Nurix Therapeutics Presents Data from Studies of Its Targeted Protein Degraders in B Cell Malignancies and Initiates Expansion of NX-2127 Phase 1b Trial in Diffuse Large B Cell Lymphoma and Mantle Cell Lymphoma Indications

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Initiation of NX-2127 Phase 1b expansion cohort in patients with diffuse large B cell lymphoma (DLBCL) was informed by a rapid and sustained complete response; Phase 1b expansion cohort also initiated in patients with mantle cell lymphoma (MCL)

Clinical biomarker data from Phase 1a trial of NX-5948 demonstrate rapid, robust, and sustained degradation of Bruton's tyrosine kinase (BTK) and support ongoing investigation of B cell malignancies

NX-5948 crosses the blood brain barrier and catalyzes robust and efficient degradation of BTK, improving survival in an intracranial patient-cell-derived preclinical model of central nervous system (CNS) lymphoma

SAN FRANCISCO, June 14, 2023 (GLOBE NEWSWIRE) -- Nurix Therapeutics, Inc. (Nasdaq: NRIX), a clinical-stage biopharmaceutical company developing targeted protein modulation drugs designed to treat patients with hematologic malignancies and solid tumors, today announced the presentation of clinical and preclinical data from its targeted protein degradation programs, NX-5948 and NX-2127, which are being evaluated in ongoing Phase 1 clinical trials in patients with relapsed/refractory B cell malignancies. These data are being presented at the 17th International Conference on Malignant Lymphoma (ICML) which is being held June 13-17, in Lugano, Switzerland.

"The positive data emerging from our two targeted BTK degrader clinical programs are guiding our strategy on how best to deploy each drug candidate's strengths and have informed our decision to initiate Phase 1b dose expansion for NX-2127 in patients with DLBCL and MCL where this drug has been well tolerated and has shown promising activity," said Robert J. Brown, M.D., executive vice president and head of early clinical development at Nurix. "The observed rapid and sustained complete response with NX-2127 as a once daily oral single agent therapy in a relapsed/refractory patient with DLBCL supports our decision to advance this program into a Phase 1b expansion cohort. This exciting result is consistent with our findings in other non-Hodgkin lymphoma indications such as mantle cell lymphoma."

Both orally available compounds are efficient degraders of BTK, a key therapeutic target in the treatment of B-cell malignancies including primary CNS lymphoma. Limitations of current covalent and non-covalent BTK inhibitors include the susceptibility to mutational escape as a basis for resistance. Recent evidence also suggests certain resistance mutations are catalytically inactive yet maintain the ability to drive cell growth through a putative scaffolding function of the protein. Nurix's BTK degraders have the potential to address these limitations of BTK inhibitors and provide a new therapeutic option for patients.

"The significant preclinical activity demonstrated in an aggressive, patient-derived CNS lymphoma model conducted in the laboratory of Dr. James Rubenstein at UCSF provides strong support for the inclusion of primary CNS lymphoma patients in our ongoing NX-5948 clinical trial," said Gwenn Hansen, chief scientific officer of Nurix. "We remain enthusiastic about NX-5948's differentiated profile, including potent and sustained BTK degradation, activity against treatment-emergent BTK mutations, and the ability to cross the blood brain barrier. Further updates from both programs are anticipated in the second half of 2023."

Details of the ICML Presentations

- A poster presentation titled "Proof of concept of NX-2127, a first-in-class Bruton's Tyrosine Kinase (BTK) dual-targeted protein degrader with immunomodulatory activity, in patients with DLBCL" disclosed updated safety and pharmacodynamic (PD) data from patients treated in the ongoing Phase 1 study of NX-2127 and highlighted case studies of two patients with DLBCL from the Phase 1a dose escalation portion of the trial demonstrating clinical activity of NX-2127. One patient, who entered the study with Stage IV DLBCL having received and failed four prior lines of systemic therapy, was treated at the 300mg once daily dose of NX-2127 and experienced a complete response at the first assessment (week 8), which was confirmed at week 16 and maintained through week 24. As of this press release, the patient remains on study with more than 12 months of follow up. A second patient treated at the lower dose of 100mg of NX-2127, also with four prior lines of systemic therapy for DLBCL, experienced stable disease followed by progressive disease. The NX-2127 Phase 1b dose expansion cohorts in DLBCL and MCL will focus on 300mg once daily dosing. Updated demographic and safety data were presented from 37 patients (14 with non-Hodgkin lymphoma and 23 with chronic lymphocytic leukemia) enrolled and treated as of January 14, 2023. Patients were heavily pre-treated with a median of four (range 2–11) prior lines of systemic therapy. The data demonstrate that NX-2127 treatment was well tolerated with safety findings consistent with prior disclosures. NX-2127 treatment resulted in rapid and sustained BTK degradation and degradation of cereblon neosubstrate

IKZF1 in the anticipated therapeutic range.

- A second poster presentation titled “Robust Bruton’s tyrosine kinase (BTK) degradation with NX-5948, an oral BTK degrader, in a first-in-human phase 1a trial in patients with relapsed/refractory B cell malignancies” disclosed initial demographics and pharmacokinetic (PK)/pharmacodynamic (PD) data as of December 1, 2022, from the first seven patients enrolled in the ongoing Phase 1a trial in patients with relapsed or refractory B cell malignancies. The data include patients in the dose-escalation portion of the trial who received daily oral doses of NX-5948 at 50 mg (n=4) or 100 mg (n=3). The study data include patients from a range of non-Hodgkin lymphoma indications including DLBCL (n=2), MCL (n=2), marginal zone lymphoma (MZL) (n=2), and follicular lymphoma (FL) (n=1). All patients had received and failed multiple prior lines of therapy (median=4, range 3–10). The data suggest that NX-5948 exhibits dose-proportional pharmacokinetics, with rapid absorption and a half-life that supports daily dosing, as well as exposures (both AUC and Cmax) that increase with dose. NX-5948 resulted in rapid, robust, and sustained BTK degradation in all patients dosed, regardless of their absolute BTK starting level or tumor type.

- A third poster presentation titled “BTK degradation as a novel therapeutic strategy in relapsed CNS lymphoma: Preclinical proof of concept studies in intracranial patient-derived model” describes preclinical results demonstrating the potential utility of NX-5948 in addressing the unmet need in patients with CNS lymphoma, which could include both primary and secondary CNS lymphoma. In this study the pharmacodynamic activity of NX-5948 was evaluated in an intracranial model of CNS lymphoma using patient-derived SC1 cells. SC1 cells are derived from a patient with highly refractory CD79b and EVT6-mutant large B-cell secondary CNS lymphoma, resistant to R-CHOP, high-dose methotrexate/rituximab, etoposide, Ara-C and irradiation. Upon intracranial implantation in RAG-/- mice, SC1 cells grow aggressively. Oral administration of NX-5948 in mice bearing established intracranial SC1 tumors yielded 98% degradation of BTK in SC1 lymphoma cells isolated six hours after NX-5948 dosing, as quantified by immunoblot analysis. Daily treatment with NX-5948 was associated with significant prolongation of survival compared to control, and to mice treated with daily ibrutinib ($p= 8.6x10^{-5}$; N=6 mice/cohort). Prolongation of survival was further evident following cessation of dosing at 100 days. Taken together, these preclinical results support the rationale for including patients with CNS lymphoma in the ongoing Phase 1 study of NX-5948.

- A fourth poster presentation titled “Drug-resistance mutations in BTK occur in distinct enzymatic classes and are overcome by BTK degradation” is an encore presentation of the oral presentation from the American Society of Hematology annual meeting in December 2022 that was for the ongoing 2023 series “Best of ASH” presented at multiple venues. The presentation highlights the discovery that Nurix’s BTK degraders are capable of overcoming treatment-emergent BTK inhibitor resistance mutations. This collaborative work from Nurix and investigators at the University of Miami and Memorial Sloan Kettering Cancer Center detail the emergence of new BTK inhibitor resistance mutations that lack BTK’s enzymatic function but still drive tumor growth. These newly identified “kinase deficient” and “kinase dead” mutations underscore the importance of BTK’s scaffolding function, which is uniquely addressable by the BTK degrader modality. In the presentation, five different clinically emergent BTK resistance mutations were analyzed and categorized as kinase proficient, kinase deficient, or kinase dead, each conferring a different spectrum of resistance to available therapies. NX-2127 was found to be broadly active against each of these mutations. These findings translated into clinically meaningful BTK degradation in the Phase 1 clinical trial and clinical activity independent of baseline BTK mutations.

Nurix’s ICML presentations are available on the Posters and Presentations section of the scientific resources page of the Nurix website.

NX-2127 Clinical Trial Update
Nurix is announcing plans to initiate two new Phase 1b dose expansion cohorts in the ongoing Phase 1a/1b clinical trial of NX-2127 in patients with relapsed or refractory B-cell malignancies. The new cohorts include patients with relapsed or refractory DLBCL who have failed at least two prior lines of therapy and patients with relapsed or refractory MCL who have failed at least two prior lines of therapy. The expansion protocol provides for treatment with once daily oral NX-2127 at a dose of 300mg. The decision to open a DLBCL and MCL expansion cohort was informed by emerging clinical activity in the Phase 1a dose escalation including the rapid, robust, and prolonged clinical response observed in the DLBCL patient described in the IMCL presentation.

About NX-2127
NX-2127 is a novel bifunctional molecule that degrades BTK and cereblon neosubstrates Ikaros (IKZF1) and Aiolos (IKZF3). NX-2127 is currently being evaluated in a Phase 1 clinical trial in patients with relapsed or refractory B cell malignancies. Additional information on the ongoing clinical trial can be accessed at www.clinicaltrials.gov (NCT04830137).

About NX-5948
NX-5948 is an investigational, orally bioavailable, small molecule degrader of BTK that, unlike NX-2127, has been designed to lack cereblon immunomodulatory activity. NX-5948 is currently being evaluated in a Phase 1 clinical trial in patients with relapsed or refractory B cell malignancies. Additional information on the ongoing clinical trial can be accessed at clinicaltrials.gov (NCT05131022).

About Nurix Therapeutics, Inc.
Nurix Therapeutics is a clinical stage biopharmaceutical company focused on the discovery, development and commercialization of small molecule therapies based on the modulation of cellular protein levels as a novel treatment approach for cancer and other challenging diseases. Leveraging extensive expertise in E3 ligases together with proprietary DNA-encoded libraries, Nurix has built

DELigase, an integrated discovery platform to identify and advance novel drug candidates targeting E3 ligases, a broad class of enzymes that can modulate proteins within the cell. Nurix's drug discovery approach is to either harness or inhibit the natural function of E3 ligases within the ubiquitin proteasome system to selectively decrease or increase cellular protein levels. Nurix's wholly owned pipeline includes targeted protein degraders of Bruton's tyrosine kinase, a B-cell signaling protein, and inhibitors of Casitas B-lineage lymphoma proto-oncogene B, an E3 ligase that regulates T cell activation. Nurix is headquartered in San Francisco, California. For additional information visit http://www.nurixtx.com.

Forward Looking Statement

This press release contains statements that relate to future events and expectations and as such constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. When or if used in this press release, the words "anticipate," "believe," "could," "estimate," "expect," "intend," "may," "outlook," "plan," "predict," "should," "will," and similar expressions and their variants, as they relate to Nurix, may identify forward-looking statements. All statements that reflect Nurix's expectations, assumptions or projections about the future, other than statements of historical fact, are forward-looking statements, including, without limitation, statements regarding the tolerability, safety profile, therapeutic potential and other advantages of NX-2127 and NX-5948; the planned timing and conduct of the clinical trials for NX-2127 and NX-5948; the planned timing for the provision of updates and findings from Nurix's clinical trials; and the extent to which Nurix's drug candidates and scientific approach may potentially address a broad range of diseases. Forward-looking statements reflect Nurix's current beliefs, expectations, and assumptions. Although Nurix believes the expectations and assumptions reflected in such forward-looking statements are reasonable, Nurix can give no assurance that they will prove to be correct. Forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and changes in circumstances that are difficult to predict, which could cause Nurix's actual activities and results to differ materially from those expressed in any forward-looking statement. Such risks and uncertainties include, but are not limited to: (i) whether Nurix will be able to successfully conduct Phase 1 clinical trials for NX-2127 and NX-5948 and receive results on its expected timelines, or, at all; (ii) the unexpected emergence of adverse events or other undesirable side effects during clinical development; (iii) whether Nurix will be able to successfully complete clinical development for NX-2127 and NX-5948; (iv) the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; (v) whether regulatory authorities will be satisfied with the results from Nurix's clinical studies; (vi) whether Nurix will be able to obtain regulatory approval of and ultimately commercialize its drug candidates; (vii) whether Nurix will be able to fund development activities and achieve development goals; (viii) the impact of macroeconomic conditions and global events on Nurix's clinical trials and operations; and (ix) other risks and uncertainties described under the heading "Risk Factors" in Nurix's Quarterly Report on Form 10-Q for the fiscal quarter ended February 28, 2023, and other SEC filings. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. The statements in this press release speak only as of the date of this press release, even if subsequently made available by Nurix on its website or otherwise. Nurix disclaims any intention or obligation to update publicly any forward-looking statements, whether in response to new information, future events, or otherwise, except as required by applicable law.

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