Nuvalent Reports Preliminary Phase 1 Clinical Data from ALKOVE-1 Trial that Support Best-In-Class Potential of NVL-655 for Patients with ALK-Positive NSCLC

Encouraging preliminary signs of activity observed in heavily pre-treated patients with ALK-positive NSCLC, including in subgroups of patients who have

previously received a 2nd generation ALK TKI and lorlatinib, have brain metastases, or have single or compound ALK resistance mutations

Favorable preliminary safety profile is consistent with an ALK-selective, TRK sparing design

Company to host a conference call today, October 13, at 8:00am EDT

CAMBRIDGE, Mass., Oct. 13, 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 updated 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. These data will be presented today at the 35th AACR-NCI-EORTC (ANE) Symposium in Boston, Massachusetts.

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.

"Significant advancements have been made with the development of three generations of ALK TKIs, and the five ALK inhibitors that are currently FDA-approved provide important treatment options for patients with advanced ALK fusion-positive cancers. However, some limitations remain with the available therapies, ranging from association with TRK-related neurologic adverse events that can limit adequate coverage of ALK single resistance mutations to the emergence of refractory compound mutations following sequential treatment with ALK TKIs," said presenting investigator **Jessica J. Lin, M.D., Assistant Professor of Medicine, Harvard Medical School and Attending Physician, Mass General Cancer Center**. "These preliminary data support the potential for NVL-655 as an ALK-selective inhibitor that may combine, for the first time, potent and selective targeting of diverse ALK fusions and secondary ALK resistance mutations, including single and compound mutations involving G1202R and I1171N, brain penetrance, and the avoidance of TRK inhibition that can be dose limiting."

As of the enrollment and data cut-off date of August 8, 2023 for the preliminary data, 93 patients have been enrolled in the Phase 1 portion of the ALKOVE-1 trial across six evaluated dose levels of NVL-655 ranging from 15 mg once daily (QD) to 200 mg QD. Enrollment in the Phase 1 portion of the trial is ongoing.

Preliminary activity data as of the cut-off date were available from 51 heavily pre-treated response-evaluable NSCLC patients. The objective response rate (ORR) by RECIST 1.1 was 39% (20/51) of patients treated at all doses, of which all were partial responses (4 pending confirmation). In the subset of 41 patients treated at dose levels of 50 mg QD or higher, the ORR was 44% (18/41).

To evaluate key target characteristics of NVL-655, activity was examined in subgroups of the 51 response-evaluable patients treated at all doses, including:

- Patients with any history of CNS metastases (ORR 52%, 15/29);
- Patients with any ALK resistance mutation (ORR 54%, 15/28), including those with compound ALK mutations (ORR 56%, 9/16) and those with ALK G1202R single or compound mutations (ORR 71%, 12/17);
- The most heavily pre-treated of patients, after receiving ≥3 prior ALK TKIs including at least one 2nd generation (2G) ALK TKI (alectinib, brigatinib, or ceritinib) plus lorlatinib, and prior chemotherapy (ORR 42%, 8/19); and,
- Lorlatinib-naïve patients who had received at least one 2G +/- 1G ALK TKI (ORR 71%, 5/7).

Preliminary pharmacokinetic (PK) analyses were available for dose levels 15 mg QD to 150 mg QD. Treatment with NVL-655 resulted in exposure above target efficacy thresholds in both the periphery and in the CNS. These preliminary PK data suggest that dose levels of 50 mg QD and above may provide increased coverage of single and compound mutations in the CNS. Preliminary pharmacodynamic analysis showed that NVL-655 induced clearance of diverse ALK resistance mutation alleles across a wide dose range.

As of the cut-off date for the preliminary data, 67% (34/51) of response-evaluable patients remained on treatment with NVL-655 with duration of treatment up to 12 months (median duration of treatment of 3.4 months). All patients with tumor response continued on treatment without disease progression. NVL-655 was well-tolerated with a preliminary safety profile that was favorable and consistent with its ALK-selective, TRK sparing design.

"We are excited to present the first look at the safety and clinical activity of NVL-655 from our ALKOVE-1 clinical trial, which we believe supports the potential for NVL-655 to address each key area of its desired target product profile," said **Christopher Turner, M.D., Chief Medical Officer of Nuvalent**. "Across a wide dose range, NVL-655 demonstrated activity in a heavily pre-treated patient population that uniquely includes patients in the post-lorlatinib setting, with a favorable preliminary safety profile consistent with its ALK-selective, TRK sparing design. Importantly, all patients with tumor response remained on treatment without disease progression as of the data cut-off date, suggesting the potential for durable responses even in this late line population."

Dr. Turner continued, "Ultimately, we view the ability to keep patients on therapeutically relevant dose levels as a key indicator of the potential for NVL-655 to drive clinically meaningful durable responses when used earlier in the treatment paradigm. In earlier lines of therapy, potent activity against ALK as well as single or compound ALK resistance mutations in both the periphery and the brain has the potential to delay or prevent the emergence of both treatment resistance and CNS progression. Furthermore, selective inhibition of wild-type ALK and its resistance variants may minimize TRK-related CNS adverse events and other off-target toxicities that can be dose limiting. We believe that the preliminary characteristics of NVL-655 observed in this heavily pre-treated patient population support its opportunity as a potential best-in-class therapy that can move up the treatment paradigm to deliver deep and durable responses for patients with ALK-positive cancers."

"With today's data, Nuvalent has presented preliminary proof-of-concept data for both of its novel parallel lead programs in ROS1 and ALK-positive cancers in just over 5 years since the company's inception," said **James Porter, Ph.D., Chief Executive Officer at Nuvalent**. "We believe this achievement is a testament to the dedication of the Nuvalent team, and to our approach of collaboration with leading physician-scientists, identification of medical needs stemming from the limitations of existing therapies, and focused application of our innovative chemistry and deep expertise in structure-based drug design to develop precisely targeted therapies according to well-defined target product profiles."

Dr. Porter continued, "Most importantly, we recognize that this achievement is made possible by the patients, caregivers, and

investigators who are participating in the ALKOVE-1 trial and offer our sincere gratitude. We look forward to discussions with investigators and regulators on the selection of a recommended Phase 2 dose (RP2D) and the transition to the planned Phase 2 portion of ALKOVE-1 for patients with lorlatinib-naïve and lorlatinib-treated ALK-positive NSCLC. We also look forward to using the preliminary data to guide discussions with physicians regarding potential development strategies for patients with TKI-naïve ALK-positive NSCLC as we work towards our goal of bringing new treatment options to all patients with ALK-positive cancers."

NVL-655 First-in-Human Preliminary Phase 1 Data
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 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 and intracranial activity of NVL-655.

As of the enrollment and data cut-off date of August 8, 2023 for the preliminary data, 93 patients were enrolled in the Phase 1 portion of the ALKOVE-1 trial, of which 91 patients had ALK-positive NSCLC and 58% (54/93) had a history of CNS metastases.

The patient population was heavily pre-treated:

- 100% (93/93) had received a 2G ALK TKI or lorlatinib;
- 77% (72/93) had received two or more ALK TKIs, including a 2G ALK TKI and lorlatinib;
- 44% (41/93) had received three or more ALK TKIs, including a 2G ALK TKI and lorlatinib; and,
- 46% (43/93) had an identified secondary ALK mutation, including 26% (24/93) with any compound ALK mutation.

Preliminary Activity Analysis
As of the cut-off date for the preliminary data, patients were treated in six NVL-655 dose cohorts of 15 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg QD. Fifty-one patients with NSCLC were response-evaluable by investigator assessment with duration of treatment up to 12 months (median duration of treatment of 3.4 months).

Key findings include early anti-tumor activity in ALK-positive NSCLC patients, including partial responses (RECIST 1.1) in:

- **Heavily pre-treated patients**: An ORR of 39% (20/51) was observed in response-evaluable patients, and all patients with tumor response continued on treatment without disease progression as of the data cut-off date.
    - For dose levels of 50 mg or greater, which may provide increased coverage of single and compound mutations in the CNS, an ORR of 44% (18/41) was observed.
    - In patients who have likely exhausted all available treatment options (≥3 prior ALK TKIs including a 2G ALK TKI and lorlatinib), the observed ORR was 40% (10/25) regardless of prior chemotherapy and 42% (8/19) with prior chemotherapy.
- **Patients with ALK single or compound resistance mutations:** An ORR of 54% (15/28) was observed in patients with any ALK resistance mutation, including an ORR of 56% (9/16) in patients with compound ALK mutations, and an ORR of 71% (12/17) in patients with ALK G1202R single or compound mutations.
- **Patients with CNS metastases**: An ORR of 52% (15/29) was observed in patients with any history of CNS metastases. All patients with tumor response who had a history of CNS disease continued on treatment without CNS progression.
- **Lorlatinib-naïve patients**: Of patients who received at least one 2G +/- 1G ALK TKI and had not previously received lorlatinib, 5 of 7 (71%) responded.

Preliminary Safety, Pharmacokinetic, and Pharmacodynamic Analysis
A favorable preliminary safety profile was observed with NVL-655 treatment in the 93 patients enrolled across the dose-escalation portion of ALKOVE-1, consistent with an ALK-selective, TRK-sparing design. Most treatment-related adverse events (TRAEs) were low-grade and manageable, with the highest incidence of TRAEs being ALT increase (19%, 18/93 any grade; 6%, 6/93 ≥ Grade 3), AST increase (18%, 17/93 any grade; 4%, 4/93 ≥ Grade 3), and nausea (10%, 9/93 of which all were Grade 1 or 2). TRAEs requiring dose modification were infrequent, with 2% (2/93) discontinuations and 5% (5/93) dose reductions. There was one dose-limiting toxicity of transient asymptomatic Grade 4 CPK increase at the 200 mg QD dose level. An MTD was not reached, and the preliminary overall safety profile was consistent with avoidance of TRK-related neurotoxicities.

The observed favorable preliminary safety profile allowed for achievement of NVL-655 exposure levels above target CNS efficacy thresholds for ALK, ALK single and compound G1202R mutations, and other recalcitrant ALK single mutations such as I1171N. Favorable PK and low intra-cohort patient PK variability were observed, with dose-proportional exposure and a half-life that is supportive of once daily dosing. This preliminary PK data suggest that dose levels of 50 mg QD or greater may provide increased coverage of single and compound mutations in the CNS.

Preliminary pharmacodynamic findings by centrally confirmed ctDNA analysis showed that treatment with NVL-655 induced clearance of diverse ALK resistance mutation alleles across a wide dose range. Notably, 100% clearance was observed in 14 of 16 patients with centrally confirmed single or compound ALK G1202R or I1171X (X = N or T) mutations, of which 13 had received prior lorlatinib.

Combined with the favorable preliminary activity observed as of the data cut-off date, these data suggest that NVL-655 has opportunity as a potential best-in-class therapy that may be able to move up the treatment paradigm for patients with ALK-positive NSCLC.

The ALKOVE-1 clinical trial is continuing to enroll patients in the Phase 1 portion of the trial and is focused on further characterizing the safety, PK, and pharmacodynamic profiles, determining the RP2D, and if applicable, the MTD of NVL-655. Upon RP2D selection, the trial is designed to transition directly into the Phase 2 portion, which will evaluate the safety and activity of NVL-655 in several expansion cohorts of patients defined based on the number and type of prior anti-cancer therapies they have received. The Phase 2 cohorts are intended to support potential registration in patients with ALK-positive NSCLC who are both lorlatinib-naïve and lorlatinib-treated.

In addition to the planned Phase 2 cohorts, Nuvalent intends to use these preliminary data in patients with heavily pre-treated ALK-positive NSCLC to guide discussions with physicians that will inform development strategies in TKI-naïve ALK-positive NSCLC.

Webcast and Conference Call Information
A conference call with management will be held today 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 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; the implications of the data readouts and presentations; timing and content of potential discussions with regulators and investigators; the design and timing of the planned Phase 2 portion of the ALKOVE-1 trial; 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 Nuvalent'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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