Relay Therapeutics Announces Preclinical Data that Support RLY-2608 as the First Known Allosteric Pan-Mutant Selective Inhibitor of PI3Kα

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RLY-2608 preferentially binds mutant PI3Kα at a novel allosteric site discovered by the Dynamo™ platform

Preclinically, achieved tumor regressions in vivo with significantly reduced impact on glucose metabolism compared to active site inhibitors

RLY-2608's pan-mutant inhibition has the potential to address over 100,000 patients per year in the U.S.

CAMBRIDGE, Mass., Oct. 07, 2021 (GLOBE NEWSWIRE) -- Relay Therapeutics, Inc. (Nasdaq: RLAY), a clinical-stage precision medicine company transforming the drug discovery process by combining leading-edge computational and experimental technologies, today shared preclinical data at the virtual AACR-NCI-EORTC Molecular Targets Conference for RLY-2608, the first allosteric, pan-mutant (H1047X, E542X and E545X) and isoform-selective PI3Kα inhibitor.

The data presented at the conference show that in preclinical models, RLY-2608 preferentially binds mutant PI3Kα at a novel allosteric site discovered by the Dynamo™ platform. Scientists at Relay Therapeutics solved the full-length structure of PI3Kα, performed long time-scale molecular dynamic simulations to elucidate differences in motion between wild-type (WT) and mutant PI3Kα, and leveraged these insights to enable the design of RLY-2608. In biochemical and cellular assays, RLY-2608 inhibited the three major classes of PI3Kα oncogenic mutations (H1047X, E542X and E545X) while sparing WT PI3Kα. The data further suggest that RLY-2608 is also highly selective against other PI3K family members and exquisitely selective across the kinome. The data suggest that projected clinically relevant doses of RLY-2608 achieved tumor regression in *PIK3CA* mutant in vivo xenograft models representing H1047R and E545K mutations with significantly reduced impact on glucose metabolism compared to non-mutant selective active site inhibitors. In higher species, dosing of RLY-2608 resulted in exposures exceeding 90% inhibition of mutant PI3Kα in cells without resulting in elevated glucose levels or histopathological changes associated with dysregulation of glucose metabolism that are seen with non-mutant selective inhibitors.

These results support advancement of RLY-2608 into clinical development as a differentiated mechanism of mutant PI3Kα inhibition with the first-in-human study anticipated to start in the first half of 2022. RLY-2608 is the lead program of multiple preclinical efforts at Relay Therapeutics to discover and develop mutant selective inhibitors of PI3Kα.

RLY-2608 has the potential to address over 100,000 patients per year in the United States, one of the largest patient populations for a precision oncology medicine. Selectivity for all three mutation hot spots (H1047X, E542X and E545X) has the potential to effectively double the addressable patient population compared to selectivity for only H1047X.

"The data shared today provide another proof point that we're developing what we believe to be the first known pan-mutant selective allosteric inhibitor of PI3Kα," said Don Bergstrom, M.D., Ph.D., executive vice president of R&D at Relay Therapeutics. "We believe RLY-2608 has the potential to address a significant unmet medical need in a large population and have validated our approach for developing mutant selective inhibitors of PI3Kα. RLY-2608 is only the start of our PI3Kα efforts, and by leveraging our Dynamo™ platform, we plan to build a franchise around this target for the long-term."

Conference Call Information
Relay Therapeutics will host a live webcast and conference call tomorrow, October 8, beginning at 12:30 pm E.T. to discuss the results of this presentation and the RLY-4008 presentation tomorrow. To access the live call, please dial (833) 540-1168 (domestic) or (929) 517-0359 (international) and refer to conference ID 4657916. A webcast of the conference call will be available under "News and Presentations" in the Media & Investors section of Relay Therapeutics' website at http://ir.relaytx.com. The archived webcast will be available on Relay Therapeutics' website approximately two hours after the conference call and will be available for 30 days following the call.

The data presentation from the AACR-NCI-EORTC Molecular Targets Conference is also available on the Relay Therapeutics website under "Publications/Presentations" near the bottom of https://relaytx.com/pipeline/.

About RLY-2608
RLY-2608 is the lead program of multiple preclinical efforts to discover and develop mutant selective inhibitors of PI3Kα. PI3Kα is the most frequently mutated kinase in all cancers, with oncogenic mutations detected in about 13% of patients with solid tumors. Traditionally, the development of PI3Kα inhibitors has focused on the active, or orthosteric, site. The therapeutic index of orthosteric inhibitors is limited by the lack of clinically meaningful selectivity for mutant versus WT PI3Kα and off-isoform activity. Toxicity related to inhibition of WT PI3Kα and other PI3K isoforms results in sub-optimal inhibition of mutant PI3Kα with reductions in dose intensity and frequent discontinuation. The Dynamo™ platform enabled the discovery of RLY-2608, the first known allosteric, pan-mutant (H1047X, E542X and E545X), and isoform-selective PI3Kα inhibitor designed to overcome these limitations. Relay Therapeutics solved the full-length cryo-EM structure of PI3Kα, performed computational long time-scale molecular dynamic simulations to elucidate conformational differences between WT and mutant PI3Kα, and leveraged these insights to support the design of RLY-2608. RLY-2608 is on path to initiate a first-in-human clinical trial in the first half of 2022, subject to submission of an investigational new drug application and acceptance by the FDA.

About Relay Therapeutics

Relay Therapeutics (Nasdaq: RLAY) is a clinical-stage precision medicines company transforming the drug discovery process by combining leading-edge computational and experimental technologies with the goal of bringing life-changing therapies to patients. Relay Therapeutics is the first of a new breed of biotech created at the intersection of disparate technologies. Relay Therapeutics' Dynamo™ platform integrates an array of leading-edge computational and experimental approaches designed to drug protein targets that have previously been intractable. Relay Therapeutics' initial focus is on enhancing small molecule therapeutic discovery in targeted oncology and genetic disease. For more information, please visit www.relaytx.com or follow us on Twitter.

Cautionary Note Regarding 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: Relay Therapeutics' strategy, business plans and focus; the progress and timing of updates on the clinical development of the programs across Relay Therapeutics' portfolio, including the timing of initiation of a first-in-human clinical trial of RLY-2608; potential therapeutic effects and anticipated clinical benefits of RLY-2608; Relay Therapeutics' plans to build a franchise around PI3Kα; the potential target patient population of RLY-2608; and whether preclinical results of RLY-2608 will be predictive of future clinical trials of RLY-2608. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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: the impact of COVID-19 on countries or regions in which Relay Therapeutics has operations or does business, as well as on the timing and anticipated results of its clinical trials, strategy and future operations; the delay of any current or planned clinical trials or the development of Relay Therapeutics' drug candidates; the risk that the results of its clinical trials may not be predictive of future results in connection with future clinical trials; Relay Therapeutics' ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of Relay Therapeutics' 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 Relay Therapeutics' Quarterly Report on Form 10-Q for the quarter ended June 30, 2021, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Relay Therapeutics' views only as of today and should not be relied upon as representing its views as of any subsequent date. Relay Therapeutics explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

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