ONO PHARMACEUTICAL CO.,LTD.

August 21, 2020

ONO Receives a Supplemental Approval in Japan for Velexbru® Tablet 80mg, a BTK Inhibitor, for Additional Indication of Waldenstrom Macroglobulinemia and Lymphoplasmacytic Lymphoma

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced today that ONO received a supplemental approval for Velexbru® (generic name: tirabrutinib hydrochloride) Tablet 80mg ("Velexbru"), a Bruton's tyrosine kinase ("BTK") inhibitor, in Japan for additional indication of Waldenstrom macroglobulinemia and lymphoplasmacytic lymphoma, for a partial change in approved items of the manufacturing and marketing approval.

This approval is based on the result from a multi-center, open-label, single-arm Phase II study (ONO-4059-05), evaluating Velexbru in patients with previously untreated, or relapsed or refractory Waldenstrom macroglobulinemia (WM) and lymphoplasmacytic lymphoma (LPL). In 27 patients who received tirabrutinib (untreated 18 patients and relapsed or refractory 9 patients) in this study, the overall response rate (partial response or greater) assessed by an independent review committee (IRC), a primary endpoint, was 88.9% (16/18 patients) (95% CI: 65.3 - 98.6) in the untreated group, and 88.9% (8/9 patients) (95% CI: 51.8 - 99.7) in the relapsed/refractory group. The secondary endpoints of progression-free survival (PFS) and overall survival (OS) were 100% at 6 months both in the untreated group and relapsed/refractory group. The most commonly observed grade ≥3 adverse events (AEs) were neutropenia and lymphopenia (11.1% each), and leukopenia (7.4%).

With this approval, Velexbru becomes the first BTK inhibitor approved for the treatment of patients with previously untreated, relapsed or refractory WM and LPL in Japan.

Velexbru 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.

About Waldenstrom macroglobulinemia ("WM") and lymphoplasmacytic lymphoma ("LPL")

WM and LPL are one of the malignant lymphomas and are classified as "indolent lymphoma" which means one with relatively slow progression*1. It is estimated that there are approximately 240 new cases*2,3 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*4. In Japan, standard treatment has not been established in patients with untreated relapsed or refractory WM and LPL, so a new treatment option is expected for these patient populations.

*1 : Center for Cancer Control and Information Services, National Cancer Center, National Research and Development Agency

*2 : Cancer Incidence of Japan 2016

*3 : Pathology International 2000;50:696–702.

*4 : Practical Guidelines for Hematological Malignancies 2018

About ONO-4059-05 Study

This study is a multi-center, open-label, single-arm Phase II study, evaluating the efficacy and safety of a monotherapy with Velexbru in patients with previously untreated, or relapsed or refractory WM and LPL. In this study, 27 patients were recruited (untreated 18 patients and relapsed or refractory 9 patients). Patients received Velexbru 480 mg (fasted) once daily and were treated until disease progression or unacceptable toxicity. The primary endpoint of this study is the overall response rate (partial response or greater) assessed by an independent review committee (IRC). The secondary endpoints are progression-free survival (PFS) and overall survival (OS).

About Velexbru

Velexbru (tirabrutinib hydrochloride), 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). Velexbru 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.

In Japan, Velexbru was approved in March 2020 and launched in May 2020 for the treatment of relapsed or refractory primary central nervous system lymphoma (PCNSL).

Overview of Velexbru® Tablet 80mg

Product Name	Velexbru® Tablet 80mg
Generic name (JAN)	Tirabrutinib hydrochloride
Indication	1. Relapsed or refractory primary central nervous system lymphoma 2. Waldenstrom macroglobulinemia and lymphoplasmacytic lymphoma
Dosage and administration	Usually, for adults, administer at 480 mg of tirabrutinib orally once a day in the fasting. The dose should be decreased based on patients' condition.
Approval date	August 21, 2020
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.

Note: Underlined parts show the revised ones according to this approval.

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