Press Release

Daiichi Sankyo to Showcase TURALIO® Research in Patients with Tenosynovial Giant Cell Tumor at CTOS

Basking Ridge, NJ – (November 13, 2024) – Daiichi Sankyo (TSE: 4568) will highlight new clinical research and real-world data from seven abstracts for TURALIO® (pexidartinib) at the Connective Tissue Oncology Society (#CTOS2024) 2024 Annual Meeting.

TURALIO is the first and only oral systemic therapy approved in the U.S. for adult patients with tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery. TGCT is a rare and typically non-malignant tumor that affects small and large joints.[1,2,3]

Data at CTOS will highlight ongoing TURALIO research, including two analyses from the ENLIVEN phase 3 trial. One analysis evaluates the efficacy of TURALIO according to surgical history and the feasibility of surgery following treatment with TURALIO. The other is an exploratory analysis examining the dose of TURALIO at the time of objective response and the first timepoint response of progressive disease in relation to adverse events.

“These latest data being presented at CTOS continue to support the role of TURALIO as a treatment option for certain patients with tenosynovial giant cell tumor,” said Dan Switzer, Head of U.S. Oncology Business, Daiichi Sankyo, Inc. “As a leader in TGCT research and development, Daiichi Sankyo has made significant progress in transforming the treatment landscape for patients with this rare, debilitating tumor and we remain committed to educating the medical community on identifying appropriate patients who may be eligible for treatment with TURALIO.”

Additional TURALIO data at CTOS include health-related quality of life (HRQOL) outcomes from a phase 4 trial evaluating the discontinuation and re-treatment in patients with TGCT previously treated with TURALIO and a trial-in-progress of a phase 4 trial evaluating the risk of idiosyncratic cholestatic hepatoxicity associated with TURALIO treatment.

Other clinical research includes interim results from an investigator-initiated phase 1 trial evaluating the safety and tolerability of TURALIO in pediatric patients and young adults with TGCT, a case study reporting

the use of TURALIO as an upfront treatment strategy for TCGT and results of a real-world assessment evaluating symptom change in patients with TGCT receiving TURALIO.

An overview of TURALIO data to be presented at CTOS includes:

Presentation Title	Author	Presentation (PST)
Pexidartinib use in patients with tenosynovial giant cell tumor: an analysis of the phase 3 randomized ENLIVEN clinical trial according to surgical history	J. Healey	Oral Presentation Saturday, November 16 3:30 – 4:30 pm
Tumor response and regrowth in relation to clinical events among pexidartinib-treated subjects in the phase 3 ENLIVEN trial	J. Desai	Poster Session Thursday, November 14 5:45 – 6:45 pm
Health-related quality of life from a phase 4 study to evaluate discontinuation and rechallenge of pexidartinib in patients with tenosynovial giant cell tumor previously treated with pexidartinib	J. Desai	Poster Session Thursday, November 14 5:45 – 6:45 pm
A long-term phase 4 study to evaluate the risk of hepatotoxicity associated with pexidartinib treatment	A. Singh	Poster Session Thursday, November 14 5:45 – 6:45 pm
Tenosynovial giant cell tumor in children: interim results from a phase 1 study of TURALIO	J. Lake	Poster Session Thursday, November 14 5:45 – 6:45 pm
Pexidartinib upfront in a case of tenosynovial giant cell tumor: proof of concept for a treatment paradigm shift	E. Palmerini	Poster Session Thursday, November 14 5:45 – 6:45 pm
Real-world experience of patients newly initiated on pexidartinib for tenosynovial giant cell tumor	D. Dai	Poster Session Thursday, November 14 5:45 – 6:45 pm

About TGCT (PVNS/GCT-TS)

TGCT, also referred to as pigmented villonodular synovitis (PVNS) or giant cell tumor of the tendon sheath (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.[3,6,10,11,12] Diffuse TGCT recurrence rates are estimated to be up to 55% following complete resection.[3,6,10,13] TGCT affects all age groups with the diffuse type on average occurring most often in people below the age of 40, and the localized type typically occurring 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 based on the results of the ENLIVEN trial.

Important Safety Information

Indication

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

- Hepatotoxicity with ductopenia and cholestasis 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 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.
- In ENLIVEN, 3 of 61 (5%) patients who received TURALIO developed signs of serious liver injury, defined as alanine aminotransferase (ALT) or alanine aminotransferase (AST) ≥3 × upper limit of normal (ULN) with total bilirubin ≥2 × ULN. In these patients, peak ALT ranged from 6 to 9 × ULN, peak total bilirubin ranged from 2.5 to 15 × ULN, and alkaline phosphatase (ALP) was ≥2 × ULN. ALT, AST and

total bilirubin improved to <2 × ULN in these patients 1 to 7 months after discontinuing TURALIO.

- Avoid TURALIO in patients with preexisting increased serum transaminases, total bilirubin, or direct bilirubin (>ULN); or active liver or biliary tract disease, including increased ALP.
- Monitor liver tests, including AST, 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. Rechallenge 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

- Requirements include: 1) prescribers must be certified by enrolling and completing training, 2) patients must complete and sign an enrollment form for inclusion in a patient registry, and 3) pharmacies must be certified and must dispense only to patients who are authorized (enrolled in the REMS patient registry).
- Further information is available at www.TURALIOREMS.com or 1-833-887-2546.

Embryo-fetal toxicity

- TURALIO may cause fetal harm when administered to a pregnant woman. Advise patients of reproductive potential of the potential risk to a fetus. 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. 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.

Potential Risks Associated with a High-Fat Meal

- Taking TURALIO with a high-fat meal increases pexidartinib concentrations, which may increase the incidence and severity of adverse reactions, including hepatotoxicity.
- Instruct patients to take TURALIO with a low-fat meal (approximately 11 to 14 grams of total fat) and to avoid taking TURALIO with a high-fat meal (approximately 55 to 65 grams of total fat).

Adverse Reactions

- The most common adverse reactions (>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%).

Drug Interactions

- Hepatotoxic products: Avoid coadministration in patients with increased serum transaminases, total bilirubin, or direct bilirubin (>ULN) or active liver or biliary tract disease.
- Moderate or strong CYP3A inhibitors and UGT inhibitors: Concomitant use may increase pexidartinib concentrations. Reduce TURALIO dosage if concomitant use cannot be avoided.
- Strong CYP3A inducers: Avoid concomitant use due to decreased pexidartinib concentrations.
- Acid-reducing agents: Avoid concomitant use of proton pump inhibitors due to decreased pexidartinib concentrations. Use histamine-2 receptor antagonists or antacids if needed.
- CYP3A substrates: Avoid concomitant use where minimal concentration changes may lead to serious therapeutic failure (e.g., hormonal contraceptives) due to decreased concentrations of CYP3A substrates.

Use in Specific Populations

- **Lactation:** Advise not to breastfeed and for at least 1 week after the final dose.
- **Renal impairment:** Reduce the dosage for patients with mild to severe renal impairment.
- **Hepatic impairment:** Reduce the dosage for patients with moderate hepatic impairment. TURALIO has not been studied in patients with severe hepatic impairment.

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 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 need. For more information, please visit www.daiichisankyo.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] Ravi V, et al. *Curr Opin Oncol*. 2011;23:361-366.
[4] Myers BW, et al. *Medicine* (Baltimore). 1980;59(3):223-238.
[5] Mastboom MJL, et al. *Acta Orthopaedica*. 2017;88(6):688-694.
[6] Ehrenstein V, et al. *J Rheumatol.* 2017; 44(10):1476-1483.
[7] Verspoor FGM, et al. *Future Oncol.* 2013;10:1515-1531.
[8] Verspoor FGM, et al. *Rheumatol.* 2014;53(11):2063-2070.
[9] Brahmi M, et al. *Curr Treat Options Oncol.* 2016;17(2):10.
[10] Gouin F, Noailles T. *Orthop Traumatol Surg Res.* 2017;103(1S):S91-S97.
[11] Palmerini E, Staals EL, Maki RG, et al. *Eur J Cancer*. 2015;51(2):210-217.
[12] Dines JS, et al. *Arthroscopy.* 2007;23(9):930-937.
[13] Xie GP, et al. *PLOS One.* 2015;10(3):e0121451.