SpringWorks Therapeutics Announces Abstracts Accepted for Presentation at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting

April 24, 2024

– Results from Phase 2b ReNeu trial of mirdametinib in NF1-PN accepted for oral presentation –

– Additional data from the Phase 3 DeFi trial of OGSIVEO® (nirogacestat) in adults with desmoid tumors also accepted for presentations at ASCO –

STAMFORD, Conn., April 24, 2024 (GLOBE NEWSWIRE) -- SpringWorks Therapeutics, Inc. (Nasdaq: SWTX), a commercial-stage biopharmaceutical company focused on severe rare diseases and cancer, today announced that data from the Phase 2b ReNeu trial evaluating mirdametinib, an investigational MEK inhibitor, in pediatric and adult patients with neurofibromatosis type 1-associated plexiform neurofibromas (NF1-PN) will be presented in an oral presentation at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting, being held May 31 to June 4, 2024. SpringWorks recently initiated a rolling submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for mirdametinib in pediatric and adult patients with NF1-PN.

Additional data from the Phase 3 DeFi trial of OGSIVEO® (nirogacestat) in adults with desmoid tumors were also accepted for presentation at ASCO, including an abstract describing the onset and resolution of ovarian toxicity for desmoid tumor patients treated with nirogacestat, as well as two additional sub-group analyses evaluating nirogacestat in desmoid tumor patients with poor prognostic factors and in those with adenomatous polyposis coli (APC) mutations.

“The Phase 2b ReNeu trial data are the cornerstone of our NDA for mirdametinib in NF1-PN, and we are very pleased that these data were accepted for an oral presentation at ASCO,” said Jim Cassidy, M.D., Ph.D., Chief Medical Officer of SpringWorks. “We also look forward to presenting additional data from our Phase 3 DeFi trial and believe the results will further reinforce the robust safety and efficacy profile of nirogacestat in adult patients with desmoid tumors.”

Details of the presentations are as follows:

Presentation Title	Presenter	Presentation Details
ReNeu: A pivotal phase 2b trial of mirdametinib in children and adults with neurofibromatosis type 1 (NF1)-associated symptomatic inoperable plexiform neurofibroma (PN)	Christopher Moertel, M.D.	**Date and Time:** June 3, 8:00 - 9:30 a.m. CDT **Type:** Rapid Oral Abstract **Session:** Developmental Therapeutics: Molecularly Targeted Agents and Tumor Biology **Abstract #:** 3016
Monitoring ovarian function in oncology studies: Results and insights from the DeFi phase 3 study of nirogacestat in desmoid tumor	Elizabeth Loggers, M.D., Ph.D.	**Date and Time:** May 31, 2:45 - 4:15 p.m. CDT **Type:** Rapid Oral Abstract **Session:** Sarcoma **Abstract #:** 11520
Efficacy of nirogacestat in patients with poor prognostic factors for desmoid tumors: Analyses from the randomized phase 3 DeFi study	Bruno Vincenzi, M.D., Ph.D.	**Date and Time:** June 1, 1:30 - 4:30 p.m. CDT **Type:** Poster **Session:** Sarcoma **Abstract #:** 11556
Efficacy and safety of nirogacestat in patients with desmoid tumor and adenomatous polyposis coli (APC) mutation: phase 3 DeFi analyses	Bernd Kasper, M.D., Ph.D.	**Date and Time:** June 1, 1:30 - 4:30 p.m. CDT **Type:** Poster **Session:** Sarcoma **Abstract #:** 11558

About the ReNeu Trial

ReNeu (NCT03962543) is an ongoing, multi-center, open-label Phase 2b trial evaluating the efficacy, safety, and tolerability of mirdametinib in patients two years of age and older with an inoperable NF1-associated PN causing significant morbidity. The study enrolled 114 patients to receive mirdametinib at a dose of 2 mg/m^2 twice daily (maximum dose of 4 mg twice daily) without regard to food. Mirdametinib was administered orally in a 3-week on, 1-week off dosing schedule and has a pediatric formulation (dispersible tablet) for patients who cannot swallow a pill. The primary endpoint of the ReNeu trial was confirmed objective response rate defined as ≥ 20% reduction in target tumor volume as measured by MRI and assessed by blinded independent central review. Secondary endpoints included safety and tolerability, duration of response, and changes from baseline in patient reported outcomes.

About NF1-PN

Neurofibromatosis type 1 (NF1) is a rare genetic disorder that arises from mutations in the NF1 gene, which encodes for neurofibromin, a key suppressor of the MAPK pathway.[1,2] NF1 is the most common form of neurofibromatosis, with an estimated global birth incidence of approximately 1 in 2,500 individuals, and approximately 100,000 patients living with NF1 in the United States.[3,4] The clinical course of NF1 is heterogeneous and manifests in a variety of symptoms across numerous organ systems, including abnormal pigmentation, skeletal deformities, tumor growth and

neurological complications, such as cognitive impairment.[5] Patients with NF1 have an eight to 15-year mean reduction in their life expectancy compared to the general population.[2]

NF1 patients have approximately a 30-50% lifetime risk of developing plexiform neurofibromas, or PN, which are tumors that grow in an infiltrative pattern along the peripheral nerve sheath and that can cause severe disfigurement, pain and functional impairment; in rare cases, NF1-PN may be fatal.[6,7] Patients with NF1-PN can also experience additional manifestations, including neurocognitive deficits and developmental delays. NF1-PNs are most often diagnosed in the first two decades of life.[6] These tumors can be aggressive and are associated with clinically significant morbidities; typically, they grow more rapidly during childhood.[8,9]

Surgical removal of these tumors is challenging due to the infiltrative tumor growth pattern along nerves and can lead to permanent nerve damage and disfigurement.[10] MEK inhibitors have emerged as a validated class of treatment for NF1-PN.[11]

About Mirdametinib

Mirdametinib is a potent, oral, allosteric small molecule MEK inhibitor in development as a monotherapy treatment for neurofibromatosis type 1-associated plexiform neurofibromas (NF1-PN) and low-grade glioma (LGG), and as a combination therapy for the treatment of several subsets of biomarker-defined metastatic solid tumors. Mirdametinib is an investigational drug for which safety and efficacy have not been established.

Mirdametinib is designed to inhibit MEK1 and MEK2, which occupy pivotal positions in the MAPK pathway. The MAPK pathway is a key signaling network that regulates cell growth and survival and that plays a central role in multiple oncology and rare disease indications when genetically altered.

The FDA and the European Commission have granted Orphan Drug designation for mirdametinib for the treatment of NF1. The FDA has also granted Fast Track designation for the treatment of patients ≥ 2 years of age with NF1-PN that are progressing or causing significant morbidity and Rare Pediatric Disease designation for the treatment of NF1.

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 (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.[12,13]

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.[14,15] It is estimated that there are 1,000-1,650 new cases diagnosed per year in the United States.[15,18,19]

Although they do not metastasize, desmoid tumors are associated with recurrence rates of up to 77% after surgical resection.[14,16,17] Desmoid tumor experts and treatment guidelines now recommend systemic therapies as first-line intervention instead of surgery for most tumor locations requiring treatment.[17]

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, the potential for mirdametinib to become an important new treatment for pediatric and adult patients with NF1-PN, the potential for the results of the Phase 2b ReNeu clinical trial to support an NDA submission, the timing of our planned NDA submission for mirdametinib, our plans for seeking regulatory approval for and making mirdametinib available to NF1-PN patients, if approved, 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 mirdametinib for patients with NF1-PN, (ii) estimates regarding the global birth incidence of NF1-PN and the number of patients living with NF1-PN in the United States and the potential market for mirdametinib, (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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