Poster MPN-555

John Mascarenhas | john.mascarenhas@mssm.edu

Trial in Progress: A Phase 3, Randomized, Double-Blind, Active-Control Study of Pelabresib (DAK539) Plus Ruxolitinib vs Placebo Plus Ruxolitinib in JAK Inhibitor-Naive Adult Patients With Myelofibrosis (MANIFEST-3)

J. Mascarenhas[1], P. Bose[2], M. Griesshammer[3], R. Komrokji[4], A. Kuykendall[4], R. Mesa[5], F. Palandri[6], F. Passamonti[7], R. Rampal[8], P. Vachhani[9], Z. Xiao[10], G. Cleary[11], H. Maier[12], S. Khanna[13], C. Harrison[14]

[1]Tisch Cancer Institute, New York, New York, United States; [2]University of Texas, Houston, Texas, United States; [3]University of Bochum, Minden, Germany; [4]Moffitt Cancer Center, Tampa, Florida, United States; [5]Wake Forest University School of Medicine, Winston-Salem, North Carolina, United States; [6]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [7]Università degli Studi di Milano, Fondazione IRCSS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [8]Memorial Sloan Kettering Cancer Center, New York, New York, United States; [9]University of Alabama, Birmingham, Alabama, United States; [10]Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [11]Novartis Ireland Limited, Dublin, Ireland; [12]Novartis Pharma AG, Basel, Switzerland; [13]Novartis Pharma S.A.S, Rueil-Malmaison, France; [14]Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom

CONCLUSIONS

- MANIFEST-3 builds on the positive findings from MANIFEST-2 (NCT04603495)[8] by evaluating the efficacy and safety of PELA+RUX versus PBO+RUX in a broad MF population, including patients with higher symptom burden
- The combination of PELA+RUX aims to achieve deeper and more durable responses, as well as address underlying disease biology, thus offering a potential shift in the MF treatment paradigm

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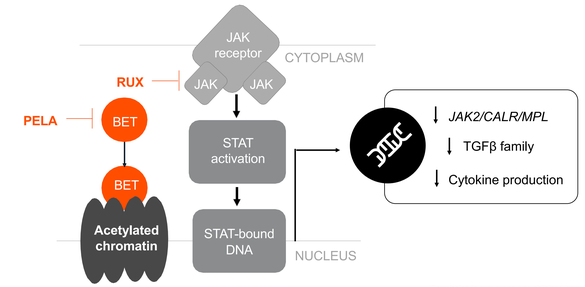
Background

- Myelofibrosis (MF) is a chronic, debilitating and progressive myeloproliferative neoplasm (MPN) with a significant disease burden that includes splenomegaly, bone marrow fibrosis (BMF), and MF-associated symptoms (fatigue, pruritus, fever, weight loss)[1-4]
- Constitutive activation of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling is central to MF pathogenesis; JAK inhibition (JAKi) monotherapy, such as ruxolitinib (RUX), is the standard of care in intermediate (int) and high-risk MF, achieving spleen and symptom improvements[1,2,5]
- There remains an unmet need for new therapeutic approaches which address the underlying disease biology and improve response depth and durability, thus potentially offering a survival advantage[6]
- Preclinical MPN models show that dual JAK and bromodomain and extraterminal domain (BET) inhibition produces synergistic effects on disease-relevant transcriptional pathways, supporting the rationale for combined JAKi/BETi therapy[7]
- Pelabresib (PELA; DAK539) is an oral, investigational, small molecule that inhibits BET proteins, altering BET-mediated expression of oncogenes, such as nuclear factor kappa beta (NF-κB), that contribute to the pathology of MF[1] **(Figure 1)**
- In the Phase III MANIFEST-2 study (NCT04603495), combined inhibition of BET and JAK pathways with PELA+RUX has deep and durable spleen responses, sustained improvements in symptoms and benefits in hemoglobin levels[8-9]

Objective

- MANIFEST-3 (NCT07357727) is a Phase III study designed to evaluate the efficacy and safety of PELA+RUX versus placebo (PBO)+RUX in JAKi-naive patients with MF, including a pre-specified, highly symptomatic patient subgroup (baseline total symptom score [TSS] ≥25)

Figure 1. PELA+RUX mechanism of action[9,10]



Study Design and Study Sites

- MANIFEST-3 is a randomized, double-blind, multicenter Phase III study that plans to enroll 460 JAKi-naive patients with primary or secondary (post-polycythemia vera [PV]/essential thrombocytopenia [ET]) MF, across 242 sites globally **(Figure 2)**
- The study is designed to explore whether adding PELA to standard therapy can further support symptom and spleen improvement across a broad range of patients, including those experiencing a substantial symptom burden (baseline TSS ≥25)
- Patients will be randomized 1:1 to PELA or PBO once daily on Days 1-14 of a 21-day cycle, in combination with RUX twice daily throughout the cycle **(Figure 3)**
- Randomization will be stratified by Dynamic International Prognostic Scoring System (DIPSS) (int-1 vs int-2 vs high-risk), baseline platelet count (>200 vs 100-200 x 10^9/L), and TSS (<25 vs ≥25)
- After end of treatment and the 30-day safety follow-up visit, patients will enter either an efficacy follow-up (if no documented progression for either splenomegaly or leukemic transformation and no new treatment started for MF), or a survival follow-up (if disease progression is documented or new treatment for MF started)

Figure 2. Study Sites

Screening and Enrollment Criteria

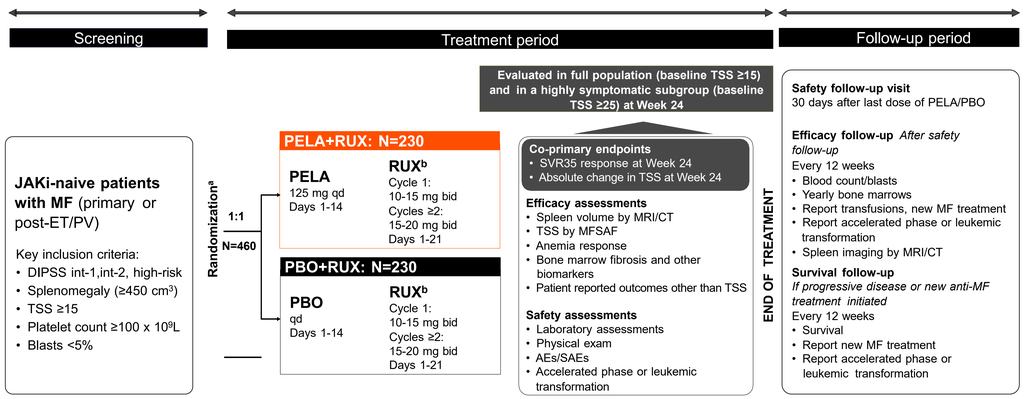
- Key eligibility criteria for study enrollment are summarized in **Table 1**
- At screening, peripheral blood blast assessment is mandatory; monitoring will be performed throughout the study

Table 1. Patient inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• JAKi-naive patients with MF (primary or post-ET/PV)* • DIPSS risk category of int-1, int-2 or high risk • Splenomegaly (≥450 cm^3) by computed tomography (CT) or magnetic resonance imaging (MRI) • Have an average TSS of ≥15 within 7 days prior to randomization using Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 • Blasts <5% in peripheral blood • Platelet count ≥100 x 10^9/L in the absence of growth factor or transfusions for the previous 4 weeks • Absolute neutrophil count ≥1 x 10^9/L in the absence of growth factor or transfusions for the previous 4 weeks • Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2	• Prior splenectomy at any time or splenic irradiation in the previous 6 months • Prior hematopoietic stem cell transplantation (HSCT) or participant anticipated to receive a HSCT <24 weeks from randomization • Blasts ≥5% in bone marrow or history of accelerated phase or leukemic transformation • Prior malignancy other than MF (primary or post-ET/PV) in previous 3 years requiring systemic treatment • Received any agent other than hydroxyurea or anagrelide for MF <14 days from the first dose of study treatment or within 5 half-lives of the agent, whichever is longer • Prior treatment with JAKi or BETi

*Diagnosis according to the International Consensus Classification of Myeloid Neoplasm and Acute Leukemia 2022.

Figure 3. MANIFEST-3 study design schema



[a] Randomization will be stratified by DIPSS (int-1 vs int-2 vs high-risk), baseline platelet count (>200 vs 100-200 x 10^9/L), and TSS score at baseline (<25 vs ≥25)
[b] RUX dose 10 or 15 mg bid in cycle 1, dependent on baseline platelet count, with mandatory dose increase by 5 mg bid at cycle 2 day 1 if specified criteria met

Pre-specified Endpoints

- The coprimary endpoints to be evaluated are ≥35% spleen volume reduction (SVR35) and absolute change in TSS at week 24 **(Table 2)**
- Coprimary endpoints will be evaluated in the full population (baseline TSS ≥15) and in a pre-specified, highly symptomatic patient subgroup (baseline TSS ≥25) **(Table 2)**
- Secondary endpoints include absolute TSS change and SVR35 over time as well as TSS50 and dual response (SVR35+TSS50) at specified timepoints **(Table 2)**
- Safety reporting for accelerated phase and leukemic transformation will be conducted throughout the study, including on study treatment and during the follow-up period **(Table 2)**

Table 2. Primary, Secondary and Safety Endpoints

Coprimary endpoint	SVR35 response at week 24 (measured by MRI/CT and centrally assessed)	Absolute change in TSS from baseline at week 24 (measured by MFSAF v4.0)
Secondary endpoints	• SVR35 response from baseline to Week 12, 36 and 48 and thereafter (MRI/CT assessed) • TSS50 from baseline to Week 12, 24, 36 and 48 and thereafter (MFSAF v4.0 assessed) • Dual response defined as achieving both SVR35 (MRI/CT assessed) and TSS50 (MFSAF v4.0 assessed) • Anemia and hemoglobin response	• Duration of response in TSS50 and SVR35 • Overall survival • Progression-free survival • Leukemia-free survival • Pharmacokinetics of PELA (plasma concentrations and parameters) • Changes in electronic patient reported outcome assessing fatigue and quality of life
Safety	Adverse events and serious adverse events, including accelerated phase and leukemic transformation	

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Abbreviations

AE, adverse event; BET, bromodomain and extraterminal domain; BETi, bromodomain and extraterminal domain inhibitor; bid, twice daily; BMF, bone marrow fibrosis; CALR, calreticulin; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ET, essential thrombocythemia; HSCT, hematopoietic stem cell transplantation, int, intermediate; JAK, Janus kinase; JAKi, Janus kinase inhibitor; JAK2, Janus kinase 2; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MPL, myeloproliferative leukemia virus oncogene; MPN, myeloproliferative neoplasm; MRI, magnetic resonance imaging; NF-κB, nuclear factor kappa B; PBO, placebo; PELA, pelabresib; PV, polycythemia vera; qd, once daily; RUX, ruxolitinib; SAE, serious adverse event; STAT, signal transducer and activator of transcription; SVR35, ≥35% spleen volume reduction; TGF-β, transforming growth factor beta; TSS50, ≥50% reduction in total symptom score.

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Disclosures

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