

Press Release

Daiichi Sankyo Presents Positive Results of the First Randomized, Controlled Trial of Uninterrupted Oral, Once-daily Lixiana[®] (edoxaban) in Atrial Fibrillation Patients Undergoing Catheter Ablation

- *ELIMINATE-AF is the first set of data presented in 2019 from the Edoxaban Clinical Research Program EDOSURE, which will deliver new evidence to support the use of Edoxaban in clinical practice*
- *Late-breaking data presented at EHRA 2019, the annual congress of the European Heart Rhythm Association, shows ELIMINATE-AF met primary efficacy and safety objectives, demonstrating low thromboembolic and bleeding event rates¹*
- *ELIMINATE-AF provides evidence that uninterrupted edoxaban treatment represents an alternative to continuous anticoagulation with VKA in patients undergoing catheter ablation of AF*

Tokyo, Japan (March 19, 2019) – Daiichi Sankyo Company, Limited (hereafter, “Daiichi Sankyo”) today announced results from ELIMINATE-AF, a prospective, randomized, open label, blinded endpoint evaluation (PROBE) design study assessing the safety and efficacy of uninterrupted oral, once-daily edoxaban (known by the brand name LIXIANA[®] outside the US and SAVAYSA[®] in the US) 60 mg versus uninterrupted vitamin K antagonists (VKA) in atrial fibrillation (AF) patients undergoing catheter ablation. The study showed the uninterrupted anticoagulation regimen with edoxaban in patients undergoing catheter ablation resulted in low event rates for both thromboembolic and bleeding events¹. The data were presented today during a late-breaker session at EHRA 2019, the annual congress of the European Heart Rhythm Association, in Lisbon, Portugal.

The primary efficacy objective of ELIMINATE-AF was to compare descriptively the time to first all-cause death, stroke, or International Society on Thrombosis and Haemostasis (ISTH)-defined major bleeding, assessed in the per-protocol population from the end of ablation procedure to the end of treatment. The incidence of the primary endpoint was 0.3% (1/316) in the edoxaban group and 2.0% (2/101) in the VKA group (HR 0.16; 95% CI 0.02, 1.73). The event rate was low and similar in both treatment arms; most events were procedure -related. All three events were major bleedings, and there were no deaths in the study. Edoxaban adherence was excellent (>97%) and VKA treatment was well managed.¹

The primary safety objective was to compare descriptively the incidence of ISTH-defined major bleeding in the edoxaban group against the VKA group in the period from date of first intake of study medication to end of treatment/Day 90. The primary safety endpoint in the mITT population occurred in 2.5% (10/405) in the edoxaban group and 1.5% (3/197) in the VKA group (HR 1.68; 95% CI 0.46, 6.07).

“Catheter ablation is a common and effective procedure for rhythm control in patients with symptomatic AF. However, the procedure is associated with a significant thromboembolic risk during and shortly after the procedure, requiring systemic anticoagulation before, during, and after ablation,” said Stefan Hohnloser, MD, Professor of Medicine and Cardiology, Head, Department of Electrophysiology, Johann Wolfgang Goethe University in Frankfurt, Germany, and principal study investigator. “These results provide evidence that uninterrupted edoxaban treatment represents an alternative to continuous anticoagulation with VKA in patients undergoing catheter ablation of AF. This is significant for this complex patient population and physicians because the management of anticoagulation around ablation is much easier with once-daily edoxaban, with low potential of interaction with concomitant drugs.”

Until recently, there has been a lack of data to support the uninterrupted peri-procedural use of non-VKA, oral anticoagulants (NOACs) during AF ablation. ELIMINATE-AF was the first randomized controlled trial on the use of edoxaban for catheter ablation of AF.

“We are encouraged by these results, which represent an important potential advancement in the way we manage thromboembolic risk surrounding catheter ablation,” said Hans Lanz, MD, Vice President, Head, Global Medical Affairs Edoxaban, Daiichi Sankyo Europe GmbH. “ELIMINATE-AF will help define the role of uninterrupted therapy with edoxaban in the clinical setting of catheter ablation of AF. These results are the first of a broad set of data to be presented in 2019 supporting the use of edoxaban in specific clinical situations and the real-world setting.”

ELIMINATE-AF is one of more than 10 randomized, controlled trials (RCTs), registries and non-interventional studies that comprise the edoxaban clinical research program, EDOSURE. More than 100,000 patients worldwide are expected to participate in EDOSURE studies, the goal of which is to generate new clinical and real-world data regarding its use in AF and VTE populations, providing physicians and patients worldwide with greater treatment confidence.

About ELIMINATE-AF

Evaluation of Edoxaban compared with VKA in subjects undergoing catheter ablation of non-valvular Atrial Fibrillation (ELIMINATE-AF) was a prospective, randomized, open-label, blinded endpoint evaluation, parallel-group phase 3b study to evaluate the efficacy and safety of once-daily edoxaban against a vitamin K antagonist in AF patients undergoing catheter ablation of AF. The primary objective was to descriptively compare the incidence of the composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined) and major bleeding (ISTH definition) in the edoxaban group against the vitamin K antagonist group in the period from the end of the catheter ablation procedure to Day 90/end-of-treatment (EOT). The primary safety objective was to descriptively compare the incidence of major bleeding (ISTH definition) in the edoxaban group against the VKA group in the period from date of first intake of study medication to Day 90/EOT. Approximately 600 patients were enrolled in ELIMINATE-AF from more than 70 clinical sites across Europe, Canada and Asia. Patients were randomized (2:1) to receive edoxaban or VKA for 21 to 28 days pre- and 90 days post-ablation period.²

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.³

AF is the most common type of heart rhythm disorder and is associated with substantial morbidity and mortality.⁴ More than six million Europeans are diagnosed with AF, and this figure is expected to at least double over the next 50 years.^{5,6} Compared to those without AF, people with the arrhythmia have a 3-5 times higher risk of stroke.⁷ One in five of all strokes are a result of AF.⁸

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. Edoxaban is currently marketed by Daiichi Sankyo and its partners in more than 20 countries around the world.

About EDOSURE – Edoxaban Clinical Research Program

More than 10 studies, more than 100,000 patients worldwide

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) designed to further build on the results of the pivotal ENGAGE-AF and Hokusai-VTE studies. More than 100,000 patients worldwide are expected to participate in the edoxaban clinical research program, EDOSURE, which is comprised of more than 10 RCTs (randomized, controlled trials), registries and non-interventional studies, including completed, ongoing and future research. The goal is to generate new clinical and real-world-data regarding its use in AF and VTE populations, providing physicians and patients worldwide with greater treatment assurance.

The RCTs include:

- ENGAGE-AF-TIMI 48 (Effective anticoagulation with factor xA next Generation in Atrial Fibrillation), in AF patients at moderate-to-high risk of thromboembolic events
- Hokusai-VTE (Edoxaban in Venous Thromboembolism), in patients with either acute symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE) or both
- 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
- ELDERCARE-AF (Edoxaban Low-Dose for Elderly CARE AF patients), in elderly AF patients in Japan
- ELIMINATE-AF (Evaluation of edoxaban compared with VKA in subjects undergoing catheter ablation of non-valvular Atrial Fibrillation)
- ENVISAGE-TAVI AF (Edoxaban Versus standard of care and their effects on clinical outcomes in patients having undergone Transcatheter Aortic Valve Implantation (TAVI) – Atrial Fibrillation)

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 nonvalvular 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
- ANAFIE (All Nippon AF In Elderly) Registry in Japan
- Cancer-VTE Registry in Japan

Through EDOSURE, 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.

For more information, please visit: <https://www.daiichisankyo.com/rd/pipeline/products/ecrp/index.html>

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 15,000 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.

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.

¹ Hohnloser SH, et al. Uninterrupted Edoxaban versus Vitamin K Antagonists for Ablation of Atrial Fibrillation: The ELIMINATE-AF Trial. EHRA Annual Meeting Abstracts [<https://bit.ly/2C85IPO>]

² Clinicaltrials.gov. Edoxaban Treatment Versus Vitamin K Antagonist (VKA) in Patients With Atrial Fibrillation (AF) Undergoing Catheter Ablation (ELIMINATE-AF). Available at <https://clinicaltrials.gov/ct2/show/NCT02942576>. [Last accessed: February 2019]

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: February 2019].

⁴ Iqbal MB, et al. Recent developments in atrial fibrillation. *BMJ*. 2005;330(7485):238–43.

⁵ Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Society of Cardiology*. 2016;37, 2893–2962.

⁶ Krijthe BP, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34(35):2746-2751.

⁷ Ball J, et al. Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century. *Int J Card*. 2013;167:1807-1824.

⁸ 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.