Incyte Presents Updated Positive Data at ASH 2025 Reinforcing the Potential of INCA033989, its First-in-Class mutCALR-Targeted Monoclonal Antibody, in Patients with Essential Thrombocythemia

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- *Nearly all (90%) of essential thrombocythemia (ET) patients treated with INCA033989 at the higher dose achieved a hematologic response (HR) with 83.3% achieving a complete HR*
- *Molecular responses were frequent, rapid, durable and correlated with hematologic responses; a reduction in mutCALR variant allele frequency (VAF) from baseline occurred in 96.2% of patients with ≥1 post-baseline VAF measurement*
- *Exploratory analyses from the clinical studies show potential direct disease-modifying activity of INCA033989*
- *Results demonstrate a favorable safety profile – no dose limiting toxicities were reported and a maximum tolerated dose was not reached*
- *The FDA granted Breakthrough Therapy designation to INCA033989 for the treatment of patients with ET harboring a Type 1 CALR mutation who are resistant or intolerant to at least one cytoreductive therapy*

WILMINGTON, Del.--(BUSINESS WIRE)--Dec. 8, 2025-- Incyte (Nasdaq:INCY) today announced updated clinical data from two Phase 1 studies evaluating the safety, tolerability and efficacy of INCA033989, a first-in-class mutant calreticulin (mutCALR)-targeted monoclonal antibody, as a treatment for patients with mutCALR-expressing myeloproliferative neoplasms (MPNs). These data, which are featured in oral presentations at the 2025 American Society of Hematology (ASH) Annual Meeting in Orlando (Session 634, Publication #1024; Session 631, Publication #71), focus on the dose escalation portion of the studies in patients with essential thrombocythemia (ET) harboring a CALR mutation who are resistant or intolerant to at least one cytoreductive therapy.

“The compelling efficacy and safety data presented today at the 2025 ASH Annual Meeting provide additional evidence of the potential for INCA033989 to provide disease modification for high-risk ET patients harboring a CALR mutation,” said Pablo J. Cagnoni, M.D., President, Head of Research and Development, Incyte. “We are proud to be advancing a portfolio of novel targeted therapies, including INCA033989, that could offer a mutation-specific treatment for patients with mutCALR-expressing MPNs.”

Results presented today evaluate the safety and efficacy of INCA033989 in patients with ET, as measured by hematologic response and reduction in mutCALR variant allele frequency (VAF), and build upon previously announced data presented at the European Hematology Association 2025 Congress.

The new results (data cut-off September 25, 2025) demonstrate rapid and durable normalization of platelet counts across all dose levels in patients with ET treated with INCA033989 (n=55), with optimal responses at higher doses. Of note, most (90%) ET patients treated with starting doses of 400 to 2,500 mg (n=30) INCA033989 achieved a hematologic response. Of those, 83.3% achieved a complete hematologic response (CHR), defined as platelet count ≤400 × 10^9/L and leukocytes <10 × 10^9/L, and nearly half (46.4%) achieved a durable (≥12 weeks) CHR. Among patients treated at lower doses (24 to 250 mg, n=25), 88% achieved a hematologic response, with 68% achieving a CHR and of those 44% achieving a durable CHR.

Additionally, molecular responses were frequent, rapid, durable and correlated with hematologic responses seen with INCA033989 monotherapy. A reduction in mutCALR VAF from baseline occurred in 96.2% of ET patients with ≥1 post-baseline VAF measurement, with approximately half (52%) achieving a ≥25% best reduction in VAF and nearly one third (31%) achieving a ≥50% best reduction in VAF. Reduction in mutCALR VAF was observed within three to six months and has maintained over time in most patients, with deeper and more consistent mutCALR VAF reductions observed at higher doses of INCA033989.

Exploratory analyses in a subset of ET patients showed that INCA033989 reduced circulating mutCALR-positive hematopoietic stem and progenitor cells (HSPC) and mutCALR-positive platelet producing cells called megakaryocytes (MK) in the bone marrow, and improved MK hyperplasia. Together, these findings demonstrate the disease-modifying activity of INCA033989 in patients with mutCALR-expressing ET.

The safety analysis (n=55) showed that INCA033989 was well tolerated across all dose cohorts (24 to 2,500 mg), with no dose-limiting toxicities observed. Only one (1) patient discontinued treatment due to treatment emergent adverse events (TEAEs). One (1) dose reduction and one (1) infusion interruption due to TEAEs were reported, and a maximum tolerated dose was not reached. Fifty-three (53) patients across the dose cohorts reported a TEAE, thirty-six (36) of which were treatment related. The most common TEAEs were fatigue (30.9%), headache (27.3%), upper respiratory tract infection (27.3%) and anemia (20%). Grade ≥3 anemia and/or neutropenia TEAEs (>1 patient) occurred in five (5) patients (3.6% and 7.3%, respectively). No Grade ≥3 thrombocytopenia TEAEs were observed.

"Approximately 25 to 35 percent of ET patients have mutCALR-expressing ET, yet current treatments are broadly myelosuppressive, not mutant targeted and have limited efficacy in reducing mutCALR allele frequency,” said John Mascarenhas, M.D., Professor of Medicine at the Icahn School of Medicine at Mt. Sinai and Director, Center of Excellence for Blood Cancers and Myeloid Disorders, The Tisch Cancer Institute. “These emerging data suggest that INCA033989 could offer a novel treatment approach by selectively targeting mutCALR in a way that enables rapid and durable hematologic responses, while maintaining safety and tolerability for ET patients who are resistant or intolerant to prior cytoreductive therapy. I'm encouraged by these findings and the potential for INCA033989 to redefine treatment paradigms for patients with ET."

INCA033989 was recently granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for the treatment of patients

with ET harboring a Type 1 CALR mutation who are resistant or intolerant to at least one cytoreductive therapy. Incyte plans to develop INCA033989 for patients with Type 1 and non-Type 1 CALR mutations and, following discussions with regulatory agencies, plans to initiate a registrational program evaluating patients with ET with a Type 1 or non-Type 1 CALR mutation who are resistant or intolerant to at least one cytoreductive therapy in the first half of next year.

More information regarding the 2025 ASH Annual Meeting can be found on the ASH website: https://www.hematology.org/meetings/annual-meeting/schedule-and-program/programs.

About Essential Thrombocythemia
Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm (MPN) characterized by persistently elevated platelet counts due to abnormal blood cell production in the bone marrow. People living with ET are at increased risk for blood clots and bleeding and a proportion of patients may progress over time to myelofibrosis or acute leukemia.

About Mutations in Calreticulin (mutCALR)
Calreticulin (CALR) is a protein involved in the regulation of cellular calcium levels and normal protein folding. Somatic, or non-inherited, DNA mutations in the CALR gene (mutCALR) can result in abnormal protein function and lead to the development of myeloproliferative neoplasms (MPNs),[1] a closely related group of clonal blood cancers in which the bone marrow functions abnormally, overproducing blood cells.[2,3] Among two types of MPNs, essential thrombocythemia (ET) and myelofibrosis (MF), mutCALR drives 25-35% of all cases.[2,3]

Incyte is at the forefront of developing novel therapies for patients with mutCALR ET or MF that target only malignant cells, sparing normal cells, including INCA033989, a first-in-class, mutCALR-specific therapy.

About the INCA033989 Trial Program
The clinical trial program for INCA033989 includes two multicenter, open-label Phase 1 studies, INCA33989-101 (NCT05936359) and INCA33989-102 (NCT06034002). The studies are evaluating the safety, tolerability and efficacy of INCA033989 in ~455 adult (≥18 years old) patients with mutCALR-expressing myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET) and myelofibrosis (MF).

The primary endpoint of the studies is measured by the number of participants with dose limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs) and the number of participants with TEAEs leading to dose modification or discontinuation. Secondary endpoints include response rates, mean change of ET total symptom score, percentage of MF patients achieving spleen volume reduction, MF patient anemia response, mean change in disease-related allele burden and various pharmacokinetics measures.

For more information on the studies, please visit: https://clinicaltrials.gov/study/NCT05936359 and https://clinicaltrials.gov/study/NCT06034002.

About Incyte
A global biopharmaceutical company on a mission to *Solve On.*, Incyte follows the science to find solutions for patients with unmet medical needs. Through the discovery, development and commercialization of proprietary therapeutics, Incyte has established a portfolio of first-in-class medicines for patients and a strong pipeline of products in Oncology and Inflammation & Autoimmunity. Headquartered in Wilmington, Delaware, Incyte has operations in North America, Europe and Asia.

For additional information on Incyte, please visit Incyte.com or follow us on social media: LinkedIn, X, Instagram, Facebook, YouTube.

Forward-Looking Statements
Except for the historical information set forth herein, the matters set forth in this press release, including statements regarding the presentation of data for Incyte's anti-mutCALR monoclonal antibody (INCA033989), the potential this monoclonal antibody offers for patients, and expectations regarding ongoing and future clinical trials, contain predictions, estimates, and other forward-looking statements.

These forward-looking statements are based on Incyte's current expectations and subject to risks and uncertainties that may cause actual results to differ materially, including unanticipated developments in and risks related to: further research and development and the results of clinical trials possibly being unsuccessful or insufficient to meet applicable regulatory standards or warrant continued development; the ability to enroll sufficient numbers of subjects in clinical trials and the ability to enroll subjects in accordance with planned schedules; determinations made by the FDA, EMA and other regulatory agencies; Incyte's dependence on its relationships with and changes in the plans of its collaboration partners; the efficacy or safety of Incyte's products and the products of Incyte's collaboration partners; the acceptance of Incyte's products and the products of Incyte's collaboration partners in the marketplace; market competition; unexpected variations in the demand for Incyte's products and the products of Incyte's collaboration partners; the effects of announced or unexpected price regulation or limitations on reimbursement or coverage for Incyte's products and the products of Incyte's collaboration partners; sales, marketing, manufacturing and distribution requirements, including Incyte's and its collaboration partners' ability to successfully commercialize and build commercial infrastructure for newly approved products and any additional products that become approved; greater than expected expenses, including expenses relating to litigation or strategic activities; variations in foreign currency exchange rates; and other risks detailed in Incyte's reports filed with the Securities and Exchange Commission, including its annual report on form 10-K and our quarterly report on Form 10-Q for the quarter ended September 30, 2025. Incyte disclaims any intent or obligation to update these forward-looking statements.

[1] Raghavan, M., Wijeyesakere S.J., Peters L.R., Del Cid N. (2013) Calreticulin in the immune system: ins and outs. *Trends in Immunology,* 34(1):13-21. Link to source (https://www.cell.com/trends/immunology/abstract/S1471-4906(12)00131-7?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1471490612001317%3Fshowall%3Dtrue)

[2] Nangalia J. Massie C.E., Baxter E.J., Nice F.L., et al. (2013) Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2.*New England Journal of Medicine,* 369(25):2391-2405. Link to source (https://www.nejm.org/doi/10.1056/NEJMoa1312542?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200www.ncbi.nlm.nih.gov)

[3] Klampfl T., Gisslinger, H., Harutyunyan A.S., et al. (2013) Somatic mutations of calreticulin in myeloproliferative neoplasms.*New England Journal of Medicine,* 369(25):2379-2390. Link to source (https://www.nejm.org/doi/10.1056/NEJMoa1311347?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200www.ncbi.nlm.nih.gov)

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