Press Release

TURALIO® New Dosing Regimen Approved in the U.S. for Certain Patients with Tenosynovial Giant Cell Tumor

- New recommended dose of 250 mg twice daily with a low-fat meal of approximately 11 to 14 grams of total fat
- Long-term efficacy data from open-label extension portion of pivotal ENLIVEN phase 3 trial of TURALIO also recently added to label, demonstrating an objective response rate of 61%

Basking Ridge, NJ – (October 17, 2022) – Daiichi Sankyo (TSE: 4568) today announced that the U.S. Food and Drug Administration (FDA) has approved a new dosing regimen and added long-term follow-up data to the label for TURALIO® (pexidartinib), the first and only FDA-approved therapy 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. Daiichi Sankyo will discontinue the 200 mg capsule of TURALIO and replace it with a new 125 mg capsule during the first quarter of 2023.

TGCT is a rare, typically non-malignant tumor that affects small and large joints. The disease can cause debilitating symptoms, can be locally aggressive and can significantly impact everyday activities in a relatively young patient population.[1,2,3]

The new recommended dose of TURALIO is 250 mg orally twice daily (taken as two 125 mg capsules) with a low-fat meal of approximately 11 to 14 grams of total fat until disease progression or unacceptable toxicity. The previous recommended dose of TURALIO was 400 mg orally twice daily (taken as two 200 mg capsules) on an empty stomach.

Patients will begin receiving the new 125 mg capsules of TURALIO and begin the 250 mg twice daily dosing regimen during the first quarter of 2023. New and existing patients will be educated on the dosing change and that once the new dosage becomes available, TURALIO is to be taken with a low-fat meal (approximately 11 to 14 grams of total fat) instead of taking the medicine on an empty stomach and not eating one hour before or two hours after having a meal or snack. Patients will continue to be carefully monitored for risk of hepatotoxicity through the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program.

The dosing change is being made due to the known effects food has on the absorption of TURALIO and the potential for drug overexposure that could happen if a patient takes the TURALIO 200 mg dose with a meal rather than on an empty stomach. Taking the 400 mg dose of TURALIO with a high-fat meal (approximately 55 to 65 grams of total fat) increases the concentration of TURALIO in the body and may increase the risk of adverse reactions, including hepatotoxicity. Therefore, as a post-marketing requirement issued by the FDA, Daiichi Sankyo conducted pharmacokinetic studies to further evaluate the effects of food when taking TURALIO. These studies demonstrated that lowering the dose of TURALIO and taking it with a low-fat meal helps to minimize the potential for drug overexposure in the event a patient did not carefully follow the dietary recommendations when taking the 200 mg capsule of TURALIO. Existing patients should continue to take the 200 mg capsule on an empty stomach until the new dosage is available and contact their healthcare providers with any questions.

"We worked closely with the FDA to establish the new dosing regimen for TURALIO based on the data from our pharmacokinetic studies," said Daniel Switzer, Head of U.S. Oncology Business, Daiichi Sankyo, Inc. "In the coming months, we will be dedicated to informing healthcare professionals about this new dosing regimen and providing resources they can share with their patients regarding the dose and instructions around compliance."

In addition, on October 6, 2022, the FDA approved inclusion of long-term efficacy data from the open-label extension part of the pivotal ENLIVEN phase 3 trial in the label. Patients who completed treatment in the double-blind, randomized part of the ENLIVEN trial were eligible to advance to an open-label extension part to continue to receive TURALIO. At the completion of the open-label extension, the objective response rate (ORR) was 61% (95% CI: 48%, 72%) in 61 patients originally randomized to the TURALIO arm as evaluated using Response Evaluation Criteria in Solid Tumors (RECIST), v1.1. The median duration of response was not reached (range: 4.6+, 63.4+ months) in the 37 patients responding to TURALIO. The safety profile remained consistent with previously reported data and there was no unexpected late emerging toxicity, including hepatotoxicity.

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 is available by prescription in the U.S. 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. Patients must complete and sign an enrollment form for inclusion in a patient registry to receive treatment. Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive TURALIO.

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. For more information on the 400 mg twice daily dosage of TURALIO on an empty stomach, please visit www.TURALIO.com for full Prescribing Information, including Boxed WARNINGS, and for additional Important Safety Information. For more information on the new recommended dose of 250 mg orally twice daily with a low-fat meal, commercially available during the first quarter of 2023, please see full Prescribing Information, including Boxed WARNINGS, and for additional Important Safety Information.

About ENLIVEN

ENLIVEN is a global pivotal, double-blind, randomized, placebo-controlled, phase 3 trial that 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. In the first part of the trial, the double-blind phase, patients were randomized (1:1) to receive either TURALIO at 1,000 mg/day for two weeks followed by 800 mg/day for 22 weeks or matching placebo. Results from this portion of the trial were published in *The Lancet.*

The major efficacy outcome measure was 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. Additional efficacy outcome measures included range of motion and response by tumor volume score.

After completing the first part of the trial, patients randomized to either TURALIO or placebo were eligible to enter the second part of ENLIVEN, a long-term, open-label portion of the trial where patients could continue to receive or start to receive TURALIO.

ENLIVEN enrolled 120 patients at multiple sites in Europe, Oceania, and North America. For more information about the trial, visit ClinicalTrials.gov.

About TGCT (PVNS/GCT-TS)

TGCT, also referred to as PVNS or GCT-TS, is a rare, typically 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 worldwide incidence of TGCT is 43 patients per million person-years.[4,5,6] TGCT is subcategorized into two types: localized, which is more common and accounts for 80% to 90% of cases, and diffuse, which accounts for 10% to 20% of cases.[5,6]

The current standard of care for TGCT is surgical resection.[1,7] However, in patients with recurrent, difficult-to-treat, or the 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% following complete resection.[2,6,10,11,12] Diffuse TGCT recurrence rates are estimated to be up to 55% following complete resection.[3,6,10,13] 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 targets colony stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication (ITD) mutation. Overexpression of the CSF1R ligand promotes cell proliferation and accumulation in the synovium.

TURALIO is approved in the U.S. for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. The treatment was granted Priority Review, Breakthrough Therapy and Orphan Drug Designation by the U.S. FDA prior to FDA approval in August 2019.

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.

In ENLIVEN, 3 of 61 (5%) patients who received TURALIO developed signs of serious liver injury, defined as ALT or AST ≥3 × ULN with total bilirubin ≥2 × ULN. ALT, AST and total bilirubin improved to <2 × ULN in these patients 1 to 7 months after discontinuing TURALIO.

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 an effective nonhormonal method of contraception, since TURALIO can render hormonal contraceptives ineffective, 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 were reported in 13% of patients who received TURALIO. The most frequent serious adverse reactions (occurring in >1 patient) included abnormal liver tests (3.3%) and hepatotoxicity (3.3%).

Permanent discontinuation due to adverse reactions occurred in 13% of patients who received TURALIO. The most frequent adverse reactions (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 adverse reactions (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 adverse reactions for all grades (>20%) were increased lactate dehydrogenase (92%), increased AST (88%), hair color changes (67%), fatigue (64%), increased ALT (64%), decreased neutrophils (44%), increased cholesterol (44%), increased ALP (39%), decreased lymphocytes (38%), eye edema (30%), decreased hemoglobin (30%), rash (28%), dysgeusia (26%), and decreased phosphate (25%).

Clinically relevant adverse reactions 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.
- Moderate or strong CYP3A inhibitors: Concomitant use of a moderate or strong CYP3A inhibitor may increase pexidartinib concentrations. Reduce TURALIO dosage if concomitant use of moderate or strong CYP3A inhibitors cannot be avoided.
- Strong CYP3A inducers: Concomitant use of a strong CYP3A inducer decreases pexidartinib concentrations. Avoid concomitant use of strong CYP3A inducers.

- Uridine diphosphate glucuronosyltransferase (UGT) inhibitors: Concomitant use of a UGT inhibitor increases pexidartinib 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 concentrations. Avoid concomitant use of PPIs. Use histamine-2 receptor antagonists or antacids if needed.
- CYP3A substrates: TURALIO is a moderate CYP3A inducer. Concomitant use of TURALIO decreases concentrations of CYP3A substrates. Avoid coadministration of TURALIO with hormonal contraceptives and other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failure. Increase the CYP3A substrate dosage in accordance with approved product labeling if concomitant use is unavoidable.

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 the 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 an effective nonhormonal method of contraception, since TURALIO can render hormonal contraceptives ineffective, 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).
- **Hepatic impairment:** Reduce the dosage of TURALIO for patients with moderate hepatic impairment (total bilirubin greater than 1.5 and up to 3 times ULN, not due to Gilbert's syndrome, with any AST). TURALIO has not been studied in patients with severe hepatic impairment (total bilirubin greater than 3 to 10 times ULN and any AST).

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.

About Daiichi Sankyo

Daiichi Sankyo is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit www.daiichisankyo.com.

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