SpringWorks Therapeutics Announces Presentation of Additional Data from Phase 3 DeFi Trial of Nirogacestat in Adults with Desmoid Tumors at the 2023 ASCO Annual Meeting

May 25, 2023

- Nirogacestat Treatment Demonstrated Rapid, Sustained and Consistent Reductions in Pain Compared to Placebo Using Multiple Assessment Tools -

- Substantial Reductions in MRI-Assessed Tumor Volume and T2 Hyperintensity Observed with Nirogacestat Compared to Placebo -

STAMFORD, Conn., May 25, 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, today announced that additional data from the Phase 3 DeFi trial assessing the impact of nirogacestat, an investigational gamma secretase inhibitor, on pain, tumor volume and T2 hypersensitivity in adults with desmoid tumors will be presented at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting, being held June 2-6, 2023. Data from the DeFi trial were previously presented at the European Society for Medical Oncology Congress in September 2022 and published in the March 9, 2023 edition of the *New England Journal of Medicine.*[1]

“Pain is the most debilitating symptom reported by patients living with desmoid tumors and reducing this burden is a key treatment goal for physicians. We are pleased with the robust data observed using multiple assessment tools demonstrating clinically significant reductions in pain with nirogacestat treatment,” said Jim Cassidy, M.D., Ph.D., Chief Medical Officer of SpringWorks. “We are also encouraged by the substantial reductions in tumor volume and T2 hyperintensity seen in the DeFi study, which are consistent with the significant improvements in progression-free survival and objective response rate previously reported, and further elaborate on the activity profile of nirogacestat in desmoid tumors. We believe that nirogacestat has the potential to be a significant advance for patients and we look forward to our continued discussions with the FDA as they review our New Drug Application.”

Poster Presentations at the 2023 ASCO Annual Meeting

Impact of nirogacestat on pain, a key symptom in patients with desmoid tumors (DT): results from the Phase 3 DeFi study (Poster #: 498)

Abstract #: 11564

Poster Session Date and Time: Saturday, June 3, 1:15 – 4:15 p.m. CT (2:15 – 5:15 p.m. ET)

As previously reported, in the DeFi trial (NCT03785964), nirogacestat met its primary endpoint of significantly improving progression-free survival compared to placebo in adult patients with progressing desmoid tumors (hazard ratio: 0.29 [95% CI, 0.15–0.55]; P<0.001). Nirogacestat also achieved a significant and clinically meaningful reduction in pain severity, a key secondary endpoint, compared with placebo at Cycle 10 (P<0.001). A manageable safety profile was observed with nirogacestat, with 95% of all treatment-emergent adverse events (TEAEs) reported as either 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%).

During the DeFi study, patients also completed three prespecified assessment tools that included pain measurements to characterize the impact of nirogacestat on this symptom. Changes from baseline in pain severity were compared between treatment arms at Cycle 10 per the prespecified exploratory endpoints. Statistically significant and clinically meaningful reductions in pain were observed with nirogacestat compared with placebo at Cycle 10 across all three assessment tools evaluated in DeFi: the Brief Pain Inventory-Short Form (BPI-SF), the GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom Scale (GODDESS-DTSS), and the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30).

The following results from the assessment tools will be presented at ASCO:

- Nirogacestat significantly reduced pain severity per the BPI-SF “worst pain” score (0–10 range) by 1.55 points, compared with 0.05 points with placebo (P<0.001) at Cycle 10.
- Nirogacestat significantly reduced pain per the GODDESS-DTSS pain score (0–10 range) by 1.78 points, compared with an increase in pain of 0.34 points with placebo (P<0.001) at Cycle 10. The GODDESS-DTSS pain score includes questions about worst pain, dull pain, and shooting pain.
- Nirogacestat significantly reduced pain per the EORTC QLQ-C30 pain subscale (0–100 range) by 22.36 points, compared with an increase in pain of 7.00 points with placebo (P<0.001) at Cycle 10. This pain sub-scale includes questions about pain and its interference with daily activities.
- A statistically significant greater proportion of patients achieved a clinically meaningful pain reduction with nirogacestat treatment compared with placebo at Cycle 10 per the BPI-SF “worst pain” score (P=0.001) and the GODDESS-DTSS pain score (P<0.001).
- Reductions in pain were rapid, becoming evident as early as Cycle 2 (the first post-treatment timepoint evaluated), and these reductions were sustained through to the end of the double-blind phase of the DeFi trial.

“Many patients with desmoid tumors live with severe, chronic pain that significantly impacts their quality of life,” said Winette T.A. van der Graaf, M.D., Ph.D., Group Leader and Medical Oncologist, Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands and

investigator in the DeFi trial. “It is very encouraging that nirogacestat demonstrated a rapid, sustained and consistent reduction in different aspects of pain during the trial, including worst pain, dull pain, shooting pain, and pain interference with people’s ability to perform daily activities.”

Tumor volume and T2 hyperintensity changes from DeFi: a Phase 3, randomized, controlled trial of nirogacestat in patients with desmoid tumors (Poster #: 448)

Abstract #: 11514

Poster Session Date and Time: Saturday, June 3, 4:30 – 6:00 p.m. CT (5:30 – 7:00 p.m. ET); Poster Discussion at 4:30 p.m. CT (5:30 p.m. ET).

Exploratory analyses were conducted to evaluate changes in MRI-assessed desmoid tumor volume and T2 signal intensity in the Phase 3 DeFi trial. Specifically, volumetric MRI and T2 hyperintensity of each patient’s largest target tumor were evaluated at screening and every 6 cycles thereafter during the double-blind phase of the study. The use of MRI to assess changes in tumor volume or T2 signal intensity represent a novel imaging technique that could have prognostic or predictive value in patients with desmoid tumors.

Treatment with nirogacestat led to significantly improved median best change from baseline in MRI-assessed tumor volume of the largest target tumor compared with placebo (–59% versus +14%; P<0.001). Treatment with nirogacestat also led to significant improvement in the median best percent change in T2 hyperintensity signal ratio of the largest target tumor compared with placebo (–55% versus –21%; P<0.001).

“The Phase 3 DeFi study is the largest trial to date to prospectively evaluate volumetric MRI and T2 hyperintensity results in patients with desmoid tumors,” said Thierry Alcindor, M.D., MSc, Medical Oncologist, Dana-Farber Cancer Institute and investigator in the DeFi trial. “These results are consistent with the significant improvements in progression-free survival and objective response rate achieved with nirogacestat compared to placebo in DeFi and represent an alternative approach to imaging patients with desmoid tumors that may better capture the asymmetric and irregular growth of these tumors.”

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, potentially morbid tumors of the soft tissues.[2,3] While they do not metastasize, desmoid tumors are associated with a high rate of recurrence.[3,4,5] Sometimes referred to as aggressive fibromatosis, or desmoid fibromatosis, these soft tissue tumors can be serious, debilitating, and in rare cases when vital organs are impacted, they can be life-threatening.[3,6]

Desmoid tumors are most commonly diagnosed in patients between the ages of 20 to 44 years, with a two-to-three times higher prevalence in females.[5,7,8,9] It is estimated that there are 1,000-1,650 new cases diagnosed per year in the United States.[8,9,10]

Historically, desmoid tumors were treated with surgical resection, but this approach has become less favored due to a high recurrence rate after surgery.[2,5,11] 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. 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. Nirogacestat is an investigational drug for which safety and efficacy have not been established.

The U.S. Food and Drug Administration (FDA) has accepted the 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.

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 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.

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, 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) 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, (iii) the success and timing of our collaboration partners' ongoing and planned clinical trials, (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) and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies, (v) 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, (vi) our ability to obtain and maintain regulatory approval of any of our product candidates, (vii) our plans to research, discover and develop additional product candidates, (viii) our ability to maintain adequate patent protection and successfully enforce patent claims against third parties, (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 II of SpringWorks' Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, as well as discussions of potential risks, uncertainties and other important factors in SpringWorks' subsequent filings.

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