Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

# Press Release

# Daiichi Sankyo, Inc. Announces New Analyses of Once-Daily SAVAYSA® (edoxaban) in Patients with Non-valvular Atrial Fibrillation to be Presented at the ACC 66th Annual Scientific Session

- *Four abstracts to feature analyses from the global phase 3 ENGAGE AF-TIMI 48 study*
- *Abstract to highlight treatment satisfaction and utilization of healthcare services from the ENSURE-AF study in patients undergoing cardioversion*

**Parsippany, NJ (March 13, 2017)** – Daiichi Sankyo, Inc., (hereafter, Daiichi Sankyo) today announced the presentation of five abstracts at the American College of Cardiology's (ACC) 66th Annual Scientific Session, March 17-19, 2017, in Washington, D.C. Four abstracts highlighting subgroup analyses from the global phase 3 ENGAGE AF-TIMI 48 study of edoxaban (known by the brand name SAVAYSA® in the US and LIXIANA® outside the US) will be presented. The studies include analyses of patients with atrial fibrillation (AF) and active malignancy, patients undergoing AF ablation procedures, the association of genetic risk score with burden of AF, and treatment outcomes in Asian vs. non-Asian populations. Additionally, a new analysis from the ENSURE-AF study in patients undergoing cardioversion will be featured in a poster session highlighting the impact of therapy on treatment satisfaction and utilization of healthcare services.

Details of the presentations include:

| **Presentation Title** | **Presenter** | **Session Details** |
|---|---|---|
| ***Poster Presentations*** | | |
| Edoxaban vs. Warfarin in Atrial Fibrillation Ablation - First Experience from the ENGAGE AF-TIMI 48 Trial | Jan Steffel, MD, TIMI Study Group, Boston, MA, USA | Friday, March 17<br>10:00 – 10:45 AM EDT<br>Location: Poster Hall, Hall C |
| Outcomes of Asian Patients with Atrial Fibrillation Compared to Non-Asians in the ENGAGE AF-TIMI 48 trial | Tze-Fan Chao, MD, Brigham and Women's Hospital | Friday, March 17<br>3:45 – 4:30 PM EDT<br>Location: Poster Hall, Hall C |

| | | |
|---|---|---|
| | Boston, MA, USA | |
| Edoxaban Therapy Increases Treatment Satisfaction and Reduces Utilization of Health Care Resources: An Analysis from the EdoxabaN versus warfarin in subjectS UndeRgoing cardiovErsion of Atrial Fibrillation (ENSURE-AF) Study | Andreas Goette, MD, St. Vincenz-Hospital Paderborn, Germany | Saturday, March 18<br>9:45 – 10:30 AM EDT<br>Location: Poster Hall, Hall C |
| Association of Genetic Risk Score with Burden of Atrial Fibrillation: An ENGAGE AF-TIMI 48 Analysis | Christian T. Ruff, MD, Brigham and Women's Hospital, Boston, MA, USA | Saturday, March 18<br>3:45 – 4:30 PM EDT<br>Location: Poster Hall, Hall C |
| ***Moderated Poster Presentation*** | | |
| Efficacy and Safety of Edoxaban in Patients with Atrial Fibrillation and Active Malignancy: An Analysis of ENGAGE AF-TIMI 48 Randomized Clinical Trial | Christina Fanola, MD, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA | Saturday, March 18<br>12:30 – 12:40 PM EDT<br>Location: Arrhythmias and Clinical EP Moderated Poster Theater, Poster Hall, Hall C |

**About the ENGAGE AF-TIMI 48 Study**

The ENGAGE AF-TIMI 48 global phase 3 study investigated once-daily edoxaban in comparison to warfarin in 21,105 patients with nonvalvular atrial fibrillation (NVAF). This represented the largest and longest trial with a novel oral anticoagulant (NOAC) in patients with AF performed to date, with a median follow-up of 2.8 years. Edoxaban demonstrated non-inferiority for stroke or systemic embolism (SE) in comparison to warfarin. Edoxaban was also found to be superior for the principal safety endpoint of major bleeding in comparison to warfarin.[1]

**About ENSURE-AF**

(**E**doxaba**N** vs. warfarin in subject**S** **U**nde**R**going cardiov**E**rsion of **A**trial **F**ibrillation) 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 with NVAF undergoing electrical cardioversion. The primary efficacy endpoint was the composite of stroke, SE, myocardial infarction, and cardiovascular mortality. The primary safety endpoint was the composite of major and clinically-relevant non-major bleeding. A total of 2,199 NVAF 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.[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] AF affects approximately 6.1 million people in the U.S.[5] Compared to those without AF, people with the arrhythmia have a 3-5 times higher risk of stroke.[6] One in five of all strokes are as a result of AF.[7]

**About Venous Thromboembolism**

Venous thromboembolism (VTE) is an umbrella term for two conditions, deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is a disease caused by a blood clot found in deep veins, usually within the lower leg, thigh or pelvis, although they can occur in other parts of the body as well.[8] PE occurs when part of a clot detaches and lodges in the pulmonary arteries, causing a potentially fatal condition.[9]

VTE is a major cause of morbidity and mortality.[10] In the U.S., it is estimated that more than 950,000 VTE events and approximately 300,000 VTE related deaths occur each year.[11,12] There is a high rate of recurrence after a first VTE event, which is reduced with anticoagulant treatment. Without anticoagulant

treatment, approximately half of patients who experience an initial VTE event have recurrent VTE within three months.[13]

**About Edoxaban**

Edoxaban is an oral, once-daily, direct factor Xa (pronounced "Ten A") inhibitor. Factor Xa is one of the key components in the coagulation cascade responsible for blood clotting. Inhibition of factor Xa reduces thrombin generation, prolongs clotting time and reduces the risk of thrombus formation.

**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 AF and VTE. The edoxaban clinical research program includes multiple randomized, controlled trials (RCTs), 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 EldeR 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

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**

Passion for Innovation.
Compassion for Patients.™

# Press Release

Daiichi-Sankyo

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 (≥5%) are bleeding and anemia
- **DVT/PE:** The most common adverse reactions (≥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, Switzerland, the U.K., Germany, Ireland, the Netherlands, Italy, Spain, Belgium, Austria, Portugal, and other European countries.

Passion for Innovation.
Compassion for Patients.™

# Press Release

Daiichi-Sankyo

**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.

**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. Giugliano R, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104.
2. Goette, A, et al. Edoxaban versus enoxaparin-warfarin in in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *The Lancet*. 2016:388(10055):1995-2003.
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 2017].

4. Iqbal MB, et al. Recent developments in atrial fibrillation. *BMJ*. 2005;330(7485):238–43.
5. Go AS, et al. Heart disease and stroke statistics--2013 update: A report from the American Heart Association. *Circulation*. 2013;127:6-245.
6. Ball J, et al. Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century. *Int J Card.* 2013;167:1807-1824.
7. 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.
8. Deep Vein Thrombosis (DVT) / Pulmonary Embolism (PE) — Blood Clot Forming in a Vein. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/ncbddd/dvt/facts.html. [Last accessed: March 2017].
9. Van Beek E, et al. Deep vein thrombosis and pulmonary embolism. New York: John Wiley & Sons, 2009. Print.
10. Cohen A, et al. Venous thromboembolism (VTE) in Europe. *Thromb Haemost.* 2007;98(4):756-764.
11. Deitelzweig S, Lin J, Johnson BH, Schulman KL. Prevalence of venous thromboembolism in the USA: now and future. *Thromb Haemost* 2009;7 (Suppl. 2):207-8 (abstract OC-WE-018).
12. Heit JA, Cohen AT, Anderson FAJ, on behalf of the VTE Impact Assessment Group. Estimated annual number of incident and recurrent, non-fatal and fatal venous thromboembolism (VTE) events in the US. ASH Annual Meeting Abstracts. 106:910. 2005.
13. Kearon C. Natural history of venous thromboembolism. *Circulation.* 2003;107(23 suppl 1):I-22-30.