Passion for Innovation.
Compassion for Patients.™

Press Release

Daiichi-Sankyo

Daiichi Sankyo to Present Findings From New Subgroup Analyses of Once-Daily SAVAYSA® (edoxaban) in NVAF and VTE at ACC's 65th Annual Scientific Session

- *Four abstracts highlight new subgroup analyses from the global phase 3 ENGAGE AF-TIMI 48 and Hokusai-VTE studies to be presented in oral and poster sessions*

Parsippany, NJ (March 24, 2016) – Daiichi Sankyo, Inc. (hereafter, Daiichi Sankyo) today announced that data from three new subgroup analyses from the phase 3 ENGAGE AF-TIMI 48 study, and one new subgroup analysis from the phase 3 Hokusai-VTE study, will be presented at the American College of Cardiology's 65th Annual Scientific Session, April 2-4, 2016, in Chicago, Illinois. Results will provide new insights into the safety and efficacy profile of once-daily edoxaban compared to warfarin in patients with non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE).

The subgroup analysis data on edoxaban (known by the brand name SAVAYSA® in the US and as LIXIANA® outside the US) will be presented. The complete list of presentations is included below:

Presentation Title	**Presenter**	**Session Details**
Oral Session		
Outcomes in 2,824 Patients With Valvular Heart Disease Treated With Edoxaban or Warfarin in the ENGAGE AF-TIMI 48 Trial (ACC Session #915-06)	Giulia Renda, MD, PhD, G. d'Annunzio University of Chieti-Pescara, Chieti, Italy	Monday, April 4, 8:30–8:42 AM CDT Location: S405
Poster Presentations		
Recurrent Venous Thromboembolism in Pulmonary Embolism Patients With Right Ventricular Dysfunction in the Hokusai-	Marjolein P.A. Brekelmans, MD, Department of Vascular Medicine,	Sunday, April 3 9:45–10:30 AM CDT Location: South Hall A1

VTE Study (ACC Abstract #1186-305/305)	Academic Medical Center, Amsterdam, Netherlands	
Sudden Cardiac Death in 21,105 Patients With Atrial Fibrillation: Insights From the ENGAGE AF- TIMI 48 Trial (ACC Abstract #1188-338/338)	Alon Eisen, MD, Brigham and Women's Hospital, Boston, MA, USA	Sunday, April 3 9:45–10:30 AM CDT Location: South Hall A1
Moderated Poster Presentation		
Edoxaban Versus Warfarin in 841 Patients With Atrial Fibrillation and Peripheral Arterial Disease: Insights From the ENGAGE AF-TIMI 48 Trial (ACC Session #1289M-03)	Jonathan Cunningham, MD, Brigham and Women's Hospital, Boston, MA, USA	Monday, April 4 12:45–12:55 PM CDT Location: South Hall A1

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 NVAF. This represented the largest and longest trial with a novel oral anticoagulant (NOAC) in patients with atrial fibrillation (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 the Hokusai-VTE Study

The Hokusai-VTE global phase 3 study was the largest single comparative trial of a NOAC in patients with VTE, which evaluated once-daily edoxaban versus warfarin in 8,292 patients with either acute symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE) or both. The Hokusai-VTE study was designed to reflect clinical practice using a flexible treatment duration of 3-12 months in a broad spectrum of VTE patients, including initial use of parenteral anticoagulant (heparin) for at least five days, the proven global standard of care. Edoxaban demonstrated non-inferiority to warfarin for the primary

efficacy endpoint of recurrence of symptomatic VTE, and was found to be superior in the primary safety endpoint of clinically relevant bleeding compared to warfarin.[2]

About AF

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 VTE

VTE is an umbrella term for two conditions, DVT and 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 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 systemic embolism (SE) in patients with non-valvular atrial fibrillation (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 a prescription medicine used to reduce the risk of stroke and blood clots in people who have atrial fibrillation not caused by a heart valve problem. Based on how well the kidneys work, SAVAYSA may not be a treatment option. Health Care Professionals should check kidney function before starting treatment.

SAVAYSA is used to treat blood clots in the veins of the legs (deep vein thrombosis) or lungs (pulmonary embolism), after treatment with an injectable blood thinner medicine for 5 to 10 days.

Important Safety Information

What is the most important information to know about SAVAYSA?

- **For people who take SAVAYSA for nonvalvular atrial fibrillation (a type of irregular heartbeat):** People with atrial fibrillation are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. SAVAYSA lowers the chance of having a stroke by helping to prevent clots from forming.

  Health Care Professionals should check kidney function before prescribing SAVAYSA. People whose kidneys work really well should not receive SAVAYSA because it may not work as well as other medications to prevent stroke.

Patients should not stop taking SAVAYSA without first talking to their doctor who prescribed it. Stopping SAVAYSA increases the patient's risk of having a stroke.

- **SAVAYSA can cause bleeding which can be serious,** and sometimes lead to death. This is because SAVAYSA is a blood thinner medicine that reduces blood clotting. While taking SAVAYSA, the patient may bruise more easily and bleeding may take longer to stop. Patients should call their doctor or get medical help right away if they experience bleeding that is severe (for example, coughing up or vomiting blood) or bleeding that cannot be controlled.

  Patients may have a higher risk of bleeding if they take SAVAYSA and take other medicines that increase their risk of bleeding, including: aspirin, long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), and blood thinners (warfarin, heparin, or other medicines to prevent or treat blood clots). Patients should tell their doctor if they take any of these medicines. Patients should ask their doctor or pharmacist if they are not sure if their medicine is one listed above.

- **SAVAYSA is not for people with mechanical heart valves or people who have moderate-to severe narrowing (stenosis) of their mitral valve.**

- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like SAVAYSA, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). The risk of developing a spinal or epidural blood clot is higher if: a thin tube called an epidural catheter is placed in the patient's back to give him/her certain medicine, the patient takes NSAIDs or a medicine to prevent blood from clotting, the patient has a history of difficult or repeated epidural or spinal punctures, and the patient has a history of problems with his/her spine or has had surgery on his/her spine.

  If a patient takes SAVAYSA and receives spinal anesthesia or has a spinal puncture, the patient's doctor should watch closely for symptoms of spinal or epidural blood clots. Patients should tell their

doctor right away if they have back pain, tingling, numbness (especially in the legs and feet), muscle weakness, loss of control of the bowels or bladder (incontinence).

Who should not take SAVAYSA?

Patients should not take SAVAYSA if they currently have certain types of abnormal bleeding.

What should patients tell their doctor before taking SAVAYSA?

- Before taking SAVAYSA, patients should tell their doctor if they: have liver or kidney problems, have ever had bleeding problems, have a mechanical heart valve, are pregnant or plan to become pregnant, are breastfeeding or plan to breastfeed.

  It is not known if SAVAYSA will harm an unborn baby. Patients should tell their doctor right away if they become pregnant during treatment with SAVAYSA.

  It is not known if SAVAYSA passes into breast milk. Patients should decide with their doctor if they will take SAVAYSA or breastfeed. Patients should not do both.

- Patients should tell all of their doctors and dentists that they are taking SAVAYSA. The health care providers should talk to the doctor who prescribed SAVAYSA before the patient has any surgery, medical or dental procedure. Patients should tell their doctor about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some other medicines may affect the way SAVAYSA works. Certain medicines may increase the risk of bleeding or stroke when taken with SAVAYSA.

How should the patient take SAVAYSA?

- Patients should take SAVAYSA exactly as prescribed. The doctor will decide how long the patient should take SAVAYSA. The patient should not change their dose or stop taking SAVAYSA unless their doctor tells them to.

  Patients can take SAVAYSA with or without food. If a dose of SAVAYSA is missed, the patient should take it as soon as he/she remembers that day and not take more than one dose at the same time. The next dose should be taken at the usual time the next day. Patients should not run out of SAVAYSA and should refill their prescriptions before running out.

- If too much SAVAYSA is taken, the patient should go to the nearest hospital emergency room or call his/her doctor right away. Patients should call their doctor right away if they fall or injure themselves, especially if they hit their heads. The doctor may need to check them.

What are the possible side effects of SAVAYSA?

Common side effects in people who take SAVAYSA include bleeding and low red blood cell count (anemia). Patients should talk to their doctor if they have any side effect that bothers them or that does not go away. Patients should call their doctor for medical advice about side effects. Side effects may be reported to FDA at 1-800-FDA-1088.

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

Edoxaban is currently marketed in South Korea, the Netherlands, Ireland, the UK, Germany, Switzerland, the US and Japan, and was approved in Taiwan. In other countries, regulatory review is ongoing.

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 17,000

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 its strong portfolio of medicines for hypertension, dyslipidemia, bacterial infections, and thrombotic disorders, the Group's research and development is focused on bringing forth novel therapies in cardiovascular-metabolic diseases, pain management, and oncology, including biologics. For more information, please visit: www.daiichisankyo.com.

Contact

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

Lydia Worms (Europe)
Daiichi Sankyo Europe GmbH
Edoxaban Communications & Product PR Europe
+49 (89) 7808751

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. Büller H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406-1415.
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 2016].
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 2016].
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.