Nuvalent Announces Clinical Progress on Parallel Lead Programs NVL-520 and NVL-655 for NSCLC and Solid Tumor Cancers

Preliminary dose-escalation data anticipated in second half of 2022 for ongoing ARROS-1 Phase 1/2 clinical trial of NVL-520 for patients with advanced ROS1-positive NSCLC and other solid

tumors

First patient dosed in ALKOVE-1 Phase 1/2 clinical trial of NVL-655 for patients with advanced ALK-positive NSCLC and other solid tumors

CAMBRIDGE, Mass., June 21, 2022 /PRNewswire/ -- Nuvalent, Inc. (Nasdaq: NUVL), a clinical-stage biopharmaceutical company focused on creating *precisely* targeted therapies for clinically proven kinase targets in cancer, today announced progress on its parallel lead clinical programs NVL-520, a novel ROS1-selective inhibitor, and NVL-655, a novel ALK-selective inhibitor. Nuvalent announced that it plans to share preliminary data from the dose-escalation portion of its ongoing ARROS-1 Phase 1/2 clinical trial for NVL-520 in patients with advanced ROS1-positive NSCLC and other solid tumors in the second half of 2022. In addition, Nuvalent announced that the first patient has been dosed in ALKOVE-1, its Phase 1/2 clinical trial evaluating NVL-655 in patients with advanced ALK-positive non-small cell lung cancer (NSCLC) and other solid tumors. NVL-520 and NVL-655 have been designed to address the clinical challenges of emergent treatment resistance, off-target CNS adverse events, and brain metastases that may limit the use of currently available ROS1 and ALK kinase inhibitors.

"Advancing two novel candidates into clinical development in a little over six months is a significant achievement that we believe demonstrates our ability to scale as a clinical stage company with our growing portfolio, and the value of continued collaboration with leading physician-scientists in the advancement of investigational opportunities for patients in need of new therapies," said Christopher Turner, M.D., Chief Medical Officer of Nuvalent. "We remain committed to the efficient and data-driven development of NVL-520 and NVL-655 through our ARROS-1 and ALKOVE-1 studies and look forward to the opportunity to share preliminary data from the dose-escalation portion of the ARROS-1 trial later this year."

ARROS-1 is a Phase 1/2, multicenter, open-label, dose-escalation and expansion trial evaluating NVL-520 in patients with advanced ROS1-positive NSCLC and other solid tumors. ARROS-1 is actively enrolling patients with previously treated ROS1-positive solid tumors in the Phase 1 portion of the study. Additional information on the ARROS-1 trial is available on www.ClinicalTrials.gov (NCT05118789).

ALKOVE-1 is a Phase 1/2, multicenter, open-label, dose-escalation and expansion trial evaluating NVL-655 in patients with advanced ALK-positive NSCLC and other solid tumors. The Phase 1 dose-escalation portion of the study is open and enrolling patients with previously treated ALK-positive solid tumors and will evaluate the overall safety and tolerability of NVL-655. Additional objectives include determination of the recommended Phase 2 dose (RP2D), characterization of the pharmacokinetic profile, and evaluation of preliminary anti-tumor activity.

Once a safe and tolerable dose is determined as the RP2D, the ALKOVE-1 trial is designed to transition directly into the Phase 2 multiple cohort expansion portion, which will evaluate the overall activity of NVL-655 in patients with advanced ALK-positive NSCLC and other 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 with the intent to expand in size, as data emerge and in collaboration with the U.S. Food and Drug Administration (FDA), into potential registrational cohorts for the treatment of previously treated patients with ALK-positive NSCLC. Additional information on the ALKOVE-1 trial is available on www.ClinicalTrials.gov (NCT05384626).

"The ALKOVE-1 study has been designed with the goal of seamlessly accelerating from first-in-human dose-exploration of NVL-655 into Phase 2 cohorts evaluating a range of ALK-positive patient populations," said Darlene Noci, A.L.M., Senior Vice President of Product Development & Regulatory Affairs for Nuvalent. "We believe the growing body of preclinical data generated to date for NVL-655 continue to demonstrate its promise as a differentiated ALK-selective inhibitor with the potential to overcome the limitations of currently available therapies, and are supportive of its development throughout the treatment paradigm for patients with ALK-positive cancers."

In addition to NVL-520 and NVL-655, Nuvalent continues to advance its pipeline expansion efforts with multiple discovery-stage research programs.

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 wild-type ROS1 and its resistance variants 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. NVL-520 is currently being investigated in the ARROS-1 study (NCT05118789), a first-in-human Phase 1/2 clinical trial for patients with advanced non-small cell lung cancer (NSCLC) and other solid tumors.

About NVL-655

NVL-655 is a novel brain-penetrant ALK-selective inhibitor created to overcome limitations observed with currently available ALK inhibitors. NVL-655 is designed to remain active in tumors that have developed resistance to first-, second-, and third-generation ALK inhibitors, including tumors with the solvent front G1202R mutation or compound mutations G1202R / L1196M ("GRLM"), G1202R / G1269A ("GRGA"), or G1202R/L1198F ("GRLF"). NVL-655 has been optimized for CNS penetrance to improve treatment options for patients with brain metastases. NVL-655 has been observed in preclinical studies to selectively inhibit wild-type ALK and its resistance variants over the structurally related tropomyosin receptor kinase (TRK) family to potentially avoid TRK-related CNS adverse events seen with dual TRK/ALK inhibitors and drive more durable responses for patients. NVL-655 is currently being investigated in the ALKOVE-1 study (NCT05384626), a first-in-human Phase 1/2 clinical trial for patients with advanced ALK-positive non-small cell lung cancer (NSCLC) and other solid tumors.

About Nuvalent

Nuvalent, Inc. (Nasdaq: NUVL) is a clinical-stage 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 programs for NVL-520 and NVL-655 and the timing thereof; the potential clinical effect of NVL-520 and NVL-655; the design and enrollment of the ARROS-1 and ALKOVE-1 studies 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; and capital allocation. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "aim," "goal," "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 or ALKOVE-1 studies or that enrollment will take longer than expected; unexpected concerns that may arise from additional data, analysis, or results obtained during clinical trials; the occurrence of adverse safety events; risks of unexpected costs, delays, or other unexpected hurdles; risks that Nuvalent may not be able to nominate drug candidates from its HER2 Exon 20 and ALK IXDN programs; the direct or indirect impact of COVID-19 or other global geopolitical circumstances on the timing and anticipated timing and results of Nuvalent's clinical trials, strategy, and future operations, including the ARROS-1 and ALKOVE-1 studies; the timing and outcome of Nuvalent's planned interactions with regulatory authorities; and obtaining, maintaining, and protecting its intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Company's Annual Report on Form 10-K for the year ended December 31, 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.

SOURCE Nuvalent, Inc.

Investor Contact:
Chelcie Lister
THRUST Strategic Communications
chelcie@thrustsc.com

Media Contact:
Amanda Sellers
Verge Scientific Communications
asellers@vergescientific.com
