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Press Release: For US media only

Once-Daily, Oral SAVAYSA® (edoxaban) Met Primary Endpoint in Investigational Hokusai-VTE CANCER Study

- *Hokusai-VTE CANCER study is a phase 3b, prospective, randomized, open-label, blind end-point (PROBE) study evaluating edoxaban versus low molecular weight heparin (LMWH) dalteparin in venous thromboembolism (VTE) associated with primarily active cancer*[1,2,3]
- *Study met primary endpoint of non-inferiority in the recurrence of VTE or ISTH-defined major bleeding*[1,2,3]

Basking Ridge, NJ (December 12, 2017) – Daiichi Sankyo, Inc., (hereafter, Daiichi Sankyo), today announced results from the Hokusai-VTE CANCER study evaluating oral edoxaban (known by the brand names SAVAYSA® in the U.S. and LIXIANA® outside the U.S.), and found that edoxaban is non-inferior to subcutaneous injectable LMWH dalteparin for the treatment of cancer-associated VTE or major bleeding[2,3]. The results of the study were simultaneously published in the *New England Journal of Medicine* (NEJM) and presented during the late-breaker session at the 59th American Society of Hematology (ASH) Annual Meeting in Atlanta, Georgia.

The Hokusai-VTE CANCER study met the primary objective of non-inferiority of edoxaban for the composite outcome of first recurrent VTE or ISTH-defined major bleeding during a 12-month study period, which occurred in 67 of 522 patients (12.8%) in the edoxaban group compared with 71 of 524 patients (13.5%) in the dalteparin group (hazard ratio with edoxaban, 0.97; 95% CI, 0.70 to 1.36; P = 0.006 for non-inferiority) for a risk difference (edoxaban minus dalteparin) of -0.7% (95% CI, -4.8 to 3.4)[2,3]. The difference in risk for recurrent VTE was -3.4% (95% CI, -7.0 to 0.2) whereas the corresponding difference in risk for major bleeding was 2.9% (95% CI, 0.1 to 5.6)[3]. The frequencies of severe major bleeding events at presentation (categories 3 and 4) were similar during treatment with edoxaban or dalteparin (12 patients in each group, respectively)[2,3]. There was no fatal bleed in the edoxaban group versus two fatal bleedings in the dalteparin arm[2,3].

The study also met the secondary outcome of event-free survival (free of recurrent VTE, major bleeds or death) at 12 months, and rates were similar between edoxaban and dalteparin (55.0% and 56.5%, respectively)[2,3]. The trial was a PROBE design study and included a broad spectrum of patients (n=1,050) with primarily active cancer; (98%), 53% of which had metastatic cancer and 72% of which were receiving cancer therapy at randomization[2,3].

"Cancer patients have a significantly increased risk of VTE, and are a high-risk population since 82% of patients have one or more pre-specified bleeding risk factors," said co-principal study investigator Professor Harry Büller, from the Department of Vascular Medicine at Academic Medical Center, Amsterdam, The Netherlands. "We saw a lower rate of recurrent VTE with edoxaban compared to dalteparin over the one-year study period. In addition, in the edoxaban arm, we saw no bleeding fatalities and similar severity of clinical presentation of major bleeding events compared to dalteparin. The risk for VTE persists beyond six months for cancer patients, therefore, the study duration of 12 months enabled the evaluation of edoxaban over a longer time period."

VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE) and is the second leading cause of death in cancer patients receiving chemotherapy[4]. The treatment of cancer-associated VTE is challenging because these patients are at increased risk of both recurrent VTE and major bleeding[2]. The occurrence of VTE increases the risk of death 2-6-fold in cancer patients[4] and can interrupt cancer treatment[5].

"Data from the Hokusai-VTE CANCER study will continue to add to the growing body of knowledge in the Edoxaban Clinical Research Program, which provides key insights into the potential effects of edoxaban in VTE and AF patients," said Hans J. Lanz, MD, Vice President, Global Medical Affairs, Daiichi Sankyo.

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About the Hokusai-VTE CANCER study

Hokusai-VTE CANCER is a multinational, prospective, randomized, open-label, blinded endpoint evaluation (PROBE) study, evaluating the efficacy and safety of once-daily edoxaban compared to dalteparin for the treatment of VTE associated with cancer[1,2,3]. The purpose of the study was to evaluate edoxaban in comparison with dalteparin in preventing the combined outcome of VTE recurrence or major bleeding in patients with VTE associated with cancer[1,2,3]. Other objectives include assessing the effects of treatment on VTE recurrence, clinically relevant bleeding and event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events and death[1,2,3]. The study enrolled 1,050 patients across 13 countries in North America, Europe, Australia and New Zealand[2,3]. Patients were randomized to receive edoxaban 60 mg once-daily (reduced to 30 mg edoxaban for patients with creatinine clearance [CrCL] 30-50 mL/min, body weight ≤ 60 kg, or concomitant use of P-glycoprotein [P-gp] inhibitors), following treatment with LMWH for at least five days; or dalteparin SC 200 IU/kg once-daily for 30 days, then 150 IU/kg once-daily for the remainder of the 12-month study[1,2,3].

For more information please visit: https://www.clinicaltrials.gov/ct2/show/NCT02073682[6].

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[7]. PE occurs when part of a clot detaches and lodges in the pulmonary arteries, causing a potentially fatal condition[8].

VTE is a major cause of morbidity and mortality[9]. In the U.S., it is estimated that more than 950,000 VTE events and approximately 300,000 VTE related deaths occur each year[10,11]. 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[11].

About VTE and Cancer

VTE is a major cause of morbidity and mortality in patients with cancer, with an annual incidence that can be as high as 20 percent depending on the cancer type, background risk and time since diagnosis [10,11]. Patients with cancer have multiple risk factors for VTE and the risk of VTE events increases in patients with cancer receiving chemotherapy [15]. In addition, patients with cancer and VTE have a lower survival rate than those without VTE[15].

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

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 thrombo-embolism (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 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
- 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 DVT and 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.

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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.

IMPORTANT SAFETY INFORMATION FOR SAVAYSA

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

- Lactation: Breastfeeding not recommended
- Pregnancy: Insufficient data to determine drug-associated risks for adverse developmental outcomes
- Impaired renal function (CrCl 15 to 50 mL/min): Reduce SAVAYSA dose to 30 mg once daily
- Moderate or severe hepatic impairment: Not recommended

Please see full Prescribing Information, including **Boxed WARNINGS** and Medication Guide.

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 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 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.

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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.

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