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Press Release

Patritumab Deruxtecan BLA Submission Receives Complete Response Letter from FDA Due to Inspection Findings at Third-Party Manufacturer

- The letter did not identify any issues with the efficacy or safety data submitted in the application

Tokyo and Basking Ridge, NJ – (June 26, 2024) – The U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter (CRL) for the Biologics License Application (BLA) seeking accelerated approval of Daiichi Sankyo (TSE: 4568) and Merck & Co., Inc., Rahway, N.J., USA's (known as MSD outside of the United States and Canada) patritumab deruxtecan (HER3-DXd) for the treatment of adult patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) previously treated with two or more systemic therapies.

The CRL results from findings pertaining to an inspection of a third-party manufacturing facility. The CRL did not identify any issues with the efficacy or safety data submitted.

Patritumab deruxtecan is a specifically engineered potential first-in-class HER3 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo and being jointly developed by Daiichi Sankyo and Merck & Co., Inc, Rahway, NJ, USA.

"We will work closely with the FDA and the third-party manufacturer to address the feedback as quickly as possible in order to bring the first HER3 directed medicine to patients with previously-treated EGFR-mutated non-small cell lung cancer," said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. "We remain confident in the ability to develop this medicine to its full potential."

"Patients with previously treated EGFR-mutated non-small cell lung cancer often experience recurrence and have limited treatment options," said Marjorie Green, MD, Senior Vice President and Head of Oncology, Global Clinical Development, MSD Research Laboratories. "We are committed to working with Daiichi Sankyo and the FDA to prioritize bringing patritumab deruxtecan to these patients in need."

The BLA is based on the primary results from the HERTHENA-Lung01 pivotal phase 2 trial that were presented at the IASLC 2023 World Conference on Lung Cancer (#WCLC23) and simultaneously published in the *Journal of Clinical Oncology*.

In HERTHENA-Lung01, patritumab deruxtecan was studied in 225 patients with EGFR-mutated locally advanced or metastatic NSCLC following disease progression with an EGFR TKI and platinum-based chemotherapy, which demonstrated an objective response rate (ORR) of 29.8% (95% CI: 23.9-36.2), including one complete response and 66 partial responses. The median duration of response (DoR) was 6.4 months (95% CI: 4.9-7.8).

The safety profile of patritumab deruxtecan observed in HERTHENA-Lung01 was consistent with previous phase 1 clinical trials in NSCLC with a treatment discontinuation rate of 7.1% due to treatment-emergent adverse events (TEAEs). Grade 3 or higher TEAEs occurred in 64.9% of patients. The most common (≥5%) grade 3 or higher TEAEs were thrombocytopenia (21%), neutropenia (19%), anemia (14%), leukopenia (10%), fatigue (6%), hypokalemia (5%) and asthenia (5%). Twelve patients (5.3%) had confirmed treatment-related interstitial lung disease (ILD) as determined by an independent adjudication committee. One grade 5 ILD event was observed.

About HERTHENA-Lung01

HERTHENA-Lung01 is a global, multicenter, open-label, two-arm phase 2 trial evaluating the safety and efficacy of patritumab deruxtecan in patients with EGFR-mutated locally advanced or metastatic NSCLC following disease progression with an EGFR TKI and platinum-based chemotherapy. Patients were randomized 1:1 to receive 5.6 mg/kg (n=225) or an uptitration regimen (n=50). The uptitration arm was discontinued as the dose of 5.6 mg/kg of patritumab deruxtecan was selected following a risk-benefit analysis conducted from the phase 1 trial assessing the doses in a similar patient population.

The primary endpoint of HERTHENA-Lung01 was ORR as assessed by blinded independent central review (BICR). Secondary endpoints included DoR, progression-free survival, disease control rate, and time to response – all assessed by both BICR and investigator assessment – as well as investigator-assessed ORR, overall survival, safety and tolerability.

HERTHENA-Lung01 enrolled patients in Asia, Europe, North America and Oceania. For more information about the trial, visit ClinicalTrials.gov.

About EGFR-Mutated Non-Small Cell Lung Cancer

Approximately 226,000 lung cancer cases were diagnosed in the U.S. in 2022.[1] Lung cancer is the third most common cancer and the leading cause of cancer-related deaths in the U.S.[1] NSCLC accounts for approximately 81% of all lung cancers in the U.S., with 52% having distant spread at diagnosis.[2,3] EGFR mutations occur in approximately one in five patients with NSCLC in Western populations.[4]

About HER3

HER3 is a member of the EGFR family of receptor tyrosine kinases.[5] It is estimated that about 83% of primary NSCLC tumors and 90% of advanced EGFR-mutated tumors express HER3 after prior EGFR TKI treatment.[6,7] HER3 is associated with poor treatment outcomes, including shorter relapse-free survival and significantly reduced survival.[8,9] There is currently no HER3 directed therapy approved for the treatment of any cancer.

About Patritumab Deruxtecan

Patritumab deruxtecan (HER3-DXd) is an investigational HER3 directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC Technology, patritumab deruxtecan is composed of a fully human anti-HER3 IgG1 monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

Patritumab deruxtecan was granted Breakthrough Therapy Designation by the U.S. Food and Drug Administration in December 2021 for the treatment of patients with EGFR-mutated locally advanced or metastatic NSCLC with disease progression on or after treatment with a third-generation TKI and platinum-based therapies.

Patritumab deruxtecan is currently being evaluated as both a monotherapy and in combination with other therapies in a global development program, which includes HERTHENA-Lung02, a phase 3 trial evaluating the efficacy and safety of patritumab deruxtecan versus platinum-based chemotherapy in patients with EGFR-mutated locally advanced or metastatic NSCLC following disease progression on or after treatment with a third-generation EGFR TKI; HERTHENA-Lung01, a phase 2 trial in metastatic or locally advanced NSCLC with an activating EGFR mutation previously treated with at least one EGFR TKI and one platinum-based chemotherapy-containing regimen; HERTHENA-PanTumor01, a phase 2 trial in locally advanced or metastatic solid tumors, including melanoma, gastric and head and neck cancer, among other types of cancer, previously treated with at least one prior systemic therapy; a phase 1 trial in combination with osimertinib in EGFR-mutated locally advanced or metastatic NSCLC; and a phase 1 trial in previously treated patients with advanced NSCLC. A phase 1/2 trial in HER3 expressing metastatic breast cancer also has been completed.

About the Daiichi Sankyo and Merck & Co., Inc., Rahway, N.J., USA Collaboration

Daiichi Sankyo and Merck & Co., Inc., Rahway, N.J., USA (known as MSD outside of the United States and Canada) entered into a global collaboration in October 2023 to jointly develop and commercialize patritumab deruxtecan (HER3-DXd), ifinatamab deruxtecan (I-DXd) and raludotatug deruxtecan (R-DXd), except in Japan where Daiichi Sankyo will maintain exclusive rights. Daiichi Sankyo will be solely responsible for manufacturing and supply.

About the DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of six ADCs in clinical development across multiple types of cancer. ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, are being jointly developed and commercialized globally with AstraZeneca. Patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd), a B7-H3 directed ADC, and raludotatug deruxtecan (R-DXd), a CDH6 directed ADC, are being jointly developed and commercialized globally with Merck & Co., Inc., Rahway, N.J., USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

Designed using Daiichi Sankyo's proprietary DXd ADC Technology to target and deliver a cytotoxic payload inside cancer cells that express a specific cell surface antigen, each ADC consists of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

Datopotamab deruxtecan, ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan and DS-3939 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

About Daiichi Sankyo

Daiichi Sankyo is an innovative global healthcare company contributing to the sustainable development of society that discovers, develops and delivers new standards of care to enrich the quality of life around the world. With more than 120 years of experience, Daiichi Sankyo leverages its world-class science and technology to create new modalities and innovative medicines for people with cancer, cardiovascular and other diseases with high unmet medical needs. For more information, please visit www.daiichisankyo.com.

Media Contacts:

Global/US Media:
Jennifer Brennan
Daiichi Sankyo, Inc.
jennifer.brennan@daiichisankyo.com
+1 908 900 3183 (mobile)

Japan Media:
DS-PR@daiichisankyo.co.jp

Investor Relations Contact:
DaiichiSankyoIR@daiichisankyo.co.jp

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