Positive Late-Breaking Data for Incyte's First-in-Class mutCALR-targeted therapy INCA033989 in Essential Thrombocythemia Presented at EHA2025

June 15, 2025

- *Data demonstrates the potential for INCA033989 to modify disease by directly inhibiting and eliminating oncogenic mutCALR cells, while sparing healthy cells and restoring normal blood cell production*
- *In high-risk patients with essential thrombocythemia (ET) with a CALR mutation (mutCALR), 86% of INCA033989-treated patients at doses 400 mg and above achieved a complete or partial hematologic response with the majority (82%) realizing a complete response*
- *A reduction in peripheral blood mutCALR variant allele frequency (VAF) was observed in 89% of evaluable patients correlating with hematologic response*
- *Initial results demonstrate a favorable safety profile – no dose limiting toxicities were reported, a maximum tolerated dose was not reached and 98% of patients remained on treatment*
- *Incyte will host an in-person analyst and investor event highlighting this data at EHA today, Sunday, June 15, 2025, from 6:00 - 7:30 a.m. EDT (12:00 -1:30 p.m. CEST)*

WILMINGTON, Del.--(BUSINESS WIRE)--Jun. 15, 2025-- Incyte (Nasdaq:INCY) today announced the first clinical data from two studies evaluating the safety, tolerability and efficacy of INCA033989, a novel, first in class, Incyte-discovered, targeted monoclonal antibody in patients with mutant calreticulin (mutCALR)-expressing myeloproliferative neoplasms (MPNs). These data – featured today in the Late-Breaking Oral Session (#LB4002) at the European Hematology Association 2025 (EHA2025) Congress in Milan, Italy – focus on the dose escalation portion of the studies in patients with high risk essential thrombocythemia (ET) who are resistant/intolerant to prior cytoreductive therapy.

The studies evaluated the safety and efficacy of INCA033989 in patients with ET as measured by hematologic response and reduction in mutCALR variant allele frequency (VAF).

Results as of April 4, 2025, showed rapid and durable normalization of platelet counts across all dose levels, with a trend toward improved responses in higher doses (≥400 mg), in patients with ET treated with INCA033989. Notably, 86% of patients at doses 400 mg and above achieved a complete or partial hematologic response, with the majority (82%) of patients achieving complete response. Eighty-nine (89) percent of evaluable patients (34/38) showed a reduction in mutCALR VAF from baseline. A partial molecular response (>50% VAF reduction) was observed in 21% of evaluable patients (8/38) after only 3 cycles of treatment.

An exploratory study using single-cell DNA (scDNA) sequencing showed that INCA033989 directly targets and reduces cells carrying mutCALR. This reduction was seen in early blood-forming (CD34-positive) cells and cells in the myeloid-erythroid (ME) lineage. At the same time, there was a clear increase in healthy (wild-type CALR) cells, suggesting that the treatment supports the return of normal blood production. Bone marrow biopsies further confirmed these effects showing fewer megakaryocytes with mutCALR protein and a notable increase in megakaryocytes without mutCALR protein. Together, these findings demonstrate the selectivity of INCA033989, allowing for normalization of healthy hematopoiesis and disease modification.

"The late-breaking data presented today highlight the impact of INCA033989, a novel agent that selectively targets mutant CALR, to inhibit and eliminate cancer-causing cells in patients with essential thrombocythemia (ET), while sparing healthy cells and normalizing healthy blood production," said Pablo J. Cagnoni, M.D., President, Head of Research and Development, Incyte. "These findings, and the further development of INCA033989, offer the potential to significantly transform the treatment of patients with CALR-mutant myeloproliferative neoplasms (MPNs)."

The results (N=49) 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, and only one (1) dose reduction due to treatment-emergent adverse events (TEAEs) was observed. No infusion interruptions due to TEAEs were reported, and a maximum tolerated dose was not reached. Forty-two (42) patients across the dose cohorts reported a TEAE. The most common TEAEs were fatigue (26.5%) and upper respiratory tract infection (20.4%), all of which were Grade ≤2. Thirteen (13) patients had Grade ≥3 TEAEs, with transient asymptomatic lipase increase as the most common (6%).

"mutCALR is the second most common oncogenic driver of MPNs, yet the therapeutic landscape lacks a targeted agent for mutCALR expressing MPNs. Currently, ET treatments aim to prevent vascular complications and improve symptoms but are limited by toxicity and tolerability issues," 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 data support the hypothesis that INCA033989 has the potential not only to normalize platelet counts and provide rapid and durable hematologic responses – but to induce molecular responses, which could potentially change the natural history of the disease."

Additional data from the INCA033989 study in patients with myelofibrosis will be submitted for presentation at a future medical meeting. Discussions with regulatory authorities are planned with the goal to initiate a Phase 3 study by early 2026.

More information regarding the EHA2025 Congress and the data from Incyte's hematology/oncology portfolio being featured at the meeting can be found on the EHA website: https://ehaweb.org/congress/eha2025-congress.

Incyte Conference Call and Webcast

Incyte will host an in-person analyst and investor event on Sunday, June 15, 2025, from 6:00 - 7:30 a.m. ET (12:00 - 1:30 p.m. CEST) to discuss key mutCALR data presented at EHA.

The event will be webcasted and can be accessed via the Events and Presentations tab of the Investor section of Incyte.com and it will be available for replay for 30 days.

About Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPNs) are a closely related group of blood cancers in which the bone marrow functions abnormally. The bone marrow is where the body's blood cells are made. MPNs are progressive blood cancers that can strike anyone at any age, but they are more common in older adults. Estimates of the prevalence of MPNs vary, but analysis of claims data suggests there may be as many as 200,000 people in the U.S. living with the most prevalent MPNs: myelofibrosis, polycythemia vera or essential thrombocythemia (ET).[1]

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),[2] a closely related group of clonal blood cancers in which the bone marrow functions abnormally, overproducing blood cells.[3,4] Among two types of MPNs, essential thrombocythemia (ET) and myelofibrosis (MF), mutCALR drives 25-35% of all cases.[2,3] There are approximately 60,000 patients in the U.S. and Europe with mutCALR positive ET.[5]

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), enrolling ~225 patients outside of the U.S. and ~140 patients in the U.S., respectively. The studies are evaluating the safety, tolerability, dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) and/or recommended dose(s) for expansion (RDE) of INCA033989 administered as a monotherapy or in combination with ruxolitinib in patients with myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET) and myelofibrosis (MF). The intent of Part 1A (dose escalation) is to identify the MTD and/or the RDE of INCA033989 among patients with MF and ET. In Part 1A INCA033989 is administered intravenously every two weeks at a protocol defined dose ranging from 24 mg. to 2,500 mg. In Part 1B (dose expansion), INCA033989 is administered at the RDE(s) identified during Part 1A.

The primary endpoint of the studies focuses on safety and tolerability as measured by: the number of participants with DLTs up to 28 days, the number of participants with treatment-emergent adverse events (TEAEs) up to 3 years and 60 days, and the number of participants with TEAEs leading to dose modification or discontinuation up to 3 years and 60 days. Secondary endpoints include response rates, mean change of ET total symptom score from baseline, percentage of MF patients achieving spleen volume reduction, MF patient anemia response, mean change in disease-related allele burden and various pharmacokinetics measures up to 3 years and 60 days.

For more information on the study, 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 March 31, 2025. Incyte disclaims any intent or obligation to update these forward-looking statements.

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[1] Data on file

[2] 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)

[3] 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)

[4] 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)

[5] Epidemiology Source: DRG, Prevalence 2026.

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