolism (VTE). The extensive edoxaban research program include multiple RCTs(randomized, controlled trials), registries and non-interventional studies, with the goal of generating new clinical and real-world-data regarding its use in AF and VTE populations. Daiichi Sankyo expects that more than 100,000 patients will participate in the edoxaban clinical research program, including completed, ongoing and future research.

The RCTs include:

- ENSURE-AF (EdoxabaN vs. warfarin in subjectS UndeRgoing cardiovErsion of Atrial Fibrillation), in AF patients undergoing electrical cardioversion;
- ENTRUST-AF PCI (EdoxabaN TReatment versUS VKA in paTients with AF undergoing PCI), in AF patients undergoing percutaneous coronary intervention;
- Hokusai-VTE Cancer (Edoxaban in Venous Thromboembolism Associated with Cancer), in patients with cancer and an acute VTE event.

In addition, global and regional registry studies will provide important real-world-data about the use of edoxaban and other oral anticoagulants in everyday practice, and include:

- ETNA-AF (Edoxaban Treatment in routiNe clinical prActice in patients with non valvular Atrial Fibrillation);
- ETNA-VTE (Edoxaban Treatment in routiNe clinical prActice in patients with Venous ThromboEmbolism);
- EMIT-AF/VTE (Edoxaban Management In diagnostic and Therapeutic procedures-AF/VTE);
- Prolongation PREFER in AF (PREvention oF thromboembolic events European Registry) in patients with AF.

We are committed to adding to the scientific body of knowledge around edoxaban in a variety of AF and VTE patients, including those who are vulnerable.

#### About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address diversified, unmet medical needs of patients in both mature and emerging markets. With over 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to a strong portfolio of medicines for hypertension and thrombotic disorders, under the Group's 2025 Vision to become a "Global Pharma Innovator with Competitive Advantage in Oncology," Daiichi Sankyo research and development is primarily focused on bringing forth novel therapies in oncology, including immuno-oncology, with additional focus on new horizon areas, such as pain management, neurodegenerative diseases, heart and kidney diseases, and other rare diseases. For more information, please visit: www.daiichisankyo.com.

# Contact

Lydia Worms (Europe) Daiichi Sankyo Europe GmbH Edoxaban Communications & Product PR Europe +49 (89) 7808751

# **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.

#### References

- 1. Goette, A, et al. Edoxaban versus enoxaparin / warfarin in subjects undergoing cardioversion of atrial fibrillation: the randomized (ENSURE-AF) study. *The Lancet*. 2016.
- 2. Goette A, et al. Edoxaban versus enoxaparin/warfarin in subjects undergoing cardioversion of atrial fibrillation: the randomized (ENSURE-AF) study. Presented at the European Society of Cardiology. August 30, 2016. Rome, Italy.
- 3. National Heart, Lung and Blood Institute What is Atrial Fibrillation. Available at: http://www.nhlbi.nih.gov/health/dci/Diseases/af/af\_diagnosis.html. [Last accessed: March 2016].
- 4. Iqbal MB, et al. Recent developments in atrial fibrillation. BMJ. 2005;330(7485):238-43.
- 5. Ball J, et al. Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century. *Int J Card.* 2013;167:1807-1824.
- 6. Camm A, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31(19):2369–2429.