SpringWorks Therapeutics Announces New England Journal of Medicine Publication of Phase 3 DeFi Trial Evaluating Nirogacestat in Adults with Desmoid Tumors

March 8, 2023

– Nirogacestat Treatment Significantly Improved Progression-Free Survival, Objective Response Rate and Key Patient Reported Outcomes –

– New Drug Application Under Review by the FDA with PDUFA Action Date of August 27, 2023 –

STAMFORD, Conn., March 08, 2023 (GLOBE NEWSWIRE) -- SpringWorks Therapeutics, Inc. (Nasdaq: SWTX), a clinical-stage biopharmaceutical company focused on developing life-changing medicines for patients with severe rare diseases and cancer, announced today that data from the Phase 3 DeFi trial of nirogacestat, an investigational oral gamma secretase inhibitor, in adult patients with progressing desmoid tumors, were published in the *New England Journal of Medicine* (*NEJM*). Results from this study were previously presented at the European Society for Medical Oncology (ESMO) Congress in September 2022.

“Desmoid tumors are aggressive soft tissue tumors that can lead to substantial negative impacts on patients’ lives,” said Mrinal M. Gounder, M.D., sarcoma medical oncologist at Memorial Sloan Kettering Cancer Center (MSK) in New York City, an investigator in the DeFi trial and first author of the *NEJM* publication. “In the Phase 3 DeFi trial, nirogacestat demonstrated significant clinical efficacy and substantially improved pain, symptom burden, physical and role functioning, and health-related quality of life in desmoid tumor patients. Importantly, nirogacestat exhibited a manageable safety profile. These results represent a noteworthy therapeutic advance for patients.”

As reported in the *NEJM* publication and previously presented at ESMO, the DeFi trial met its primary endpoint of improving progression-free survival (PFS), demonstrating a statistically significant improvement for nirogacestat 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. Nirogacestat improved PFS across pre-specified subgroups, including sex, tumor location, focality, prior treatment status (including treatment-naïve or previous treatment with chemotherapy or tyrosine kinase inhibitors), prior surgery, mutation status, and history of familial adenomatous polyposis. Confirmed objective response rate (complete response + partial response) based on RECIST 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 statistically significant and clinically meaningful improvements in patient-reported outcomes (PROs), which were key secondary endpoints of the study. Specifically, at Cycle 10 nirogacestat significantly reduced pain (p<0.001) and other desmoid tumor-specific symptoms (p<0.001) and also significantly improved physical/role functioning (p<0.001) and overall health-related quality of life (p≤0.01).[1] Improvements in most PROs occurred early (at Cycle 2, the first post-treatment timepoint evaluated) and were sustained throughout the trial.

At the time of primary analysis data cutoff on April 7, 2022, the median follow-up for PFS was 15.9 months. Nirogacestat exhibited a manageable safety profile in the DeFi trial, with 95% of all treatment-emergent adverse events (TEAEs) reported as Grade 1 or 2. The most frequently reported TEAEs that occurred in participants receiving nirogacestat were diarrhea (84%), nausea (54%), fatigue (51%), hypophosphatemia (42%), and maculopapular rash (32%). Ovarian dysfunction, which was defined by events of amenorrhea, premature menopause, menopause, and ovarian failure, was observed in 75% (27/36) of women of childbearing potential receiving nirogacestat. As of the extended follow-up date of July 20, 2022, these events resolved in 74% (20/27) of the affected participants, including 64% (9/14) of participants who remained on nirogacestat treatment and 100% (11/11) of participants who were off of treatment for any reason.

“There is a great unmet need for patients with desmoid tumors as there are no approved therapies. We are very pleased that nirogacestat provided benefit across all prespecified subgroups in the study, which underscores the potential to broadly serve desmoid tumor patients regardless of tumor location, prior treatments or surgery, or genetic mutation,” said Saqib Islam, Chief Executive Officer of SpringWorks. “We look forward to working with the FDA as they review our NDA, and we are excited by the opportunity to make a profound impact on this underserved patient population.”

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[1] 2-sided p-values are shown here to be consistent with *NEJM* publication standards.

About the DeFi Trial

DeFi (NCT03785964) is a global, randomized (1:1), double-blind, placebo-controlled 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, 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 are rare, aggressive, locally invasive, and potentially morbid tumors of the soft tissues.[1,2] While they do not metastasize, desmoid tumors are associated with a high rate of recurrence.[2,3,4] Sometimes referred to as aggressive fibromatosis, or desmoid fibromatosis, these soft tissue tumors can be serious, debilitating, and, in rare cases when vital structures are impacted, they can be life-threatening.[2,5]

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.[4,6,7,8] It is estimated that there are 1,000-1,650 new cases diagnosed per year in the United States.[7,8,9]

Historically, desmoid tumors were treated with surgical resection, but this approach has become less favored due to a high recurrence rate after surgery.[1,4,10] There are currently no FDA-approved therapies for the treatment of desmoid tumors.

About Nirogacestat

Nirogacestat is an oral, selective, small molecule gamma secretase inhibitor in Phase 3 clinical development for desmoid tumors and in Phase 2 clinical development for ovarian granulosa cell tumors. Nirogacestat is an investigational drug for which safety and efficacy have not been established.

Gamma secretase cleaves multiple transmembrane protein complexes, including Notch, which is believed to play a role in activating pathways that contribute to growth of desmoid and ovarian granulosa cell tumors. Gamma secretase has also been shown to directly cleave membrane-bound B cell maturation antigen (BCMA), resulting in the release of the BCMA extracellular domain (ECD) from the cell surface. By inhibiting gamma secretase, membrane-bound BCMA can be preserved, increasing target density while reducing levels of soluble BCMA ECD, which may serve as decoy receptors for BCMA-directed therapies. Nirogacestat's ability to enhance the activity of BCMA-directed therapies has been observed in preclinical models of multiple myeloma. SpringWorks is evaluating nirogacestat as a BCMA potentiator and has several collaborations with industry-leading BCMA developers to evaluate nirogacestat in combinations across modalities. SpringWorks has also formed research collaborations with Fred Hutchinson Cancer Research Center and Dana-Farber Cancer Institute to further characterize the ability of nirogacestat to modulate BCMA and potentiate BCMA-directed therapies using a variety of preclinical multiple myeloma models.

The U.S. Food and Drug Administration (FDA) has accepted a New Drug Application (NDA) for nirogacestat for the treatment of adults with desmoid tumors, which is being reviewed under the FDA's Real-Time Oncology Review program. The NDA was granted Priority Review designation and has been given a Prescription Drug User Fee Act (PDUFA) action date of August 27, 2023. The FDA also granted Fast Track and Breakthrough Therapy Designations to nirogacestat for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis. In addition, nirogacestat has received Orphan Drug Designation from the FDA for the treatment of desmoid tumors and from the European Commission for the treatment of soft tissue sarcoma.

About SpringWorks Therapeutics

SpringWorks is a clinical-stage biopharmaceutical company applying a precision medicine approach to acquiring, developing and commercializing life-changing medicines for patients living with severe rare diseases and cancer. SpringWorks has a differentiated targeted oncology pipeline spanning solid tumors and hematological cancers, including two late-stage clinical trials in rare tumor types as well as several programs addressing highly prevalent, genetically defined cancers. SpringWorks' strategic approach and operational excellence in clinical development have enabled it to rapidly advance its two lead product candidates into late-stage clinical trials while simultaneously entering into multiple shared-value partnerships with innovators in industry and academia to unlock the full potential for its portfolio and create more solutions for patients with cancer. For more information, visit www.springworkstx.com and follow @SpringWorksTx on Twitter and LinkedIn.

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 plans, our preclinical and clinical results, the potential for nirogacestat to become an important new treatment for patients with desmoid tumors, expectations regarding the timing and results of the FDA's review of the NDA for nirogacestat, including the FDA's PDUFA target action date for the NDA, and the adequacy of the data contained in the NDA to serve as the basis for an approval of nirogacestat for the treatment of adults with desmoid tumors, 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 press release 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 press release, including, without limitation, risks relating to: (i) the success and timing of our product development activities, including the initiation and completion of SpringWorks' clinical trials, (ii) our expectations regarding the potential clinical benefit to patients with desmoid tumors based upon the results of our DeFi trial, (iii) the fact that topline or interim data from a clinical study 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 success and timing of our collaboration partners' ongoing and planned clinical trials, (v) 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) and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; (vi) whether FDA or other regulatory authorities will require additional information or further studies, or may fail or refuse to approve or may delay approval of our drug candidates, including nirogacestat, (vii) our ability to obtain and maintain regulatory approval of any of our product candidates, (viii) our plans to research, discover and develop additional product candidates, (ix) our ability to enter into collaborations for the development of new product candidates, (x) our ability to establish manufacturing capabilities, and our and our collaboration partners' abilities to manufacture our product candidates and scale production, (xi) our ability to meet any specific milestones set forth herein, and (xii) uncertainties and assumptions regarding the impact of the COVID-19 pandemic on SpringWorks' business, operations, clinical trials, supply chain, strategy, goals and anticipated timelines.

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, 2022, as well as discussions of potential risks, uncertainties and other important factors in SpringWorks' subsequent filings.

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