Shionogi announces European Union Marketing Authorisation for lusutrombopag for the treatment of severe thrombocytopenia in adults with chronic liver disease undergoing invasive procedures

OSAKA, Japan, and LONDON, UK, 22nd February 2019 – Shionogi & Co., Ltd. (hereafter "Shionogi"), a research-driven pharmaceutical company, announced today that the European Commission (EC) has granted Marketing Authorisation (MA) for lusutrombopag for the treatment of severe thrombocytopenia (TCP) in adult patients with chronic liver disease (CLD) undergoing invasive procedures.

This decision by the EC has followed the positive opinion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in December 2018.

"We are very pleased that the EC has approved lusutrombopag as the first pharmacological therapy in Europe for adult patients living with chronic liver disease and TCP who undergo invasive procedures" said John Keller, Chief Executive Officer of Shionogi Ltd. "With CLD patients often requiring procedures that could put them at increased risk of bleeding, this approval represents a milestone in terms of offering them and the physicians that care for them, a well-tolerated and effective new treatment option."

"Adult patients with advanced chronic liver disease often have to undergo invasive procedures for various medical reasons, but currently the only available treatment for TCP is supportive care with platelet transfusions. New and more effective pharmacological treatment options are urgently needed," said Professor Markus Peck-Radosavljevic, chairman at the Department of Gastroenterology & Hepatology, Endocrinology and Nephrology at Klinikum Klagenfurt in Klagenfurt, Austria. "Lusutrombopag has convincingly demonstrated its efficacy and safety in raising platelet counts and avoiding platelet transfusions in clinical trials, and I welcome the EC's decision to grant MA."

Professor Adrian Newland, consultant haematologist at Barts Health NHS Trust in London, UK, said: "It is very good news to have MA for this new treatment option to cover invasive procedures in this condition. The pivotal Phase 3 trials show excellent clinical responses without any significant increase in adverse events, and I welcome its approval".

CLD is a major public health issue, affecting approximately 29 million people in Europe,[1] and is an increasing cause of morbidity and mortality worldwide.[2] Thrombocytopenia is the most common blood-related complication of CLD, occurring in up to 78% of patients with the condition.[3] Severe thrombocytopenia is less common, occurring in up to 11% of patients.[4] In patients with severe thrombocytopenia who require an invasive procedure, there is an increased risk of bleeding and subsequent need for platelet cover, which is currently provided through platelet transfusions.[5,6]

The safety and efficacy of lusutrombopag has been established in two pivotal Phase 3 randomised clinical trials, L-PLUS1 and L-PLUS2, where 312 patients with CLD, severe thrombocytopenia with a platelet count of <50,000/µL and a scheduled invasive procedure received either lusutrombopag or placebo once daily for up to seven days.[7,8] Lusutrombopag met the pre-specified primary and all key secondary endpoints with statistically significant results. In L-PLUS1, 75.5% (37/49) of patients receiving lusutrombopag required no platelet transfusion prior to the primary invasive procedure or rescue therapy for bleeding within seven days post-procedure, compared with 12.5% (6/48) who received placebo (P< 0.0001).[9] In L-PLUS2, 64.8% (70/108) of patients who received lusutrombopag required no platelet transfusion prior to the primary invasive procedure or rescue therapy for bleeding within seven days post-procedure, compared to 29% (31/107) receiving placebo (P< 0.0001).[9] The most common adverse reactions were headache, nausea, portal vein thrombosis and rash; the frequency of portal vein thrombosis was comparable between lusutrombopag and placebo treatment groups.

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Lusutrombopag, which has already been approved for routine use in the US[10] and Japan[11], is an orally active, small molecule agonist of the human thrombopoietin receptor that triggers the production of endogenous platelets, taken once daily in tablet form for 7 days. It has been granted Promising Innovative Medicine Designation (PIM) by the UK Medicines and Healthcare Products Regulatory Agency (MHRA), confirming its potential for CLD patients with severe TCP undergoing an invasive procedure.

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About Thrombocytopenia in Chronic Liver Disease
Thrombocytopenia is a common complication of chronic liver disease (CLD) and may be caused by multiple mechanisms including splenic sequestration and decreased production of thrombopoietin.[3] There is evidence that the annual health care cost of a CLD patient with thrombocytopenia is more than three times that of a CLD patient without thrombocytopenia.[6] In addition to the potential of thrombocytopenia, especially severe thrombocytopenia, to aggravate procedural or traumatic bleeding, it may also significantly complicate routine diagnostic procedures and patient care, such as liver biopsy and medically indicated or elective procedures for cirrhotic patients, resulting in delayed or cancelled curative treatment.[12]

About Shionogi
Shionogi & Co., Ltd. ("Shionogi") is a Japanese major research-driven pharmaceutical company dedicated to bringing benefits to patients based on its corporate philosophy of "supplying the best possible medicine to protect the health and wellbeing of the patients we serve." The company currently markets products in several therapeutic areas including anti-infectives, pain, CNS disorders, cardiovascular diseases and gastroenterology. Shionogi's research and development currently target two therapeutic areas: infectious diseases and pain/CNS disorders. For more information on Shionogi, please visit http://www.shionogi.co.jp/en/.

Forward Looking Statement
This announcement contains forward-looking statements. These statements are based on expectations in light of the information currently available, assumptions that are subject to risks and uncertainties which could cause actual results to differ materially from these statements. Risks and uncertainties include general domestic and international economic conditions such as general industry and market conditions, and changes of interest rate and currency exchange rate. These risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. Also for existing products, there are manufacturing and marketing risks, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials and entry of competitive products. The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.

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