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Press Release

Daiichi-Sankyo

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

- *Hokusai-VTE CANCER study is a phase 3b, prospective, randomised, 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]

Tokyo, Japan (December 13, 2017) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo), today announced results from the Hokusai-VTE CANCER study evaluating oral edoxaban (known by the brand names LIXIANA® outside the U.S. and SAVAYSA® in the U.S.), and found that edoxaban is non-inferior to subcutaneous injectable LMWH dalteparin for the treatment of cancer-associated VTE and 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.

Hokusai-VTE CANCER is the first study with a direct oral anticoagulant (DOAC), edoxaban, to meet pre-specified non-inferiority criteria versus the standard of care dalteparin in this patient population.[2,3] The 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.[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 randomisation.[2,3] This is the largest prospectively randomised clinical trial to have studied the benefit risk of DOACs in cancer patients versus the current injectable standard of care, dalteparin. Hokusai-VTE CANCER is the first study to demonstrate that a DOAC, edoxaban, is non-inferior to the standard of care, injectable LMWH (dalteparin), in this population.[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] Current guidelines recommend LMWH for at least six months as the standard of care in cancer patients,[5,6,7] and currently there is poor adherence to VTE cancer treatment guidelines due to the requirement for daily injections. 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.[8]

"The use of an oral anticoagulant that alleviates the burdens associated with a daily injectable drug, without loss of clinical benefit, would represent an advance for cancer patients with VTE," said Hans J. Lanz, MD, Vice President, Global Medical Affairs, Daiichi Sankyo. "The data will continue to add to the growing

body of knowledge in the Edoxaban Clinical Research Programme, which provides key insights into the potential effects of edoxaban in VTE and AF patients."

About the Hokusai-VTE CANCER study

Hokusai-VTE CANCER is a multinational, prospective, randomised, 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 randomised 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.[9]

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.[10] PE occurs when part of a clot detaches and lodges in the pulmonary arteries, causing a potentially fatal condition.[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.[12,13] Patients with cancer have multiple risk factors for VTE and the risk of VTE events increases in patients

with cancer receiving chemotherapy.[14] In addition, patients with cancer and VTE have a lower survival rate than those without VTE.[14]

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 20 countries around the world.

About Edoxaban Clinical Research Programme (ECRP)

Daiichi Sankyo is committed to expanding scientific knowledge about edoxaban, as demonstrated through our research programmes evaluating its use in a broad range of cardiovascular conditions, patient types and clinical settings in AF and VTE. The edoxaban clinical research programme includes multiple RCTs (randomised, 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 programme, 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 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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