



SpringWorks Therapeutics Announces Publication of the Pivotal Phase 2b ReNeu Trial Evaluating Mirdametinib in Adults and Children with NF1-PN in the Journal of Clinical Oncology

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- Mirdametinib treatment demonstrated significant confirmed objective response rates and a manageable safety profile in adults and children with NF1-PN –
- Patients achieved deep and durable reductions in tumor volume and early, sustained and clinically meaningful improvements in pain and health-related quality of life –
- New Drug and Marketing Authorization Applications under review; U.S. PDUFA action date set for February 28, 2025 –

STAMFORD, Conn., Nov. 11, 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 pivotal, Phase 2b ReNeu trial of mirdametinib, an investigational MEK inhibitor, in adult and pediatric patients with neurofibromatosis type 1-associated plexiform neurofibromas (NF1-PN), were published online in the *Journal of Clinical Oncology* (JCO). Data from ReNeu, which is a multi-center, single arm trial, were previously presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting. The JCO e-publication can be accessed at the following link: <https://ascopubs.org/doi/pdf/10.1200/JCO.24.01034>.

"Plexiform neurofibromas can cause extreme pain, disfigurement, compression of internal organs, and impaired physical function. There is a substantial unmet need for a highly effective and well tolerated systemic therapy for these patients," said Christopher Moertel, M.D., Medical Director, Pediatric Neuro-Oncology and Neurofibromatosis Programs and Kenneth and Betty Jayne Dahlberg Professor of Pediatrics, University of Minnesota and lead author of the JCO publication. "The deep tumor volume reductions and significant improvements in pain and other quality of life measures that we saw in the ReNeu trial, as well as having a formulation option for young children or those who have difficulty swallowing, underscore the potential for mirdametinib to be a valuable new treatment option for adults and children with NF1-PN."

As of the data cutoff of September 20, 2023, the ReNeu trial met its primary endpoint of confirmed objective response rate (ORR), as assessed by blinded independent central review. During the 24-cycle treatment phase (approximately 22 months), the ORR was 41% (95% CI, 29 to 55; n=24/58) in adults and 52% (95% CI, 38 to 65; n=29/56) in children receiving mirdametinib treatment. An efficacy analysis that also included patients who achieved a confirmed objective response after 24 cycles of mirdametinib treatment resulted in an ORR of 45% in adults (n=26/58) and 54% in pediatric (n=30/56) patients. Of the patients who achieved a confirmed objective response during the treatment phase, 96% of adults and 100% of children had durable responses at the time of data cut-off, with 75% of adults and 76% of children having met or exceeded 12 months in response. The median time to onset of confirmed response was 7.8 months (range: 4 to 19) in adults and 7.9 months (range: 4.1 to 18.8) in children. The median duration of treatment at data cutoff was 21.8 months (range: 0.4 to 45.6) in adults and 22 months (range: 1.6 to 40.0) in children, and the median duration of response had not been reached in either cohort.

Tumor volume reductions were deep and durable during the course of the study. The median best percentage change in target PN volume was -41% (range: -90 to 13%) in adults and -42% (range: -91 to 48%) in children. Among those with a confirmed objective response, 62% of adults and 52% of children achieved a best percent reduction in target tumor volume from baseline of >50%. From baseline to Cycle 13, both cohorts reported significant and clinically meaningful improvement in patient- or parent proxy-reported secondary endpoint outcome measures of worst tumor pain severity, pain interference, and health-related quality of life that began early and were sustained during treatment. These improvements began early and were generally sustained at the majority of timepoints over the course of the study. In addition, through an exploratory analysis, the tablet for oral suspension formulation of mirdametinib demonstrated high acceptability by patients and caregivers, providing a dosing option for patients with swallowing difficulties such as young children and adults with tumors in the head and neck region.

Mirdametinib was generally well tolerated in the ReNeu trial, with the majority of adverse events (AEs) being Grade 1 or 2. The most commonly reported treatment-related adverse events (TRAEs) occurring in ≥20% of adults were dermatitis acneiform (78%), diarrhea (48%), nausea (36%), vomiting (28%) and fatigue (21%). The most commonly reported TRAEs occurring in ≥20% of children were dermatitis acneiform (43%), diarrhea (38%), paronychia (30%; infection of the tissue adjacent to a fingernail or toenail), nausea (21%), ejection fraction decreased (20%), and increased blood creatine phosphokinase (20%). Among all study participants, 22% of adults and 9% of children discontinued treatment due to AEs.

"ReNeu is the largest multicenter trial conducted to date in patients with NF1-PN and we are very pleased that the JCO publication will serve as an important resource to further disseminate the robust efficacy and safety data of mirdametinib to the broader scientific and clinical community," said Jim Cassidy, M.D., Ph.D., Chief Medical Officer, SpringWorks Therapeutics. "We look forward to continuing to work with the FDA and EMA as they review our applications and are excited by the opportunity to make a meaningful impact on this underserved patient community."

About the ReNeu Trial

ReNeu ([NCT03962543](#)) is an ongoing, multi-center, open-label, single arm, Phase 2b trial evaluating the efficacy, safety, and tolerability of mirdametinib in patients ≥2 years of age with an inoperable NF1-associated PN causing significant morbidity. The trial enrolled 114 patients to receive mirdametinib at a dose of 2 mg/m² 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 as either a capsule or tablet for oral suspension. The primary endpoint is confirmed objective response rate assessed by proportion of patients with a ≥20% reduction in target tumor volume on consecutive scans during the 24 cycle treatment phase, as measured by MRI and assessed by blinded independent central review. Secondary endpoints include safety and tolerability, duration of response, and changes in patient reported outcomes from baseline to Cycle 13. The treatment phase of the trial is complete, and results were presented at the 2024

American Society of Clinical Oncology Annual Meeting. Patients who completed the treatment phase were eligible to continue receiving treatment in the optional long-term follow up portion of the study, which is ongoing.

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 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 8 to 15-year mean reduction in their life expectancy compared to the general population.⁴

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} 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, CNS-penetrant, 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 plays a central role in multiple cancers and rare diseases when genetically altered.

The U.S. Food and Drug Administration (FDA) has accepted a New Drug Application (NDA) for mirdametinib in adults and children with NF1-PN. The NDA was granted Priority Review designation and has been given a Prescription Drug User Fee Act (PDUFA) action date of February 28, 2025. The European Medicines Agency (EMA) has validated the Marketing Authorization Application (MAA) for mirdametinib for the treatment of adult and pediatric patients with NF1-PN.

In addition, the FDA and the European Commission previously 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 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](https://twitter.com/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, whether the preclinical and clinical results of the mirdametinib studies will meet the regulatory requirements for an approval by the FDA or by the EMA of mirdametinib for the treatment of pediatric and adult patients with NF1-PN, the potential for mirdametinib to become an important new treatment for patients with NF1-PN, our plans for seeking regulatory approval for and making mirdametinib available for 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 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) our limited experience as a commercial company, (ii) the success and timing of our product development activities, including the initiation and completion of our clinical trials, (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 FDA, 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, (vi) our ability to obtain regulatory approval of any of our product candidates or maintain regulatory approvals granted for our products, (vii) our plans to research, discover and develop additional product candidates, (viii) our ability to enter into collaborations for the development of new product candidates and our ability to realize the benefits expected from such collaborations, (ix) our ability to maintain adequate patent protection and successfully enforce patent claims against third parties, (x) our ability to establish manufacturing capabilities, and our and our collaboration partners' abilities to manufacture our product candidates and scale production, and (xi) 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 II of SpringWorks' Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, as well as discussions of potential risks, uncertainties and other important factors in SpringWorks' subsequent filings.

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