

Press Release

FDA Approves Daiichi Sankyo's TURALIO™ (pexidartinib) for the Treatment of Select Patients with TGCT, a Rare and Debilitating Tumor

- TURALIO is the first and only approved therapy for adult patients with symptomatic tenosynovial giant cell tumor (TGCT) 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
- To mitigate the risk of serious liver injury, Daiichi Sankyo proactively developed a Risk Evaluation and Mitigation Strategy (REMS) Program and patient registry to ensure appropriate prescribing and monitoring
- TURALIO is the second of seven new products that Daiichi Sankyo is committed to delivering from its oncology pipeline by 2025

Tokyo, Munich and Basking Ridge, NJ – (August 2, 2019) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced that the U.S. Food and Drug Administration (FDA) approved TURALIO™ (pexidartinib) as the first and only treatment for adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. TGCT is a rare, non-malignant tumor that affects small and large joints. The disease can cause debilitating symptoms and can be locally aggressive.^{1,2,3}

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“The FDA approval of TURALIO represents a paradigm shift in the treatment of carefully selected TGCT patients who face significant disease morbidity and for whom surgery is not an option,” said William D. Tap, MD, Chief of the Sarcoma Medical Oncology Service at Memorial Sloan Kettering Cancer Center, New York, and lead investigator for the pivotal phase 3 ENLIVEN study. “We now have a new oral treatment option that can have a meaningful clinical benefit in select patients, including a reduction in tumor size.”

“We are proud to be a part of today’s landmark approval and offer a much-needed treatment advancement for TGCT patients whose disease is not amenable to improvement with surgery, and who, until now, have had no approved systemic treatment options,” said Antoine Yver, MD, MSc, Executive Vice President and Global Head, Oncology Research and Development, Daiichi Sankyo, Inc. “With patients at the center of everything we do, Daiichi Sankyo believes patient safety and providing effective medicines are our most important responsibilities. As such, we are committed to educating patients and the healthcare providers who care for

them about the benefits and risks associated with TURALIO to ensure appropriate prescribing and monitoring.”

The FDA approval of TURALIO is based on the results of the pivotal phase 3 ENLIVEN study, the first placebo-controlled study of a systemic therapy in patients with TGCT. Study results showed the primary endpoint of tumor response rate by Response Evaluation Criteria v1.1 in Solid Tumors (RECIST) was 38 percent (95% CI: 27%, 50%) in TURALIO-treated patients and zero percent (95% CI: 0%, 6%) for placebo-treated patients at Week 25 (TURALIO N=61, placebo N=59; p<0.0001). In addition, overall response rate by tumor volume score (TVS) was 56 percent (95% CI: 43%, 67%) in patients randomized to the TURALIO arm and zero percent in patients randomized to the placebo arm at Week 25 (TURALIO N=61, placebo N=59; p<0.0001). Furthermore, the analysis of mean change from baseline in range of motion at Week 25 (TURALIO N=45, placebo N=43) demonstrated a statistically significant improvement in patients treated with TURALIO, compared to placebo.

TURALIO is approved with a Boxed Warning for hepatotoxicity due to the risk of serious and potentially fatal liver injury. Hepatotoxicity with ductopenia and cholestasis has occurred in patients treated with TURALIO. Across 768 patients who received TURALIO in clinical trials, there were two irreversible cases of cholestatic liver injury. One patient died with advanced cancer and ongoing liver toxicity and one patient required a liver transplant. The mechanism of cholestatic hepatotoxicity is unknown and its occurrence cannot be predicted. It is unknown whether liver injury occurs in the absence of increased transaminases.

Because of the risk of hepatotoxicity, TURALIO will be available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program. Under this program, only certified healthcare providers may prescribe TURALIO. Biologics by McKesson, an independent specialty pharmacy for oncology and other complex therapeutic areas, has been selected to be the exclusive specialty pharmacy provider for TURALIO.

TURALIO is available by prescription in the U.S. Daiichi Sankyo is committed to ensuring that patients in the U.S. who are prescribed TURALIO can access the medication and receive necessary financial support. Provider and patient support related to access, reimbursement and distribution for TURALIO in the U.S. will be accessible through Daiichi Sankyo Access Central by visiting www.DSIAccessCentral.com or calling 1-866-4-DSI-NOW (1-866-437-4669).

Further information is available at www.TURALIOREMS.com. Please visit www.TURALIO.com for full [Prescribing Information](#), including Boxed Warning, and for additional Important Safety Information.

About the ENLIVEN Study

ENLIVEN, a double-blind, randomized, placebo-controlled, global multi-center, pivotal phase 3 study, evaluated TURALIO in patients with symptomatic 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 TURALIO at 1000 mg/day for 2 weeks followed by 800 mg/day for 22 weeks or matching placebo, to evaluate the efficacy and safety of TURALIO versus placebo. The major efficacy outcome measure was overall response rate (ORR) at Week 25, which was the percentage of patients achieving a complete or partial response after 24 weeks of treatment as assessed by blinded independent central review (BICR). Additional efficacy outcome measures included range of motion and response by tumor volume score (TVS). After completing the first part of the study, patients randomized to either TURALIO or placebo were eligible to enter the second part of ENLIVEN, a long-term, open-label portion of the study where patients could continue to receive or start to receive TURALIO.

About TGCT (PVNS/GCT-TS)

TGCT, also referred to as PVNS or 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 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 80 percent to 90 percent of cases, and diffuse, which accounts for 10 percent to 20 percent of cases.^{5,6}

The current standard of care for TGCT is surgical resection.^{1,7} However, in patients with a recurrent, difficult-to-treat, or diffuse form of TGCT, the tumor may wrap around bone, tendons, ligaments and other parts of the joint. In these cases, the tumor may be difficult to remove and/or may not be amenable to improvement with surgery. Multiple 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 TURALIO

TURALIO (pexidartinib) is an oral small molecule that inhibits CSF1R (colony stimulating factor-1 receptor), which is a primary growth driver of abnormal cells in the synovium that cause TGCT. TURALIO also inhibits KIT and *FLT3*-ITD. TURALIO was discovered by Plexxikon Inc., the small molecule structure-guided R&D center of Daiichi Sankyo.

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. TURALIO was granted Priority Review, Breakthrough Therapy designation and Orphan Drug status by the U.S. FDA. Pexidartinib is currently under regulatory review for the treatment of TGCT with the European Medicines Agency (EMA) and has received Orphan Drug designation.

Indication and Important Safety Information

Indication and Usage

TURALIO™ (pexidartinib) is indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

WARNING: HEPATOTOXICITY

- TURALIO can cause serious and potentially fatal liver injury.
- Monitor liver tests prior to initiation of TURALIO and at specified intervals during treatment. Withhold and dose reduce or permanently discontinue TURALIO based on severity of hepatotoxicity.
- TURALIO is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program.

Contraindications

None.

Warnings and Precautions

Hepatotoxicity

TURALIO can cause serious and potentially fatal liver injury and is available only through a restricted program called the TURALIO REMS. Hepatotoxicity with ductopenia and cholestasis has occurred in patients treated with TURALIO. Across 768 patients who received TURALIO in clinical trials, there were 2 irreversible cases of cholestatic liver injury. One patient with advanced cancer and ongoing liver toxicity died and one patient required a liver transplant.

The mechanism of cholestatic hepatotoxicity is unknown and its occurrence cannot be predicted. It is unknown whether liver injury occurs in the absence of increased transaminases. Please see Adverse Reactions.

Avoid TURALIO in patients with preexisting increased serum transaminases, total bilirubin, or direct bilirubin (>upper limit of normal [ULN]) or patients with active liver or biliary tract disease including increased alkaline phosphatase (ALP). Taking TURALIO with food increases drug exposure by 100% and may increase the risk of hepatotoxicity. Administer TURALIO on an empty stomach, either 1 hour before or 2 hours after a meal or snack. Monitor liver tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, ALP, and gamma-glutamyl transferase (GGT), prior to initiation of TURALIO, weekly for the first 8 weeks, every 2 weeks for the next month, and every 3 months thereafter. Withhold and dose reduce, or permanently discontinue TURALIO based on the severity of the hepatotoxicity. Rechallenging with a reduced dose of TURALIO may result in a recurrence of increased serum transaminases, bilirubin, or ALP. Monitor liver tests weekly for the first month after rechallenge.

TURALIO REMS

TURALIO is available only through a restricted program under a REMS, because of the risk of hepatotoxicity. Notable requirements of the TURALIO REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Patients must complete and sign an enrollment form for inclusion in a patient registry.
- Pharmacies must be certified with the program and must dispense only to patients who are authorized (enrolled in the REMS patient registry) to receive TURALIO.

Further information is available at turalioREMS.com or by calling 1-833-887-2546.

Embryo-fetal toxicity

Based on animal studies and its mechanism of action, TURALIO may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TURALIO and for 1 month after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TURALIO and for 1 week after the final dose.

Adverse Reactions

The safety of TURALIO was evaluated in ENLIVEN, in which patients received TURALIO without food at a dose of 400 mg in the morning and 600 mg in the evening orally for 2 weeks followed by 400 mg orally twice daily until disease progression or unacceptable toxicity.

Serious adverse reactions (ARs) were reported in 13% of patients who received TURALIO. The most frequent serious ARs (occurring in >1 patient) included abnormal liver tests (3.3%) and hepatotoxicity (3.3%).

Permanent discontinuation due to ARs occurred in 13% of patients who received TURALIO. The most frequent ARs (occurring in >1 patient) requiring permanent discontinuation included increased ALT (4.9%), increased AST (4.9%), and hepatotoxicity (3.3%).

Dose reductions or interruptions occurred in 38% of patients who received TURALIO. The most frequent ARs (occurring in >1 patient) requiring a dosage reduction or interruption were increased ALT (13%), increased AST (13%), nausea (8%), increased ALP (7%), vomiting (4.9%), increased bilirubin (3.3%), increased GGT (3.3%), dizziness (3.3%), and abdominal pain (3.3%).

The most common ARs (>20%) were increased lactate dehydrogenase, increased AST, hair color changes, fatigue, increased ALT, decreased neutrophils, increased cholesterol, increased ALP, decreased lymphocytes, eye edema, decreased hemoglobin, rash, dysgeusia, and decreased phosphate.

Clinically relevant ARs occurring in <10% of patients were blurred vision, photophobia, diplopia, reduced visual acuity, dry mouth, stomatitis, mouth ulceration, pyrexia, cholangitis, hepatotoxicity, liver disorder, cognitive disorders (memory impairment, amnesia, confusional state, disturbance in attention, and attention

deficit/hyperactivity disorder), alopecia, and skin pigment changes (hypopigmentation, depigmentation, discoloration, and hyperpigmentation).

Drug Interactions

- Use with hepatotoxic products: TURALIO can cause hepatotoxicity. In patients with increased serum transaminases, total bilirubin, or direct bilirubin (>ULN) or active liver or biliary tract disease, avoid coadministration of TURALIO with other products known to cause hepatotoxicity.
- Strong CYP3A inhibitors: Concomitant use of a strong CYP3A inhibitor increases pexidartinib plasma concentrations. Reduce TURALIO dosage if concomitant use of strong CYP3A inhibitors cannot be avoided.
- Strong CYP3A inducers: Concomitant use of a strong CYP3A inducer decreases pexidartinib plasma concentrations. Avoid concomitant use of strong CYP3A inducers.
- Uridine diphosphate glucuronosyltransferase (UGT) inhibitors: Concomitant use of a UGT inhibitor increases pexidartinib plasma concentrations. Reduce TURALIO dosage if concomitant use of UGT inhibitors cannot be avoided.
- Acid-reducing agents: Concomitant use of a proton pump inhibitor (PPI) decreases pexidartinib plasma concentrations. Avoid concomitant use of PPIs. Use histamine-2 receptor antagonists or antacids if needed.

Use in Specific Populations

- **Pregnancy:** TURALIO may cause embryo-fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus.
- **Lactation:** Because of the potential for serious adverse reactions in the breastfed child, advise women to not breastfeed during treatment with TURALIO and for at least 1 week after their final dose.
- **Females and males of reproductive potential:** Verify pregnancy status in females of reproductive potential prior to the initiation of TURALIO. Advise females of reproductive potential to use effective contraception during treatment with TURALIO and for 1 month after the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TURALIO and for 1 week after the final dose.
- **Renal impairment:** Reduce the dose when administering TURALIO to patients with mild to severe renal impairment (CLcr 15 to 89 mL/min, estimated by Cockcroft-Gault [C-G] using actual body weight).

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc, at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see accompanying full Prescribing Information, including **Boxed WARNING**, and Medication Guide.

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About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical therapies to improve standards of care and address diversified, unmet medical needs of people globally by leveraging our world-class science and technology. With more than 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 cardiovascular diseases, under the Group's 2025 Vision to become a "Global Pharma Innovator with Competitive Advantage in Oncology," Daiichi Sankyo is primarily focused on providing novel

therapies in oncology, as well as other research areas centered around rare diseases and immune disorders. 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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