Nuvalent Announces First Patient Dosed in ARROS-1 Phase 1/2 Clinical Trial of NVL-520, its Novel ROS1-selective Inhibitor

ARROS-1 trial enrolling patients with advanced ROS1-positive NSCLC and other solid tumors

Clinical development for parallel lead program, NVL-

655, in ALK-positive cancers expected to begin in first half of 2022

CAMBRIDGE, Mass., Jan. 7, 2022 /PRNewswire/ -- Nuvalent, Inc. (Nasdaq: NUVL), a biotechnology company creating *precisely* targeted therapies for clinically proven kinase targets in cancer, today announced that the first patient has been dosed in ARROS-1, its Phase 1/2 clinical trial evaluating NVL-520 in patients with advanced ROS1-positive non-small cell lung cancer (NSCLC) and other advanced solid tumors. NVL-520, Nuvalent's lead product candidate, is a novel ROS1-selective inhibitor designed to address the clinical challenges of emergent treatment resistance, CNS adverse events, and brain metastases that may limit the use of currently available ROS1 kinase inhibitors.

"The initiation of patient dosing with NVL-520 in ARROS-1 is a significant milestone for Nuvalent as we transition from a preclinical to clinical stage company," said Christopher Turner, M.D., Chief Medical Officer of Nuvalent. "We designed NVL-520 with the goal of fulfilling a specific target product profile developed in collaboration with leading physician-scientists who are actively treating patients with ROS1-driven cancers today. We are encouraged by the preclinical data generated to date, which provide evidence that NVL-520 represents a differentiated ROS1-selective inhibitor with the potential to overcome the limitations of current tyrosine kinase inhibitor therapies and provide a new therapeutic option for patients in need."

ARROS-1 is a Phase 1/2, multicenter, open-label, dose-escalation and expansion trial evaluating NVL-520 as an oral monotherapy. The Phase 1 dose-escalation portion of the study is open and enrolling patients with advanced ROS1-positive solid tumors who have been previously treated with at least one prior ROS1 tyrosine kinase inhibitor (TKI) therapy, and will evaluate the overall safety and tolerability of NVL-520 as well as determine the recommended Phase 2 dose (RP2D), characterize the pharmacokinetic profile, and evaluate preliminary anti-tumor activity.

Once a safe and tolerable dose is determined as the RP2D, the trial is designed to transition directly into the Phase 2 multiple cohort expansion portion, which will evaluate the overall activity of NVL-520 in patients with advanced ROS1-positive NSCLC and other advanced solid tumors. The Phase 2 portion will examine several cohorts of patients based on the number and type of prior anti-cancer therapies they have received. The Phase 2 cohorts are designed to support potential registration in ROS1-positive patients with NSCLC who are kinase inhibitor-naïve and in those who have been previously treated with ROS1 kinase inhibitors.

"Nuvalent thoughtfully designed the ARROS-1 trial to support the goal of seamless acceleration from first-in-human dose-exploration of NVL-520 into Phase 2 cohorts that are structured to evaluate multiple opportunities for potential registration," said Darlene Noci, A.L.M., Senior Vice President of Product Development & Regulatory Affairs for Nuvalent. "Through parallel evaluation of NVL-520 in TKI-naïve and clearly defined cohorts of pre-treated patients, we aim to generate data to comprehensively evaluate NVL-520 throughout the treatment paradigm for ROS1-driven cancers."

In addition to NVL-520, Nuvalent is advancing a robust pipeline including the development of NVL-655 as a parallel lead program for the potential treatment of patients with ALK-positive NSCLC, along with multiple discovery-stage research programs.

"Our focus in 2022 is on establishing Nuvalent as an operationally efficient, clinical-stage biotech company with an active in-house R&D pipeline. We are on track for the planned IND submission for NVL-655 which we expect to enable the opening of our second Phase 1/2 clinical trial for enrollment in the first half of the year, and continue to plan for portfolio expansion with multiple internally discovered novel drug candidates," said James Porter, Ph.D., Chief Executive Officer at Nuvalent. "Through the prioritization of a pipeline of novel small molecules designed to overcome the dual challenges of kinase resistance and selectivity, we aim to deliver new medicines that may not only provide additional therapeutic options, but have the potential to advance earlier in the treatment paradigm and become best-in-class treatments for patients with cancer."

Nuvalent ended 2021 with $288.4 million in cash, cash equivalents and marketable securities (unaudited), which, based on its current operating plans, is expected to fund its operations into 2024.

About NVL-520

NVL-520 is a brain-penetrant ROS1-selective inhibitor designed to remain active in tumors that have developed resistance to currently available ROS1 inhibitors, including tumors with the prevalent G2032R resistance mutation and those with the S1986Y/F, L2026M, or D2033N resistance mutations. NVL-520 has been optimized for brain penetrance to potentially improve treatment options for patients with brain metastases. NVL-520 has been observed in preclinical studies to selectively inhibit ROS1 over the structurally related tropomyosin receptor kinase (TRK) family to potentially avoid TRK-related CNS adverse events seen with dual TRK/ROS1 inhibitors and drive more durable responses for patients with ROS1-mutant variants. NVL-520 is currently being investigated in the ARROS-1 study, a first-in-human Phase 1/2 clinical trial for patients with advanced non-small cell lung cancer (NSCLC) and other solid tumors.

About Nuvalent

Nuvalent, Inc. (Nasdaq: NUVL) is a biopharmaceutical company focused on creating *precisely* targeted therapies for patients with cancer, designed to overcome the limitations of existing therapies for clinically proven kinase targets. Leveraging deep expertise in chemistry and structure-based drug design, we develop innovative small molecules that have the potential to overcome resistance, minimize adverse events, address brain metastases, and drive more durable responses. Nuvalent is advancing a robust pipeline with parallel lead programs in ROS1-positive and ALK-positive non-small cell lung cancer (NSCLC), along with multiple discovery-stage research programs. We routinely post information that may be important to investors on our website at www.nuvalent.com. Follow us on Twitter (@nuvalent) and LinkedIn.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding Nuvalent's strategy, business plans, and focus; the clinical development program for NVL-520 and NVL-655 and the timing thereof; the potential clinical effect of NVL-520; the design and enrollment of the ARROS-1 study and the timing thereof; the potential of Nuvalent's pipeline programs, including NVL-520 and NVL-655; Nuvalent's research and development programs for the treatment of cancer; risks and uncertainties associated with drug development; capital allocation; and Nuvalent's future financial and operating results and its expectations related thereto. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" or the negative of these terms and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. You should not place undue reliance on these statements or the scientific data presented.

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 that Nuvalent may not fully enroll the ARROS-1 study or it will take longer than expected; unexpected concerns that may arise from additional data, analysis, or results obtained during the ARROS-1 study; the occurrence of adverse safety events; risks of unexpected costs, delays, or other unexpected hurdles; risks associated with: the impact of COVID-19 on countries or regions in which Nuvalent has operations or does business, as well as on the timing and anticipated timing and results of its clinical trials, strategy, and future operations, including the ARROS-1 study; the timing and outcome of Nuvalent's planned interactions with regulatory authorities; obtaining, maintaining, and protecting its intellectual property; and potential changes in estimated cash, cash equivalents, and marketable securities based on the completion of financial closing procedures and release of complete fiscal 2021 results. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Nuvalent's views only as of today and should not be relied upon as representing its views as of any subsequent date. Nuvalent explicitly disclaims any obligation to update any forward-looking statements.

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