

November 27, 2019

## **ONO Submits an Application for Manufacturing and Marketing Approval in Japan for Tirabrutinib Hydrochloride (ONO-4059), a BTK Inhibitor, for the Treatment of Waldenstrom Macroglobulinemia and Lymphoplasmacytic Lymphoma**

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; “ONO”) announced today that ONO submitted an application of tirabrutinib hydrochloride (ONO-4059) (“Tirabrutinib”), a Bruton’s tyrosine kinase (“BTK”) inhibitor, for the manufacturing and marketing approval in Japan for the treatment in patients with Waldenstrom macroglobulinemia (“WM”) and lymphoplasmacytic lymphoma (“LPL”).

This application is based on the result from a multi-center, open-label, uncontrolled Phase II study (ONO-4059-05) evaluating Tirabrutinib in 27 patients with untreated recurrent or refractory WM and LPL, Tirabrutinib was designated as an orphan drug for the indication of WM and LPL by the Ministry of Health, Labour and Welfare (MHLW) in Japan on November 19, 2019.

WM and LPL are one of the malignant lymphomas and are classified as “indolent lymphoma” which means one with relatively slow progression\*<sup>1</sup>. It is estimated that there are approximately 240 new cases\*<sup>2,3</sup> with LPL per year in Japan.

WM and LPL generally grow and spread slowly in the clinical course, with a median survival of more than 5 years, but these are intractable diseases that cannot be cured with existing therapies\*<sup>4</sup>. In Japan, standard treatment has not been established in patients with untreated recurrent or refractory WM and LPL, so a new treatment option is expected for these patient populations.

\*<sup>1</sup> : Center for Cancer Control and Information Services, National Cancer Center, National Research and Development Agency

\*<sup>2</sup> : Cancer Incidence of Japan 2016

\*<sup>3</sup> : Pathology International 2000;50:696–702.

\*<sup>4</sup> : Practical Guidelines for Hematological Malignancies 2018

On August 28, 2019, ONO submitted an application of Tirabrutinib for the manufacturing and marketing approval in Japan for the treatment of recurrent or refractory primary central nervous system lymphoma (PCNSL).

### **About Tirabrutinib**

Tirabrutinib, discovered and developed by ONO, is a highly selective, oral BTK inhibitor and has been developed for the treatment in patients with B-cell tumors and autoimmune diseases in Japan. B cell receptor (“BCR”) signaling plays a core role in the survival, activation, proliferation, maturation and differentiation of B cell lymphocyte. The BCR signaling pathway is known to be permanently activated, particularly B cell non-Hodgkin lymphoma (B-NHL) and chronic lymphocytic leukemia (CLL). Tirabrutinib is expected to have a therapeutic effect because it inhibits BTK, a mediator located downstream of BCR.

In December 2014, ONO out-licensed Tirabrutinib to Gilead Sciences, Inc. (Gilead) to allow Gilead the right to develop and commercialize the product in all countries of the world, except Japan, South Korea, Taiwan, China and ASEAN countries where ONO retains the development and commercialization rights of the product.

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