SpringWorks Therapeutics Initiates Rolling Submission of New Drug Application to the FDA for Mirdametinib for the Treatment of Children and Adults with NF1-PN

March 4, 2024

STAMFORD, Conn., March 04, 2024 (GLOBE NEWSWIRE) -- SpringWorks Therapeutics, Inc. (Nasdaq: SWTX), a commercial-stage biopharmaceutical company focused on severe rare diseases and cancer, announced today that the Company has initiated a rolling submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for mirdametinib, an investigational MEK inhibitor, in pediatric and adult patients with neurofibromatosis type 1-associated plexiform neurofibromas (NF1-PN).

“There is tremendous potential for mirdametinib to address the substantial needs that exist for children and adults with NF1-PN, and the initiation of our rolling NDA submission brings us one step closer toward our goal of providing these patients with a best-in-class therapy that could make a significant impact on their lives,” said Saqib Islam, Chief Executive Officer of SpringWorks. “We are excited to advance the regulatory filing for our second product and look forward to working closely with the FDA on their review of our application.”

The NDA submission includes data from the Phase 2b ReNeu trial, a multi-center, open-label study that opened across 50 sites in the U.S. and enrolled 114 patients across two cohorts (pediatric and adult). The primary endpoint was confirmed objective response rate (ORR), defined as ≥ 20% reduction in target tumor volume as measured by MRI and assessed by Blinded Independent Central Review (BICR). As of the data cutoff date of September 20, 2023, the BICR-confirmed objective response rate was 52% in pediatric patients and 41% in adult patients. Mirdametinib treatment showed deep and durable responses and demonstrated significant improvements in key secondary patient-reported outcome measures. Pediatric and adult patients in the ReNeu trial experienced statistically significant improvements from baseline in pain, quality of life, and physical function, as assessed across multiple patient-reported outcome tools. Mirdametinib was generally well tolerated in the trial, with the majority of adverse events (AEs) being Grade 1 or Grade 2. The most frequently reported AEs were rash, diarrhea, and vomiting in the pediatric cohort and rash, diarrhea, and nausea in the adult cohort.

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. In July 2023, the FDA granted mirdametinib Rare Pediatric Disease designation for the treatment of NF1, which provides eligibility for a priority review voucher upon FDA approval. SpringWorks expects to complete the NDA submission in the second quarter of 2024.

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 is 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 is confirmed objective response rate defined as ≥ 20% reduction in target tumor volume as measured by MRI and assessed by BICR. Secondary endpoints include 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.[9] These tumors can be aggressive and are associated with clinically significant morbidities; typically, they grow more rapidly during childhood.[10,11]

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.[12] MEK inhibitors have emerged as a validated class of treatment for NF1-PN.[13]

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 U.S. Food and Drug Administration (FDA) and the European Commission granted Orphan Drug designation for mirdametinib for the treatment of NF1, and the FDA granted Fast Track designation for the treatment of patients ≥ 2 years of age with NF1-PN that are progressing or causing significant morbidity.

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, and expectations regarding the receipt of a priority review voucher upon the potential approval of mirdametinib, 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.

Contacts

Kim Diamond
Vice President, Communications and Investor Relations
Phone: 203-561-1646
Email: kdiamond@springworkstx.com

Samantha Hilson Sandler
Senior Director, Investor Relations
Phone: 203-461-5501
Email: samantha.sandler@springworkstx.com

References

1. Yap YS, McPherson JR, Ong CK, et al. The NF1 gene revisited - from bench to bedside. *Oncotarget*. 2014;5(15):5873-5892. doi:10.18632/oncotarget.2194.
2. Rasmussen S, Friedman J. NF1 Gene and Neurofibromatosis 1. *Am J Epidemiol*. 2000;151(1):33-40. doi:10.1093/oxfordjournals.aje.a010118.
3. CTF: Children's Tumor Foundation. New and Improved: The way to talk about NF. Press release. May 9, 2023. Accessed February 2, 2024.
4. Lee: Lee TJ, et al. Incidence and prevalence of neurofibromatosis type 1 and 2: a systematic review and meta-analysis. Orphanet J Rare Dis. 2023;18(1):292. Published 2023 Sep 14. doi:10.1186/s13023-023-02911-2)
5. Weiss BD, Wolters PL, Plotkin SR, et al. NF106: A Neurofibromatosis Clinical Trials Consortium Phase II Trial of the MEK Inhibitor Mirdametinib (PD-0325901) in Adolescents and Adults With NF1-Related Plexiform Neurofibromas. *Journal of*

Clinical Oncology. 2021;JCO.20.02220.doi.org/10. 1200/JCO.20.02220.
6. Prada: Prada CE, Rangwala FA, Martin LJ, et al. Pediatric plexiform neurofibromas: impact on morbidity and mortality in neurofibromatosis type 1. J Pediatr. 2012;160(3):461-467.
7. Miller: Miller DT, et al. Health Supervision for Children With Neurofibromatosis Type 1. Pediatrics. 2019;143(5):e20190660.
8. Ferner R. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. *The Lancet Neurology*. 2007;6(4):340-351. doi:10.1016/s1474-4422(07)70075-3.
9. Prada C, Rangwala F, Martin L, et al. Pediatric Plexiform Neurofibromas: Impact on Morbidity and Mortality in Neurofibromatosis Type 1. *J Pediatr*. 2012;160(3):461-467. doi:10.1016/j.jpeds.2011.08.051.
10. Gross A, Singh G, Akshintala S, et al. Association of plexiform neurofibroma volume changes and development of clinical morbidities in neurofibromatosis 1. *Neuro Oncol*. 2018;20(12):1643-1651. doi:10.1093/neuonc/noy067.
11. Nguyen R, Dombi E, Widemann B, et al. Growth dynamics of plexiform neurofibromas: a retrospective cohort study of 201 patients with neurofibromatosis 1. *Orphanet J Rare Dis*. 2012;7(1):75. doi:10.1186/1750-1172-7-75.
12. Needle M, Cnaan A, Dattilo J, et al. Prognostic signs in the surgical management of plexiform neurofibroma: The Children's Hospital of Philadelphia experience, 1974-1994. J Pediatr. 1997;131(5):678-682. doi:10.1016/s0022-3476(97)70092-1.
13. Ferner R. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. The Lancet Neurology. 2007;6(4):340-351. doi:10.1016/s1474-4422(07)70075-3.