Nuvalent Announces Positive Pivotal Data from ARROS-1 Clinical Trial of Zidesamtinib for TKI Pre-treated Patients with Advanced ROS1-positive NSCLC

Aligned with FDA on NDA submission strategy for TKI pre-treated patients with advanced ROS1-positive NSCLC and participation in Real-Time Oncology Review; the company

plans to initiate a rolling NDA submission in July 2025 with target completion in the third quarter of 2025

In 117 ROS1 TKI pre-treated patients, including 50% who had received ≥ 2 prior ROS1 TKIs ± chemotherapy, ORR by BICR was 44% (95% CI: 34, 53) with initial estimated durability of response of 78% at the 12-month landmark and 62% at the 18-month landmark

In the subset of 55 patients

treated with 1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy, ORR was 51% (95% CI: 37, 65) with initial estimated durability of response of 93% at the 12- and 18-month landmarks

Zidesamtinib demonstrated intracranial responses, activity against tumors with a ROS1 G2032R resistance mutation, and a generally well-tolerated safety profile, including low rates of dose reduction (10%) and discontinuation (2%), consistent

with its ROS1-selective, TRK-sparing design

Company announces progress in the front-line development strategies for its parallel lead programs in ROS1-positive and ALK-positive NSCLC

Company to host a conference call today, June 24th at 8:00am ET

CAMBRIDGE, Mass., June 24, 2025 /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 positive pivotal data for zidesamtinib, a novel ROS1-selective inhibitor, in TKI (tyrosine kinase inhibitor) pre-treated patients with advanced ROS1-positive non-small cell lung cancer (NSCLC) from the global ARROS-1 Phase 1/2 clinical trial.

In addition, Nuvalent announced progress on the front-line development strategies for its parallel lead programs in ROS1-positive and ALK-positive NSCLC, including:

- The first report of preliminary data from the Phase 2 TKI-naïve cohort in its ARROS-1 clinical trial, in which global enrollment is ongoing; and,
- The advancement of clinical startup activities to support the global initiation of the ALKAZAR Phase 3, randomized, controlled trial. The trial is designed to evaluate neladalkib, a novel ALK-selective inhibitor, versus alectinib, a front-line standard of care, for the treatment of patients with TKI-naïve ALK-positive NSCLC, and the company expects to begin enrollment early in the second half of 2025.

The company completed a pre-New Drug Application (NDA) meeting with the U.S. Food and Drug Administration (FDA) and

aligned on its plans to move forward with an NDA submission seeking an indication for the treatment of zidesamtinib for TKI pre-treated patients with locally advanced or metastatic ROS1-positive NSCLC. The FDA agreed to accept the NDA for participation in the Real-Time Oncology Review (RTOR) pilot program, which facilitates earlier submission of topline data to support an earlier start to the FDA's evaluation of the application. The company plans to initiate a rolling NDA submission in July 2025 with completion targeted for the third quarter of 2025, and continues to engage with the FDA on potential opportunities for line-agnostic expansion.

"Continued innovation for patients with ROS1-positive NSCLC is needed. Limitations of currently available ROS1 TKIs can lead to trade-offs between efficacy and tolerability in the front-line, and there is no clear targeted therapy care standard for TKI pre-treated patients," **said Alexander Drilon, MD, ARROS-1 trial investigator and Chief of the Early Drug Development Service at Memorial Sloan Kettering Cancer Center**. "These data demonstrate the potential for zidesamtinib to deliver meaningful clinical outcomes for TKI pre-treated patients, including those progressing with brain metastases or treatment-emergent resistance mutations, and to offer a favorable tolerability profile consistent with its goal of avoiding off-target side effects through ROS1-selectivity."

"Bringing a drug from ideation to pivotal data in just a few short years is a rare opportunity, and I would like to express my sincere gratitude for the tireless dedication of the Nuvalent team and for the patients, caregivers, and investigators that have helped us achieve this milestone for zidesamtinib," **said James Porter, Ph.D., Chief Executive Officer at Nuvalent**. "Today's announcement brings us a critical step closer to achieving our goal of becoming a fully integrated, commercial-stage biopharmaceutical company able to deliver a new, potential best-in-class treatment option to ***all*** patients with advanced ROS1-positive NSCLC."

"Ongoing research and efforts to develop more effective, targeted therapies for people living with ROS1-positive lung cancer align closely with our mission at The ROS1ders," **said Janet Freeman-Daily, Co-Founder and President of The ROS1ders** "Today's announcement brings renewed hope to our community—for more options and the potential for more precious time with our loved ones."

Summary of Pivotal Data

Zidesamtinib is being evaluated in ARROS-1, a first-in-human Phase 1/2 clinical trial for patients with advanced ROS1-positive NSCLC and other solid tumors. The recommended phase 2 dose (RP2D) for zidesamtinib of 100 mg once daily (QD) was determined during the Phase 1 dose-escalation portion of the trial. The ongoing global, single arm, multi-cohort, open label Phase 2 portion is designed to evaluate zidesamtinib at the RP2D with registrational intent for both TKI-naïve and TKI pre-treated patients with advanced ROS1-positive NSCLC.

In this pivotal dataset for the TKI pre-treated ROS1-positive NSCLC population, data are pooled across Phase 1 and 2 and reported for the primary objective of objective response rate (ORR, RECIST 1.1) by blinded independent central review (BICR). Key secondary objectives include duration of response (DOR), intracranial ORR (IC-ORR), and safety.

As of the data cut-off date of March 21, 2025, 514 patients with ROS1-positive solid tumors had received zidesamtinib at any starting dose across the Phase 1 and Phase 2 portions of the ARROS-1 clinical trial. Of these, 432 patients with advanced ROS1-positive NSCLC were treated with zidesamtinib at the RP2D.

Efficacy Analysis in TKI Pre-treated Advanced ROS1-positive NSCLC

The primary analysis population consisted of 117 TKI pre-treated patients with advanced ROS1-positive NSCLC with measurable disease who received zidesamtinib at the RP2D by May 31, 2024, with DOR follow-up of at least 6 months available for nearly all responders.

The primary analysis population was distinct from the ROS1 TKI pre-treated populations that have been reported for the current available and investigational ROS1 TKIs:

- Patients received a median of 2 prior lines of therapy (range, 1 – 11) and 53% had received prior chemotherapy.
- 47% of patients received crizotinib or entrectinib, the most commonly used front-line TKIs, as their only ROS1 TKI± prior chemotherapy. Within this subset, 51% of patients received prior crizotinib and 49% of patients received prior entrectinib; 47% of patients received prior chemotherapy.
- 50% of patients had received 2 or more prior ROS1 TKIs± prior chemotherapy, of which 93% had received prior lorlatinib, repotrectinib, or taletrectinib.
- 36% of patients had a secondary ROS1 resistance mutation, a key driver of disease progression.
- 49% of patients had active CNS disease by BICR, including cases of disease progression following treatment with the brain-penetrant TKIs lorlatinib, repotrectinib, and/or taletrectinib.

Activity was observed across subsets of TKI pre-treated patients, and durability of response was assessed as the probability of patients remaining in response for at least 6, 12 and 18 months by Kaplan-Meier estimate (Table 1). Median duration of response (mDOR) continues to mature.

Table 1.	**All TKI Pre-treated** [a]	**1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy** [b]
n	117	55
ORR, % (n/N) (95% CI)	44% (51/117) [c] (34, 53)	51% (28/55) [d] (37, 65)
% DOR ≥ 6 months [e] (95% CI)	84% (71, 92)	93% (74, 98)
% DOR ≥ 12 months [e] (95% CI)	78% (62, 88)	93% (74, 98)
% DOR ≥ 18 months [e] (95% CI)	62% (28, 84)	93% (74, 98)
G2032R mutation [f]		
n	26	6
ORR, % (n/N) (95% CI)	54% (14/26) (33, 73)	83% (5/6) (36, 100)
% DOR ≥ 6 months [e] (95% CI)	79% (47, 93)	80% (20, 97)
% DOR ≥ 12 months [e] (95% CI)	60% (28, 81)	80% (20, 97)

NE = not estimable.

a The median duration of follow-up was 11.1 months (range 0.2 – 25.6) and mDOR continue to mature. For responders, the emerging mDOR was 22.0 months (95% CI: 17.2, NE) overall and 17.2 months (95% CI: 3.7, NE) for the subset with G2032R.

b The median duration of follow-up was 11.8 months (range 1.2 – 25.6) and mDOR continue to mature. For responders, the emerging mDOR was 22.0 months (95% CI: 22.0, NE) overall and NE (95% CI: 1.9, NE) for the subset with G2032R.

c Includes responses observed in patients previously treated with at least 2 prior ROS1 TKIs ± chemotherapy (22/58, ORR = 38%), and in patients previously treated with repotrectinib (8/17, ORR = 47%) or taletrectinib (3/7, ORR = 43%).

d For patients receiving crizotinib only ± chemotherapy, ORR was 68% (19/28) with no progression events among responders. For patients receiving entrectinib only ± chemotherapy, ORR was 33% (9/27) with three progression events among responders.

e Estimated for responders by Kaplan-Meier analysis.

f ROS1 G2032R mutation identified in local or central testing of blood (ctDNA) or tissue.

In patients that had measurable CNS lesions by BICR at baseline (n = 56), the IC-ORR was 48% with 20% (11/56) intracranial complete responses (CR) and 2 unconfirmed partial responses (PR), and IC-DOR ≥ 12 months of 71% (95% CI: 46, 87).

- In patients that had only received prior crizotinib, which has limited brain penetrance,**±** chemotherapy (n = 13), the IC-ORR was 85% with 54% (7/13) intracranial CRs. There was only one CNS progression event among CNS responders.
- Intracranial responses were also observed in patients previously treated with the brain-penetrant TKIs entrectinib, lorlatinib, repotrectinib or taletrectinib.

Safety Analyses in Advanced ROS1-positive NSCLC

Zidesamtinib demonstrated a well-tolerated safety profile consistent with its ROS1-selective, TRK-sparing design.

In the 432 patients with advanced ROS1-positive NSCLC treated at RP2D as of the data cut-off date, the median duration of exposure was 5 months (range, 0, 32). The most frequent treatment-emergent adverse events (TEAEs) occurring in ≥ 15% of patients were peripheral edema (36%), constipation (17%), blood CPK increase (16%), fatigue (16%), and dyspnea (15%).

Dose reductions due to TEAEs occurred in 10% of patients and 2% of patients discontinued treatment due to TEAEs.

Preliminary Data for TKI-Naïve Patients with Advanced ROS1-positive NSCLC

Encouraging preliminary data were available for 35 TKI-naïve patients with advanced ROS1-positive NSCLC treated with zidesamtinib at RP2D as of August 31, 2024. Patients may have received up to one prior line of chemotherapy.

The preliminary ORR was 89% (31/35) and DOR ranged from 1.9+ to 13.9+ months with DOR ≥ 6 months and 12 months of 96% (95% CI: 76, 99). In 6 patients with measurable intracranial lesions, the IC-ORR was 83% (5/6) and the intracranial CR rate was 67% (4/6). The IC-DOR ranged from 4.6+ to 11.1+ months with no CNS progression among responders.

As of June 16, 2025, a total of 104 patients had been enrolled in the ongoing TKI-naïve cohort of the ARROS-1 trial.

Webcast and Conference Call Information

A conference call with management will be held today at8:00 am ET. To access the call, please 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 zidesamtinib, 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 Neladalkib and the ALKAZAR Phase 3 Clinical Trial

Neladalkib is a novel brain-penetrant ALK-selective inhibitor created with the aim to overcome limitations observed with currently available ALK inhibitors. Neladalkib 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, neladalkib 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. Neladalkib 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.

ALKAZAR is a Phase 3 global, randomized, controlled trial designed to enroll approximately 450 patients with TKI-naïve ALK-positive NSCLC. Patients will be randomized 1:1 to receive neladalkib monotherapy or ALECENSA® (alectinib) monotherapy. 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.

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 expected timing of data announcements, clinical trial initiations, FDA submissions and potential product approval; the clinical development programs for zidesamtinib and neladalkib; the potential clinical effects of zidesamtinib and neladalkib; the design and enrollment of Nuvalent's clinical trials, including for the ARROS-1 and ALKAZAR trials their intended pivotal registration-directed design; the potential of Nuvalent's pipeline programs, including zidesamtinib and neladalkib; the implications of data readouts and presentations; timing and content of potential discussions with FDA regarding potential accelerated approval pathways; 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 its clinical trials or that enrollment will take longer than expected; unexpected concerns that may arise from additional data, analysis, or results obtained during preclinical studies and clinical trials; the risk that preliminary results of clinical trials may not be predictive of future results from the same or other 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 zidesamtinib and neladalkib; 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 trial and the ALKAZAR 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 Nuvalent's Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, 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.

Dr. Drilon has financial interests related to Nuvalent.

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