Nuvalent Presents New Data Demonstrating Expanded Preclinical Activity with ROS1-Selective Inhibitor NVL-520 and ALK-Selective Inhibitor NVL-655 at AACR Annual Meeting 2022

NVL-520 showed strong preclinical activity against diverse ROS1 fusion partners

and kinase-domain resistance mutations, as well as in a ROS1-driven model of glioblastoma

NVL-655 demonstrated differentiation through broad preclinical activity across diverse ALK oncoproteins, resistance mutations, and tumor types while maintaining strong selectivity for ALK over TRKB

Supports broad investigation in advanced ROS1+ and

ALK+ NSCLC and other solid tumors through the ongoing Phase 1/2 ARROS-1 study of NVL-520 and planned Phase 1/2 ALKOVE-1 study of NVL-655 beginning Q2 2022

CAMBRIDGE, Mass., April 8, 2022 /PRNewswire/ -- Nuvalent, Inc., (Nasdaq: NUVL) a clinical-stage biopharmaceutical company creating *precisely* targeted therapies for patients with cancer, today announced new data to support broad clinical exploration of its parallel lead programs NVL-520 – a ROS1-selective inhibitor – and NVL-655 – an ALK-selective inhibitor. NVL-520 and NVL-655 are central nervous system (CNS)-penetrant kinase inhibitors designed to specifically solve for the dual challenges of kinase resistance and selectivity commonly observed with currently available inhibitors.

The data are available via two posters presented at the American Association for Cancer Research (AACR) Annual Meeting 2022, which runs from April 8 through April 13. The posters will also be available on the Nuvalent website at www.nuvalent.com/news/.

"We are pleased to share new data today resulting from our continued collaborations with leading investigators in ROS1 and ALK research, which we believe further demonstrate the potential for our highly selective inhibitors to be differentiated within the dynamic treatment landscapes for non-small cell lung cancer (NSCLC) and beyond," said James Porter, Ph.D., Chief Executive Officer of Nuvalent. "These preclinical data support the inclusion of various fusion partners and resistance mutations in our ARROS-1 and ALKOVE-1 clinical trials for ROS1- and ALK-positive NSCLC, respectively, as well as the inclusion of exploratory cohorts for other advanced solid tumors outside of NSCLC."

Monika Davare, Ph.D. is an Associate Professor of Pediatrics, Division of Hematology and Oncology at Oregon Health & Science University School of Medicine and leading expert in ROS1 oncoprotein biology. Professor Davare's research is directed towards overcoming therapeutic bottlenecks in oncology, including those that arise from the lack of validated translational research models for genomic subsets of cancer.

"Translational models of ROS1-driven cancers have centered on NSCLC, where the clinical impact of fusion partners is not yet well characterized and new treatment-resistant variants continue to emerge. Hypothesizing that broad coverage of fusion partners and resistance mutations is a beneficial feature for next-generation ROS1 inhibitors, we conducted an extensive comparative analysis of NVL-520 versus currently approved as well as investigational ROS1 inhibitors," said Professor Davare. "In contrast to comparator compounds, NVL-520 exhibited consistently high potency (IC_{50} < 10 nM) across all models tested, and in particular displayed potencies against the recurrently problematic G2032R solvent front mutation that were ≥ 1-order of magnitude higher than all comparative agents tested."

"While models of ROS1-driven cancers outside of NSCLC are sparse, we further present data that NVL-520 induces regression in a human cell-line derived model of glioblastoma driven by a ROS1 fusion," continued Professor Davare. "This suggests potential for clinical utility outside of NSCLC and highlights the importance of developing additional research models to help accelerate the development of new therapies for genomically-driven cancers."

Luc Friboulet, Ph.D. is an investigator at Gustave Roussy focused on investigating molecular mechanisms of tumor adaptation to kinase inhibitors in solid tumors, with particular expertise in understanding resistance to ALK kinase inhibitors.

"ALK oncogenic activations as well as mutations conferring resistance to current ALK inhibitors have been characterized across a range of tumor types, suggesting that broad activity across diverse ALK-driven cancers is a beneficial feature for next-generation ALK inhibitors," said Dr. Friboulet. "In a comparative analysis of NVL-655 versus currently approved as well as investigational ALK inhibitors, NVL-655 exhibited strong activity across a wide range of fusion partners, activating mutations, and disease backgrounds, suggesting potential for broad clinical utility. Importantly, this expansive activity of NVL-655 against ALK does not come at the expense of its ability to avoid inhibition of TRKB, a limitation that has been observed with other investigational ALK inhibitors."

NVL-520 is currently under investigation in the Phase 1 portion of the Phase 1/2 ARROS-1 study (NCT05118789) for advanced ROS1-positive NSCLC and other solid tumors. Nuvalent recently announced the IND clearance for NVL-655 and plans to initiate the Phase 1 portion of the Phase 1/2 ALKOVE-1 study for advanced ALK-positive NSCLC and other solid tumors in the second quarter of 2022. In addition to these parallel lead programs, Nuvalent is advancing a robust discovery pipeline with plans to nominate two new development candidates in 2022 for ALK IXDN compound mutations and HER2 exon 20 insertions.

AACR Presentation Overview:

*** Presenting authors**

Title: NVL-520: Preclinical Activity of NVL-520 in ROS1-Driven Cancer Models with Diverse Fusion Partners and Kinase-Domain Mutations
Authors: Anupong Tangpeerachaikul*^, Clare Keddy^, Katelyn Nicholson, Monika A. Davare, and Henry E. Pelish*
^ Equal contributions
Poster Number: 14
Permanent Abstract: 3336
Session Category: Experimental and Molecular Therapeutics
Session Title: Tyrosine Kinase and Phosphatase Inhibitors
Session Date and Time: Tuesday April 12, 2022 from 1:30 – 5:00 p.m. Central Time
Location: New Orleans Convention Center, Exhibit Halls D-H, Poster Section 26

Summary of Presentation:

- NVL-520 shows high activity against diverse ROS1 fusion partners tested including CD74, CEP85L, EZR, GOPC(L), GOPC(S), and SLC34A2 and induces regression in a ROS1-driven model of glioblastoma harboring GOPC(L)-ROS1.
- NVL-520 shows high activity against diverse ROS1 kinase-domain mutations tested including S1986F, F2004C/V, L2026M, G2032R, D2033N, and G2101A.
- NVL-520 shows a differentiated preclinical activity and selectivity profile compared to other inhibitors tested.
- Preclinical activity against diverse ROS1 fusion partners and kinase domain mutations suggests broad potential clinical utility of NVL-520.

Title: NVL-655: Preclinical Activity of NVL-655 in ALK-Driven Cancer Models beyond Non-Small Cell Lung Cancer
Authors: Anupong Tangpeerachaikul*, Ludovic Bigot, Luc Friboulet, and Henry E. Pelish*
Poster Number: 15
Permanent Abstract: 3337
Session Category: Experimental and Molecular Therapeutics
Session Title: Tyrosine Kinase and Phosphatase Inhibitors
Session Date and Time: Tuesday April 12, 2022 from 1:30 – 5:00 p.m. Central Time
Location: New Orleans Convention Center, Exhibit Halls D-H, Poster Section 26

Summary of Presentation:

- NVL-655 shows strong activity in diverse preclinical models of ALK-driven cancers: cholangiocarcinoma, neuroblastoma, lymphoma, and soft-tissue sarcoma.
- Among all inhibitors tested, NVL-655 shows the broadest activity for diverse ALK oncoproteins including fusions, point mutations, and partial N-terminal deletions.

- NVL-655 shows larger ALK-vs-TRK selectivity windows than lorlatinib and TPX-0131.
- Preclinical activity against diverse ALK oncoproteins (fusions, mutations, and partial deletions) in multiple tumor types suggests broad potential clinical utility of NVL-655.

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), along with 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 clinical development programs for NVL-520, NVL-655, ALK IXDN compound resistance mutations and HER2 exon 20 insertions and the timing thereof; the potential clinical effect of NVL-520 and NVL-655; the design and enrollment of the ARROS-1 study and the timing thereof; the design and initiation of the ALKOVE-1 Phase 1/2 study and the timing thereof; the potential of Nuvalent's pipeline programs, including NVL-520 and NVL-655; and Nuvalent's research and development programs for the treatment of cancer. 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 associated with: risks that Nuvalent may not fully enroll the ARROS-1 study or it will take longer than expected; unexpected concerns that may arise from additional data, analysis, or results obtained during clinical trials; the occurrence of adverse safety events; risks of unexpected costs, delays, or other unexpected hurdles; the impact of COVID-19 on countries or regions in which Nuvalent has operations or does business, as well as on the timing and anticipated timing and results of its clinical trials, strategy, and future operations, including the global ARROS-1 study and the planned initiation of the ALKOVE-1 Phase 1/2 study; 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 Annual Report on Form 10-K for the year ended December 31, 2021, as well as any 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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