Nuvalent Announces Publication in Molecular Cancer Therapeutics Reinforcing Rational Molecular Design of Zidesamtinib as a Novel ROS1-Selective Inhibitor

CAMBRIDGE, Mass., April 29, 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 the publication of a manuscript in *Molecular Cancer Therapeutics*, a journal of the American Association for Cancer Research, which supports the rational molecular design of zidesamtinib, its novel and selective ROS1 inhibitor. Zidesamtinib is currently being evaluated in the ongoing ARROS-1 Phase 1/2 trial for patients with advanced ROS1-positive non-small cell lung cancer (NSCLC) and other solid tumors, which is designed with registrational intent for tyrosine kinase inhibitor (TKI) pre-treated and TKI-naïve patients with advanced ROS1-positive NSCLC.

The publication, entitled "Zidesamtinib Selective Targeting of Diverse ROS1 Drug-Resistant Mutations," is published online and can be accessed here: http://doi.org/10.1158/1535-7163.MCT-25-0025

"Zidesamtinib was specifically designed with the goal of addressing the combined medical needs of treating tumors that have developed resistance, treating brain metastases and avoiding off-target adverse events. Structural studies play a critical role in the development and optimization of novel therapeutics, particularly when aiming to solve for multiple, and at times competing, challenges. To date, structural studies for ROS1-positive cancers have been hindered by a lack of ROS1 G2032R crystal structures, despite G2032R being the most commonly occurring ROS1 resistance mutation," **said first author Anupong Tangpeerachaikul, Ph.D., Director, Biology at Nuvalent.** "With this publication in *Molecular Cancer Therapeutics*, we are pleased to have shared what is, to our knowledge, the first structure of ROS1 G2032R, or any ROS1 mutation, offering a framework for understanding ROS1 TKI activity against these important drivers of disease progression. This structure further illustrates the intentional design of zidesamtinib and adds to the growing body of preclinical data supporting its ROS1-selective and TRK-sparing design."

The manuscript explores the activity of zidesamtinib and other approved or investigational ROS1 TKIs at clinically relevant concentrations against ROS1 resistance mutations, including the most commonly occurring resistance mutation, ROS1

G2032R, in preclinical mutagenesis screens and an intracranial ROS1 G2032R xenograft model. Findings presented in the manuscript show that, at clinically relevant concentrations, zidesamtinib suppressed on-target resistance in ENU mutagenesis screens simulating first-line and later-line treatment and inhibited ROS1 G2032R brain tumors more effectively than the other ROS1 TKIs evaluated. This favorable preclinical activity suggests the potential for zidesamtinib to delay tumor progression, both peripherally and intracranially.

In addition, the manuscript details the first crystal structure of ROS1 G2032R in complex with zidesamtinib, which further supports zidesamtinib's molecular design and provides structural insights into how the ROS1 G2032R mutation affects TKI binding. Zidesamtinib was designed with the goal of being active against ROS1 and ROS1 resistance mutations while avoiding the inhibition of the structurally related tropomyosin receptor kinase (TRK) family in the central nervous system (CNS), which has been associated with neurological adverse events that can be dose limiting. The crystal structure elucidates zidesamtinib's preclinical affinity for ROS1 G2032R and selectivity for ROS1 over TRK.

The company expects to report pivotal clinical data for TKI pre-treated patients with advanced ROS1-positive NSCLC from the ARROS-1 Phase 1/2 trial in the first half of 2025 in support of an anticipated New Drug Application submission by mid-year 2025, with an initial target indication of TKI pre-treated patients with advanced ROS1-positive NSCLC.

About Zidesamtinib
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.

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 and FDA submissions; the clinical development program for and potential effects of zidesamtinib; the potential of Nuvalent's pipeline programs, including zidesamtinib; 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 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 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-1trial; 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 Annual Report on Form 10-K for the fiscal year ended December 31, 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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