

Nuvalent Reports Preliminary Phase 1 Clinical Data from ARROS-1 Trial that Support Best-In-Class Potential of NVL-520 for Patients with ROS1- Positive NSCLC

Favorable preliminary safety profile of NVL-520 suggests potential for a highly ROS1-selective, TRK sparing design, with no dose-limiting

toxicities, treatment-related serious adverse events, treatment-related dizziness, or adverse events leading to treatment reductions or discontinuations as of the data cut-off date

Encouraging preliminary signs of activity observed across all dose levels in heavily pre-treated patients with ROS1-positive NSCLC, including in subgroups of patients with G2032R resistance mutation or with

brain metastases

Company to host conference call today at 8:30 am EDT

CAMBRIDGE, Mass., Oct. 28, 2022 [/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 initial data from the Phase 1 dose-escalation portion of its ongoing ARROS-1 Phase 1/2 clinical trial of NVL-520 for patients with advanced ROS1-positive non-small cell lung cancer (NSCLC) and other solid tumors. These data will be presented today in the "New Drugs on the Horizon" oral plenary session at the 34th EORTC-NCI-AACR (ENA) Symposium in Barcelona, Spain.

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

"Currently approved and investigational ROS1 TKIs are important treatment options for advanced ROS1 fusion-positive cancers. However, these drugs can have key limitations. These include the inability to treat on-target resistance and brain metastases effectively, and an association with neurologic adverse events," said Alexander Drilon, M.D., Chief, Early Drug Development Service, Memorial Sloan Kettering Cancer Center (MSK) and presenting investigator. "These preliminary data support NVL-520 as a potential best-in-class ROS1-selective inhibitor that may combine, for the first time, potent and selective targeting of diverse ROS1 fusions and secondary ROS1 resistance mutations including G2032R, brain penetrance, and the avoidance of TRK inhibition that can be dose limiting."

As of September 1, 2022, 35 subjects have been enrolled in the Phase 1 portion of the ARROS-1 trial. Treatment with NVL-520 across five evaluated dose levels ranging from 25 mg once daily (QD) to 125 mg QD resulted in exposures above all target efficacy thresholds. As of the preliminary data cut-off date of September 13, 2022, no dose-limiting toxicities (DLTs), treatment-related serious adverse events (SAEs), treatment-emergent dizziness, or adverse events leading to treatment reductions or discontinuations were observed.

Preliminary activity data reported as of the data cut-off date were available from 21 heavily pre-treated response-evaluable NSCLC patients, of which partial responses were observed in 48% (10/21). To evaluate key target characteristics of NVL-520, activity was examined in subgroups including:

- Patients with ROS1 G2032R mutations (Objective Response Rate (ORR) 78%, 7/9);
- Patients with a history of CNS metastases (ORR 73%, 8/11);
- The most heavily pre-treated of patients, receiving two or more prior ROS1 TKIs and one or more prior lines of chemotherapy (ORR 53%, 9/17); and
- Patients previously treated with lorlatinib or repotrectinib (ORR 50%, 9/18).

As of the preliminary data cut-off date, 76% (16/21) of response-evaluable patients continued on NVL-520 treatment. Enrollment in the Phase 1 portion of the trial is ongoing.

"We are excited to present the first look at the safety and clinical activity of NVL-520 from our ARROS-1 clinical trial, which we believe supports NVL-520 as a potential best-in-class ROS1-selective inhibitor that may be capable of overcoming the limitations of current approved and investigational ROS1 TKIs," said Christopher Turner, M.D., Chief Medical Officer of Nuvalent. "Across all evaluated dose levels, NVL-520 exhibited activity in a heavily pre-treated patient population, many of whom have exhausted all available treatment options and would have been excluded from other investigational ROS1 TKI studies. Importantly, the favorable safety profile and lack of dose reductions or discontinuations due to adverse events reflected in this preliminary data suggest that NVL-520 has the potential to provide deep and durable responses and may be able to move up in the

treatment paradigm for patients with ROS1-driven cancers."

"We believe today's preliminary results further support Nuvalent's approach of applying innovative chemistry and structure-based drug design to well-defined target product profiles focused on addressing medical needs that have been identified in collaboration with leading physician-scientists," said James Porter, Ph.D., Chief Executive Officer at Nuvalent. "Not only has this approach rapidly delivered the encouraging preliminary results for NVL-520 presented today, it underpins our work across our entire pipeline, including parallel lead candidate NVL-655 for ALK-positive NSCLC, and our recently announced development candidate for HER2ex20-driven cancers, NVL-330. I congratulate the entire Nuvalent team for their dedication and tireless efforts, and offer sincere gratitude to the patients, caregivers and investigators who are participating in the ARROS-1 trial."

NVL-520 First-In-Human Preliminary Phase 1 Data

NVL-520 is currently being evaluated in the ongoing ARROS-1 Phase 1/2 clinical trial, a first-in-human study of NVL-520 in patients with advanced ROS1-positive NSCLC and other solid tumors. The Phase 1 dose escalation portion is enrolling ROS1-positive NSCLC patients who have previously received at least one ROS1 TKI, or patients with other ROS1-positive solid tumors who have been previously treated. The Phase 1 portion of the trial is designed to evaluate the overall safety and tolerability of NVL-520, with additional objectives including determination of the recommended Phase 2 dose (RP2D), characterization of the pharmacokinetic profile, and evaluation of preliminary anti-tumor activity.

As of September 1, 2022, 35 subjects were enrolled in the Phase 1 portion of the ARROS-1 trial, of which 34 patients had ROS1-positive NSCLC and 51% (18/35) had a history of CNS metastases.

The patient population was heavily pre-treated:

- 77% (27/35) had received three or more prior lines of anti-cancer therapy;
- 71% (25/35) had received two or more prior ROS1 TKIs and one or more lines of chemotherapy; and
- 80% (28/35) had received a ROS1 TKI other than crizotinib or entrectinib, including lorlatinib (57%, 20/35) or repotrectinib (34%, 12/35).

Preliminary Safety and Pharmacokinetic Analysis

Preliminary safety and pharmacokinetics of NVL-520 were evaluated as of the data cut-off date of September 13, 2022. Patients were treated in five dose cohorts of 25 mg, 50 mg, 75 mg, 100 mg, or 125 mg once daily with NVL-520.

NVL-520 demonstrated exposure above all target efficacy thresholds (ROS1 wild type and ROS1 G2032R in both the periphery and in the CNS). Favorable pharmacokinetics and low intra-cohort patient PK variability were observed, with exposure increasing with increasing dose level and half-life supportive of once daily dosing.

A favorable preliminary safety profile was observed with NVL-520 treatment in the 35 patients enrolled across the dose-escalation portion of ARROS-1, suggesting the potential for a highly ROS1-selective, TRK sparing design. There were no DLTs, no treatment-related SAEs, no treatment related dizziness, and no adverse events leading to dose reduction or discontinuation of NVL-520 through the preliminary data cut-off date.

Most treatment-related adverse events (TRAEs) were low-grade and manageable, and the favorable preliminary safety profile allowed for achievement of exposure levels well above target thresholds for both ROS1 and ROS1 resistance variants in both the CNS and the periphery. To date, a maximum tolerated dose has not been reached and Phase 1 is ongoing to determine the RP2D.

Preliminary Activity Analysis

As of the preliminary data cut-off date of September 13, 2022, 21 patients with NSCLC were response-evaluable by investigator assessment with duration of treatment ranging from one to more than eight months.

Key findings include early anti-tumor activity in ROS1-positive NSCLC patients, including objective responses (RECIST 1.1) in:

- **Heavily pre-treated patients:** Partial Responses (PRs) were observed in 48% (10/21) of all response-evaluable patients, with 76% (16/21) continuing on treatment. Responses were observed in 53% (9/17) of patients who received two or more prior TKIs and one or more prior lines of chemotherapy, in 50% (9/18) of patients previously treated with lorlatinib or repotrectinib, and across all dose levels evaluated.
- **Patients with ROS1 G2032R resistance mutation:** Of nine patients with known ROS1 G2032R resistance mutation, responses were observed in 78% (7/9) including in two of three patients previously treated with repotrectinib, and tumor shrinkage was observed in 100% (9/9). Notably, complete clearance of G2032R allele was observed in all seven patients with G2032R detected on central ctDNA analysis.
- **Patients with CNS metastases:** Intracranial PRs were observed in 100% (3/3) patients with measurable (>10 mm) CNS metastases. Responses were observed in 73% (8/11) of patients with a history of CNS

metastases, and no CNS progression was observed in any of the 35 treated patients.

Combined with the favorable tolerability observed across the dose levels evaluated through the preliminary data cut-off date, these data also suggest that NVL-520 is a potential best-in-class therapy that may be able to move up the treatment paradigm for patients with ROS1-positive NSCLC.

The ARROS-1 clinical trial is continuing to enroll patients in the Phase 1 portion of the trial and is focused on further characterizing the safety profile of NVL-520, its pharmacokinetic profile, and determining the RP2D.

Once a safe and tolerable dose is determined as the RP2D, the trial is designed to transition directly into the Phase 2 portion, which will evaluate the overall activity of NVL-520 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 designed to support potential registration in patients with ROS1-positive NSCLC who are kinase inhibitor-naïve and in those who have been previously treated with ROS1 kinase inhibitors.

Webcast and Conference Call Information

Nuvalent will host a live webcast and conference call today at 8:30am EDT to discuss these results. The event is accessible through the "Events" section of the Investors page of www.nuvalent.com or by dialing (866) 652-5200 (domestic) or (412) 317-6060 (international) and referring to conference ID 10171503. A replay and accompanying slides will be archived on the Nuvalent website for 30 days.

About NVL-520

NVL-520 is a novel 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](https://clinicaltrials.gov/ct2/show/study/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](https://twitter.com/nuvalent)) and [LinkedIn](https://www.linkedin.com/company/nuvalent).

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-520, NVL-655 and NVL-330; the potential clinical effect of NVL-520 and NVL-655; the design and enrollment of the ARROS-1 and ALKOVE-1 trials; the potential of Nuvalent's pipeline programs, including NVL-520, NVL-655 and NVL-330; data readouts and presentations; 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 or ALKOVE-1 studies 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 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 ALK IXDN and other discovery programs; the direct or indirect impact of COVID-19 or other 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; and obtaining, maintaining, and protecting its 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, 2022, 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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<https://investors.nuvalent.com/2022-10-28-Nuvalent-Reports-Preliminary-Phase-1-Clinical-Data-from-ARRS-1-Trial-that-Support-Best-In-Class-Potential-of-NVL-520-for-Patients-withROS1-Positive-NSCLC>