SpringWorks Therapeutics Announces European Medicines Agency Validation for Marketing Authorization Application of Nirogacestat for the Treatment of Adults with Desmoid Tumors

February 29, 2024

Application based on Phase 3 DeFi trial in which nirogacestat significantly improved progression-free survival and objective response rate compared to placebo, with rapid and sustained improvements in symptom burden including pain, physical and role functioning, and quality of life

STAMFORD, Conn., Feb. 29, 2024 (GLOBE NEWSWIRE) -- SpringWorks Therapeutics, Inc. (Nasdaq: SWTX), a commercial-stage biopharmaceutical company focused on severe rare diseases and cancer, announced today that the European Medicines Agency (EMA) has validated the Marketing Authorization Application (MAA) for nirogacestat, an oral gamma secretase inhibitor, for the treatment of adults with desmoid tumors. If approved, nirogacestat will be the first therapy to receive marketing authorization in the European Union (EU) for the treatment of desmoid tumors. Nirogacestat previously received Orphan Drug designation from the European Commission for the treatment of soft tissue sarcoma.

“The validation of our marketing authorization application is an important step towards bringing nirogacestat to patients with desmoid tumors in the European Union who currently do not have an approved therapy,” said Saqib Islam, Chief Executive Officer of SpringWorks. “We look forward to working with the EMA on this important submission.”

The MAA submission is based on results from the Phase 3 DeFi trial. In DeFi, nirogacestat met the primary endpoint of improving progression-free survival (PFS), demonstrating a statistically significant improvement over placebo with a 71% reduction in the risk of disease progression (hazard ratio (HR) = 0.29 (95% CI: 0.15, 0.55); p< 0.001). Median PFS was not reached in the nirogacestat arm and was 15.1 months in the placebo arm. Confirmed objective response rate (ORR) based on blinded independent central review of Response Evaluation Criteria in Solid Tumors v1.1 was 41% with nirogacestat versus 8% with placebo (p<0.001); the complete response rate was 7% in the nirogacestat arm and 0% in the placebo arm. Nirogacestat also demonstrated early and sustained improvements in patient-reported outcomes (PROs) measured as of the cycle 10 assessment, including pain (p<0.001), desmoid tumor-specific symptoms (p<0.001), physical/role functioning (p<0.001), and overall health-related quality of life (p≤0.01). Nirogacestat exhibited a manageable safety and tolerability profile. The most common adverse events (>15%) reported in patients receiving nirogacestat were diarrhea, ovarian toxicity, rash, nausea, fatigue, stomatitis, headache, abdominal pain, cough, alopecia, upper respiratory tract infection, and dyspnea. The DeFi trial results were published in the March 9, 2023 edition of the *New England Journal of Medicine* and presented during a Presidential Symposium at the European Society for Medical Oncology Congress 2022.[1, 2]

“Desmoid tumors can have a significant impact on patients’ lives and there is a pressing need for a new treatment for patients in Europe,” said Bernd Kasper, M.D., Ph.D., University of Heidelberg, Mannheim Cancer Center, Mannheim, Germany and Principal Investigator of the DeFi trial. “In the DeFi trial, nirogacestat demonstrated significant improvements across progression-free survival, objective response rate, and patient-reported outcomes, and had a safety profile that supports long-term dosing. These results support that nirogacestat will be a practice-changing therapy if approved by the EMA.”

In November 2023, the U.S. Food and Drug Administration approved OGSIVEO™ (nirogacestat) for the treatment of adults with progressing desmoid tumors who require systemic treatment. The U.S. prescribing information includes the following Warnings & Precautions: diarrhea, ovarian toxicity, hepatotoxicity, non-melanoma skin cancers, electrolyte abnormalities, and embryo-fetal toxicity. **Please see below for additional Important Safety Information.**

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.[3,4]

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. [5,6] In the European Union, the incidence of desmoid tumors is estimated to be approximately 3-5 cases per million per year.[7]

Although they do not metastasize, desmoid tumors are associated with recurrence rates of up to 77% after surgical resection.[5,8,9] Desmoid tumor experts and treatment guidelines now recommend systemic therapies as first-line intervention instead of surgery for most tumor locations requiring treatment.[9]

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 occurred in 84% of patients treated with OGSIVEO. Grade 3 events occurred in 16% of patients. 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 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:** Oral administration of nirogacestat to pregnant rats during the period of organogenesis resulted in embryo-fetal toxicity 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, ovarian toxicity, rash, nausea, fatigue, stomatitis, headache, abdominal pain, cough, alopecia, upper respiratory tract infection, and dyspnea.
- 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.

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, the market potential of OGSIVEO for adult patients with desmoid tumors, expectations regarding timing and results of the EMA's review of the MAA for nirogacestat, including the adequacy of the data contained in the MAA to serve as the basis for marketing approval of nirogacestat for the treatment of desmoid tumors in the European Union, 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) our expectations regarding the potential clinical benefit of nirogacestat for patients with

desmoid tumors, (ii) estimates regarding the number of adult patients who are diagnosed with desmoid tumors annually per year in Europe and the potential market for nirogacestat, (iii) 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, (iv) 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, (v) 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, (vi) our ability to obtain regulatory approval of any of our product candidates or maintain regulatory approvals granted for our products, (vii) our ability to maintain adequate patent protection and successfully enforce patent claims against third parties, and (viii) 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 I of SpringWorks' Annual Report on Form 10-K for the year ended December 31, 2023, as well as discussions of potential risks, uncertainties and other important factors in SpringWorks' subsequent filings.

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