Nuvalent Initiates the Phase 2 Portion of ALKOVE-1 Clinical Trial for Patients with ALK-Positive NSCLC and other Solid Tumors

Alignment with US Food and Drug Administration on a Recommended Phase 2 Dose for NVL-655 of 150 mg once daily

Phase 2 Designed with

Registrational Intent for TKI Pre-Treated Patients with ALK-Positive NSCLC and Enables Preliminary Evaluation in the TKI-naïve Setting

CAMBRIDGE, Mass., Feb. 12, 2024 /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 the initiation of the Phase 2 portion of ALKOVE-1, its Phase 1/2 clinical trial of NVL-655 for patients with ALK-positive non-small cell lung cancer (NSCLC) and other solid tumors, following alignment with the US Food and Drug Administration (FDA) on a recommended Phase 2 dose (RP2D) of 150 mg once daily (QD).

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 inhibition of the structurally-related tropomyosin receptor kinase (TRK) family that may limit the use of currently available ALK TKIs.

In the Phase 1 portion of ALKOVE-1, six dose levels (15 mg to 200 mg QD) of NVL-655 were evaluated in heavily pre-treated patients with ALK-positive solid tumors, and a maximum tolerated dose was not reached. The RP2D of 150 mg QD maintained steady state plasma levels above target efficacy thresholds (ALK wild type fusions and ALK single and compound mutations in both the periphery and in the CNS).

"The transition of our NVL-655 program into Phase 2 advances a second, parallel opportunity towards our goal of bringing potential best-in-class therapies to patients as efficiently as possible," **said Darlene Noci, A.L.M., Chief Development Officer at Nuvalent.** "This sense of urgency is reflected in the thoughtful design of the Phase 2 portion of the ALKOVE-1 trial which aims to accelerate the clinical investigation that may support a potential marketing application towards an initial approval for previously treated patients with ALK-positive NSCLC. The Phase 2 portion also includes a TKI-naïve cohort which may provide an opportunity to generate early data, and could be conducted in parallel with a front-line registration-directed trial."

Ms. Noci continued, "Support for the design of the Phase 2 cohorts includes the broad clinical activity and favorable tolerability observed to date in heavily pre-treated patients in the Phase 1 portion of ALKOVE-1. Combined with the demonstrated nonclinical activity of NVL-655 in the periphery and in the CNS, and its selective inhibition of ALK and ALK single and compound drug-resistance mutations over the structurally-related TRK kinases, we believe there is the potential for NVL-655 to provide durable responses while minimizing adverse events and dose limiting toxicities for patients with ALK-positive cancers throughout the treatment paradigm."

"With today's announcement, we've delivered on the first of the key 2024 milestones laid out in our OnTarget 2026 operating plan, an achievement made possible by the tireless dedication of our team to our mission of delivering *precisely* targeted therapies to patients with cancer," **said James Porter, Ph.D., Chief Executive Officer at Nuvalent**. "With all of our programs, our goal is to not only address the existing medical needs for later-line patients but to ultimately deliver therapies that can move up the treatment paradigm, and our multi-

pronged development strategy for NVL-655 exemplifies this approach. We look forward to sharing an update from the ALKOVE-1 trial as well as more detail on our broader front-line development strategy for ALK later this year."

ALKOVE-1 Phase 2 Design

The Phase 2 portion of the ALKOVE-1 trial will be conducted globally across North America, Europe, Asia, and Australia. The single arm, open label Phase 2 portion is designed with registrational intent for TKI pre-treated patients with ALK-positive NSCLC and to enable preliminary investigation for patients with ALK-positive NSCLC who are TKI naïve. The Phase 2 cohorts are designed to evaluate NVL-655 in:

- **TKI Pre-Treated ALK-Positive NSCLC**
  - **2 – 3 Prior TKIs:** Patients with locally advanced or metastatic NSCLC harboring an ALK rearrangement, who have received 2-3 prior ALK TKIs. Up to 2 prior lines of chemotherapy and/or immunotherapy are allowed.
  - **1 Prior 2G TKI:** Patients with locally advanced or metastatic NSCLC harboring an ALK rearrangement who have received 1 prior second-generation (2G) ALK TKI (ceritinib, alectinib, or brigatinib). Up to 2 prior lines of chemotherapy and/or immunotherapy are allowed.
  - **1 Prior 3G TKI:** Patients with locally advanced or metastatic NSCLC harboring an ALK rearrangement, who have received lorlatinib (third-generation, 3G) as the only prior ALK TKI therapy. Up to one prior line of chemotherapy and/or immunotherapy received prior to lorlatinib is allowed.
- **TKI-Naïve ALK-Positive NSCLC**
  - Patients with locally advanced or metastatic NSCLC harboring an ALK rearrangement, who are naïve to ALK TKI therapy. Up to one prior line of chemotherapy and/or immunotherapy is allowed.
- **Other**
  - **Other ALK-Positive NSCLC:** Patients with locally advanced or metastatic NSCLC harboring an ALK rearrangement, not eligible for other Phase 2 cohorts.
  - **Other ALK-Positive Solid Tumors:** Patients with other solid tumors harboring an ALK rearrangement or activating ALK mutation, who have received ≥1 prior systemic anticancer therapy, or for whom no satisfactory standard therapy exists.

Additional details can be found on www.clinicaltrials.gov (NCT05384626).

Selection of NVL-655 RP2D

The selection of 150 mg QD as the RP2D for NVL-655 was supported by the FDA based on clinical data from the Phase 1 dose escalation portion of the ALKOVE-1 trial. The company believes that the preliminary Phase 1 data support the opportunity for NVL-655 as a potential best-in-class therapy that may be able to move up the treatment paradigm for patients with ALK-positive NSCLC.

The selection was based on the following considerations:

- The dose level of 150 mg QD maintained steady state plasma levels above target efficacy thresholds (ALK wild type fusions and ALK single and compound mutations in both the periphery and in the CNS).
- Favorable tolerability of NVL-655 was observed at the 150 mg QD dose level, continuing to suggest the potential for a highly ALK-selective, TRK sparing safety profile.
- Early anti-tumor activity was observed in ALK-positive NSCLC patients across a broad range of doses, including 150 mg QD. Objective responses (RECIST 1.1) were observed in heavily pre-treated patients including patients who had received one or more second-generation TKIs (alectinib, brigatinib, or ceritinib) plus lorlatinib, patients who were lorlatinib-naïve, patients with ALK single and compound resistance mutations, and patients with CNS metastases.

Preliminary Phase 1 data were presented in October 2023, and the company expects to share an update from the ALKOVE-1 trial at a medical meeting in 2024.

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 both single or compound treatment-emergent ALK mutations such as G1202R. In addition, NVL-655 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. NVL-655 has received orphan drug designation for ALK-positive non-small cell lung cancer (NSCLC) and 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 NSCLC and other solid tumors.

About OnTarget 2026

OnTarget 2026 delineates Nuvalent's 3-year operating plan towards bringing new, potential best-in-class medicines to patients with cancer. As part of this plan announced in January 2024, Nuvalent outlined the following anticipated milestones throughout 2024, leading to the company's first potential pivotal data in 2025 and first potential approved product in 2026:

- ***2024: Execute on Global Registrational Strategies***
    - Progress the Phase 2 portion of the ARROS-1 trial of NVL-520 in patients with advanced ROS1-positive NSCLC with registrational intent;
    - Initiate the Phase 2 portion of the ALKOVE-1 trial of NVL-655 in patients with advanced ALK-positive NSCLC, including cohorts in pretreated patients with registrational intent;
    - Launch the front-line development strategy for its ALK program;
    - Present interim data from the ongoing ARROS-1 and ALKOVE-1 clinical trials at medical meetings; and,
    - Initiate the Phase 1 trial for its HER2 program.
- ***2025: First Pivotal Data***
- ***2026: First Approved Product***

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-positive 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, clinical trial initiations, and FDA product approvals; the preclinical and clinical development programs for NVL-520, NVL-655 and NVL-330; the potential clinical effect of NVL-655; the design and enrollment of the ARROS-1 and ALKOVE-1 trials, including their intended pivotal registration-directed design; the potential of Nuvalent's pipeline programs, including NVL-520, NVL-655 and NVL-330; the implications of 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 ARROS-1 and ALKOVE-1 trials; Nuvalent's research and development programs for the treatment of cancer; and risks and uncertainties associated with drug development. The words "may," "might," "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 trials 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; 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 our product candidates; 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 ARROS-1 and ALKOVE-1 trials; the timing and outcome of Nuvalent's planned interactions with regulatory authorities; 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 quarterly period ended September 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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