CHUGAI PHARMACEUTICAL CO., LTD.

Roche Group

Translation

Chugai Pharmaceutical Co., Ltd.
Roche Diagnostics K.K.

New Drug Application Filed for "Vemurafenib" for the Treatment of Melanoma with BRAF^{V600} Mutation and a Companion Diagnostic to Detect the BRAF Mutation

April 9, 2014 (Tokyo) - Chugai Pharmaceutical Co., Ltd. [Main Office: Chuo-ku, Tokyo. Chairman & CEO: Osamu Nagayama (hereafter, "Chugai")] announced today that it has filed a new drug application to the Ministry of Health, Labour and Welfare (MHLW) on April 9, 2014, for oral, selective BRAF kinase inhibitor "vemurafenib (Development code: RG7204)" for the treatment of melanoma with BRAF^{V600} mutation.
Also, Roche Diagnostics K.K. [Main Office: Minato-ku, Tokyo. President & CEO: Makoto Ogasawara (hereafter, "Roche Diagnostics")] has filed a new drug application to MHLW for *in vitro* diagnostics to detect the BRAF mutation "cobas® 4800 BRAF V600 Mutation Test," as a companion diagnostics for vemurafenib on March 14, 2014. Roche Diagnostics is aimed at simultaneous approval of vemurafenib.

Chugai filed the application with the MHLW based on the results from the global phase III clinical trial (NO25026, The BRIM3 study) and the Japanese phase I/II clinical trial (The JO28178 study).
The BRIM3 study compared vemurafenib to dacarbazine, a standard of care, in 675 patients with previously chemotherapy naïve metastatic melanoma with BRAF^{V600} mutation, diagnosis by cobas® 4800 BRAF V600 Mutation Test. As a result, the risk of death was reduced by 63 percent for people who received vemurafenib compared to those who received dacarbazine (hazard ratio=0.37, $p<0.001$). Patients who received vemurafenib had a 74 percent reduced risk of the disease getting worse or dying (progression free survival: PFS) compared to those who received dacarbazine (hazard ratio=0.26, $p<0.001$). Median PFS was 5.3 months for those who received vemurafenib compared to 1.6 months for those who received dacarbazine.
The common adverse events in patients receiving vemurafenib were joint pain, rash, fatigue and skin tumor. The tolerability of vemurafenib was confirmed, based on the fact that for most adverse events, patients were able to continue the treatment with vemurafenib by receiving additional treatments for adverse events, or by temporarily halting the administration of vemurafenib or changing of the dose.

The JO28178 study was conducted in two phases in 11 patients of Melanoma with BRAF^{V600} mutation, diagnosis by cobas® 4800 BRAF V600 Mutation Test; the phase 1 portion was conducted to evaluate initial safety, and the phase 2 portion was conducted to evaluate the efficacy and safety. The result showed that the efficacy and the tolerability of vemurafenib in Japanese patients with melanoma are confirmed.

cobas® 4800 BRAF V600 Mutation Test is a genetic testing kit to detect the $BRAF^{V600}$ mutation in genomic DNA extracted from melanoma tissue. It is the first diagnostic tool to detect the BRAF mutation using the measurement principle of real-time PCR method, for use prior to the administration of vemurafenib.

Chugai and Roche Diagnostics, a member of the Roche Group and pioneer in personalized healthcare, will work for the early approval to provide vemurafenib as a new treatment option for patients and medical professionals for melanoma, a disease with poor prognosis and with high unmet medical need, and to provide cobas® 4800 BRAF V600 Mutation Test to properly diagnose the patients expected to be effectively treated by vemurafenib. We will continue to contribute to provide treatment options to suit individual patients.

About vemurafenib

Vemurafenib, created by Plexxikon, a member of the Daiichi Sankyo Group, is an oral, small molecule BRAF kinase inhibitor that is designed to selectively inhibit a cancer-driving mutated form of the BRAF protein. In overseas, vemurafenib is being co-developed under a 2006 license and collaboration agreement between F. Hoffmann-La Roche, Ltd. [Head Office: Basel, Switzerland / CEO: Severin Schwan (hereafter, “Roche”)] and Plexxikon. Vemurafenib was approved for the treatment of adult patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation in the U.S. in 2011, or with $BRAF^{V600}$ mutation in Europe in 2012. Chugai entered into a license agreement with Roche and obtains exclusive rights for the development and marketing of vemurafenib in Japan.

Vemurafenib and Roche Personalized Healthcare

Roche is the leading company in the world working on personalised healthcare medicines. The cobas® 4800 BRAF V600 Mutation Test is used to identify patients eligible for treatment of vemurafenib for melanoma. The cobas® 4800 BRAF V600 Mutation Test is a polymerase chain reaction-based diagnostic test developed by Roche Molecular Systems, Inc, was approved for the companion diagnostics in the US, and was CE-marked in the EU. Vemurafenib is a drug candidate that matches with personalized healthcare that selects an appropriate drug for patients expected to obtain the therapeutic effect by using biomarkers and/or diagnostic tools.

About melanoma

It is reported that each year 1,300-1,400 patients (Globocan 2012) in Japan are newly diagnosed with malignant melanoma (all stages), the deadliest and most aggressive form of skin cancer. Of these patients, 26.7-41.8% are reported to have the BRAF gene mutation[1, 2)].

The BRAF protein is a key component of the RAS-RAF pathway involved in normal cell growth and survival. BRAF gene mutations lead to uncontrollable cell growth and survival by activation of BRAF protein which results in a defect in the signal pathway.

1. Uhara H., et al.: Journal of Dermatological Science 66: 240-242, 2012
2. Yamazaki N., et al.: ESMO poster presentation: Presented at the 17th ECCO - 38th ESMO - 32nd ESTRO European Cancer Congress; Amsterdam, The Netherlands, September 27-October 1, 2013

About Chugai

Chugai Pharmaceutical is one of Japan's leading research-based pharmaceutical companies with strengths in biotechnology products. Chugai, based in Tokyo, specializes in prescription pharmaceuticals and is listed on the 1st section of the Tokyo Stock Exchange. As an important member of the Roche Group, Chugai is actively involved in R&D activities in Japan and abroad. Specifically, Chugai is working to develop innovative products which may satisfy the unmet medical needs, mainly focusing on the oncology area.

In Japan, Chugai's research facilities in Gotemba and Kamakura are collaborating to develop new pharmaceuticals and Ukima is conducting research for technology development for industrial production. Overseas, Chugai Pharmabody Research was established in Singapore in January 2012 for conducting research focusing on the generation of new antibody drugs by utilizing Chugai's proprietary innovative antibody engineering technologies. Chugai Pharma USA and Chugai Pharma Europe are engaged in clinical development activities in the United States and Europe.

The consolidated revenue in 2013 of Chugai totaled 423.7 billion yen and the operating income was 79.9 billion yen in IFRS core basis. We are aiming at the consolidated revenue of 451.0 billion yen and operating profit of 71.0 billion yen in IFRS core basis, in 2013.

Additional information is available on the Internet at http://www.chugai-pharm.co.jp/english.

About Roche Diagnostics K.K.

Roche Diagnostics K.K. is the Japanese affiliate of the Diagnostics Division of F. Hoffmann-La Roche, one of the world's leading healthcare companies, based on Basel, Switzerland. With 783 employees and sales branches in 9 cities across Japan as well as a logistics center in Kawasaki, Roche Diagnostics K.K. provides innovative diagnostic solutions for customers ranging from research, clinical diagnostics to patient self-monitoring in Diabetes Care. Our aim is to continuously provide tests with increased medical value and to improve testing efficiency that ultimately empower healthcare professionals to make better and timely clinical decisions for the people in Japan.

Please visit www.roche-diagnostics.jp

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