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Press Release

Daiichi-Sankyo

# FDA Oncologic Drugs Advisory Committee Votes in Favor of Daiichi Sankyo's Pexidartinib for the Treatment of Select Patients with TGCT, a Rare, Debilitating Tumor

- If approved by the FDA, pexidartinib would be the first and only approved therapy for tenosynovial giant cell tumor (TGCT), which is associated with severe morbidity or functional limitations, and not amenable to improvement with surgery
- TGCT, also referred to as pigmented villonodular synovitis (PVNS) or giant cell tumor of the tendon sheath (GCT-TS), can be locally aggressive and debilitating, and for some patients, surgery is not an option
- Pexidartinib is among the seven new molecular entities that Daiichi Sankyo is committed to delivering from its oncology pipeline by 2025

**Tokyo and Basking Ridge, NJ – (May 14, 2019)** – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced that the U.S. Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) voted (Vote: 12 yes, 3 no, zero abstained) that the demonstrated benefit of pexidartinib outweighs the risks in the treatment of adult patients with symptomatic TGCT, which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

"Today's vote in favor of pexidartinib marks a significant step toward delivering the first approved systemic therapy for select TGCT patients whose disease is not amenable to improvement with surgery," said Antoine Yver, MD, MSc, Executive Vice President and Global Head, Oncology Research and Development, Daiichi Sankyo. "Some people living with TGCT experience debilitating symptoms and need innovative treatment options. We believe that pexidartinib has the potential to help address this need by offering carefully selected TGCT patients an important treatment advancement, and we look forward to working with the FDA as it completes its review of our application."

The New Drug Application (NDA) for pexidartinib is currently under Priority Review in the U.S., and the FDA is expected to decide whether to approve the application by the PDUFA date of August 3, 2019. The FDA will consider today's vote as it reviews the NDA, although it is not obligated to follow the Committee's recommendation. The NDA submission is based on the results of the pivotal phase 3 ENLIVEN study of oral pexidartinib, the first placebo-controlled study of a systemic investigational therapy in patients with TGCT.

The ENLIVEN study met its primary endpoint of tumor response rate by RECIST, which was 39 percent in pexidartinib-treated patients and zero percent for placebo-treated patients at week 25 ($p < 0.0001$). In the ENLIVEN study, hepatic toxicities were more frequent with pexidartinib versus placebo (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3X the upper limit of normal [ULN]: 33 percent, total bilirubin ≥2X ULN: 5 percent, N=61). In the randomized Part 1 of the study, eight (13%) patients discontinued pexidartinib due to adverse events (AEs); one discontinuation was due to hypertension and seven were due to liver-related AEs occurring within the first two months of treatment. Of the liver-related AEs, three were serious nonfatal AEs with increased bilirubin, one lasting ~7 months. In non-TGCT development studies using pexidartinib, two severe liver toxicity cases (one required liver transplant, one was associated with death) were observed.

**About TGCT (PVNS/GCT-TS)**

Tenosynovial giant cell tumor (TGCT), also referred to as pigmented villonodular synovitis (PVNS) or giant cell tumor of the tendon sheath (GCT-TS), is a rare, non-malignant tumor that can be locally aggressive. TGCT affects the synovium-lined joints, bursae, and tendon sheaths, resulting in swelling, pain, stiffness and reduced mobility in the affected joint or limb.[1,2,3]

While the exact incidence of TGCT is not known, it is estimated that the incidence of TGCT is 11 to 50 cases per million person-years, based on studies from three countries.[4,5,6] TGCT is subcategorized into two types: localized, which is more common and accounts for 90 percent of cases, and diffuse, which accounts for 10 percent of cases.[5,6] The current standard of care for TGCT is surgical resection.[1,2] However, in patients with a recurrent, difficult to treat, or diffuse form where the tumor can wrap around bone, tendons, ligaments and other parts of the joint, it is more difficult to remove or might not be amenable to improvement with surgery due to the risk of morbidity and potential recurrence. Additional surgeries for more severe cases can lead to significant joint damage, debilitating functional impairments, and reduced quality of life and amputation may be considered.[7,8,9]

Recurrence rates for localized TGCT are estimated to be up to 15 percent following complete resection.[2,10,11,12] Diffuse TGCT recurrence rates are estimated to be about 20 percent to 50 percent following complete resection.[3,10,13] TGCT affects all age groups; the diffuse type on average occurs most often in people below the age of 40 and the localized type typically occurs in people between 30 and 50 years old.[1,4,5,6]

**About Pexidartinib**

Pexidartinib is an investigational, novel, oral small molecule that potently inhibits CSF1R (colony stimulating factor-1 receptor), which is a primary growth driver of abnormal cells in the synovium that cause TGCT.

Pexidartinib also inhibits c-kit and FLT3-ITD. Pexidartinib was discovered by Plexxikon Inc., the small molecule structure-guided R&D center of Daiichi Sankyo.

Pexidartinib is currently under regulatory review with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT), which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery. In addition to Priority Review designation, pexidartinib has been granted Breakthrough Therapy designation for the treatment of patients with pigmented villonodular synovitis (PVNS) or giant cell tumor of the tendon sheath (GCT-TS), where surgical resection may result in potentially worsening functional limitation or severe morbidity, and Orphan Drug designation for PVNS/GCT-TS by the FDA. Pexidartinib also has received Orphan Drug designation from the European Commission for the treatment of TGCT. Pexidartinib is an investigational compound that has not been approved for any indication in any country. Safety and efficacy have not been established.

**About Daiichi Sankyo Cancer Enterprise**

The mission of Daiichi Sankyo Cancer Enterprise is to leverage our world-class, innovative science and push beyond traditional thinking to create meaningful treatments for patients with cancer. We are dedicated to transforming science into value for patients, and this sense of obligation informs everything we do. Anchored by three pillars including our investigational Antibody Drug Conjugate Franchise, Acute Myeloid Leukemia Franchise and Breakthrough Science, we aim to deliver seven distinct new molecular entities over eight years during 2018 to 2025. Our powerful research engines include two laboratories for biologic/immuno-oncology and small molecules in Japan, and Plexxikon Inc., our small molecule structure-guided R&D center in Berkeley, CA. Compounds in pivotal stage development include: [fam-] trastuzumab deruxtecan, an antibody drug conjugate (ADC) for HER2 expressing breast, gastric and other cancers; quizartinib, an oral selective FLT3 inhibitor, for newly-diagnosed and relapsed/refractory FLT3-ITD acute myeloid leukemia (AML); and pexidartinib, an oral CSF1R inhibitor, for tenosynovial giant cell tumor (TGCT). For more information, please visit: www.DSCancerEnterprise.com.

**About Daiichi Sankyo**

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address diversified, unmet medical needs of patients in both mature and emerging markets. With over 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 15,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to a strong portfolio of medicines for hypertension and thrombotic disorders, under the Group's 2025 Vision to become a "Global Pharma Innovator with Competitive Advantage in Oncology,"

Daiichi Sankyo research and development is primarily focused on bringing forth novel therapies in oncology, including immuno-oncology, with additional focus on new horizon areas, such as pain management, neurodegenerative diseases, heart and kidney diseases, and other rare diseases. For more information, please visit: www.daiichisankyo.com. Daiichi Sankyo, Inc., headquartered in Basking Ridge, New Jersey, is a member of the Daiichi Sankyo Group. For more information on Daiichi Sankyo, Inc., please visit: www.dsi.com.

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