SpringWorks Therapeutics Announces Clinical Data Presentations of Nirogacestat in Combination with BCMA-Directed Therapies at the European Hematology Association 2023 Congress

May 11, 2023

STAMFORD, Conn., May 11, 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 two collaborator-sponsored clinical studies evaluating nirogacestat, an investigational oral gamma secretase inhibitor, in combination with B-cell maturation agent (BCMA) therapies in patients with relapsed or refractory multiple myeloma (RRMM) will be presented at the European Hematology Association (EHA) 2023 Congress, taking place in Frankfurt, Germany from June 8-11, 2023. Updated clinical data from the Phase 1/2 study sponsored by GSK plc (LSE/NYSE: GSK) evaluating nirogacestat in combination with low-dose belamaf (belantamab mafodotin-blmf), GSK's antibody-drug conjugate targeting BCMA, in patients with RRMM will be presented in a poster presentation. In addition, new data from the Phase 1b clinical trial sponsored by Janssen Research & Development, LLC (Janssen) evaluating nirogacestat in combination with teclistamab, Janssen's bispecific antibody targeting BCMA and CD3, will be presented in an oral presentation.

"These data provide further validation of the mechanistic approach supporting nirogacestat's ability to enhance the activity of BCMA-directed therapies across modalities. We are pleased that updated data from the GSK-sponsored trial continue to support our thesis that the combination with nirogacestat may further optimize the benefit-risk profile of belamaf monotherapy. We are also encouraged that the Janssen-sponsored trial establishes an initial tolerability, safety and efficacy profile for combining nirogacestat with a BCMA bispecific antibody," said Saqib Islam, Chief Executive Officer of SpringWorks. "Our goal is to improve the outcomes for patients with multiple myeloma and we believe that developing a robust clinical data set across BCMA modalities and treatment lines can help us demonstrate where within the multiple myeloma treatment landscape nirogacestat has the greatest opportunity to maximize clinical benefit."

Poster Presentation at the EHA 2023 Congress

Low-dose belantamab mafodotin (belamaf) in combination with nirogacestat vs belamaf monotherapy in patients with relapsed/refractory multiple myeloma (RRMM): Phase 1/2 DREAMM-5 Platform Sub-study 3

Abstract #: P913

Session Date and Time: Friday, June 9, 18:00-19:00 CEST (12:00-1:00 p.m. ET)

This ongoing Phase 1/2 trial, which is sub-study 3 of GSK's DREAMM-5 platform trial (NCT04126200), aims to determine if low-dose belamaf in combination with nirogacestat results in similar efficacy with an improved ocular toxicity profile compared to belamaf alone at a higher dose. Patients were randomized 1:1 to 0.95 mg/kg belamaf every three weeks (Q3W, low-dose) combined with 100 mg twice daily nirogacestat or belamaf 2.5 mg/kg Q3W monotherapy.

Initial results from the pre-planned interim analysis were presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting. Updated data from a randomized cohort expansion in which 34 patients received low-dose belamaf plus nirogacestat and 37 patients received belamaf monotherapy will be presented at EHA. Patients had a median of 5 (range 3-14) prior lines of therapy. As of the December 9, 2022 data cut-off, patients received a median of 4 (range 1-20) cycles of the combination and a median of 3 (range 1-9) monotherapy cycles.

Overall response rate (ORR) in the low-dose belamaf (0.95 mg/kg Q3W) plus nirogacestat arm was 29%, with 1 patient (3%) achieving a complete response (CR), 5 patients (15%) achieving a very good partial response (VGPR), and 4 patients (12%) achieving a partial response (PR). ORR in the belamaf monotherapy arm (2.5 mg/kg Q3W) was 38%, with no patient achieving a CR, 5 patients (14%) achieving a VGPR, and 9 patients (24%) achieving a PR. Per the prespecified analysis plan, ORR was also calculated incorporating prior ORR for low-dose belamaf plus nirogacestat from the dose exploration cohort of this DREAMM-5 sub-study 3 and from the DREAMM-2 belamaf monotherapy study; ORR across these studies was 36% in the low-dose belamaf plus nirogacestat combination arm and 33% in the belamaf monotherapy arm.

Safety results showed a substantial reduction of high-grade ocular events in the low-dose belamaf plus nirogacestat arm compared to the monotherapy arm of belamaf at a higher dose. Specifically, Grade 3 ocular events were 29% for low-dose belamaf + nirogacestat versus 59% for belamaf monotherapy (per the KVA scale); no Grade 4 ocular events or new toxicities occurred in either arm.

"These clinical data suggest that combining nirogacestat with a low dose of belamaf may result in comparable efficacy to a higher monotherapy belamaf dose, while simultaneously substantially reducing the frequency high-grade ocular adverse events," said Jim Cassidy, M.D., Ph.D., Chief Medical Officer of SpringWorks. "We are encouraged by these results and we look forward to the further evaluation of this combination with standard of care agents in relapsed refractory multiple myeloma as well as its potential in earlier lines of therapy."

Oral Presentation at the EHA 2023 Congress

Teclistamab (tec) + nirogacestat (niro) in relapsed/refractory multiple myeloma (RRMM): the Phase 1b MajesTEC-2 study

Session Title: MM Clinical: New combinations and novel targets

Abstract #: S194

Session Date and Time: Saturday, June 10, 12:30-12:45 CEST (6:30-6:45 a.m. ET)

This ongoing Phase 1b trial (NCT04722146), which is part of a multi-arm trial being conducted by Janssen, aims to evaluate the safety, tolerability and preliminary efficacy of nirogacestat in combination with teclistamab in patients with RRMM. Patients in the study had received ≥3 prior lines of therapy or were double refractory to a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) and triple exposed to a PI, an IMiD, and an anti-CD38 antibody, with progressive disease within 12 months of their last line of therapy. Three dose levels were evaluated: 1) teclistamab 720 µg/kg weekly plus concurrent nirogacestat 100 mg twice daily starting with the first dose of teclistamab (n=8); 2) teclistamab 720 µg/kg weekly plus once daily nirogacestat 100 mg starting after teclistamab step-up dosing (n=7); and 3) 1500 µg/kg (which is the FDA-approved dose) weekly plus once daily nirogacestat 100 mg starting after teclistamab step-up dosing (n=13).

As of the December 16, 2022 data cut-off, 28 patients received the combination of teclistamab and nirogacestat across three different dose levels. Median prior lines of therapy was 4 (range 2-12) and median duration of treatment was 9.4 months (range 0.13-19.7) for teclistamab and 4.7 months for nirogacestat (range 0.16-13.0).

The most frequent (>20%) treatment-emergent adverse events (TEAEs) for all doses were neutropenia (82%), cytokine release syndrome, or CRS (75%), diarrhea (64%), injection-site erythema (54%), decreased appetite (50%), fatigue (42.9%), and anemia (35%). Of eight patients who received teclistamab 720 µg/kg plus concurrent nirogacestat, two dose-limiting toxicities were reported (one Grade 3 GI bleed and Grade 3 diarrhea; one Grade 3 immune effector cell-associated neurotoxicity syndrome, or ICANS). In addition, one patient had Grade 3 CRS and one patient had Grade 3 confusional state. These events led to the decision to delay the starting dose of nirogacestat in subsequent cohorts. In the dose level 2 and dose level 3 cohorts, when nirogacestat was added after teclistamab step-up dosing and reduced to once daily, no dose-limiting toxicities or Grade 3 CRS or neurologic adverse events were reported.

The overall response rate was 71% for dose level 1, 57% for dose level 2, and 92% for dose level 3. The total ORR across the three dose levels was 78% and all responses were VGPR or better. The percentage of patients experiencing complete response (CR) or stringent CR (sCR) was 43%, 57% and 54%, respectively (total percentage of CR or sCR across the three cohorts was 52%).

“This is the first clinical data set of nirogacestat in combination with a BCMA bispecific agent. We believe these data provide important insights into a tolerable treatment schedule and early evidence of an encouraging ORR, including promising CR and sCR rates, when combining nirogacestat with this BCMA modality,” commented Dr. Cassidy. “Nirogacestat is being evaluated in combination with three other bispecific agents and we look forward to generating more data with these combinations.”

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, 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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