Nuvalent Announces Positive Topline Pivotal Data from ALKOVE-1 Clinical Trial of Neladalkib for TKI Pre-treated Patients with Advanced ALK-positive NSCLC

- *In 253 ALK TKI pre-treated patients, ORR by BICR was 31% (95% CI: 26, 37), with initial estimated durability of response of 64% and 53% at the 12-month and 18-month landmarks, respectively*
- *In the subset of 63 TKI pre-treated patients who were lorlatinib-naïve, ORR by BICR was 46% (95% CI: 33, 59), with initial estimated durability of response of 80% and 60% at the 12- and 18-month landmarks, respectively*
- *Neladalkib demonstrated intracranial responses, ability to address key drivers of disease progression, and a generally well-tolerated safety profile with low rates of dose discontinuation (5%) and dose reduction (17%) due to TEAEs, consistent with its ALK-selective, TRK-sparing design*
- *Company plans to discuss pivotal data for the TKI pre-treated ALK-positive NSCLC population with the FDA at a pre-NDA meeting; detailed study results are planned for presentation at a future medical meeting*
- *Company to host a conference call today, November 17th at 8:00am ET*

CAMBRIDGE, Mass., Nov. 17, 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 positive topline pivotal data for neladalkib, an investigational ALK-selective inhibitor, in tyrosine kinase inhibitor (TKI) pre-treated patients with advanced ALK-positive non-small cell lung cancer (NSCLC) from the global ALKOVE-1 Phase 1/2 clinical trial. Additionally, the company shared the first report of preliminary data from the Phase 2 exploratory cohort for TKI-naïve patients with advanced ALK-positive NSCLC from the ALKOVE-1 study.

"Today's announcement adds to the growing body of research that is transforming potential outcomes for ALK-positive lung

cancer and offering new hope to patients," **said Kirk Smith, patient and President of the Board of ALK Positive Inc** "We encourage the continued innovation and development of new therapeutic options for patients, with the hope that one day, advanced ALK-positive NSCLC could be managed as a chronic condition more often than as a life-threatening disease."

"In treating ALK-positive lung cancer, our goal is not only to help patients live longer, but also to help them live well with their disease," **said Alice T. Shaw, M.D., Ph.D., a thoracic oncologist at Dana-Farber Cancer Institute and ALKOVE-1 trial investigator.** "These encouraging topline data suggest that neladalkib may represent a new and differentiated treatment option for ALK positive lung cancer, offering durable clinical benefit while potentially reducing the risk of side effects that can affect quality of life."

"We are deeply grateful to the patients, caregivers and investigators who have made this milestone possible for our neladalkib program. I continue to be inspired by the unwavering dedication of the Nuvalent team to making a difference for patients, and humbled by the courage and conviction of the over 1,000 patients that have already chosen to receive neladalkib through either our ALKOVE-1 trial or our global Expanded Access Program," **said James Porter, Ph.D., Chief Executive Officer at Nuvalent**. "Our focus remains on delivering our*precisely* targeted therapies to patients as quickly as possible, and we look forward to discussing these pivotal data with the FDA and aligning on a potential registration path for neladalkib in TKI pre-treated patients with advanced ALK-positive NSCLC."

Summary of Topline Pivotal Data

Neladalkib is being evaluated in ALKOVE-1, a first-in-human Phase 1/2 clinical trial for patients with advanced ALK-positive NSCLC and other solid tumors. The recommended Phase 2 dose (RP2D) for neladalkib of 150 mg once daily (QD) was determined during the Phase 1 dose-escalation portion of the trial. The global, single-arm, multi-cohort, open-label Phase 2 portion is designed to evaluate neladalkib at the RP2D with registrational intent for TKI pre-treated patients with advanced ALK-positive NSCLC. Global enrollment in ALKOVE-1 remains ongoing for adult and adolescent patients with ALK-positive solid tumors other than NSCLC, and for adolescent patients with ALK-positive NSCLC.

In this topline pivotal dataset for the TKI pre-treated ALK-positive NSCLC population, data are pooled across Phase 1 and 2 and reported for the primary objective of objective response rate (ORR, RECIST 1.1) by blinded independent central review (BICR). Key secondary objectives include duration of response (DOR), intracranial ORR (IC-ORR), and safety.

As of the data cut-off date of August 29, 2025, 781 patients with ALK-positive solid tumors had received neladalkib at any starting dose across the Phase 1 and Phase 2 portions of the ALKOVE-1 clinical trial. Of these, 656 patients with advanced ALK-positive NSCLC were treated with neladalkib at the RP2D.

Efficacy Analysis in TKI Pre-treated Advanced ALK-positive NSCLC

The pivotal primary analysis population consisted of 253 TKI pre-treated patients with advanced ALK-positive NSCLC with measurable disease by BICR who received neladalkib at the RP2D by September 30, 2024, with DOR follow-up of at least 6 months available for nearly all responders.

The pivotal primary analysis population was distinct from the ALK TKI pre-treated populations that have been reported for the currently available ALK TKIs:

- Patients received a median of 3 prior lines of therapy (range, 1 – 11) and 51% had received prior chemotherapy.
- 78% of patients had received 2 or more prior ALK TKIs**±** prior chemotherapy, of which 91% had received prior lorlatinib. No approved therapies have demonstrated activity after lorlatinib.
- 19% of patients had a secondary ALK G1202R resistance mutation, and 17% had a compound ALK resistance mutation, which are key drivers of disease progression.
- 40% of patients had active CNS disease by BICR at baseline.

Of the overall TKI pre-treated population, 25% (63/253) of patients were lorlatinib-naïve. Within this subpopulation:

- 25% received prior chemotherapy.
- 100% had received ≥ 1 prior 2G ALK TKI**±** prior chemotherapy, of which 70% received prior alectinib only. No patients received crizotinib as their only ALK TKI.
- 19% of patients had a secondary ALK G1202R mutation.
- 35% had active CNS disease by BICR at baseline.

Activity was observed across subsets of TKI pre-treated patients, and durability of response was assessed as the probability of patients remaining in response for at least 6, 12, and 18 months by Kaplan-Meier estimate (Table 1).

Table 1.	**Any prior ALK TKI ± chemotherapy** [a]	**TKI Pre-treated, Lorlatinib-naïve** [b]

n	253	63
ORR, % (n/N) (95% CI)	31% (79/253) [c,d] (26, 37)	46% (29/63) [e] (33, 59)
% DOR ≥ 6 months [f] (95% CI)	76% (64, 84)	89% (69, 96)
% DOR ≥ 12 months [f] (95% CI)	64% (51, 75)	80% (58, 91)
% DOR ≥ 18 months [f] (95% CI)	53% (34, 68)	60% (19, 85)
G1202R mutation [g]		
n	47	12
ORR, % (n/N) (95% CI)	68% (32/47) [h, i] (53, 81)	83% (10/12) (52, 98)
% DOR ≥ 6 months [f] (95% CI)	84% (65, 93)	90% (47, 99)
% DOR ≥ 12 months [f] (95% CI)	80% (61, 91)	77% (34, 94)
% DOR ≥ 18 months [f] (95% CI)	70% (42, 86)	77% (34, 94)
Measurable CNS lesions		
n	92 [j]	24 [k]
IC-ORR, % (n/N) (95% CI)	32% (29/92) [l, m] (22, 42)	63% (15/24) [l] (41, 81)
IC-CR, % (n/N)	13% (12/92) [n]	21% (5/24) [n]
% IC-DOR ≥ 6 months [f] (95% CI)	81% (59, 91)	92% (57, 99)
% IC-DOR ≥ 12 months [f] (95% CI)	71% (48, 85)	92% (57, 99)
% IC-DOR ≥ 18 months [f] (95% CI)	71% (48, 85)	92% (57, 99)

[a] Median DOR (mDOR) not reached with median follow-up of 11.3 months.

[b] mDOR not reached.

[c] Includes 2 unconfirmed partial responses (uPRs).

[d] Includes responses in patients previously treated with lorlatinib (ORR = 26% [50/190 including 2 uPRs] with mDOR = 17.6 months [95% CI: 6.9, NE]).

[e] For patients receiving only 1 prior 2nd generation ALK TKI (alectinib [n = 44] or brigatinib [n = 2]) ± chemotherapy, ORR was 48% (22/46) with mDOR not reached, and DOR ≥ 12 and 18 months of 74% (95% CI: 48, 88).

[f] Estimated for responders by Kaplan-Meier analysis.

[g] ALK G1202R mutation identified in local or central testing of blood (ctDNA) or tissue. Patients may have had other mutations in addition to ALK G1202R.

[h] Includes responses in patients with compound ALK mutations (≥2 ALK mutations, cis allelic configuration not determined in all cases) after ≥ 2 prior ALK TKIs (ORR = 58% [25/43, including 1 uPR] with DOR ≥ 12 months of 69% [95% CI: 45, 84]) and in patients with ALK resistance mutations other than G1202R, including C1156Y, I1171N, I1171T, F1174C, F1174L, V1180L, L1196M, L1198F, D1203N, E1210K, and G1269A.

[i] Includes 1 uPR.

[j] For intracranial (IC) responders, the emerging IC-mDOR was 21.6 months (95% CI: 10.1, NE) and continues to mature.

[k] For IC-responders, the emerging IC-mDOR was 21.6 months (95% CI: 21.6, NE) and continues to mature.

[l] Includes 2 IC-uPRs.

[m] IC responses were also observed in lorlatinib-experienced patients with measurable CNS lesions at baseline (IC-ORR = 21%, 14/68) with IC-mDOR not reached, IC-DOR ≥ 6 months of 71% (95% CI: 41, 88), and IC-DOR ≥ 12 and 18 months of 55% (95% CI: 26, 77).

[n] Includes 1 IC-uCR with prior confirmed IC-PR.

Preliminary Data from Exploratory Cohort for TKI-Naïve Patients with Advanced ALK-positive NSCLC

Encouraging preliminary data were available for 44 TKI-naïve patients with advanced ALK-positive NSCLC and measurable disease by BICR. These patients were treated with neladalkib at RP2D in an exploratory cohort of ALKOVE-1, with data cut-off of August 29, 2025. Patients may have received up to one prior line of chemotherapy.

The preliminary ORR was 86% (38/44; 2 uPRs) and a CR rate of 9% (4/44; 1 uCR with prior confirmed PR) was observed. DOR ranged from 1.7+ to 14.8+ months with DOR ≥ 6 and 12 months of 91% (95% CI: 70, 98) and only two progression events among responders. In 9 patients with measurable intracranial lesions, the IC-ORR was 78% (7/9) and the intracranial CR rate was 44% (4/9; 1 IC-uCR with prior confirmed IC-PR). The IC-DOR ranged from 3.1+ to 7.0+ months with no CNS progression among responders.

Global enrollment of TKI-naïve patients is ongoing in ALKAZAR, Nuvalent's Phase 3 randomized controlled trial of neladalkib versus alectinib.

Safety Analyses in Advanced ALK-positive NSCLC

Neladalkib demonstrated a generally well-tolerated safety profile consistent with its ALK-selective, TRK-sparing design.

In the 656 patients with advanced ALK-positive NSCLC treated at RP2D as of the data cut-off date, the median duration of exposure was 6.0 months (range, 0.1, 28.4). The most frequent treatment-emergent adverse events (TEAEs) occurring in ≥ 15% of patients were alanine aminotransferase increased (47%), aspartate aminotransferase increased (44%), constipation (28%), dysgeusia (23%), peripheral edema (18%), cough and nausea (16% each).

The most common TEAE of transaminase elevations were generally observed to be asymptomatic lab abnormalities that were low-grade, transient, and reversible with dose interruptions or reductions. Preliminary data suggest increased incidence in less heavily pre-treated patients. Enhanced monitoring for transaminase elevations and prompt dose interventions have been implemented in the protocol for the ALKAZAR Phase 3 randomized, controlled trial.

Across the 656 patients treated in ALKOVE-1 at RP2D, dose reductions due to TEAEs occurred in 17% of patients and 5% of patients discontinued treatment due to TEAEs.

The company plans to discuss the topline pivotal data for TKI pre-treated ALK-positive NSCLC with the U.S. Food and Drug Administration (FDA) at a pre-New Drug Application (NDA) meeting. Additionally, Nuvalent plans to present detailed study results at a future medical meeting.

Webcast and Conference Call Information

A conference call with management will be held today at8:00 am ET. To access the call, please dial +1 (800) 836-8184 (domestic) or +1 (646) 357-8785 (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 Neladalkib
Neladalkib is an investigational 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 from the U.S. Food and Drug Administration (FDA) 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 the ALKOVE-1 Phase 1/2 and ALKAZAR Phase 3 Clinical Trials
The ALKOVE-1 trial (NCT05384626) is a first-in-human Phase 1/2 clinical trial for patients with advanced ALK-positive NSCLC and other solid tumors. The completed Phase 1 portion enrolled ALK-positive NSCLC patients who previously received at least one ALK TKI, or patients with other ALK-positive solid tumors who had been previously treated or for whom no satisfactory standard of care exists. The Phase 1 portion of the trial was designed to evaluate the overall safety and tolerability of neladalkib, with additional objectives including determination of the recommended Phase 2 dose (RP2D), characterization of the pharmacokinetic profile, and evaluation of preliminary anti-tumor activity. The global, single arm, open label Phase 2 portion is designed with registrational intent for TKI pre-treated patients with advanced ALK-positive NSCLC. Global enrollment in ALKOVE-1 remains ongoing for adult and adolescent patients with ALK-positive solid tumors outside of NSCLC, and adolescent patients with ALK-positive NSCLC.

The ALKAZAR trial (NCT06765109) is a global, randomized, controlled trial designed to enroll approximately 450 patients with TKI-naïve ALK-positive NSCLC. Patients are randomized 1:1 to receive neladalkib or ALECENSA® (alectinib). The primary endpoint is progression free survival (PFS) based on Blinded Independent Central Review (BICR). Secondary endpoints include PFS based on investigator's assessment, and BICR assessment of objective response rate (ORR), intracranial objective response rate (IC-ORR), overall survival (OS), and safety.

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 programs for our investigational product candidates, including neladalkib; the potential clinical effects of our investigational product candidates, including neladalkib; the design and enrollment of Nuvalent's clinical trials, including for the ALKOVE-1 and ALKAZAR trials their intended pivotal registration-directed design; the potential of Nuvalent's pipeline programs, including neladalkib, zidesamtinib and NVL-330; the

implications of data readouts and presentations; timing and content of FDA submissions and interactions; 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 zidesamtinib and 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 ALKOVE-1 and ALKAZAR trials; the timing and outcome of Nuvalent's planned interactions with regulatory authorities and the ability of Nuvalent to interact with such officials as a result of government shutdowns or other political circumstances; 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 September 30, 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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