

Press Release

Daiichi Sankyo, Inc. Initiates ENVISAGE-TAVI AF Study Investigating Once-Daily SAVAYSA® (edoxaban) in Patients with Atrial Fibrillation Undergoing Transcatheter Aortic Valve Implantation

- *ENVISAGE-TAVI AF is the first study to evaluate the effects of a direct oral anticoagulant on clinical outcomes exclusively in atrial fibrillation patients following successful transcatheter aortic valve implantation*
- *Study adds to the growing Edoxaban Clinical Research Program (ECRP) evaluating its use in a broad range of cardiovascular conditions, patient types and clinical settings*

Parsippany, NJ (May 1, 2017) – Daiichi Sankyo, Inc., (hereafter, Daiichi Sankyo) today announced that the first patient has been enrolled into the ENVISAGE-TAVI AF study. The multinational, randomized phase 3b study will evaluate a treatment regimen based on the company’s oral, once-daily direct factor Xa-inhibitor edoxaban (known by the brand name LIXIANA® outside the US and SAVAYSA® in the US) against a vitamin K antagonist based regimen, with or without antiplatelet therapy, in patients with atrial fibrillation (AF) following successful transcatheter aortic valve implantation (TAVI). The study will investigate the incidence of net adverse clinical events (NACE), including the composite of all-cause death, myocardial infarction (MI), ischemic stroke, systemic thromboembolism (SEE), valve thrombosis, and major bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition). Approximately 1,400 patients will be enrolled in ENVISAGE-TAVI AF from 200 clinical sites across Europe, the United States and Canada.¹

“ENVISAGE-TAVI AF is an important study because it will evaluate the safety and efficacy of an edoxaban-based versus a vitamin K antagonist-based regimen in non-valvular AF patients with indication for chronic oral anticoagulation after successful TAVI in a sufficiently powered study. In this study, edoxaban will be used with the approved dosage regimen for stroke risk reduction in AF,” said George Dangas, MD, PhD, Professor of Medicine, Mount Sinai School of Medicine and co-principal study investigator.

TAVI has become an increasingly frequent procedure to treat aortic stenosis.² Aortic stenosis is a progressing disease, and may turn into a life threatening condition.³ In patients undergoing a TAVI procedure, AF is a frequent comorbidity which requires chronic oral anticoagulation therapy.^{4,5}

“At present, ENVISAGE-TAVI AF is the only study of patients undergoing TAVI designed to compare exclusively non-valvular AF patients on a direct oral anticoagulant regimen against a vitamin K antagonist-based regimen,” said Nicolas M. van Mieghem, MD, PhD, Erasmus University of Rotterdam and co-principal study investigator.

“ENVISAGE-TAVI AF will add to the growing body of knowledge in the Edoxaban Clinical Research Program, providing important insights into the potential effects of edoxaban in AF patients undergoing TAVI procedures, a high-risk population,” said Hans J. Lanz, MD, Executive Director, Global Medical Affairs, Daiichi Sankyo.

About ENVISAGE-TAVI AF

Edoxaba**N** Versus 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 – in **A**trial **F**ibrillation (ENVISAGE-TAVI AF) is 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. The primary efficacy endpoint is incidence of NACE, i.e., the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (ISTH definition). The primary safety endpoint is major bleeding (ISTH definition). Approximately 1,400 patients will be enrolled in ENVISAGE-TAVI AF from 200 clinical sites across Europe, the United States and Canada. Edoxaban will be used with the approved dosage regimen for stroke risk reduction in AF patients in each country.¹

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

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.⁶

AF is the most common type of heart rhythm disorder, and is associated with substantial morbidity and mortality.⁷ AF affects approximately 6.1 million people in the U.S.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 as a result of AF.¹⁰

About Edoxaban Clinical Research Program (ECRP)

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 edoxaban clinical research program includes 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
- 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 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
- ANAFIE (All Nippon AF In Elderly) Registry in Japan
- Cancer-VTE Registry in Japan

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 SAVAYSA® (edoxaban)

Edoxaban, also known as SAVAYSA in the U.S., is an oral, once-daily anticoagulant that specifically inhibits factor Xa, which is an important factor in the coagulation system that leads to blood clotting. The global edoxaban clinical trial program included two phase 3 clinical studies, Hokusai-VTE and ENGAGE AF-TIMI 48, with nearly 30,000 patients combined. The results from these trials formed the basis of the regulatory filing in the U.S. for SAVAYSA for the reduction in risk of stroke and SE in patients with NVAF, as well as for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant. According to the U.S. label, SAVAYSA should not be used in NVAF patients with creatinine clearance (CrCL) levels greater than 95 mL/min because in that population there is an increased risk of ischemic stroke compared to warfarin.

Indication

SAVAYSA® (edoxaban) is indicated to reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF). SAVAYSA should not be used in patients with creatinine clearance (CrCl) >95 mL/min because of an increased risk of ischemic stroke compared to warfarin.

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant.

BOXED WARNINGS

- **REDUCED EFFICACY IN NVAF PATIENTS WITH CRCL >95 ML/MIN**
SAVAYSA should not be used in patients with CrCl >95 mL/min. In the ENGAGE AF-TIMI 48 study, NVAF patients with CrCl >95 mL/min had an increased rate of

ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used.

- **PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS**

Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance in the Prescribing Information.

- **SPINAL/EPIDURAL HEMATOMA**

- Epidural or spinal hematomas may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures
- Factors that can increase the risk of developing epidural or spinal hematomas in these patients include: use of indwelling epidural catheters; concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants; a history of traumatic or repeated epidural or spinal punctures; a history of spinal deformity or spinal surgery
- Optimal timing between the administration of SAVAYSA and neuraxial procedures is not known

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

SAVAYSA is contraindicated in patients with active pathological bleeding.

WARNINGS AND PRECAUTIONS

Bleeding Risk

SAVAYSA increases the risk of bleeding and can cause serious and potentially fatal bleeding. Promptly evaluate any signs or symptoms of blood loss. Discontinue SAVAYSA in patients with active

pathological bleeding. Concomitant use of drugs affecting hemostasis may increase the risk of bleeding. These include aspirin and other antiplatelet agents, other antithrombotic agents, fibrinolytic therapy, chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). There is no established way to reverse the anticoagulant effects of SAVAYSA, which can be expected to persist for approximately 24 hours after the last dose. The anticoagulant effect of SAVAYSA cannot be reliably monitored with standard laboratory testing. A specific reversal agent for edoxaban is not available. Hemodialysis does not significantly contribute to edoxaban clearance. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse its anticoagulant activity.

Mechanical Heart Valves or Moderate to Severe Mitral Stenosis

The safety and efficacy of SAVAYSA has not been studied in patients with mechanical heart valves or moderate to severe mitral stenosis. SAVAYSA is not recommended in these patients.

ADVERSE REACTIONS

- **NVAF:** The most common adverse reactions ($\geq 5\%$) are bleeding and anemia
- **DVT/PE:** The most common adverse reactions ($\geq 1\%$) are bleeding, rash, abnormal liver function tests and anemia

DISCONTINUATION FOR SURGERY AND OTHER INTERVENTIONS

Discontinue SAVAYSA at least 24 hours before invasive or surgical procedures because of the risk of bleeding. SAVAYSA can be restarted after the surgical or other procedure as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- **Anticoagulants, Antiplatelets, and Thrombolytics:** Coadministration of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding
- **P-gp Inducers:** Avoid concomitant use of SAVAYSA with rifampin
- **P-gp Inhibitors (DVT/PE only):** Coadministration of certain P-gp inhibitor medications requires a dose reduction of SAVAYSA to 30 mg once daily

SPECIAL POPULATIONS

- Nursing mothers: Discontinue drug or discontinue nursing

- Impaired renal function (CrCl 15 to 50 mL/min): Reduce SAVAYSA dose to 30 mg once daily
- Moderate or severe hepatic impairment: Not recommended
- Pregnancy Category C

Please see the full Prescribing Information, including **Boxed WARNINGS** and Medication Guide at savaysa.com.

Edoxaban is currently marketed in Japan, the U.S., South Korea, Hong Kong, Taiwan, Thailand, Switzerland, the U.K., Germany, Ireland, the Netherlands, Italy, Spain, Belgium, Austria, Portugal, and other European countries.

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

Kimberly Wix
Daiichi Sankyo, Inc.
Senior Director, Public Affairs
+1 973 944 2338

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. Clinicaltrials.gov. Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation (ENVISAGE-TAVI AF). Available at: <https://clinicaltrials.gov/ct2/show/NCT02943785>. [Last accessed: March 2017].
2. Webb J, Cribier A. Percutaneous transarterial aortic valve implantation: what do we know? *Eur Heart J*. 2011;32(2):140-7.
3. Otto CM, Prendergast B. Aortic-valve stenosis- from patients at risk to severe valve ablation. *N Engl J Med*. 2014;371(8):744-56.
4. Biviano AB, et al. Atrial fibrillation is associated with increased mortality in patients undergoing transcatheter aortic valve replacement: insights from the placement of aortic transcatheter valve (PARTNER) trial. *Circ Cardiovasc Interv*. 2016;9(1):e002766. doi:10.1161/CIRCINTERVENTIONS.115.002766.
5. Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-2962.
6. 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 2017].
7. Iqbal MB, et al. Recent developments in atrial fibrillation. *BMJ*. 2005;330(7485):238–43.
8. Go AS, et al. Heart disease and stroke statistics--2013 update: A report from the American Heart Association. *Circulation*. 2013;127:6-245.
9. Ball J, et al. Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century. *Int J Card*. 2013;167:1807-1824.
10. 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.