MANIFEST-2, a Global, Phase 3, Randomized, Double-Blind, Active-Control Study of Pelabresib (CPI-0610) and Ruxolitinib vs Placebo and Ruxolitinib in JAK Inhibitor-Naïve Myelofibrosis Patients

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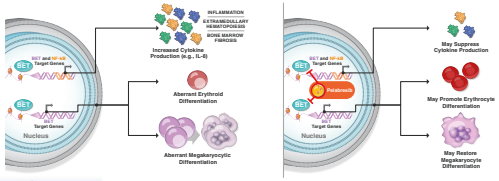
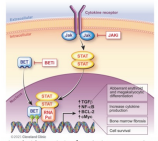
INTRODUCTION

- MF is a life-threatening myeloproliferative disorder caused by the overproduction of megakaryocytes[1,2]
- The four hallmarks of MF are splenomegaly, symptoms, cytopenias and bone marrow fibrosis[3–5]
- JAKi ruxolitinib and fedratinib are the current SOC in higher-risk MF patients with platelets ≥50 × 10⁹/L and ineligible for allogeneic stem cell transplant[6]
- Despite clinical successes with JAKi therapy, unmet medical still exists due to:
  - <50% of patients achieving a spleen response (SVR35 response rates of 29–42% at Week 24 in previous pivotal studies of ruxolitinib or fedratinib)[7–10]
  - <50% of patients achieving total symptom score reduction (TSS50 rates of 34–46% in previous pivotal studies of ruxolitinib or fedratinib)[7,9,10]
- In addition, patients on these treatments experience progressive disease and toxicity, which frequently lead to JAKi discontinuation[6, 11–13]
- Pelabresib (CPI-0610) is an investigational, oral, small-molecule BET inhibitor
- BET proteins regulate transcription of specific genes integrating an array of oncogenic signals[14,15]
- BET inhibition could modify critical components of MF pathobiology:
  - Megakaryocyte differentiation and proliferation[14,15]
  - Reduction in proinflammatory cytokine expression via the NF-κB signaling pathway[16,17]
- In patients refractory to or intolerant/ineligible for JAKi treatment, pelabresib monotherapy demonstrated clinical activity through the achievement of splenic responses and symptom improvement[18]





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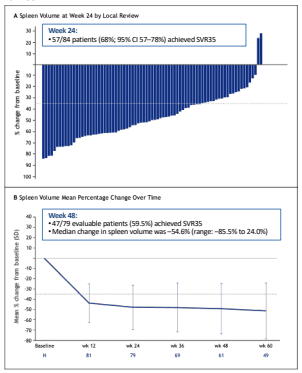
- Preclinical *in vitro* and *in vivo* data showed synergistic effect of BET and JAK inhibition in MF[19]
- Arm 3 of the Phase 2 MANIFEST study (NCT02158858) with JAKi-naïve MF patients treated with pelabresib and ruxolitinib demonstrated strong response rates for both SVR35 (68% of patients) and TSS50 (56% of patients) at Week 24, and durable spleen responses (59.5% SVR35 at Week 48)[20]
- Here we describe the design of the Phase 3 MANIFEST-2 (NCT04603495) study, which will evaluate the efficacy and safety of pelabresib in combination with ruxolitinib versus placebo in combination with ruxolitinib in patients with JAKi treatment-naïve MF

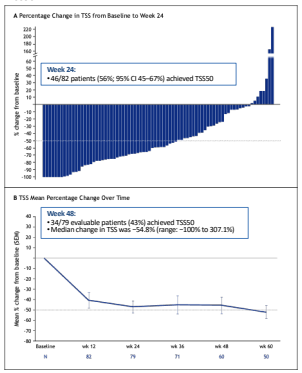
Phase 2 MANIFEST Arm 3 Data *(September 10, 2021 data cut-off)*[20]

- Pelabresib combined with ruxolitinib demonstrated efficacy in the Phase 2 MANIFEST study of JAKi-naïve patients with MF
- Primary endpoint was SVR35 at 24 weeks

SVR35

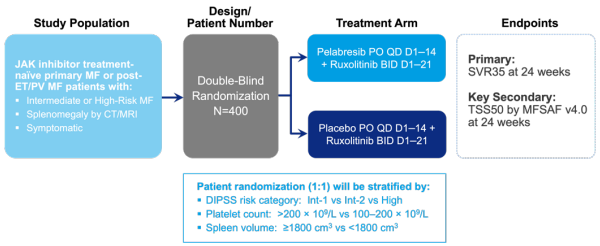


TSS50



MANIFEST-2 STUDY DESIGN

- **MANIFEST-2 (NCT04603495) is a global Phase 3, multicenter, randomized, double-blind, placebo-controlled study of pelabresib in combination with ruxolitinib vs placebo in combination with ruxolitinib in JAKi-naïve patients with MF**
  - Following a screening period of ≤28 days, eligible patients are randomized in a 1:1 ratio to their designated treatment arm
- **All patients will receive either pelabresib or placebo 125 mg QD for 14 consecutive days, followed by a 7-day break (21-day cycle)**
  - The starting dose of ruxolitinib is administered BID for all 21 days of each cycle at either 10 or 15 mg BID, depending on patient baseline platelet counts
  - Dose increase(s) and reduction(s) are permitted as per protocol criteria
  - Patients are treated until disease progression or discontinuation/withdrawal of treatment, and are followed up for PFS and OS
  - Patients enrolled in the placebo and ruxolitinib group, who experience disease progression after 24 weeks of treatment, may be crossed over to the pelabresib and ruxolitinib group



Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Confirmed diagnosis of MF (primary MF, post-polycythemia vera MF or post-essential thrombocythemia MF) • Adequate hematologic, renal and hepatic function • Have ≥2 symptoms with an average score ≥3 or an average total score of ≥10 over the 7-day period prior to randomization using the MFSAF v4.0 • Prognostic risk-factor score of intermediate-1 or higher per DIPSS • Spleen volume of ≥450 cm^3 • ECOG performance status of ≤2	• Splenectomy or splenic irradiation within 6 months prior to anticipated C1D1 • Chronic or active conditions and/or concomitant medication use that would prohibit participation in study • Prior treatment with any JAKi or BETi for the treatment of a myeloproliferative neoplasm

Study Endpoints

Study Endpoint	Endpoint(s) Description
Primary	• Splenic response at Week 24 vs baseline (defined as SVR35 measured by MRI or CT)
Key Secondary	• TSS50 at Week 24 vs baseline, measured by the MFSAF v4.0
Other Secondary	• Percentage change in TSS at Week 24 vs baseline • Improvement in bone marrow fibrosis by ≥1 grade at Week 24 vs baseline • SVR35 and TSS50 response at Week 48 vs baseline • Conversion from RBC transfusion dependence to independence • Adverse events of all grades and serious adverse events

Planned Enrollment

Approximately 400 patients will be enrolled in the study (200 in each treatment group) such that sequential testing of the primary (SVR35) and key secondary (TSS50) endpoints are adequately powered for 2-group continuity corrected χ^2 test

Participating Countries

Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Malaysia, The Netherlands, Poland, Romania, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom and United States

MANIFEST-2 STUDY DESIGN CONT.

Study Procedures

Screening	Treatment Period				
	Disease status assessments	Patient-reported outcomes*	Safety assessment and AE review	PK assessment	PD assessment
• Patient demographics • Complete medical history • Spleen volume measured by MRI/CT • Completion of MFSAF v4.0 and EQ-5D • Hematology • Safety baseline assessment	• Hematology • Transfusion history • MF-associated symptoms • Spleen size by palpation and by MRI and/or CT • Bone marrow fibrosis grading by bone marrow biopsy	• MFSAF v4.0 daily • PGIC weekly • EQ-5D weekly	• TEAE review per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0†	• Plasma pelabresib and ruxolitinib concentrations	• Biomarker assessments

**Starting at either C1D1 or initiation of crossover treatment and continuing until 12 weeks after end of treatment.*
†For all TEAEs, the investigator will determine if these can be attributed to either pelabresib or, in the case of Gormany, the study drugs.

Statistics: Analysis of Primary and Key Secondary Endpoints

- Primary analysis will take place after all randomized patients have either completed their Week 24 visit or discontinued prematurely
- SVR35 and TSS50 will be compared sequentially using the Cochran–Mantel–Haenszel test controlling for these baseline factors:
  - DIPSS (Intermediate-1 vs Intermediate-2 vs High)
  - Platelet count (100–200 × 10⁹/L vs >200 × 10⁹/L)
  - Spleen volume (<1800 cm^3 vs ≥1800 cm^3)

MANIFEST STUDY EHA 2022 ABSTRACTS

Oral Presentation: Saturday, June 11, 11:30 am–12:45 pm CEST

– BET Inhibitor Pelabresib (CPI-0610) Combined With Ruxolitinib in Patients With Myelofibrosis — JAK Inhibitor-Naïve or With Suboptimal Response to Ruxolitinib — Preliminary Data From the MANIFEST Study

Oral Presentation: Saturday, June 11, 4:30pm–5:45pm CEST

– Single-Cell RNA Profiling of Myelofibrosis Patients Reveals Pelabresib-Induced Decrease of Megakaryocytic Progenitors and Normalization of CD4+ T Cells in Peripheral Blood

Poster: Friday, June 10, 4:30pm–5:45pm CEST

– Matching-Adjusted Indirect Comparison (MAIC) of Pelabresib (CPI-0610) in Combination With Ruxolitinib vs Ruxolitinib or Fedratinib Monotherapy in Patients With Intermediate or High-Risk Myelofibrosis

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- https://www.manifestclinicaltrials.com/
- https://clinicaltrials.gov/ct2/show/NCT04603495

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ABBREVIATIONS: AE, adverse event; BCL-2, B-cell lymphoma 2; BET, bromodomain and extraterminal domain; BETi, bromodomain and extraterminal domain inhibitor; BID, twice daily; C1D1, Cycle 1 Day 1; CI, confidence interval; c-Myc, cellular Myc; CT, computerized tomography; D, day; DIPSS, Dynamic International Prognostic Scoring System; ECOG, Eastern Cooperative Oncology Group; ET, essential thrombocythemia; HSCT, hematopoietic stem cell transplant; IL-8, interleukin-8; Int-1, Intermediate-1; Int-2, Intermediate-2; JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MPN, myeloproliferative neoplasm; MRI, magnetic resonance imaging; NF-κB, nuclear factor kappa B; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PGIC, Patient Global Impression of Change; PK, pharmacokinetics; PO, by mouth; PV, polycythemia vera; QD, once daily; RBC, red blood cell; RNA pol, ribonucleic acid polymerase; SD, standard deviation; SEM, standard error of the mean; SOC, standard of care; STAT, signal transducer and activator of transcription; SVR35, ≥35% spleen volume reduction from baseline; TEAE, treatment-emergent adverse event; TGFβ , transforming growth factor β; TSS, reduction in total symptom score from baseline; TSS50, reduction in total symptom score of ≥50% from baseline; wk, week.