Prelude Therapeutics Presents Data at the 2025 ASH Annual Meeting from its Myeloproliferative Neoplasm (MPN) Programs

December 6, 2025 4:00 PM EST

First disclosure of PRT12396, a JAK2V617F-selective JH2 inhibitor demonstrates disease modifying potential in myeloproliferative neoplasms

PRT12396 has completed GLP toxicology studies and is on track for IND filing in the first quarter 2026

First disclosure of a mutant calreticulin (mCALR) targeted degrader antibody conjugate (DAC) with a novel CDK9 degrader payload

JAK2V617F and mCALR are the two primary driver mutations responsible for disease progression and poor prognosis in the majority of MPN patients

WILMINGTON, Del., Dec. 06, 2025 (GLOBE NEWSWIRE) -- Prelude Therapeutics Incorporated (Nasdaq: PRLD) ("Prelude" or the "Company"), a precision oncology company, presented earlier today the first preclinical data on its JAK2V617F mutant selective JH2 inhibitors and additional preclinical data from its mCALR-targeted degrader antibody conjugate (DAC) discovery program. Both oral presentations took place at the American Society of Hematology (ASH) 67th Annual Meeting in Orlando, FL. These presentations can be found at Publications - Prelude Therapeutics.

"Since JAK2V617F was first identified as a major driver mutation in JAK2 enzyme in myeloproliferative neoplasms two decades ago, our industry has been searching for an inhibitor that can selectively target the mutant JAK2 enzyme without disrupting normal JAK2 function" stated Kris Vaddi, Ph.D., Chief Executive Officer of Prelude. "We are proud to have made significant advances in the discovery of such molecules and to share preclinical data demonstrating that our lead candidate meaningfully differentiates between mutant and wild-type JAK2 and potentially overcomes dose-limiting toxicities associated with current therapies. This work underscores the potential for a disease-modifying approach beyond what is achievable with today's JAK2 inhibitors, and we look forward to advancing this molecule into the clinic in early 2026."

Continued Vaddi, "Beyond JAK2, mCALR is the other most common driver mutation in MPNs. Clinical data with an mCALR-directed antibody has now demonstrated meaningful therapeutic benefit for patients. Our degrader antibody conjugate (DAC) approach is designed to build on this validation by delivering a disease-relevant payload, such as our highly potent CDK9 degrader, directly to mCALR-positive cells. We believe this innovative strategy offers a differentiated, and potentially even more efficacious approach as we seek to advance the next wave of disease-modifying therapies for MPN patients. We were pleased to share these initial results from both programs today at ASH."

In the oral presentation, titled *"Discovery and preclinical characterization of orally bioavailable JAK2V617F mutant selective JH2 inhibitors with disease modification potential in myeloproliferative neoplasms,"* the authors presented data from preclinical studies showing that PRT12396 selectively inhibits JAK2V617F activity in a cellular context while preserving WT JAK2-medited cytokine signaling. Additionally, PRT12396 demonstrated robust preclinical activity in multiple preclinical MPN models, superior to ruxolitinib. PRT12396 also showed selective inhibition of the proliferation of JAK2VF stem and progenitor cells both *in vitro* and *in vivo* and was well-tolerated in toxicological studies with minimal effects on hematologic parameters.

The Company has completed GLP toxicology studies and anticipates filing the IND and initiating a phase 1 study in the first quarter of 2026. The Company's JAK2V617F inhibitor program is subject to an exclusive option agreement with Incyte announced in November 2025.

Additionally, the Company presented data from its mutant calreticulin (mCALR) degrader antibody conjugates (DACs) discovery program. In the oral presentation, titled "*Discovery of First-in-Class Calreticulin-targeted Precision Antibody Drug Conjugates Delivering a CDK9 Degrader Payload for the Treatment of CALR-mutated MPNs*," the authors demonstrated that an mCALR x CDK9 degrader antibody conjugate delivers a CDK9 degrader selectively to malignant clones. Through this approach, deep mutant-selective killing across cell lines, HSPCs and primary cultures was shown, highlighting disease modifying potential, supported by compelling *in vivo* efficacy data. mCALR x CDK9 DACs were also shown to spare healthy hematopoietic cells, indicating potential for a favorable therapeutic index.

About mutant selective JAK2V617F JH2 inhibitor program
JAK2V617F is the primary driver mutation responsible for disease progression in the majority of patients living with myeloproliferative neoplasms (MPNs). The mutation impacts approximately 95% of patients with polycythemia vera (PV), 60% of patients with essential thrombocythemia (ET) and 55% of patients with myelofibrosis (MF). Identifying JAK2 JH2 inhibitors that selectively target V617F+ cells has long been a shared goal and challenge for industry. Prelude has discovered novel allosteric inhibitors that bind into the JAK2 JH2 "deep pocket" where the V617F mutation resides. These candidates demonstrate mutant specific inhibition in multiple preclinical models of MPNs. Prelude believes this approach may have the potential to reduce mutant allele burden, slow or even reverse disease progression, and transform treatment outcomes for MPN patients.

About mutant calreticulin (mCALR) targeted degrader antibody conjugates (DACs)
Mutant CALR is a neoantigen presented on the cell surface of malignant myeloid cells but not normal cells and is found in approximately 25-35% of patients with MF and ET. Recently, a mCALR-targeted monoclonal antibody demonstrated robust clinical activity in high-risk ET patients. Prelude is seeking to further optimize this modality by developing mCALR-targeted DACs using the Company's proprietary degrader payloads. The Company presented the first preclinical data from this discovery effort at the European Hematology Association 2025 Congress in June.

About Prelude Therapeutics
Prelude Therapeutics is a leading precision oncology company developing innovative medicines in areas of high unmet need for cancer patients. Our pipeline features highly selective KAT6A degraders and JAK2V617F mutant selective JH2 inhibitors – new approaches to clinically validated targets with transformative potential for patients. We are leveraging our expertise in targeted protein degradation to discover and develop next generation degrader antibody conjugates (DACs) with novel payloads. We are on a mission to extend the promise of precision medicine to every cancer patient in need. Our corporate presentation can be found at Events & Presentations - Prelude Therapeutics. For more information, visit preludetx.com.

Cautionary Note Regarding Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform

Act of 1995, including, but not limited to, anticipated discovery, preclinical and clinical development activities for Prelude's product candidates, the potential safety, efficacy, benefits and addressable market for Prelude's product candidates, the expected timeline for clinical trial results for Prelude's product candidates, and the sufficiency of Prelude's cash runway. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. The words "believes," "anticipates," "estimates," "plans," "expects," "intends," "may," "could," "should," "potential," "likely," "projects," "continue," "will," "schedule," and "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are predictions based on the Company's current expectations and projections about future events and various assumptions. Although Prelude believes that the expectations reflected in such forward-looking statements are reasonable, Prelude cannot guarantee future events, results, actions, levels of activity, performance or achievements, and the timing and results of biotechnology development and potential regulatory approval is inherently uncertain. Forward-looking statements are subject to risks and uncertainties that may cause Prelude's actual activities or results to differ significantly from those expressed in any forward-looking statement, including risks and uncertainties related to Prelude's ability to advance its product candidates, the receipt and timing of potential regulatory designations, approvals and commercialization of product candidates, clinical trial sites and our ability to enroll eligible patients, supply chain and manufacturing facilities, Prelude's ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of preclinical and clinical trials, Prelude's ability to fund development activities and achieve development goals, Prelude's ability to protect intellectual property, and other risks and uncertainties described under the heading "Risk Factors" in Prelude's Annual Report on Form 10-K for the year ended December 31, 2024, its Quarterly Reports on Form 10-Q and other documents that Prelude files from time to time with the Securities and Exchange Commission. These forward-looking statements speak only as of the date of this press release, and Prelude undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof, except as may be required by law.

Investor Contact:
Robert A. Doody, Jr.
Senior Vice President, Investor Relations
Prelude Therapeutics Incorporated
484.639.7235
rdoody@preludetx.com