SpringWorks Therapeutics Announces Long-Term Efficacy and Safety Data from Phase 3 DeFi Trial of OGSIVEO® (nirogacestat) in Adults with Desmoid Tumors to be Presented at the Connective Tissue Oncology Society (CTOS) 2024 Annual Meeting

November 7, 2024

– Long-term follow-up data highlight further reductions in tumor size, increase in ORR with additional CRs, sustained improvement in desmoid tumor symptoms, and consistent safety profile, now with a median duration of therapy of approximately 3 years –

STAMFORD, Conn., Nov. 07, 2024 (GLOBE NEWSWIRE) -- SpringWorks Therapeutics, Inc. (Nasdaq: SWTX), a commercial-stage biopharmaceutical company focused on severe rare diseases and cancer, today announced that long-term efficacy and safety data from the Phase 3 DeFi trial of nirogacestat in adults with progressing desmoid tumors will be presented as a late-breaking oral presentation at the Connective Tissue Oncology Society (CTOS) 2024 Annual Meeting, being held November 13-16, 2024, in San Diego, CA. These results, utilizing an August 2024 data cutoff date, showed that longer-term treatment with nirogacestat was associated with further reductions in tumor size, increase in objective response rate (ORR) with additional partial responses (PRs) and complete responses (CRs), sustained improvements in desmoid tumor symptoms including pain, and a consistent safety profile compared to the April 2022 data cut utilized for the primary results of the trial.

“Our findings demonstrate that longer-term nirogacestat treatment was associated with durable tumor size reductions, evidence of deepening responses, and sustained benefits in pain, physical functioning and other desmoid tumor symptoms,” said Ravin Ratan, M.D., M.Ed., Associate Professor, Department of Sarcoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center in Houston, and DeFi study investigator presenting the data at CTOS. “Given the oftentimes persistent and debilitating nature of desmoid tumors, these results are meaningful for patients and clinicians as they provide valuable insights on the longer-term use of this medicine.”

“We are pleased that the growing body of evidence from the DeFi trial continues to support the significant benefits that OGSIVEO is providing for patients with desmoid tumors,” said Jim Cassidy, M.D., Ph.D., Chief Medical Officer of SpringWorks Therapeutics. “It is also gratifying that feedback from the real-world setting is consistent with our clinical trial experience, with patients reporting rapid, sustained and continued symptomatic relief, which is contributing to their overall improved quality of life.”

Additional DeFi data to be presented at CTOS include an oral presentation of a post-hoc analysis assessing the effect of nirogacestat in subgroups of patients with desmoid tumors who have risk factors associated with poor prognosis and a poster on patients with *CTNNB1* and *APC* mutations.

Oral Presentations at the CTOS 2024 Annual Meeting

Nirogacestat treatment in adult patients with desmoid tumors: Long-term efficacy and safety from the Phase 3 DeFi trial
Date and Time: November 16, 3:30-4:30 p.m. PT (6:30-7:30 p.m. ET)

As previously reported, 70 patients were randomized to nirogacestat in the double-blind (DB) portion of the Phase 3 DeFi trial (NCT03785964); these patients achieved statistically and clinically significant improvement in progression-free survival (PFS) and ORR, as well as rapid and sustained improvement in pain, physical functioning, role functioning and overall quality of life, as compared to those randomized to placebo. At the primary analysis data cut-off date (April 2022), the median (range) duration of nirogacestat treatment was 20.6 (0.3-33.6) months. Following the DB portion of the study, patients could continue to receive nirogacestat as part of the open-label extension (OLE). As of this long-term follow-up analysis (August 2024 data cut-off date), the median (range) duration of nirogacestat treatment in these patients was 33.6 (0.3 to 60) months. The data being presented at CTOS evaluated the overall efficacy and safety of continuous nirogacestat treatment in patients initially randomized to nirogacestat in DeFi and further explored safety and efficacy analyses at milestones of one, two, three, and four years on treatment.

Results demonstrated that:

- Three new PRs and three new CRs were reported using the August 2024 versus the April 2022 data cut-off date, resulting in an ORR of 45.7% (34.3% PR, 11.4% CR) (N=70).
- The median best percent reduction from baseline in target tumor size by RECIST 1.1 with continuous nirogacestat treatment was −32.3% at year one (n=46) and −75.8% for patients completing at least four years (n=15) of treatment.
- Improvement in patient reported outcomes (PROs) of pain, desmoid tumor-specific symptom severity, and desmoid tumor-specific physical functioning, which occurred early (at Cycle 2, the first post-treatment timepoint evaluated as disclosed at the primary analysis) and were sustained with up to 45 months of treatment with nirogacestat.
- The most frequently reported treatment emergent adverse events (TEAEs) that occurred in ≥20% of patients receiving nirogacestat over the entire treatment period were diarrhea, nausea, fatigue, hypophosphatemia, and headache, and were generally consistent between the April 2022 and August 2024 data cutoffs. Most events were Grade 1 or 2, with first onset occurring in the first year of treatment for most patients. Overall, the incidence and severity of frequently reported TEAEs decreased through years two, three and four of treatment.

Efficacy of nirogacestat in patients with poor prognostic factors for desmoid tumors: patient-reported outcomes, progression-free survival, and objective response in the phase 3 DeFi trial
Date and Time: November 16, 3:30-4:30 p.m. PT (6:30-7:30 p.m. ET)

A post hoc analysis of the DeFi trial was conducted to assess the effect of nirogacestat on PFS, ORR and PROs in subgroups of patients with desmoid tumors who have risk factors associated with a poor prognosis: larger tumor size (>10 cm), younger age (≤30 years), specific types of *CTNNB1* gene mutations, and presence of pain at baseline. Results include:

- Treatment with nirogacestat led to consistent improvements in PFS, ORR and PROs versus placebo regardless of the patient subgroups.
- The ORR risk difference between nirogacestat and placebo ranged from 18.1% to 56.0%, favoring nirogacestat.
- Compared with placebo, patients treated with nirogacestat generally reported greater improvement from baseline at cycle 10 in PROs (pain, desmoid tumor-specific symptom burden, physical and role functioning, and overall quality of life) across subgroups of patient-related and tumor-related poor prognostic factors.
- The authors concluded that nirogacestat demonstrates uniform efficacy and consistent improvement in PROs across the desmoid tumor population.

Poster Presentations at the CTOS 2024 Annual Meeting

Descriptive evaluation of patients with desmoid tumor and co-occurring somatic mutations of *CTNNB1* and *APC* in the Phase 3 DeFi trial
Date and Time: November 14, 5:45-6:45 p.m. PT (8:45-9:45 p.m. ET)

This analysis identified three patients with desmoid tumors enrolled in the DeFi trial who had co-occurring somatic mutations of *CTNNB1* and *APC*, including two treated with nirogacestat. Both patients achieved a best overall response of partial response (with time to response of 6.0 and 13.8 months). Although the small number of patients limited a formal analysis, descriptive results suggest that patients with this mutational profile benefit from nirogacestat treatment in a manner that is generally consistent with the overall DeFi study population but may take longer to experience a treatment response.

About the DeFi Trial

DeFi (NCT03785964) is a global, randomized (1:1), multicenter, double-blind, placebo-controlled pivotal Phase 3 trial evaluating the efficacy, safety and tolerability of nirogacestat in adult patients with progressing desmoid tumors. The double-blind phase of the study randomized 142 patients (nirogacestat, n=70; placebo n=72) to receive 150 mg of nirogacestat or placebo twice daily. Key eligibility criteria included tumor progression by ≥20% as measured by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) within 12 months prior to screening. The primary endpoint was progression-free survival (PFS), as assessed by blinded independent central review, or death by any cause. Secondary and exploratory endpoints include safety and tolerability measures, objective response rate (ORR), duration of response, changes in tumor volume assessed by magnetic resonance imaging (MRI), and changes in patient-reported outcomes (PROs). DeFi includes an open-label extension phase, which is ongoing.

About Desmoid Tumors

Desmoid tumors (sometimes referred to as aggressive fibromatosis, or desmoid fibromatosis) are rare, aggressive, locally invasive tumors of the soft tissues that can be serious, debilitating, and, in rare cases when vital structures are impacted, life-threatening.[1,2]

Desmoid tumors are most commonly diagnosed in patients between the ages of 20 and 44 years, with a two-to-three times higher prevalence in females.[3,4] It is estimated that there are 1,000-1,650 new cases diagnosed per year in the United States.[4,5,6]

Although they do not metastasize, desmoid tumors are associated with recurrence rates of up to 77% after surgical resection.[3,7,8] Desmoid tumor experts and treatment guidelines now recommend systemic therapies as first-line intervention instead of surgery for most tumor locations requiring treatment.[8]

About OGSIVEO® (nirogacestat)

OGSIVEO (nirogacestat) is an oral, selective, small molecule gamma secretase inhibitor approved in the United States for the treatment of adult patients with progressing desmoid tumors who require systemic treatment.

OGSIVEO is not approved for the treatment of any other indication in the United States, or for any indication in any other jurisdiction by any other health authority.

SpringWorks is also evaluating nirogacestat as a potential treatment for patients with ovarian granulosa cell tumors and for patients with multiple myeloma as part of several B-cell maturation agent (BCMA) combination therapy regimens in collaboration with leaders in industry and academia.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Diarrhea:** Diarrhea, sometimes severe, can occur in patients treated with OGSIVEO. Diarrhea occurred in 84% of patients treated with OGSIVEO, and included Grade 3 events in 16% of patients. Median time to first diarrhea event was 9 days (range: 2 to 434 days). Monitor patients and manage using antidiarrheal medications. Modify dose as recommended.
- **Ovarian Toxicity:** Female reproductive function and fertility may be impaired in patients treated with OGSIVEO. Impact on fertility may depend on factors like duration of therapy and state of gonadal function at time of treatment. Long-term effects of OGSIVEO on fertility have not been established. Advise patients on the potential risks for ovarian toxicity before initiating treatment. Monitor patients for changes in menstrual cycle regularity or the development of symptoms of estrogen deficiency, including hot flashes, night sweats, and vaginal dryness.
- **Hepatotoxicity:** ALT or AST elevations occurred in 30% and 33% of patients, respectively. Grade 3 ALT or AST elevations (>5 × ULN) occurred in 6% and 2.9% of patients. Monitor liver function tests regularly and modify dose as recommended.

- **Non-Melanoma Skin Cancers:** New cutaneous squamous cell carcinoma and basal cell carcinoma occurred in 2.9% and 1.4% of patients, respectively. Perform dermatologic evaluations prior to initiation of OGSIVEO and routinely during treatment.
- **Electrolyte Abnormalities:** Decreased phosphate (65%) and potassium (22%) occurred in OGSIVEO-treated patients. Phosphate <2 mg/dL occurred in 20% of patients. Grade 3 decreased potassium occurred in 1.4% of patients. Monitor phosphate and potassium levels regularly and supplement as necessary. Modify dose as recommended.
- **Embryo-Fetal Toxicity:** OGSIVEO can cause fetal harm when administered to pregnant women. Oral administration of nirogacestat to pregnant rats during the period of organogenesis resulted in embryo-fetal toxicity and death at maternal exposures below human exposure at the recommended dose of 150 mg twice daily. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment with OGSIVEO and for 1 week after the last dose.

ADVERSE REACTIONS

- The most common (≥15%) adverse reactions were diarrhea (84%), ovarian toxicity (75% in the 36 females of reproductive potential), rash (68%), nausea (54%), fatigue (54%), stomatitis (39%), headache (30%), abdominal pain (22%), cough (20%), alopecia (19%), upper respiratory tract infection (17%), and dyspnea (16%).
- Serious adverse reactions occurred in 20% of patients who received OGSIVEO. Serious adverse reactions occurring in ≥2% of patients were ovarian toxicity (4%).
- The most common laboratory abnormalities (≥15%) were decreased phosphate, increased urine glucose, increased urine protein, increased AST, increased ALT, and decreased potassium.

DRUG INTERACTIONS

- **CYP3A Inhibitors and Inducers:** Avoid concomitant use with strong or moderate CYP3A inhibitors (including grapefruit products, Seville oranges, and starfruit) and strong or moderate CYP3A inducers.
- **Gastric Acid Reducing Agents:** Avoid concomitant use with proton pump inhibitors and H2 blockers. If concomitant use cannot be avoided, OGSIVEO can be staggered with antacids (e.g., administer OGSIVEO 2 hours before or 2 hours after antacid use).
- Consult the full Prescribing Information prior to and during treatment for important drug interactions.

USE IN SPECIFIC POPULATIONS

- Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with OGSIVEO and for 1 week after the last dose.

To report suspected adverse reactions, contact SpringWorks Therapeutics at 1-888-400-SWTX (1-888-400-7989) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full U.S. Prescribing Information for OGSIVEO for more information.

About SpringWorks Therapeutics

SpringWorks is a commercial-stage biopharmaceutical company applying a precision medicine approach to developing and delivering life-changing medicines for people with severe rare diseases and cancer. OGSIVEO® (nirogacestat), approved in the United States for the treatment of adult patients with progressing desmoid tumors who require systemic treatment, is the Company's first FDA-approved therapy. SpringWorks also has a diversified targeted therapy pipeline spanning solid tumors and hematological cancers, with programs ranging from preclinical development through advanced clinical trials. In addition to its wholly owned programs, SpringWorks has also entered into multiple collaborations with innovators in industry and academia to unlock the full potential for its portfolio and create more solutions for patients in need.

For more information, visit www.springworkstx.com and follow @SpringWorksTx on X (formerly Twitter), LinkedIn, and YouTube.

SpringWorks Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, relating to our business, operations, and financial conditions, including but not limited to current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development and commercialization plans, our preclinical and clinical results, as well as relating to other future conditions. Words such as, but not limited to, "look forward to," "believe," "expect," "anticipate," "estimate," "intend," "plan," "would," "should" and "could," and similar expressions or words, identify forward-looking statements. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Any forward-looking statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks relating to: (i) the fact that topline or interim data from clinical studies may not be predictive of the final or more detailed results of such study or the results of other ongoing or future studies, (ii) the timing of our planned regulatory submissions and interactions, including the timing and outcome of decisions made by the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies, (iii) whether FDA, EMA, or other regulatory authorities will require additional information or further studies, or may fail or refuse to approve or may delay approval of our product candidates, including nirogacestat and mirdametinib, (iv) our ability to obtain regulatory approval of any of our product candidates or maintain regulatory approvals granted for our products,

(v) our ability to maintain adequate patent protection and successfully enforce patent claims against third parties, and (vi) our ability to meet any specific milestones set forth herein.

Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

For further information regarding the risks, uncertainties and other factors that may cause differences between SpringWorks' expectations and actual results, you should review the "Risk Factors" in Item 1A of Part II of SpringWorks' Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, as well as discussions of potential risks, uncertainties and other important factors in SpringWorks' subsequent filings.

Contacts

Media:
Media@Springworkstx.com

Investors:
Investors@Springworkstx.com

References

1. Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. *Pathologica*. 2021;113(2):70-84. doi:10.32074/1591-951X-213.
2. Penel N, Chibon F, Salas S. Adult desmoid tumors: biology, management and ongoing trials. *Curr Opin Oncol*. 2017;29(4):268-274. doi:10.1097/CCO.0000000000000374.
3. Skubitz KM. Biology and treatment of aggressive fibromatosis or desmoid tumor. *Mayo Clin Proc*. 2017;92(6):947-964. doi:10.1016/j.mayocp.2017.02.012.
4. van Broekhoven DLM, Grünhagen DJ, den Bakker MA, van Dalen T, Verhoef C. Time trends in the incidence and treatment of extra-abdominal and abdominal aggressive fibromatosis: a population-based study. *Ann Surg Oncol*. 2015;22(9):2817-2823. doi:10.1245/s10434-015-4632-y.
5. Orphanet Report Series: Rare Diseases collection. Prevalence and incidence of rare diseases: bibliographic data. Number 1, January 2022. Accessed November 5, 2024. https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf.
6. U.S. Department of Commerce. News Blog. U.S. population estimated at 332,403,650 on Jan. 1, 2022. Accessed November 5, 2024. https://www.commerce.gov/news/blog/2022/01/us-population-estimated-332403650-jan-1-2022.
7. Easter DW, Halasz NA. Recent trends in the management of desmoid tumors. Summary of 19 cases and review of the literature. *Ann Surg*. 1989;210(6):765-769. doi:10.1097/00000658-198912000-00012.
8. Gronchi A, Kasper B, et al. Desmoid Tumor Working Group. The management of desmoid tumours: a joint global consensus-based guideline approach for adult and paediatric patients. *Eur J Cancer*. 2020;127:96-107. doi:10.1016/j.ejca.2019.11.013.