



Press Release

Daiichi Sankyo Presents Positive Results of the ENTRUST-AF PCI Study of LIXIANA® (edoxaban) in Patients with Atrial Fibrillation

- *ENTRUST-AF PCI study achieved the primary safety endpoint of non-inferiority in bleeding for edoxaban-based dual therapy compared with VKA-based triple antithrombotic therapy (using a risk-based duration of ASA for at least one month) in AF patients following stent placement*
- *Data contributes to growing body of evidence supporting edoxaban in combination with a P2Y₁₂ inhibitor as an alternative to the current VKA triple therapy*
- *Data presented during ESC Congress 2019 Hot Line Session and simultaneously published in [The Lancet](#)*

Tokyo, Japan, and Munich, Germany (September 4, 2019) – Daiichi Sankyo Company, Limited, (hereafter, Daiichi Sankyo) today announced results from ENTRUST-AF PCI, the first large randomised study to evaluate the efficacy and safety of once-daily edoxaban (brand name as LIXIANA®) plus a P2Y₁₂ inhibitor against a regimen of vitamin K antagonist (VKA) plus P2Y₁₂ inhibitor and acetyl salicylic acid (ASA) in atrial fibrillation (AF) patients following successful percutaneous coronary intervention (PCI). The study showed the edoxaban-based regimen is non-inferior compared with the VKA-based triple therapy regimen on the composite endpoint of major or clinically-relevant non-major bleeding over 12 months.^{1,2} The results were presented in a late-breaking presentation during the Hot Line Session at ESC Congress 2019 in Paris, France and published in [The Lancet](#).

It is estimated that about 20% to 40% of patients with AF also present with coronary artery disease (CAD), a sizeable proportion of whom requires revascularisation using percutaneous coronary intervention (PCI) and stent implantation.³ Current treatment guidelines for these patients recommend VKA-based triple therapy including a P2Y₁₂ inhibitor and ASA, however, triple therapy has been associated with significantly increased risk of bleeding.⁴ ENTRUST-AF PCI was a multinational, multicenter, randomised, open-label, blinded outcome evaluation Phase 3b study that evaluated a 12-month antithrombotic regimen of edoxaban 60 mg once-daily in combination with a P2Y₁₂ inhibitor compared to a VKA in combination with a P2Y₁₂ inhibitor and 100 mg of ASA for a risk adapted duration for one to 12 months in patients with AF following

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successful stent placement for ACS or stable CAD. The primary safety outcome was the composite of major or clinically relevant non-major bleeding, as defined by the International Society of Thrombosis and Haemostasis.¹

“For patients with atrial fibrillation receiving PCI, an antithrombotic treatment strategy that prevents both bleeding and potential coronary events is critical,” said Andreas Goette, MD, Chief Physician, St. Vincez-Hospital Paderborn, Germany, Department of Cardiology and Intensive Care Medicine and principal study investigator. “These results from the ENTRUST-AF PCI study support the use of a dual antithrombotic therapy with edoxaban plus a P2Y₁₂ inhibitor as an alternative option with an equivalent safety profile compared to VKA-based triple therapy, including a P2Y₁₂ inhibitor, plus risk adapted ASA for a duration of one to 12 months.”

The ENTRUST-AF PCI study enrolled 1,506 patients with AF following successful stent placement for ACS (51.6%) or stable CAD (48.4%). Patients were randomised to receive once-daily edoxaban (60 mg or 30 mg per dose reduction criteria) plus a P2Y₁₂ inhibitor for 12 months or a VKA in combination with a P2Y₁₂ inhibitor plus 100 mg of ASA. Major or clinically relevant non-major bleeding, the study’s primary endpoint, occurred in 128 (17.0%; annualised: 20.7%) patients in the edoxaban group and 152 (20.1%; annualised: 25.6%) patients in the VKA group (HR: 0.83, 95% CI: 0.654-1.047), demonstrating non-inferiority of the edoxaban-based dual therapy for the 12 months post PCI (p=0.001, pre-specific non-inferiority margin=1.2). There was a trend toward less bleeding with edoxaban, though, results did not show statistical superiority (p=0.115).¹ Similar rates of the main efficacy composite outcome of cardiovascular death, stroke, systemic embolic events, spontaneous myocardial infarction, and definite stent thrombosis were observed for the edoxaban-based dual therapy regimen and the VKA-based triple therapy regimen.

“These results reinforce the value of the approved regimen of edoxaban for AF treatment in post-PCI patients, providing the potential for less bleeding compared to current standard-of-care VKA-based triple therapies without significant differences in ischemic events,” said Hans Lanz, MD, Vice President, Global Medical Affairs Specialty & Value Products, Daiichi Sankyo. “ENTRUST-AF PCI is part of EDOSURE, our edoxaban clinical research programme designed to address a broad range of cardiovascular conditions

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and patient types including the elderly. We are encouraged by these results which represent an important advancement in our understanding of how to best manage AF patients post-PCI.”

In the ENTRUST-AF PCI study, bleeding events were consistent across all commonly applied bleeding definitions (ISTH, TIMI, BARC). Intracranial hemorrhage occurred in four (0.58% per year) of edoxaban-treated patients and nine (1.32% per year) VKA-treated patients. Fatal bleeding occurred in one patient receiving edoxaban and seven patients receiving VKA treatment.

ENTRUST-AF PCI is one of more than 10 randomised, controlled trials (RCTs), registries and non-randomised clinical studies that comprise the Edoxaban Clinical Research Programme, EDOSURE. More than 100,000 patients worldwide are expected to participate in EDOSURE studies, with the goal of generating new clinical and real-world data regarding edoxaban use in AF and venous thromboembolism populations, providing physicians and patients worldwide with greater treatment confidence.

About ENTRUST-AF PCI

EdoxabaN TRreatment VersUS Vitamin K Antagonist in PaTients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF PCI) is a prospective, multinational, multicenter, randomised, open-label with blinded endpoint evaluation phase 3b study. The ENTRUST-AF PCI trial was designed to evaluate the safety and accrue exploratory information on the efficacy of an edoxaban-based antithrombotic regimen compared to a VKA-based antithrombotic regimen in patients with AF following successful PCI with stent implantation. The primary objective of the ENTRUST-AF PCI trial was to compare the incidence of major or clinically relevant non-major International Society on Thrombosis and Haemostasis (ISTH)-defined bleeding over a 12-month period of an edoxaban-based antithrombotic regimen against a VKA-based regimen. 1,506 patients were enrolled in ENTRUST-AF PCI from 186 clinical sites across Europe and Asia. Participants were randomly allocated in a 1:1 ratio to a 12-month antithrombotic regimen of edoxaban and a P2Y₁₂ inhibitor or to a standard therapy with a vitamin K antagonist (VKA) and P2Y₁₂ inhibitor plus ASA for one to 12 months.¹

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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.⁵

AF is the most common type of heart rhythm disorder and is associated with substantial morbidity and mortality.⁶ More than six million Europeans are diagnosed with AF, and this figure is expected to at least double over the next 50 years.^{7,8} Compared to those without AF, people with the arrhythmia have a 3-5 times higher risk of stroke.⁹ One in five of all strokes are a result of AF.⁷

About EDOSURE – Edoxaban Clinical Research Programme

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

Daiichi Sankyo is committed to expanding scientific knowledge about edoxaban, as demonstrated through research programmes 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 programme, EDOSURE, which is comprised of more than 10 RCTs (randomised, controlled trials), registries and non-randomised clinical studies, including completed, ongoing and future research. Our goal is to generate new edoxaban 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



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- 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)
- STABLED Study (Stroke secondary prevention with catheter ablation and Edoxaban for patients with non-valvular atrial fibrillation) in Japan
- ENRICH-AF (Edoxaban for Intracranial Hemorrhage survivors with Atrial Fibrillation, an investigator initiated phase III study)

In addition, global and regional registry and non-randomised clinical studies provide important real-world and clinical data about the use of edoxaban and other oral anticoagulants in everyday practice; these 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
- RYOUMA (Real world ablation therapy with anti-coagulants in Management of Atrial fibrillation) Registry in Japan

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- KYU-RABLE (Multicenter study associated with KYU-shu to evaluate the efficacy and safety of edoxaban in patients with non-valvular Atrial fibrillation undergoing catheter ablation) in Japan
- BPV-AF (Atrial Fibrillation with BioProsthetic valve) 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.

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 30 countries and regions around the world.

About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical therapies to improve standards of care and address diversified, unmet medical needs of people globally by leveraging our world-class science and technology. With more than 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 cardiovascular diseases, under the Group’s 2025 Vision to become a “Global Pharma Innovator with Competitive Advantage in Oncology,” Daiichi Sankyo is primarily focused on providing novel therapies in oncology, as well as other research areas centered around rare diseases and immune disorders. 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



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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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