Preliminary Phase 1 Dose-Escalation Data from ALKOVE-1 Trial of NVL-655 Demonstrated Activity in Heavily Pre-Treated Patients with ALK-Positive NSCLC and an ALK-Selective, TRK-Sparing Safety Profile

Updated preliminary data to be presented at the 35th AACR-NCI-EORTC Symposium

Company plans to host a conference call on October 13, 2023 at 8:00am EDT

CAMBRIDGE, Mass., Oct. 4, 2023 /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 preliminary data from the Phase 1 dose-escalation portion of its ongoing ALKOVE-1 Phase 1/2 clinical trial of NVL-655 for patients with advanced ALK-positive non-small cell lung cancer (NSCLC) and other solid tumors as reported in an abstract accepted for presentation at the 35th AACR-NCI-EORTC (ANE) Symposium in Boston, Massachusetts. Updated preliminary data will be presented at the conference and during a live webcast and conference call with management on October 13th at 8:00am EDT.

NVL-655 is a novel brain-penetrant ALK-selective tyrosine kinase inhibitor (TKI) created with the aim to simultaneously overcome the clinical challenges of emergent treatment resistance, brain metastases, and off-target central nervous system (CNS) adverse events associated with tropomyosin receptor kinase (TRK) inhibition that may limit the use of currently available ALK TKIs.

NVL-655 is currently being evaluated in the ALKOVE-1 Phase 1/2 clinical trial, a first-in-human study of NVL-655 in patients with advanced ALK-positive NSCLC and other solid tumors (NCT05384626). The Phase 1 dose escalation portion is enrolling ALK-positive NSCLC patients who have previously received at least one ALK TKI and patients with other ALK-positive solid tumors who have been previously treated with at least one prior systemic anticancer therapy. The primary objectives are to determine the recommended Phase 2 dose (RP2D) and if applicable, the maximum tolerated dose (MTD) of NVL-655 in patients with ALK-positive solid tumors. Additional objectives include characterization of the overall safety, tolerability, and pharmacokinetic profile, and evaluation of the preliminary anti-tumor activity of NVL-655.

As of June 12, 2023, 57 patients (54 NSCLC, 3 other solid tumors) received NVL-655 orally at dose levels ranging from 15 to 200 mg once daily in the Phase 1 dose escalation portion of ALKOVE-1.

The patient population was heavily pre-treated and included:

- patients with baseline CNS metastases (51%);
- patients with ALK resistance mutations (47%), including compound ALK mutations (32%);
- patients who had received ≥3 prior ALK TKIs (53%); and,
- patients who had received ≥1 2nd generation ALK TKI (alectinib, brigatinib, ceritinib) and the 3rd generation ALK TKI lorlatinib (77%).

Preliminary activity of NVL-655 was demonstrated in this heavily pre-treated patient population as measured by objective response rate (ORR) per RECIST 1.1. Partial responses were observed in 45% (15/33; 8 pending confirmation) of response-evaluable patients with ALK-positive NSCLC who received NVL-655 at doses ranging from 15-150 mg once daily. An ORR of 65% (11/17) was observed in patients with baseline ALK resistance mutations, and an ORR of 41% (12/29) was observed in patients post-lorlatinib, including cases with compound resistance mutations. Early indicators of CNS activity were also observed.

Preliminary pharmacokinetic analysis demonstrated dose-proportional exposure, and preliminary pharmacodynamic analysis showed reductions, including clearance, of ALK fusion and mutation variants in ctDNA.

NVL-655 was well-tolerated and treatment-related adverse events (TRAEs) were generally mild. The most frequent TRAEs were nausea (12%), transaminase elevation (12%), fatigue (9%), and constipation (7%). Grade ≥3 TRAEs were transaminase elevation (n=2), CPK elevation (n=1), and fatigue (n=1). An MTD was not identified and Phase 1 was ongoing to determine the RP2D.

"We are strongly encouraged by these preliminary safety and clinical activity data from the Phase 1 portion of our ALKOVE-1 clinical trial, which demonstrate the potential for NVL-655 to achieve its target product profile of potent and selective targeting of ALK fusions and secondary ALK single and compound resistance mutations, brain penetrance, and the avoidance of TRK inhibition," said Christopher Turner, M.D., Chief Medical Officer of Nuvalent. "We look forward to presenting an update to this

data at the AACR-NCI-EORTC Symposium later this month."

Details for the presentation are as follows:
Title: Safety and preliminary activity of the selective ALK inhibitor NVL-655 in patients with ALK fusion-positive solid tumors
Abstract Number: 35177
Poster Number: B154
Session: Poster Session B
Session Date and Time: Friday, October 13, 12:30 pm-4:00 pm EDT
Presenting Author: Jessica J Lin, Massachusetts General Hospital (MGH),Boston, MA

Webcast and Conference Call Information

A conference call with management will be held on October 13th at 8:00 am EDT. To access the call, please dial +1 (866) 652-5200 (domestic) or +1 (412) 317-6060 (international) at least 10 minutes prior to the start time and ask to be joined to the Nuvalent call. Accompanying slides and a live video webcast will be available in the Investors section of the Nuvalent website at https://investors.nuvalent.com/events. A replay and accompanying slides will be archived on the Nuvalent website for 30 days.

About NVL-655

NVL-655 is a novel brain-penetrant ALK-selective inhibitor created with the aim 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 designed 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 clinical trial (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), a program in HER2 Exon 20 Insertion positive cancers, and 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 expected timing of data announcements; the preclinical and clinical development programs for NVL-655; the potential clinical effect of NVL-655; the design and enrollment of the ALKOVE-1 clinical trial; the potential of NVL-655; Nuvalent's research and development programs for the treatment of cancer; and risks and uncertainties associated with drug development. 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 ALKOVE-1 clinical trial or that enrollment will take longer than expected; unexpected concerns that may arise from additional data, analysis, or results obtained during preclinical studies or clinical trials, including ALKOVE-1; 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 discovery programs; the direct or indirect impact of public health emergencies or global geopolitical circumstances on the timing and anticipated timing and results of Nuvalent's clinical trials, strategy, and future operations, including the ALKOVE-1 clinical trial; the timing and outcome of Nuvalent's planned interactions with regulatory authorities; and risks related to obtaining, maintaining, and protecting Nuvalent's intellectual property. 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 quarterly period ended June 30, 2023, as well as any prior and 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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