Press Release

TURALIO® Final Long-Term Data Showed Sustained Clinical Benefit in Patients with Tenosynovial Giant Cell Tumor from Open-Label Extension of ENLIVEN Phase 3 Trial

Basking Ridge, NJ – (July 9, 2025) - Final long-term efficacy and safety results from the open-label extension of the ENLIVEN phase 3 trial showed a sustained clinical benefit from long-term treatment with TURALIO® (pexidartinib) in patients with symptomatic tenosynovial giant cell tumor (TGCT) not amenable to improvement with surgery. These results, consistent with the primary analysis of the trial, were recently published in *The Oncologist*.

TURALIO is the first oral systemic therapy approved in the U.S. for adult patients with 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]

"Prior to the approval of TURALIO, the first FDA-approved systemic therapy for TGCT, there were limited treatment options beyond additional surgery," said Andrew Wagner, MD, PhD, medical oncologist, Dana-Farber Cancer Institute and Harvard Medical School. "The final results of the ENLIVEN trial show the potential for long-term tumor responses with TURALIO treatment with a safety profile consistent with earlier findings."

Approval of TURALIO was based on results from the first part of the ENLIVEN phase 3 trial where 120 patients with advanced TGCT not amenable for surgery were randomized to TURALIO (n=61) or placebo (n=59). Efficacy outcomes were measured by overall response rate (ORR) by RECIST version 1.1, ORR by tumor volume score (TVS) and mean change in baseline in range of motion of the affected joint at Week 25. Study results from the first part of ENLIVEN showed an ORR of 38% (95% confidence interval [CI]: 27-50) in patients treated with TURALIO compared to an ORR of 0% (95% CI: 0-6) in patients treated with placebo as assessed by RECIST. An ORR by TVS of 56% (95% CI: 43-67) in patients treated with TURALIO and 0% in patients treated with placebo also was shown. Patients that completed the first part of ENLIVEN were able to participate in the second part, the open-label extension of the study, which included 30 patients that crossed over from placebo to receive TURALIO.

Final long-term data from the second part of ENLIVEN showed an ORR of 60% (95% CI: 50-70) as assessed by RECIST and an ORR of 68% (95% CI: 58-77) as assessed by TVS in patients with symptomatic advanced TGCT not eligible for surgery (n=91) with a median follow-up of 31.2 (range: 2-66) months. The median duration of response (DOR) for all responders was not reached with a median follow-up of 50 months for RECIST (range: 0.03-63.4) and TVS (range: 0.03-63.5). A total of 91 patients received TURALIO during the second part of the study as of data cut-off of April 30, 2021.

"The final results of ENLIVEN contribute to the body of evidence supporting the long-term benefit of TURALIO," said Patricia Judson, MD, Vice President, U.S. Medical Affairs, Daiichi Sankyo, Inc. "Daiichi Sankyo is proud to have led the discovery and development of the first FDA-approved oral medicine for this rare disease. Since its approval nearly six years ago, more than 750 patients in the U.S. have been treated with TURALIO and we remain committed to working closely with healthcare professionals to help identify appropriate patients who may benefit from this treatment."

The safety profile of TURALIO in the second part of ENLIVEN was consistent with the previous analysis from the first part of the trial, with no new safety signals identified. The most common grade 3 or higher treatment emergent adverse events (TEAEs) in patients treated with TURALIO were aspartate aminotransferase (AST) increase (9%), alanine aminotransferase (ALT) increase (10%), and hypertension (8%). Twenty-eight (31%) patients had three times or more than the upper limit of normal AST or ALT, while 17 (19%) patients had five times or more than the upper limit of normal AST or ALT. Serious TEAEs were reported in 23.1% of patients who received TURALIO in the ENLIVEN study. Due to the risk of hepatotoxicity, TURALIO is only available through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program. TURALIO can cause serious and potentially fatal liver injury, including vanishing bile duct syndrome. Please see the additional Important Safety Information, including **Boxed WARNING**, below.

Long-Term Results from Open-Label Extension of ENLIVEN

Best Overall Response and Duration of Response	Randomized to Placebo (Part 1 only) (n=59)	Randomized to TURALIO (Part 1 and 2) (n=61)	Cross-over to TURALIO (Part 2 only) (n=30)	All TURALIO Treated (Part 1 and 2) (n=91)
Response Per RECIST v1.1				
ORR % (n; 95% CI)	0% (0; 0-6)	61% (37; 48-72)	60% (18; 42-75)	60% (55; 50-70)
SD % (n; 95% CI)	61% (36; 48-72)	23% (14; 14-35)	27% (8; 14-44)	24% (22; 17-34)
PD % (n; 95% CI)	2% (1; 0.3-9)	2% (1; 0.3-9)	0% (0; 0-11)	1% (1; 0.2-6)
Not Evaluable % (n; 95% CI)	37% (22; 26-50)	15% (9; 8-26)	13% (4; 5-30)	14% (13; 9-23)
DOR (median range; months)		NR (4.6+ to 63.4+)	NR (0.03+ to 56.0+)	NR (0.03+ to 63.4+)
Response Per TVS				
ORR % (n; 95% CI)	0% (0; 0-6)	67% (41; 55-78)	70% (21; 52-83)	68% (62; 58-77)
SD % (n; 95% CI)	59% (35; 47-71)	20% (12; 12-31)	17% (5; 7-34)	19% (17; 12-28)
PD % (n; 95% CI)	3% (2; 1-12)	0% (0; 0-6)	0% (0; 0-11)	0% (0; 0-4)
Not Evaluable % (n; 95% CI)	37% (22; 26-50)	13% (8; 7-24)	13% (4; 5-30)	13% (12; 8-22)
DOR (median range; months)		NR (0.03+ to 63.5+)	NR (8.0+ to 56.0+)	NR (0.03+ to 63.5+)

Data per April 30, 2021 cut-off
ORR=overall response rate. PD=progressive disease. RECIST=Response Evaluation Criteria in Solid Tumors, version 1.1. SD=stable disease. TVS=tumor volume score. DOR=duration of response.

About ENLIVEN

ENLIVEN is a global, double-blind, randomized, placebo-controlled, phase 3 trial that evaluated TURALIO in patients with symptomatic TGCT where 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, 120 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.

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 Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Additional efficacy outcome measures included response by TVS, a novel method designed specifically for TGCT, and range of motion. Results from this portion of the trial were published in *The Lancet*.

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 91 patients either crossed over from placebo to receive TURALIO 800 mg twice a day (without loading dose) or continued the dose of TURALIO received at the end of part 1 until tumor progression, toxicity, or study completion. Results from this portion of the trial were published in *The Oncologist*.

ENLIVEN enrolled 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 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 discovered by Daiichi Sankyo 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, including vanishing bile duct syndrome.**
- **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. Monitoring and prompt cessation of TURALIO may not eliminate the risk of serious and potentially fatal liver injury.**
- **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, including liver failure and life-threatening vanishing bile duct syndrome (VBDS), ductopenia, and symptomatic cholestasis (including severe pruritus) can occur in patients treated with TURALIO and can occur despite monitoring and prompt drug cessation.
- The mechanism of cholestatic hepatotoxicity is unknown and its occurrence cannot be predicted. It is unknown whether liver injury can also occur in the absence of increased transaminases.
- Of the first 609 patients who received TURALIO under the REMS program, 32 (5.3%) developed a liver injury event of concern, defined as any serious liver-related outcome or any liver abnormality that triggers drug discontinuation per the US Prescribing Information. These 32 patients developed liver toxicity within 71 days of the first dose of TURALIO; ten required hospitalization and two developed VBDS. Sixteen of the 32 patients had not fully recovered at the time of the analysis, including 6 patients followed for at least 6 months after discontinuation.
- Among 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 with a confirmed case of VBDS required a liver transplant.
- In ENLIVEN, 3 of 61 (5%) patients who received TURALIO developed signs of serious liver injury, defined as alanine aminotransferase (ALT) or aspartate 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 three 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. Refer patients to a hepatologist if liver tests do not return to normal. Rechallenge

with a reduced dose of TURALIO may result in a recurrence of increased serum transaminases, bilirubin, ALP or other signs of liver injury. 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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