Nuvalent Highlights Presentation of Clinical Data at ESMO 2024 for Parallel Lead Programs for ROS1 and ALK-positive NSCLC and Accelerated Development Timelines

Updated Phase 1 dose-escalation data from ARROS-1 and ALKOVE-1 clinical trials continue to support potential best-in-class profiles for

zidesamtinib and NVL-655

Rapid enrollment in Phase 2 portions of the ARROS-1 and ALKOVE-1 clinical trials; Pivotal data from both ROS1 and ALK programs now anticipated in 2025

Initiation of ALKAZAR Phase 3 randomized, controlled trial of NVL-655 for treatment-naïve patients with advanced ALK-positive NSCLC anticipated in the first half of 2025

Company to host a conference

call today at 8:30 a.m. ET/2:30 p.m. CEST

CAMBRIDGE, Mass., Sept. 14, 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 highlighted the presentation of updated data from the fully enrolled Phase 1 dose-escalation portions of the ongoing ARROS-1 Phase 1/2 clinical trial of zidesamtinib, a novel ROS1-selective inhibitor, and ALKOVE-1 Phase 1/2 clinical trial of NVL-655, a novel ALK-selective inhibitor, during two oral presentations at the European Society for Medical Oncology (ESMO) Congress 2024 in Barcelona, Spain.

In addition, the company announced progress and provided updates on the development strategy and timelines for its parallel-lead programs zidesamtinib and NVL-655, including its development strategy for tyrosine kinase inhibitor (TKI)-naïve ALK-positive non-small cell lung cancer (NSCLC):

- **Phase 2 portion of the ARROS-1 trial of zidesamtinib for TKI-naïve and TKI pre-treated patients with advanced ROS1-positive NSCLC and other solid tumors:** Between September 2023 and September 1, 2024, 227 patients were enrolled in the ongoing single-arm, multi-cohort Phase 2 portion of the ARROS-1 trial, which is designed with registrational intent. The company expects to report pivotal data from this trial in 2025.
- **Phase 2 portion of the ALKOVE-1 trial of NVL-655 for TKI-naïve and TKI pre-treated patients with advanced ALK-positive NSCLC and other solid tumors:** Between February 2024 and September 1, 2024, 229 patients were enrolled in the ongoing single-arm, multi-cohort Phase 2 portion of the ALKOVE-1 trial, which is designed with registrational intent for TKI pre-treated patients. The company also expects to report pivotal data from this trial in 2025.
- **ALKAZAR Phase 3 randomized, controlled trial of NVL-655 for TKI-naïve patients with advanced ALK-positive NSCLC:** The Phase 3 ALKAZAR trial will be a global, randomized, controlled trial designed to evaluate NVL-655 versus the current standard of care for the treatment of patients with TKI-naïve ALK-positive NSCLC. Patients will be randomized 1:1 to receive NVL-655 monotherapy or ALECENSA® (alectinib) monotherapy, reflecting input from collaborating physician-scientists and alignment with the U.S. Food and Drug Administration (FDA). The company plans to initiate the ALKAZAR study in the first half of 2025.

"The Phase 1 portions of our ARROS-1 and ALKOVE-1 studies have established preliminary clinical proof-of-concept for zidesamtinib and NVL-655 as selective, brain-penetrant, TRK-sparing TKIs that have the potential to move up the treatment paradigm, as demonstrated by the preliminary safety profile indicating favorable tolerability, and the durability of responses observed across patient subsets presented today at ESMO," said Christopher Turner, M.D., Chief Medical Officer at Nuvalent. "We believe zidesamtinib and NVL-655 have the potential to not only address clear medical needs in the third line where no approved therapies have demonstrated clinical benefit, but also provide differentiated options in the second line including for patients who have experienced disease progression due to CNS metastases or resistance mutations, and ultimately deliver deep, durable responses in the front line."

"We are grateful for the strong investigator enthusiasm for our programs, exemplified by the accelerated Phase 2 enrollment in our ARROS-1 and ALKOVE-1 trials. We now anticipate reporting pivotal datasets from both Phase 2 trials in 2025," said Darlene Noci, A.L.M., Chief Development Officer at Nuvalent. "With the announcement of our planned ALKAZAR randomized, controlled Phase 3 study, we are thrilled to also establish a potential registration path for TKI-naïve patients with advanced ALK-positive NSCLC. Through our multi-pronged strategies, our goal is to bring potential best-in-class therapies that can move up the treatment paradigm to patients as efficiently as possible. We look forward to initiating the ALKAZAR study in the first half of 2025."

The ALKAZAR trial is designed to enroll approximately 450 patients with TKI-naïve ALK-positive NSCLC. 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.

"At the outset of this year, we announced our OnTarget 2026 operating plan delineating our path towards a potential first approval in 2026 from our pipeline of novel kinase inhibitors. With today's updates, we have successfully achieved all of the supporting milestones laid out for 2024 and believe we are now on track to share pivotal datasets from both of our parallel-lead programs in 2025, a testament to the tireless dedication of our team," said James Porter, Ph.D., Chief Executive Officer at Nuvalent. "I am incredibly proud of what we have accomplished thus far and am optimistic about the road ahead. With the foundation of encouraging Phase 1 proof-of-concept data, strong enrollment momentum in our global Phase 2 trials, alignment

with the FDA on the design of our Phase 3 ALKAZAR study, and the dedication of our proven team, we are confident in our ability to continue advancing our programs towards our goal of delivering them as quickly as possible to the patients that need them."

ARROS-1 Phase 1 Update at ESMO 2024

From January 2022 to August 2023, the Phase 1 portion of ARROS-1 enrolled 104 patients (99 NSCLC, 5 other solid tumors). Patients received zidesamtinib orally at dose levels ranging from 25 to 150 mg once daily (QD), and 100 mg QD was selected as the recommended Phase 2 dose (RP2D). No clinically significant exposure-response relationships for safety and efficacy were observed and data are reported across all doses.

The patient population was heavily pre-treated, with a median of 3 prior lines of therapy (range 1 – 11). 69% (72/104) of patients had ≥2 prior ROS1 TKIs, and 66% (69/104) had prior chemotherapy. Notably, 55% (57/104) of patients received prior lorlatinib and 21% (22/104) received prior repotrectinib, highlighting the differentiated nature of this population from prior trials of other ROS1 inhibitors. 52% (54/104) had history of CNS metastases, including cases of disease progression following treatment with the brain-penetrant TKIs lorlatinib and/or repotrectinib.

As of the cut-off date of July 1, 2024, 71 pre-treated patients with ROS1-positive NSCLC were response-evaluable. The median follow-up for the all-treated population was 12.1 months (range, 0.8 – 29.4).

Treatment with zidesamtinib resulted in durable clinical responses (ORR by RECIST 1.1) across key subgroups of response-evaluable patients. As of the data cut-off date:

ROS1-positive NSCLC response-evaluable	**Zidesamtinib, All Doses**			
	ORR	**mDOR (months)**	**DOR ≥ 6 months***	**DOR ≥ 12 months***
Any Prior Therapies (1 – 4 prior ROS1 TKIs ± chemotherapy)	44% (31/71, 2 CRs)	NR	83%	67%
Repotrectinib-naive	51% (27/53)	NR	88%	71%
≥2 prior ROS1 TKIs** (≥ 3rd Line; ± chemotherapy)	41% (21/51)	12.1	75%	54%
Prior crizotinib only (2nd Line; ± chemotherapy)	73% (8/11)	NR***	100%***	100%***

NR = not reached
* Analyses of DOR based on Kaplan-Meier estimates.
** Zidesamtinib has received FDA breakthrough therapy designation for the treatment of patients with ROS1-positive metastatic NSCLC who have been previously treated with 2 or more ROS1 TKIs.
*** No disease progression among responders.

In the subset of patients with confirmed ROS1 G2032R resistance mutation, the ORR was 72% (13/18) for repotrectinib-naïve patients.

IC-ORR was 50% (4/8) in intracranial response-evaluable patients with measurable CNS lesions, of which 7/8 patients had been previously treated with the brain-penetrant TKIs lorlatinib and/or repotrectinib. The mIC-DOR was not reached, with no CNS progression observed among confirmed CNS responders.

Zidesamtinib was well-tolerated with a preliminary safety profile that was favorable and consistent with its ROS1-selective, TRK sparing design. Among the 104 treated patients at all doses, the most frequent treatment-related adverse events (TRAEs) were oedema peripheral (19%), ALT increase, AST increase, and weight increase (each 11%). Among these most frequent TRAEs, there was a single grade 3 event of weight increase. No discontinuation due to TRAEs occurred. Dose reductions due to TRAEs occurred in 8% of patients. A maximum tolerated dose was not identified.

The company believes these preliminary data demonstrate the potential for zidesamtinib to address a medical need for the

third-line treatment of ROS1-positive NSCLC where no approved therapies have demonstrated clinical benefit, and to provide a differentiated option in the second line where there also remains a medical need. Additionally, the company believes that these data in heavily pre-treated patients could have the potential to translate to deep, durable responses in the front-line setting.

Further investigation of zidesamtinib for both TKI-naïve and TKI pretreated patients with ROS1-positive NSCLC is underway in the Phase 2 portion of the ARROS-1 clinical trial, designed with registrational intent. The company expects to report pivotal data in 2025.

ALKOVE-1 Phase 1 Update at ESMO 2024

From June 2022 to February 2024, the Phase 1 portion of ALKOVE-1 enrolled 133 patients (131 NSCLC, 2 other solid tumors). Patients received NVL-655 orally at dose levels ranging from 15 to 200 mg QD, and 150 mg QD was selected as the RP2D.

The patient population was heavily pre-treated, with a median of 3 prior lines of therapy (range 1 – 9). 46% (61/133) of patients had ≥3 prior ALK TKIs, and 56% (74/133) had prior chemotherapy. Notably, 84% (111/133) of patients received prior lorlatinib and 51% (68/133) had any secondary ALK resistance mutation including 26% (34/133) with compound (≥2) ALK mutations, highlighting the differentiated nature of this population from prior trials of investigational ALK inhibitors. 56% (75/133) had history of CNS metastases, including cases of disease progression following treatment with the brain-penetrant TKI lorlatinib.

As of the cut-off date of June 15, 2024, 103 heavily pre-treated patients with ALK-positive NSCLC treated across all doses were response-evaluable, of whom 39 were treated at the RP2D. The median follow-up for the all-treated population was 8.0 months (range 0.2, 22.5).

Treatment with NVL-655 resulted in durable clinical responses (ORR by RECIST 1.1) across key subgroups of response-evaluable patients treated at the RP2D and across all dose levels. As of the data cut-off date:

ALK-positive NSCLC response-evaluable	**NVL-655 at RP2D**			**NVL-655, All Doses**		
	ORR	**mDOR (months)**	**DOR ≥ 6 months***	**ORR**	**mDOR (months)**	**DOR ≥ 6 months***
Any Prior Therapies (1 – 5 prior ALK TKIs ± chemotherapy)	38% (15/39)	NR	100%	38% (39/103)	14.4	78%
Lorlatinib pre-treated (≥ 3rd Line**; ± chemotherapy)	35% (11/31)	NR	100%	35% (30/85)	9.2	75%
With compound ALK resistance mutations	64% (7/11)	NR	100%	54% (15/28)	14.4	80%
Lorlatinib-naïve (≥ 2nd Line; ± chemotherapy)	57% (4/7)	NR	100%	53% (9/17)	NR	88%
With ALK resistance mutation(s)	80% (4/5)	NR***	100%***	88% (7/8)	NR***	100%***

NR = not reached
* Analyses of DOR based on Kaplan-Meier estimates.
** NVL-655 has received FDA breakthrough therapy designation for the treatment of patients with locally advanced or metastatic ALK-positive NSCLC who have been previously treated with 2 or more ALK TKIs
*** No disease progression among responders.

CNS responses were observed in patients with either measurable or unmeasurable CNS lesions across all doses, including complete intracranial responses in patients who previously received the brain-penetrant TKI lorlatinib. No CNS progression was observed among all confirmed CNS responders.

NVL-655 was well-tolerated with a preliminary safety profile that was favorable and consistent with its ALK-selective, TRK sparing design. Among the 133 patients treated at all doses, the most frequent TRAEs were ALT increase (34%), AST increase (30%), constipation (16%), dysgeusia (13%), and nausea (12%). Among these most frequent TRAEs, 13% of patients experienced grade 3 ALT increase, one patient experienced grade 4 ALT increase, and 9% of patients experienced grade 3

AST increase. Transaminase elevations were generally transient and reversible.

Discontinuations due to TRAEs occurred in 2% of patients and dose-reductions occurred in 15% of patients. A maximum tolerated dose was not identified.

The company believes these preliminary data demonstrate the potential for NVL-655 to address a medical need for the third-line treatment of ALK-positive NSCLC where no approved therapies have demonstrated clinical benefit, and to provide a differentiated option in the second line. The ongoing Phase 2 portion of the ALKOVE-1 clinical trial is designed with registrational intent for TKI pre-treated patients with ALK-positive NSCLC, and the company expects to report pivotal data in 2025.

Additionally, the company believes that these data in heavily pre-treated patients could have the potential to translate to deep, durable responses in the front-line setting. The company plans to initiate the Phase 3 randomized, controlled, ALKAZAR study with registrational intent for TKI-naïve patients in the first half of 2025.

Conference Call Information

Following oral presentations at the ESMO Congress 2024 inBarcelona, Spain, management will host a live webcast and conference call on Saturday, September 14, 2024 at 8:30 a.m. ET/2:30 p.m. CEST.

To access the call, register online here for the live webcast or 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 Zidesamtinib and the ARROS-1 Phase 1/2 Clinical Trial

Zidesamtinib is a novel brain-penetrant ROS1-selective inhibitor created with the aim to overcome limitations observed with currently available ROS1 inhibitors. Zidesamtinib is designed to remain active in tumors that have developed resistance to currently available ROS1 inhibitors, including tumors with treatment-emergent ROS1 mutations such as G2032R. In addition, zidesamtinib 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/ROS1 inhibitors and to drive deep, durable responses for patients across all lines of therapy. Zidesamtinib has received breakthrough therapy designation for the treatment of patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) who have been previously treated with 2 or more ROS1 tyrosine kinase inhibitors and orphan drug designation for ROS1-positive NSCLC.

Zidesamtinib is currently being investigated in the ARROS-1 trial (NCT05118789), a first-in-human Phase 1/2 clinical trial for patients with advanced ROS1-positive NSCLC and other solid tumors. The completed Phase 1 portion enrolled ROS1-positive NSCLC patients who previously received at least one ROS1 TKI, or patients with other ROS1-positive solid tumors who had been previously treated. The Phase 1 portion of the trial was 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. The ongoing global, single arm, open label Phase 2 portion is designed with registrational intent for TKI naïve and TKI pre-treated patients with ROS1-positive NSCLC.

About NVL-655 and the ALKOVE-1 Phase 1/2 Clinical Trial

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 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 breakthrough therapy designation 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.

NVL-655 is currently being evaluated in the Phase 2 portion of 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 completed Phase 1 portion enrolled ALK-positive NSCLC patients who previously received at least one ALK TKI and patients with other ALK-positive solid tumors who had been previously treated with at least one prior systemic anticancer therapy. The primary objectives were to determine the recommended Phase 2 dose (RP2D) and if applicable, the maximum tolerated dose (MTD) of NVL-655 in patients with ALK-positive solid tumors. Additional objectives included characterization of the overall safety, tolerability, and pharmacokinetic profile, and evaluation of the preliminary anti-tumor activity of NVL-655. The ongoing global, 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.

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 clinical development programs for zidesamtinib and NVL-655; the expected timing of reporting data readouts from Nuvalent's clinical trials of zidesamtinib and NVL-655; the design and timing of the ALKAZAR trial, including alignment with the FDA regarding the design of the trial; the potential clinical effects of zidesamtinib and NVL-655; the potential of Nuvalent's pipeline programs, including zidesamtinib and NVL-655; the implications of 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, ALKOVE-1 or ALKAZAR 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; risks that Nuvalent may not achieve the goals and milestones set forth in its OnTarget 2026 operating plan; the occurrence of adverse safety events; risks that the FDA, European Medicines Agency or other foreign regulators 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, ALKOVE-1 and ALKAZAR trials; 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 Nuvalent's Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2024, 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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