Nuvalent Announces Initiation of ALKAZAR Phase 3 Randomized, Controlled Trial Evaluating Neladalkib for Patients with TKI-naïve ALK-positive NSCLC

CAMBRIDGE, Mass., July 21, 2025 /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 that the first patient has been dosed in ALKAZAR, the company's global Phase 3 randomized, controlled trial evaluating neladalkib for TKI-naïve patients with advanced ALK-positive non-small cell lung cancer (NSCLC), versus ALECENSA® (alectinib), a front-line standard of care.

"Neladalkib is rationally designed with the goal of addressing the combined medical needs of treating key drivers of disease progression such as brain metastases and treatment-emergent resistance mutations, while also offering a generally safe and well-tolerated safety profile supportive of long-term treatment," said **Darlene Noci, A.L.M., Chief Development Officer at Nuvalent**. "We have been encouraged by neladalkib's clinical profile to date, which we believe not only supports its potential to address clear medical needs for TKI pre-treated patients with advanced ALK-positive NSCLC, but also to translate to deep, durable responses for patients in the front-line setting. The initiation of the registration-directed ALKAZAR study enables us to explore this potential by comparing neladalkib to a front-line standard of care in a randomized, controlled clinical trial setting, and advances us towards our ultimate goal of bringing neladalkib to all patients with advanced ALK-positive NSCLC."

The ALKAZAR trial is designed to enroll approximately 450 TKI-naïve patients with advanced ALK-positive NSCLC. Patients will be randomized 1:1 to receive neladalkib monotherapy or alectinib monotherapy, reflecting input from collaborating physician-scientists and alignment with global regulatory agencies. The primary endpoint is progression free survival (PFS) based on Blinded Independent Central Review (BICR). Secondary endpoints include overall survival, PFS based on investigator's assessment, time to intracranial response, and BICR assessment of intracranial objective response rate (IC-ORR), intracranial duration of response (IC-DOR), objective response rate (ORR), duration of response (DOR), time to intracranial progression, and safety. Additional details can be found on www.clinicaltrials.gov (NCT06765109).

Neladalkib is also being evaluated in the Phase 2 portion of the ALKOVE-1 Phase 1/2 trial for TKI pre-treated patients with advanced ALK-positive NSCLC. Phase 1 data demonstrated that treatment with neladalkib resulted in durable clinical responses

in heavily pre-treated patients. This included subgroups of patients who had likely exhausted all available therapies, including lorlatinib, had a history of brain metastases, and/or had single or compound ALK resistance mutations. Additionally, neladalkib demonstrated a generally safe and well-tolerated preliminary safety profile consistent with its ALK-selective, TRK-sparing design. The company expects to report topline pivotal data for TKI pre-treated patients with advanced ALK-positive NSCLC from the Phase 2 portion of ALKOVE-1 by year-end 2025.

"The currently available therapies represent important scientific advancements that provide hope for patients with ALK-positive NSCLC. However, these therapies have limitations that can lead to challenging treatment decisions for newly diagnosed patients and their health care providers," **said Kirk Smith, President of the Board of ALK Positive Inc** "We encourage continued innovation and the investigation of new treatment opportunities for all patients with ALK-positive NSCLC and look forward to following the progress of the ALKAZAR study."

About Neladalkib
Neladalkib is a novel brain-penetrant ALK-selective inhibitor created with the aim to overcome limitations observed with currently available ALK inhibitors. Neladalkib is designed to remain active in tumors that have developed resistance to first-, second-, and third-generation ALK inhibitors, including tumors with single or compound treatment-emergent ALK mutations such as G1202R. In addition, neladalkib is designed for central nervous system (CNS) penetrance to improve treatment options for patients with brain metastases, and to avoid inhibition of the structurally related tropomyosin receptor kinase (TRK) family. Together, these characteristics have the potential to avoid TRK-related CNS adverse events seen with dual TRK/ALK inhibitors and to drive deep, durable responses for patients across all lines of therapy. Neladalkib has received breakthrough therapy designation for the treatment of patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who have been previously treated with 2 or more ALK tyrosine kinase inhibitors and orphan drug designation for ALK-positive NSCLC.

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 investigational candidates for ROS1-positive, ALK-positive, and HER2-altered non-small cell lung cancer, and multiple discovery-stage research programs.

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 clinical development program for neladalkib; the potential clinical effects of neladalkib; the design and enrollment of Nuvalent's clinical trials, including for the ALKAZAR trial its intended pivotal registration-directed design; the potential of Nuvalent's pipeline programs, including neladalkib; the implications of data readouts; 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 its clinical trials or that enrollment will take longer than expected; unexpected concerns that may arise from additional data, analysis, or results obtained during preclinical studies and clinical trials; the risk that preliminary results of clinical trials may not be predictive of future results from the same or other trials; the risk that results of earlier clinical trials may not be predictive of the results of later-stage clinical trials; the risk that data from our clinical trials may not be sufficient to support registration and that Nuvalent may be required to conduct one or more additional studies or trials prior to seeking registration of neladalkib; the occurrence of adverse safety events; risks that the FDA may not approve our potential products on the timelines we expect, or at all; 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 ALKAZAR 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 Nuvalent's Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, 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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