

## Press Release

# FDA Grants Priority Review for Daiichi Sankyo's New Drug Application for CSF1R Inhibitor Pexidartinib for Treatment of 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) when associated with severe morbidity or functional limitations, and not amenable to improvement with surgery
- TGCT is also referred to as pigmented villonodular synovitis (PVNS) or giant cell tumor of the tendon sheath (GCT-TS)
- The NDA was based on results of the phase 3 ENLIVEN study, the first placebo-controlled study of a systemic investigational therapy in patients with TGCT, and which met its primary endpoint of overall response rate
- Pexidartinib was discovered at Plexxikon and is the second compound in the Daiichi Sankyo pipeline in less than four months to be accepted for Priority Review by the U.S. FDA, helping advance the Company's mission to deliver seven distinct new molecular entities in cancer by 2025

**Tokyo, Munich and Basking Ridge, NJ – February 5, 2019** – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) announced that the U.S. Food and Drug Administration (FDA) has accepted a New Drug Application (NDA) and granted Priority Review for pexidartinib 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. TGCT, also referred to as pigmented villonodular synovitis (PVNS) or giant cell tumor of the tendon sheath (GCT-TS), is a non-malignant tumor of the joint or tendon sheath, which can be locally aggressive and debilitating in some patients. There are no currently approved systemic therapies for TGCT.

A Priority Review designation is granted by the FDA to drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications. Under Priority Review, the FDA aims to take action on an application within six months, as compared to ten months under standard review. The FDA has designated August 3, 2019 as the PDUFA Action date for this application.

On January 31, 2019, the American Society of Clinical Oncology (ASCO) recognized “Progress in Treating Rare Cancers” as the “Advance of the Year”, and selected pexidartinib as one of five significant advancements in rare disease treatment, calling it the first promising investigational therapy for TGCT.

The NDA is based on 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. Results of the phase 3

ENLIVEN study were presented during an oral presentation at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

“We are pleased to announce that the FDA has accepted our application for pexidartinib with Priority Review designation, potentially bringing a treatment option to patients for whom there is no approved therapy,” said Dale Shuster, Ph.D., Executive Director, Global Oncology R&D, Daiichi Sankyo. “Current treatment options for TGCT are largely limited to surgery, but for some patients the disease is debilitating and not amenable to improvement with surgery. We are committed to working with the FDA to potentially bring pexidartinib to carefully-selected patients as soon as possible.”

“We are excited about the first-in-class potential of pexidartinib, another targeted therapy discovered by Plexxikon,” said Gideon Bollag, Ph.D., Chief Executive Officer of Plexxikon Inc., Daiichi Sankyo’s small molecule structure-guided R&D center in Berkeley, CA and a member of the Daiichi Sankyo Group. “Our drug discovery process uses structural data and a specialized scaffold-like screening library to identify and optimize novel drug candidates.”

ENLIVEN is a pivotal, double-blind, randomized, global multi-center phase 3 study that evaluated pexidartinib in patients with symptomatic advanced TGCT for whom surgical removal of the tumor would be associated with potentially worsening functional limitation or severe morbidity. The first part of the study, the double-blind phase, enrolled 120 patients who were randomized (1:1) to receive either pexidartinib or placebo at 1000 mg/d for 2 weeks followed by 800 mg/d for 22 weeks in order to evaluate the efficacy and safety of pexidartinib versus placebo. The primary endpoint of the study was the percentage of patients achieving a complete or partial response after 24 weeks of treatment (Week 25), as assessed with centrally-read MRI scans using RECIST 1.1 criteria. Key secondary endpoints included range of motion, response by tumor volume score, PROMIS physical function, stiffness and measures of pain reduction.

The ENLIVEN study met its primary endpoint of overall response rate. In the ENLIVEN study, hepatic toxicities were more frequent with pexidartinib versus placebo (AST or ALT  $\geq 3X$  ULN: 33 percent, total bilirubin  $\geq 2X$  ULN: 5 percent, N=61). Eight patients discontinued pexidartinib due to hepatic adverse events (AEs); four 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, usually 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.<sup>1,2</sup> Patients are commonly diagnosed in their 20s to 50s, and depending on the type of TGCT, women can be up to twice as likely to develop a tumor as men.<sup>3,4</sup>

While the exact incidence of TGCT is not known, it is estimated that the incidence of TGCT is 11 to 50 cases per million, based on studies from three countries.<sup>5-7</sup> 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.<sup>6,7</sup> Recurrence rates for localized TGCT are estimated to be up to 15 percent following complete resection.<sup>2,8,9,10</sup> Diffuse TGCT recurrence rates are estimated to be about 20 percent to 50 percent following complete resection.<sup>4,8,11</sup>

Primary treatment of TGCT includes surgery to remove the tumor. 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. 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.<sup>3,12,13</sup>

### **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.

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 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 U.S. Food and Drug Administration (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](http://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](http://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](http://www.dsi.com).

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### **References:**

1. de Saint Aubain, et al. WHO. 2013;100-103
2. Rao AS, et al. J Bone Joint Surg AM. 1984;66(1):76-94.
3. Verspoor FGM, et al. Future Oncol. 2013;10:1515-1531.
4. Ravi V, et al. Curr Opin Oncol. 2011;23:361-366.
5. Myers BW, et al. Medicine (Baltimore). 1980;59(3):223-238.
6. Mastboom MJL., et al. Acta Orthopaedica. 2017;88(6):688-694.
7. Ehrenstein V, et al. J Rheumatol. 2017; 44(10):1476-1483.
8. Gouin F, Noailles T. Orthop Traumatol Surg Res. 2017;103(1S):S91-S97.
9. Palmerini E, Staals EL, Maki RG, et al. Eur J Cancer. 2015;51(2):210-217.
10. Dines JS, et al. Arthroscopy. 2007;23(9):930-937.
11. Xie G-P, et al. PLOS One. 2015;10(3):e0121451.
12. Verspoor FGM, et al. Rheumatol. 2014;53(11):2063-2070.

13. Brahmi M, et al. *Curr Treat Options Oncol*. 2016;17(2):10.