Nuvalent Initiates the Phase 2 Portion of ARROS-1 Clinical Trial for Patients with ROS1-Positive NSCLC and other Solid Tumors

Alignment with US Food and Drug Administration on a Recommended Phase 2 Dose for NVL-520 of 100 mg daily

CAMBRIDGE, Mass., Sept. 5, 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 the initiation of the Phase 2 portion of ARROS-1, its Phase 1/2 clinical trial of NVL-520 for patients with ROS1-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 100 mg daily.

NVL-520 is a novel brain-penetrant ROS1-selective tyrosine kinase inhibitor (TKI) created with the aim to simultaneously overcome the clinical challenges of emergent treatment resistance, off-target central nervous system (CNS) adverse events associated with TRK inhibition, and brain metastases that may limit the use of

currently available ROS1 TKIs.

"The ARROS-1 trial was designed to support a seamless transition from first-in-human dose-exploration in a heavily pre-treated population to a Phase 2 portion designed with the potential to support registration. We are thrilled to achieve this milestone towards our goal of bringing a potential best-in-class therapy to patients with ROS1-positive NSCLC as efficiently as possible," said Darlene Noci, A.L.M., Chief Development Officer at Nuvalent.

"The Phase 2 portion of the ARROS-1 trial includes multiple cohorts which enable the parallel investigation of NVL-520 for patients with ROS1-positive NSCLC who are either TKI naïve or pre-treated with a ROS1 TKI," Ms. Noci continued. "Support for the Phase 2 cohort design includes the demonstrated nonclinical activity of NVL-520 in the periphery and in the CNS, and its selective inhibition of ROS1 and ROS1 drug-resistance mutant G2032R over the structurally-related TRK kinases. Combined with the broad clinical activity and favorable tolerability observed to date in heavily pre-treated patients in the Phase 1 portion of ARROS-1, we believe there is the potential for NVL-520 to provide durable responses while minimizing adverse events and dose limiting toxicities for patients with ROS1-positive cancers throughout the treatment paradigm."

In the Phase 1 portion of ARROS-1, six dose levels (25 mg to 150 mg daily) of NVL-520 were evaluated in heavily pre-treated patients with ROS1-positive solid tumors. A maximum tolerated dose (MTD) was not reached, and no clinically significant exposure-response relationships for safety and efficacy were observed across the dose levels evaluated. The RP2D of 100 mg daily maintained steady state plasma levels above all target efficacy thresholds (ROS1 wild type and ROS1 G2032R in both the periphery and in the CNS).

"With the advancement of the first of our parallel lead programs into a Phase 2 trial with registrational intent, the Nuvalent team demonstrates its continued ability to scale while maintaining ambitious timelines towards our goal of delivering *precisely* targeted therapies to patients with cancer," said James Porter, Ph.D., Chief Executive Officer at Nuvalent. "We look forward to providing an update from the ARROS-1 trial at a medical meeting in 2024."

ARROS-1 Phase 2 Design

The Phase 2 portion of the ARROS-1 trial will be conducted globally across North America, Europe, Asia and Australia with planned enrollment of approximately 225 TKI naïve and TKI pre-treated patients with ROS1-positive NSCLC and other solid tumors. The single arm, open label Phase 2 cohorts are designed to evaluate NVL-520 across the treatment paradigm for patients with ROS1-positive NSCLC, and include both potentially registration-directed pivotal cohorts and an additional exploratory cohort:

- **Potential Pivotal Cohorts**
    - **Cohort 2a**: Patients with advanced/metastatic ROS1-positive NSCLC naïve to TKI therapy. Up to one prior line of chemotherapy and/or immunotherapy is allowed.
    - **Cohort 2b**: Patients with advanced/metastatic ROS1-positive NSCLC treated with 1 prior ROS1 TKI (either crizotinib or entrectinib) and no prior chemotherapy or immunotherapy allowed.
    - **Cohort 2c**: Patients with advanced/metastatic ROS1-positive NSCLC treated with 1 prior ROS1 TKI (either crizotinib or entrectinib) and 1 prior line of platinum-based chemotherapy with or without immunotherapy.
    - **Cohort 2d**: Patients with advanced/metastatic ROS1-positive NSCLC treated with at least 2 prior ROS1 TKIs (with crizotinib or entrectinib as the initial ROS1 TKI) and up to 1 line of chemotherapy and/or immunotherapy.
- **Exploratory Cohort**
    - **Cohort 2e**: Patients with any advanced/metastatic ROS1-positive solid tumor (including patients with ROS1-positive NSCLC not otherwise eligible for any other cohorts) and progressed on any prior therapy (includes, but is not limited to, patients who have progressed on prior ROS1 TKIs).

Additional details can be found on www.clinicaltrials.gov (NCT05118789).

Selection of NVL-520 RP2D

The selection of 100 mg daily as the RP2D for NVL-520 was discussed and supported by FDA based on clinical data from the Phase 1 dose escalation portion of the ARROS-1 trial with a data cut-off of May 17, 2023. These data included a safety database of 87 ROS1-positive patients enrolled across six dose levels from 25 mg to 150 mg daily, including 37 patients at dose levels of ≥100 mg daily. The selection was based on the following considerations:

- The dose level of 100 mg daily maintained steady state plasma levels above all target efficacy thresholds (ROS1 wild type and ROS1 G2032R in both the periphery and in the CNS).
- Favorable tolerability of NVL-520 was observed across all dose levels to date.
- No clinically significant exposure-response relationships for safety and efficacy were observed across the dose levels evaluated (25 mg – 150 mg daily).

Based on these data, early anti-tumor activity continued to be observed in ROS1-positive NSCLC patients, including objective responses (RECIST 1.1) in heavily pre-treated patients, patients previously treated with lorlatinib or repotrectinib, patients with ROS1 G2032R resistance mutations, and patients with CNS metastases. A favorable preliminary safety profile continued to suggest the potential for a highly ROS1-selective, TRK sparing design. Overall, the company believes these findings to be consistent with the conclusions from a preliminary data disclosure in October 2022 with data cut-off date of September 13, 2022, and believes that these data continue to support the opportunity for NVL-520 as a potential best-in-class therapy that may be able to move up the treatment paradigm for patients with ROS1-positive NSCLC.

The company expects to share an update from the ARROS-1 trial at a medical meeting in 2024.

About NVL-520
NVL-520 is a brain-penetrant ROS1-selective inhibitor designed to remain active in tumors that have developed resistance to currently available ROS1 inhibitors, including tumors with the prevalent G2032R resistance mutation and those with the S1986Y/F, L2026M, or D2033N resistance mutations. NVL-520 has been designed for brain penetrance to potentially improve treatment options for patients with brain metastases. NVL-520 has been observed in preclinical studies to selectively inhibit wild-type ROS1 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/ROS1 inhibitors and drive more durable responses for patients. NVL-520 is currently being investigated in the ARROS-1 trial (NCT05118789), a first-in-human Phase 1/2 clinical trial for patients with advanced 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-520 and other product candidates; the potential clinical effect of NVL-520; the design and enrollment of the ARROS-1 trial, including its intended pivotal registration-directed design; the potential of NVL-520; 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 ARROS-1 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 ARROS-1; the risk that results of earlier ARROS-1 clinical trials may not be predictive of the results of later-stage clinical trials; the risk that the data from the ARROS-1 Phase 2 trial 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 NVL-520; 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 ARROS-1 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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