Poster No. MPN-135

# Safety and Efficacy of Pelabresib in Combination With Ruxolitinib for JAK Inhibitor-Naïve Patients With Myelofibrosis: Latest Data From the Phase 3 MANIFEST-2 Study


**John Mascarenhas**[1], Raajit K. Rampal[2], Sebastian Grosicki[3], Dominik Chraniuk[4], Elisabetta Abruzzese[5], Prithviraj Bose[6], Aaron Gerds[7], Alessandro M. Vannucchi[8], Francesca Palandri[9], Sung-Eun Lee[10], Vikas Gupta[11], Alessandro Lucchesi[12], Stephen T. Oh[13], Andrew T. Kuykendall[14], Andrea Patriarca[15], Alberto Álvarez-Larrán[16], Ruben Mesa[17], Jean-Jacques Kiladjian[18], Moshe Talpaz[19], David Lavie[20], Morgan Harris[21], Sarah-Katharina Kays[22], Anna-Maria Jegg[22], Manlei Wu[23], Barbara Brown[21], Claire Harrison[24]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Department of Hematology and Cancer Prevention, Medical University of Silesia, Katowice, Poland; [4]Hematology Ward, Wojewódzki Szpital Zespolony im. L. Rydygiera, Torun, Poland; [5]Department of Hematology, S. Eugenio Hospital, Tor Vergata University, Rome, Italy; [6]Leukemia Department, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [8]Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy; [9]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [10]Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [11]Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada; [12]Hematology Unit, IRCCS Istituto Romagnolo per lo Studio e la Cura dei Tumori (IRST) "Dino Amadori", Meldola (FC), Italy; [13]Washington University School of Medicine in St. Louis, St. Louis, MO, USA; [14]Moffitt Cancer Center, Tampa, FL, USA; [15]Hematology Unit, AOU Maggiore della Carità and University of Eastern Piedmont, Novara, Italy; [16]Hematology Department, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain; [17]Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC, USA; [18]Clinical Investigation Center, Hôpital Saint-Louis, Université de Paris, Paris, France; [19]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; [20]Department of Hematology and Bone Marrow Transplantation, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; [21]Constellation Pharmaceuticals, a MorphoSys Company, Boston, MA, USA; [22]MorphoSys AG, Planegg, Germany; [23]MorphoSys US Inc., Boston, MA, USA; [24]Department of Haematology, Guy's and St Thomas' NHS Foundation Trust, London, UK


## SUMMARY


Myelofibrosis (MF) is a debilitating and progressive disease, characterized by splenomegaly, MF-associated symptoms, cytopenias (eg, anemia), and impairment of the bone marrow (BM) microenvironment (including fibrosis). This study presents efficacy and safety outcomes in patients with MF treated with pelabresib + ruxolitinib versus placebo + ruxolitinib in Janus kinase (JAK) inhibitor–naïve patients at Week 24.

The Phase 3 MANIFEST-2 study (NCT04603495) met its primary endpoint, showing a statistically significant higher proportion of patients with ≥35% reduction in spleen volume from baseline (SVR35) at Week 24 with pelabresib + ruxolitinib versus placebo + ruxolitinib (p<0.001). Treatment with pelabresib + ruxolitinib resulted in rapid, deep, and sustained splenic responses with a higher proportion of patients maintaining SVR35 versus patients treated with placebo + ruxolitinib.

The findings from the study demonstrate that pelabresib + ruxolitinib showed significantly reduced splenomegaly, a trend toward improved symptom score, and improvements in the BM microenvironment and in multiple measures of anemia versus placebo + ruxolitinib, impacting the four hallmarks of MF. Additionally, the safety profiles of both treatment arms were generally comparable.



**References: 1.** Tefferi A. Primary myelofibrosis: 2021 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2021;96(1):145–162; **2.** Beversdorf J, et al. P1030: Spleen volume reduction predicts survival in myelofibrosis patients on pacritinib but not best available therapy: PERSIST-2 landmark overall survival analysis. *Hemasphere*. 2023;7(S3):1965–1966; **3.** Kleppe M, et al. Dual targeting of oncogenic activation and inflammatory signaling increases therapeutic efficacy in myeloproliferative neoplasms. *Cancer Cell*. 2018;33(1):29–43; **4.** Rose P, Verstovsek S. JAK inhibitors for the treatment of myelofibrosis: limitations and future perspectives. *Hemasphere*. 2020;4(4):e424; **5.** Harrison CN, et al. Phase III MANIFEST-2: pelabresib + ruxolitinib vs placebo + ruxolitinib in JAK inhibitor treatment-naive myelofibrosis. *Future Oncol*. 2022;18(27):2987–2997; **6.** Albrecht BK, et al. Identification of a benzoxazolobenzazepine inhibitor (CPI-0610) of the bromodomain and extra-terminal (BET) family as a candidate for human clinical trials. *J Med Chem*. 2016;59(4):1330–1339; **7.** Mascarenhas J, et al. MANIFEST: pelabresib in combination with ruxolitinib for Janus kinase inhibitor treatment-naïve myelofibrosis. *J Clin Oncol*. 2023:41(32):4993-5004.



**Acknowledgments:** We thank the patients, caregivers, and study investigators involved in this study. This study was supported by Constellation Pharmaceuticals, Inc., a MorphoSys Company. The development of pelabresib was funded, in part, by the Leukemia & Lymphoma Society. Editorial and writing support was provided by Laura Travers, PhD, of LINK Health Group, funded by MorphoSys AG.


**Abbreviations:** *ASXL1*, ASXL transcriptional regulator 1; BET, bromodomain and extraterminal domain; BM, bone marrow; BMF, bone marrow fibrosis; *CALR*, calreticulin; CI, confidence interval; COVID-19, coronavirus disease 2019; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; *EZH2*, enhancer of zeste 2 polycomb repressive complex 2 subunit; Hb, hemoglobin; HMR, high molecular risk; *IDH1/2*, isocitrate dehydrogenase 1/2; INT, intermediate; ITT, intent-to-treat; IWG-MRT, International Working Group–Myeloproliferative Neoplasms Research and Treatment; JAK, Janus kinase; JAKi, Janus kinase inhibitor; LSM, least squares mean; max, maximum; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; min, minimum; *MPL*, MPL proto-oncogene, thrombopoietin receptor; N/A, not applicable; RBC, red blood cell; SD, standard deviation; *SRSF2*, serine and arginine rich splicing factor; STAT, signal transducer and activator of transcription; SVR35, ≥35% reduction in spleen volume from baseline; TEAE, treatment-emergent adverse event; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline; *U2AF1*, U2 small nuclear RNA auxiliary factor 1; WT, wild type.

**Pelabresib (CPI-0610) is an investigational, oral, small molecule drug that inhibits BET proteins and decreases the elevated BET-mediated gene expression involved in MF pathogenesis. Pelabresib is being investigated as a treatment for MF and has not yet been evaluated or approved by any regulatory authorities.**


Presented at the Society of Hematologic Oncology (SOHO) Annual Meeting; September 4–7, 2024; Houston, TX, USA


## OBJECTIVE

To assess the efficacy and safety of the combination of pelabresib + ruxolitinib compared with placebo + ruxolitinib in JAK inhibitor (JAKi)–naïve patients with MF from the Phase 3 MANIFEST-2 study (NCT04603495).

## INTRODUCTION

- MF is a debilitating and progressive disease characterized by splenomegaly, MF-associated symptoms, cytopenias (eg, anemia), and impairment of the BM microenvironment (including fibrosis).[1] Reduction in spleen size has been associated with improved overall survival[2]
- MF results from the dysregulation of the JAK/STAT pathway and bromodomain and extraterminal domain (BET)–mediated gene modulation[3]
- JAK inhibition is the standard of care in intermediate-risk and high-risk MF.[4] However, unmet medical need persists due to the limited depth and durability of response and treatment-emergent adverse events[1,5]
- Pelabresib (CPI-0610) is an investigational, oral, small molecule drug that inhibits BET proteins and subsequent BET–mediated gene expression involved in MF pathogenesis[6,7]
- MANIFEST-2, a global, randomized, double-blind, Phase 3 study, investigated the efficacy and safety of pelabresib + ruxolitinib versus placebo + ruxolitinib in JAKi–naïve patients with MF

## METHODS

- Eligible patients had Dynamic International Prognostic Scoring System (DIPSS) ≥INT-1 risk, platelet count ≥100 × $10^9$/L, spleen volume ≥450 $cm^3$, ≥2 symptoms with an average score ≥3 or total symptom score (TSS) ≥10 (MF Symptom Assessment Form [MFSAF] v4.0), peripheral blast count <5%, and ECOG PS ≤2 (**Table 1**)
- Pelabresib or placebo was administered (daily for 14 consecutive days of 21) with ruxolitinib (twice daily for 21 days [one cycle])
- The primary endpoint was SVR35 at Week 24 and key secondary endpoints were absolute change in TSS and ≥50% reduction in TSS from baseline (TSS50) at Week 24
- Other secondary endpoints included safety, hemoglobin response (≥1.5 g/dL mean increase from baseline without transfusions in the prior 12 weeks) and BM fibrosis (BMF)
- Informed consent was obtained from all patients

## RESULTS

### Table 1. Baseline Disease Characteristics

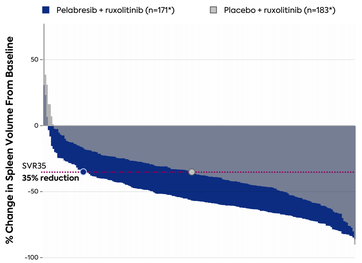
| Characteristic | | Pelabresib + ruxolitinib (N=214) | Placebo + ruxolitinib (N=216) |
|---|---|---|---|
| **Age — years** | Median (min, max) | 66 (19, 84) | 66 (26, 88) |
| **Sex — n (%)** | Female / male | 85 (39.7) / 129 (60.3) | 94 (43.5) / 122 (56.5) |
| **Race — n (%)** | White / Asian / Black | 160 (74.8) / 35 (16.4) / 2 (0.9) | 163 (75.5) / 42 (19.4) / 0 |
| | American Indian or Alaska Native | 1 (0.5) | 0 |
| | Not reported / Unknown | 15 (7.0) / 1 (0.5) | 11 (5.1) / 0 |
| **Myelofibrosis subtype — n (%)** | Primary myelofibrosis | 107 (50.0) | 110 (50.9) |
| | Post-polycythemia vera myelofibrosis | 45 (21.0) | 53 (24.5) |
| | Post-essential thrombocytopenia myelofibrosis | 62 (29.0) | 53 (24.5) |
| **Dynamic International Prognostic Scoring System — n (%)** | Intermediate-1 | 128 (59.8) | 127 (58.8) |
| | Intermediate-2 | 75 (35.0) | 74 (34.3) |
| | High-risk | 11 (5.1) | 15 (6.9) |
| **Mutations — n (%)** | *JAK2* V617F | 125 (58.4) | 122 (56.5) |
| | *CALR* | 45 (21.0) | 49 (22.7) |
| | *MPL* | 11 (5.1) | 13 (6.0) |
| | Triple negative* | 8 (3.7) | 6 (2.8) |
| | HMR mutations† | 72 (33.6) | 88 (40.7) |
| **Hemoglobin — g/dL** | Median (range) | 10.9 (5.8–18.0) | 11.0 (6.7–17.9) |
| | ≤10 — n (%) | 70 (32.7) | 76 (35.2) |
| **Platelets — × $10^9$/L** | Median (min, max) | 285 (99, 1303) | 287 (66, 1084) |
| | >200 × $10^9$/L — n (%) | 154 (72) | 157 (72.7) |
| **Peripheral blasts** | Mean (SD) | 0.8 (1.18)‡ | 0.8 (1.25)‡ |
| **RBC transfusions§ — patient n (%)** | Requiring RBC transfusion at baseline | 22 (10.3) | 21 (9.7) |
| **Transfusion dependent at enrollment‖ — patient n (%)** | | 8 (3.7) | 2 (0.9) |
| **ECOG PS — n (%)** | 0 | 107 (50.0) | 109 (50.5) |
| | 1 | 97 (45.3) | 95 (44.0) |
| | ≥2 | 10 (4.7) | 10 (4.6) |
| | Missing | 0 | 2 (0.9) |
| **Spleen volume (central read)#** | Median spleen volume (range) — cc | 1308.89 (200.24–7117.03) | 1382.97 (277.87–5540.45) |
| **Total symptom score**** | Median total symptom score (range) | 26.6 (7.3–66.4) | 24.7 (9.0–68.4) |

**Data cutoff date: August 31, 2023.** *Triple-negative status was missing for 55 patients (28 in the pelabresib + ruxolitinib arm and 27 in the placebo + ruxolitinib arm). †HMR mutations include *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SRSF2* and *U2AF1* mutations. ‡n=208, n=207. §RBC transfusions refer to number of patients who received any RBC transfusion during the 12-week baseline period prior to dosing. ‖Transfusion dependent at enrollment is defined as having received ≥6 units of RBC transfusions during the 12-week baseline period prior to dosing. #Randomization of patients was based on local read. **Patients with baseline TSS values of <10 have at least two individual symptoms score ≥3 at baseline.

- As of August 31, 2023, 72.0% (154/214) and 74.1% (160/216) of patients continued on double-blind treatment in the pelabresib + ruxolitinib and placebo + ruxolitinib arms, respectively
- SVR35 response at Week 24 was significantly greater (**Figure 1**) and was consistently higher in the pelabresib + ruxolitinib arm versus placebo + ruxolitinib arm across all predefined and hematologic subgroups (data not shown)
- Pelabresib and ruxolitinib demonstrated rapid, deep and sustained SVR35 responses (**Figure 2**); furthermore, SVR35 response was independent of driver and high molecular risk (HMR) mutation status (**Figure 3**)

### Figure 1. SVR35 at Week 24

**SVR35 response at Week 24 was significantly greater in patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib**




ITT population

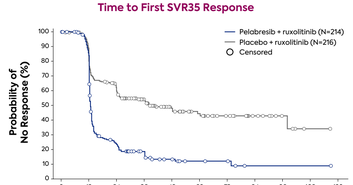
| | Pelabresib + ruxolitinib (N=214) | Placebo + ruxolitinib (N=216) | p-value |
|---|---|---|---|
| **SVR35 response at Week 24** | 65.9% | 35.2% | <0.001 |
| **Difference‡ (95% CI)** | 30.4 (21.6, 39.3) | | |
| **Mean % change in spleen volume at Week 24†** | -50.6 (n=171) | -30.6 (n=183) | N/A§ |
| **95% CI** | -53.2, -48.0 | -33.7, -27.5 | |

**Data cutoff date: August 31, 2023.** Spleen volume assessed by central read. *Waterfall plots represent patients who have baseline and Week 24 data. †Calculated by stratified Cochran–Mantel–Haenszel test. ‡Patients without Week 24 assessment are considered non-responders. §Percentage change in spleen volume at Week 24 is an exploratory endpoint.

### Figure 2. Splenic Response Over Time

**Rapid SVR35 response with a higher proportion of patients who maintained responses with pelabresib + ruxolitinib versus placebo + ruxolitinib**

Time to First SVR35 Response




Number of at-risk patients

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pelabresib + ruxolitinib | 214 | 172 | 45 | 22 | 11 | 6 | 5 | 1 | 1 | 1 | 0 |
| Placebo + ruxolitinib | 216 | 190 | 130 | 79 | 45 | 30 | 20 | 11 | 5 | 1 | 0 |

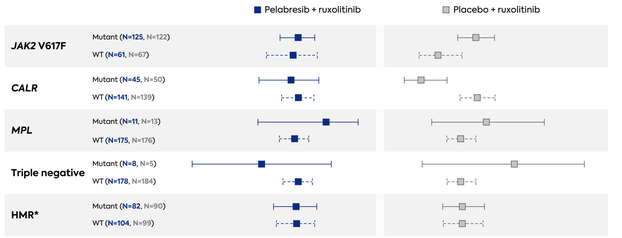
Loss of Splenic Response

| | Pelabresib + ruxolitinib (N=172)* | Placebo + ruxolitinib (N=108)* |
|---|---|---|
| **Loss of SVR35 response** | 13.4% | 27.8% |
| **Loss of SVR35 response and over 25% increase in spleen volume from nadir** | 9.3% | 14.8% |

**Data cutoff date: August 31, 2023.** Spleen volume assessed by central read. *Anytime SVR35 responder.

### Figure 3. Mutation Status and Splenic Response

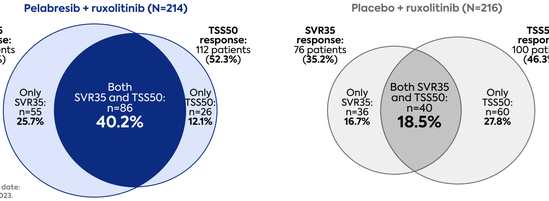
**SVR35 response with pelabresib + ruxolitinib was independent of driver and HMR mutation status**




**Data cutoff date: August 31, 2023.** *HMR mutations include *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SRSF2* and *U2AF1* mutations. †Clopper–Pearson 95% CI.

- At Week 24, overall, large reductions in symptoms were observed for both treatment arms, with numerically greater improvements observed for patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib:
  - Absolute change in TSS: least squares mean (LSM) change from baseline was −15.99 versus −14.05 (difference: −1.94 [95% CI −3.92, 0.04]; p=0.0545)
  - TSS50 response: 52.3% versus 46.3% (Cochran–Mantel–Haenszel difference: 6.0% [95% CI −3.5, 15.5]; nominal p=0.216)
  - Modified TSS (excludes fatigue subdomain) equivalent on 70-point scale: LSM change from baseline was −15.83 versus −13.73 (difference: −2.10 [95% CI −4.04, 0.15]; nominal p=0.035)
- Dual SVR35 and TSS50 response was observed in 40.2% (86/214) versus 18.5% (40/216) of patients in the pelabresib + ruxolitinib versus placebo + ruxolitinib arms, respectively, at Week 24 (**Figure 4**)

### Figure 4. Dual SVR35/TSS50 Responders at Week 24




Data cutoff date: August 31, 2023.

- A numerically greater proportion of patients had a hemoglobin response with pelabresib + ruxolitinib versus placebo + ruxolitinib (**Figure 5**)
- BMF improvement of ≥1 grade in evaluable patients was reported in 38.3% versus 25.3% of patients in the pelabresib + ruxolitinib versus placebo + ruxolitinib arms at Week 24 (nominal p=0.045)

### Figure 5. Hemoglobin Response

**A numerically greater proportion of patients had a hemoglobin response with pelabresib + ruxolitinib versus placebo + ruxolitinib**




Number of patients

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pelabresib + ruxolitinib | 212 | 204 | 209 | 199 | 193 | 189 | 186 | 185 | 184 |
| Placebo + ruxolitinib | 214 | 206 | 211 | 209 | 207 | 205 | 204 | 199 | 196 |

Hemoglobin response*

| | Pelabresib + ruxolitinib (N=214) | Placebo + ruxolitinib (N=216) |
|---|---|---|
| **Hb response† ≥1.5 g/dL mean increase (n/n) [95% CI]** | 10.7% (23/214) [6.60, 14.90] | 6.0% (13/216) [2.85, 9.19] |
| **Hb response‡ in patients with anemia (baseline Hb <10 g/dL) (n/n) [95% CI]** | 16.4% (11/67) [7.55, 25.29] | 14.1% (10/71) [5.99, 22.18] |

RBC transfusions§

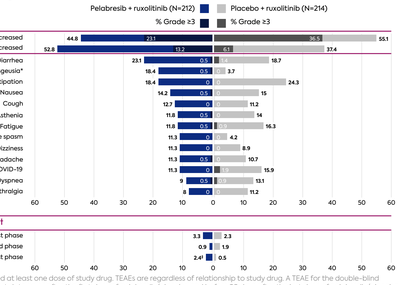
| | Pelabresib + ruxolitinib (N=195) | Placebo + ruxolitinib (N=201) |
|---|---|---|
| **Patients requiring RBC transfusion during screening,‖ n (%)** | 22 (11.3) | 21 (10.4) |
| **Patients requiring RBC transfusion during first 24 weeks of study treatment, n (%)** | 59 (30.3) | 81 (40.3) |

**Data cutoff date: August 31, 2023.** *Hemoglobin response in the ITT population. †Hemoglobin response is defined as a ≥1.5 g/dL mean increase in hemoglobin from baseline in the absence of transfusions during the previous 12 weeks. Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. A similar effect was seen across DIPSS categories. ‡RBC transfusion evaluable patients are patients who have been on the study for 24 weeks without starting new anti-MF treatment. §RBC transfusions refer to number of patients who received any RBC transfusion during the 12-week baseline period prior to dosing. ‖Screening period is the 12-week baseline period prior to dosing.

- The safety profile of pelabresib + ruxolitinib was generally comparable to the established safety profile of ruxolitinib, with fewer Grade ≥3 events versus the placebo + ruxolitinib arm: 49.1% versus 57.0%, respectively. Leukemic transformation (accelerated- and blast-phase progression) continues to be followed up (**Figure 6**)

### Figure 6. Summary of Safety Data

**% TEAEs of all grades that were reported in ≥10% of patients in either arm**




Accelerated- and blast-phase progression†




**Data cutoff date: August 31, 2023.** Safety population: received at least one dose of study drug. TEAEs are regardless of relationship to study drug. A TEAE for the double-blind treatment period is defined as an adverse event that has a start date on or after the first dose of pelabresib/placebo and before 30 days after the last dose of pelabresib/placebo or before the start of alternative (off-study) treatment for MF, whichever occurs first. *Dysgeusia was successfully managed in most patients by dose reductions of pelabresib. †Assessment based on local laboratory results, adverse events, and documented disease progression. Accelerated phase defined as ≥2 consecutive peripheral blast counts ≥10 to <20% or bone marrow myeloblast of 10–19%. Blast phase defined as blast counts ≥20% (IWG-MRT). ‡One of the five patients treated with pelabresib + ruxolitinib with blast phase according to this assessment was diagnosed with lymphoproliferative neoplasm and not blast-phase transformation.