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Press Release

ENVISAGE-TAVI AF Data Published in *The NEJM* Demonstrates Edoxaban's Noninferiority to VKAs in High-risk AF Patients Following Successful Heart Valve Procedure

- *ENVISAGE-TAVI AF study met its primary endpoint, with edoxaban being noninferior to well managed VKA for the composite of net adverse clinical events*[1]
- *Edoxaban exhibited higher rates of major bleeding with numerically lower rates of all-cause mortality, ischemic stroke, and intracranial hemorrhage*[1]
- *Findings suggest that edoxaban is an appropriate treatment option for AF patients with severe aortic stenosis following successful transcatheter aortic valve implantation*[1]

Tokyo, Japan – (August 30, 2021) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) has announced the results from the multinational, randomized, controlled, phase 3b ENVISAGE-TAVI AF study, comparing the efficacy and safety of edoxaban with vitamin-K-antagonists (VKAs) in patients with atrial fibrillation (AF) having undergone successful transcatheter aortic valve implantation (TAVI).[1] Findings from the trial were presented at a Hot-Line session at ESC Congress 2021, organized by the European Society of Cardiology, and simultaneously published in *The New England Journal of Medicine (NEJM)*.

In ENVISAGE-TAVI AF, 1,426 elderly patients with multiple comorbidities were included and followed for up to three years.[1,2] The study results suggest that edoxaban is an appropriate treatment option for AF patients with severe aortic stenosis following successful TAVI.[1,2] To date, this is the only sufficiently large and statistically powered study that compares a non-vitamin K oral anticoagulant (NOAC) with VKAs in AF patients after TAVI.[1,2]

"TAVI is an established treatment option for patients with severe aortic valve stenosis, including those with AF and multiple comorbidities," said George Dangas, MD, PhD, Professor of Medicine (Cardiology) and Director of Cardiovascular Innovation at the Zena and Michael A. Weiner Cardiovascular Institute at the Icahn School of Medicine at Mount Sinai, New York City, USA. "In AF patients, anticoagulation is

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required to prevent stroke, which can be a devastating complication following TAVI. ENVISAGE-TAVI AF shows that treatment with edoxaban can be valuable in the management of this high-risk population of AF patients after TAVI."

The study met its primary endpoint of edoxaban being noninferior to VKAs for the composite of net adverse clinical events (NACE), which included all-cause mortality, myocardial infarction, ischemic stroke, systemic thromboembolism, valve thrombosis, and International Society on Thrombosis and Haemostasis (ISTH)-defined major bleeding.[1,2] NACE occurred in 170 edoxaban-treated patients (17.3% per year) and, similarly, in 157 VKA-treated patients (16.5% per year).[1,2]

Edoxaban also showed numerically lower rates of all-cause mortality and ischemic stroke (two of the six individual clinical events included in the composite of NACE):[1,2]

- All-cause mortality occurred in 85 edoxaban-treated patients and 93 VKA-treated patients (7.8% versus 9.1% per year, respectively).
- Ischemic stroke occurred in 22 edoxaban-treated patients and 28 VKA-treated patients (2.1% versus 2.8% per year, respectively).

The study did not meet its primary safety endpoint of ISTH-defined major bleeding, due to more gastrointestinal (GI) bleeds in the edoxaban arm.[1,2] Other major bleeding events, including intracranial hemorrhage (ICH), as well as fatal and life-threatening bleeds, were similarly rare in both the edoxaban and VKA treatment arms:[1,2]

Major bleeding occurred in 98 edoxaban-treated patients and 68 VKA-treated patients (9.7% versus 7.0% per year, respectively), which included the following:[1,2]

- Major GI bleeding occurred in 56 edoxaban-treated patients and 27 VKA-treated patients (5.4% versus 2.7% per year, respectively).
- ICH occurred in 16 edoxaban-treated patients and 21 VKA-treated patients (1.5% versus 2.1% per year, respectively).

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- Fatal bleeding occurred in 11 edoxaban-treated patients and 10 VKA-treated patients (1.0% versus 1.0% per year, respectively).
- Life threatening bleeding occurred in 17 edoxaban-treated patients and 19 VKA-treated patients (1.6% versus 1.9% per year, respectively).

"These findings present evidence that edoxaban is an appropriate treatment option in AF patients post-TAVI, who are typically elderly and frail," said Prof. Nicolas Van Mieghem, global co-lead investigator from Erasmus University Medical Center in Rotterdam, The Netherlands. "We found more major bleedings with edoxaban driven by more gastrointestinal bleedings that were well managed with no significant difference in intracranial or fatal bleedings."

The ENVISAGE TAVI-AF study is part of EDOSURE, which is an extensive clinical research program for edoxaban consisting of more than 10 randomised controlled trials, registries and non-interventional studies in a broad range of cardiovascular conditions, patient types and clinical settings in AF and venous thromboembolism (VTE), involving over 100,000 patients worldwide.

About ENVISAGE-TAVI AF

Edoxaba**N** **V**ersus standard of care and the**I**r effect**S** on clinical outcomes in p**A**tients havin**G** undergon**E** **T**ranscatheter **A**ortic **V**alve **I**mplantation – **A**trial **F**ibrillation (ENVISAGE-TAVI AF) was a prospective, randomized, open-label, blinded endpoint evaluation, parallel-group phase 3b study, evaluating the efficacy and safety of once-daily edoxaban against a regimen of a vitamin K antagonist, with or without antiplatelet therapy, in AF patients following successful TAVI.[1,2,3] The primary efficacy endpoint was incidence of NACE, i.e., the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (ISTH definition).[1,2,3] The primary safety endpoint was major bleeding (ISTH definition).[1,2,3] At the completion of the trial, 1,426 patients were enrolled in ENVISAGE-TAVI AF from 173 clinical sites across Europe, North America, and Asia. Edoxaban was used with the approved dosage regimen for stroke prevention in AF in each country.[1,2]

For more information, please visit: https://clinicaltrials.gov/ct2/show/NCT02943785

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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.[4]

AF is the most common type of heart rhythm disorder and is associated with substantial morbidity and mortality.[5] More than 37 million people are estimated to have been diagnosed with AF worldwide and its prevalence is predicted to increase by at least 60% by 2050.[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 as 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 40 countries and regions around the world.

About EDOSURE (the 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, 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:

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- 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 ElderR 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)

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- 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 **A**trial fibrillation) Registry in Japan
- 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 the Edoxaban Clinical Research Programme, 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 is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 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 to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit: www.daiichisankyo.com.

References

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