Poster No. MPN-136

Pelabresib Plus Ruxolitinib Combination Therapy in JAK Inhibitor-Naïve Patients With Myelofibrosis in the Phase 3 MANIFEST-2 Study: Preliminary Evidence of Bone Marrow Recovery

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SUMMARY

Myelofibrosis (MF) is a debilitating and progressive disease, characterized by four hallmarks; splenomegaly, MF-associated symptoms, cytopenias (eg, anemia), and impairment of the bone marrow (BM) microenvironment (including fibrosis).

In the Phase 3 MANIFEST-2 study (NCT04603495), analyses of exploratory endpoints and correlation with clinical benefits indicate that pelabresib + ruxolitinib has the potential to enhance clinical responses versus ruxolitinib monotherapy.

Compared with placebo + ruxolitinib, pelabresib + ruxolitinib showed deeper and sustained reductions in levels of disease-relevant proinflammatory cytokines and showed an improvement of the bone marrow, with deeper reductions in reticulin fiber density and megakaryocyte density, and an increase in the proportion of erythrocyte progenitor cells (EPCs) in the BM, as well as an early trend toward greater reduction in Janus kinase 2 (*JAK2*) V617F variant allele fraction (VAF).

This study investigated the impact of pelabresib + ruxolitinib on exploratory endpoints (ie, changes in the BM microenvironment in patients with MF). Improvements in the BM microenvironment and correlations with clinical outcomes suggest that pelabresib + ruxolitinib could lead to more sustained splenic responses in patients with MF compared with placebo + ruxolitinib.

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.** Bose P, Verstovsek S. JAK inhibition 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–naïve myelofibrosis. *Future Oncol*. 2022;18(27):2987–2997. **6.** Albrecht BK, et al. Identification of a benzoxazoloazepine 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; **8.** Rampal R, et al. Pelabresib in combination with ruxolitinib for Janus kinase inhibitor treatment-naïve patients with myelofibrosis: results of the MANIFEST-2 randomized, double-blind, Phase 3 study. Presented at American Society of Hematology (ASH) Annual Meeting and Exposition; December 9–12, 2023; San Diego, CA, USA. Oral presentation 628.

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: B2M, beta-2 microglobulin; BET, bromodomain and extraterminal domain; BM, bone marrow; CD, cluster of differentiation; CI, confidence interval; CRP, C-reactive protein; DIPSS, Dynamic International Prognostic Scoring System; EPC, erythrocyte progenitor cell; IL, interleukin; INT, intermediate; JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MIP, macrophage inflammatory protein; MPIF, myeloid progenitor inhibitory factor; NF-κB, nuclear factor kappa B; NGS, next-generation sequencing; RANTES, regulated upon activation, normal T cell expressed and secreted; STAT, signal transducer and activator of transcription; SVR35, ≥35% reduction in spleen volume from baseline; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline; VAF, variant allele fraction; VCAM, vascular cell adhesion protein.

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 further investigate the impact of pelabresib + ruxolitinib compared with placebo + ruxolitinib on exploratory endpoints (ie, changes in the BM microenvironment) and correlations with clinical outcomes 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]
- Combined BET and JAK inhibition therapy has potential for synergistic effects that may improve clinical outcomes for patients with MF[3]
- 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[8]
- In the Phase 3 MANIFEST-2 study, pelabresib + ruxolitinib showed significantly reduced spleen size, meeting the primary endpoint, and showed a trend toward improved total symptom score (TSS), improvements in multiple measures of anemia, and improvements in the BM microenvironment compared with placebo + ruxolitinib, impacting the four hallmarks of MF[8]

METHODS

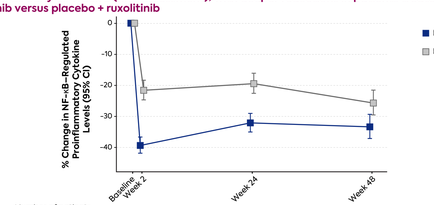
- Eligible patients had Dynamic International Prognostic Scoring System (DIPSS) ≥INT-1 risk, platelet count ≥100 × 10^9/L, spleen volume ≥450 cm^3, ≥2 symptoms with an average score ≥3 or TSS ≥10 (MF Symptom Assessment Form [MFSAF] v4.0). Pelabresib or placebo was administered (daily for 14 consecutive days of 21) with ruxolitinib (twice daily for 21 days [one cycle])
- The primary endpoint was ≥35% spleen volume reduction (SVR35) from baseline at Week 24. Secondary endpoints included absolute change in TSS and ≥50% reduction in TSS from baseline (TSS50) at Week 24, and safety
- Exploratory endpoints included changes in NF-κB–regulated proinflammatory cytokine levels from baseline at Week 24 measured by bead-based multiplex assay from plasma; changes in BM microenvironment from baseline at Week 24, including reticulin fiber density, CD61+ megakaryocytes, and CD71+ EPCs assessed by digital pathology; changes in *JAK2* V617F VAF from baseline at Week 48 conducted from peripheral blood samples by next-generation sequencing (NGS). Biomarkers were all assessed centrally
- Informed consent was obtained from all patients

RESULTS

- Rapid and sustained reductions in levels of proinflammatory cytokine levels were observed early (**Figure 1**), with greater reductions observed in patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib (**Figure 1** and **Figure 2**). Independent of treatment, lower levels of proinflammatory cytokines were correlated with SVR35 response at Week 24 (**Figure 3**)

Figure 1. NF-κB–Regulated Proinflammatory Cytokine Levels

Rapid and sustained reductions from baseline in NF-κB–regulated proinflammatory cytokine levels were observed as early as Week 2 (first assessment), with deeper reductions in patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib

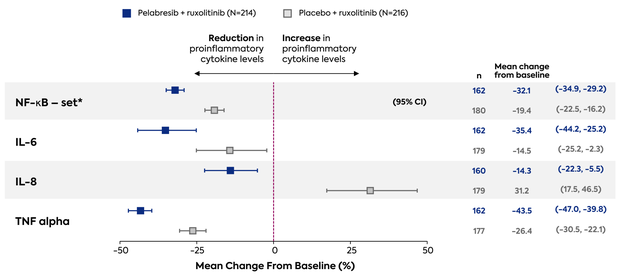


Number of patients				
Pelabresib + ruxolitinib	203	176	162	72
Placebo + ruxolitinib	210	184	180	81

Data cutoff date: August 31, 2023. Proinflammatory cytokine levels were measured by bead-based multiplex assay from plasma. NF-κB set includes B2M, CRP, CD40–L, hepcidin, IL–8, IL–12p40, MIP-1 beta, MPIF-1, RANTES, TNFR2, TNF alpha, VCAM-1

Figure 2. Disease-Relevant Proinflammatory Cytokines at Week 24

Greater reduction from baseline in proinflammatory cytokine levels at Week 24 in patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib

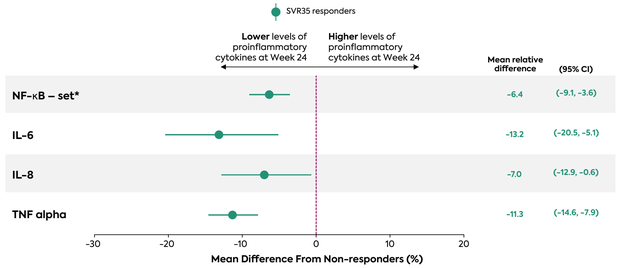


	n	Mean change from baseline	(95% CI)
NF-κB – set*	162	-32.1	(-34.9, -29.2)
	180	-19.4	(-22.5, -16.2)
IL-6	162	-35.4	(-44.2, -25.2)
	179	-14.5	(-25.2, -2.3)
IL-8	160	-14.3	(-22.3, -5.5)
	179	31.2	(17.5, 46.5)
TNF alpha	162	-43.5	(-47.0, -39.8)
	177	-26.4	(-30.5, -22.1)

Data cutoff date: August 31, 2023. Proinflammatory cytokine levels were measured by bead-based multiplex assay from plasma. *NF-κB set includes B2M, CRP, CD40–L, hepcidin, IL–8, IL–12p40, MIP-1 beta, MPIF-1, RANTES, TNFR2, TNF alpha, VCAM-1

Figure 3. Proinflammatory Cytokines Levels in SVR35 Responders

Independent of treatment, lower levels of proinflammatory cytokines were observed in patients with SVR35 response compared with non-responders at Week 24



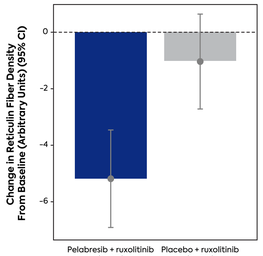
	Mean relative difference	(95% CI)
NF-κB – set*	-6.4	(-9.1, -3.6)
IL-6	-13.2	(-20.5, -5.1)
IL-8	-7.0	(-12.9, -0.6)
TNF alpha	-11.3	(-14.6, -7.9)

Data cutoff date: August 31, 2023. Proinflammatory cytokine levels were measured by bead-based multiplex assay from plasma. *NF-κB set includes B2M, CRP, CD40–L, hepcidin, IL–8, IL–12p40, MIP-1 beta, MPIF-1, RANTES, TNFR2, TNF alpha, VCAM-1

- Potential recovery of the BM was observed, with greater reductions in reticulin fiber density and CD61+ megakaryocyte density in the BM of patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib at Week 24 (**Figure 4** and **Figure 5**)
- In addition, an increase in EPC proportions was observed with pelabresib + ruxolitinib versus placebo + ruxolitinib (**Figure 6**)

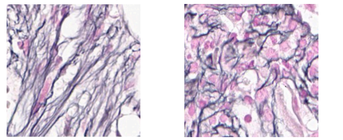
Figure 4. Reticulin Fiber Density at Week 24

Greater reduction in reticulin fiber density from baseline in patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib at Week 24



	Pelabresib + ruxolitinib (N=116)	Placebo + ruxolitinib (N=126)	Nominal p-value mean difference
Reticulin fiber density reduction (arbitrary units) (mean, 95% CI)	-5.2 (-6.9, -3.5)	-1.0 (-2.7, 0.6)	<0.001

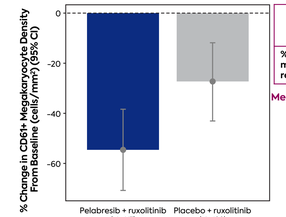
Reticulin fiber density in a patient treated with pelabresib and ruxolitinib*



Data cutoff date: August 31, 2023. Density assessed by digital pathology. *Assessed by immunohistochemistry

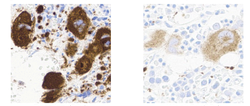
Figure 5. Megakaryocyte Density at Week 24

Greater reduction from baseline in CD61+ megakaryocyte density in the BM of patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib at Week 24



	Pelabresib + ruxolitinib (N=117)	Placebo + ruxolitinib (N=129)	Nominal p-value mean difference
% Change in CD61+ megakaryocyte density reduction (mean, 95% CI)	-54.5 (-70.8, -38.3)	-27.4 (-43.0, -11.9)	0.012

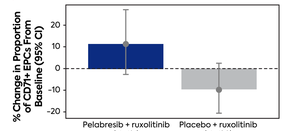
Megakaryocyte density in a patient treated with pelabresib and ruxolitinib*



Data cutoff date: August 31, 2023. BM immunohistochemistry was conducted for CD61+ megakaryocytes. Digital images were analyzed by an automated quantitative cell-specific detection analysis. *Slide pair was stained for CD61.

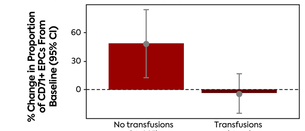
Figure 6. EPC Proportions at Week 24 and Transfusion Requirement

Increase in proportion of EPCs from baseline observed with pelabresib + ruxolitinib, and a decrease with placebo + ruxolitinib



	Pelabresib + ruxolitinib (N=121)	Placebo + ruxolitinib (N=130)	Nominal p-value mean difference
% Change in proportion of EPCs from baseline (mean, 95% CI)	11.4 (-2.4, 27.2)	-9.8 (-20.6, 2.6)	0.019

Patients who did not require red blood cell transfusions* had a greater increase in the proportion of EPCs



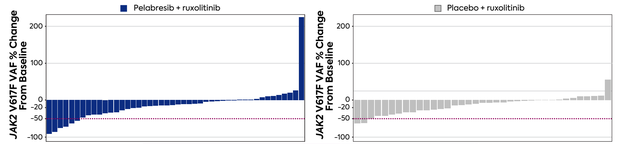
	No transfusions (N=207)	Transfusions (N=44)	Nominal p-value mean difference
% Change in proportion of EPCs from baseline (mean, 95% CI)	48.27 (12.73, 83.8)	-4.01 (-24.57, 16.56)	0.004

Data cutoff date: August 31, 2023. BM immunohistochemistry staining was conducted for CD71+ EPCs. Digital images were analyzed by an automated quantitative cell-specific detection analysis. *Patients who received transfusion between Week 20 and Week 24 on treatment.

- An early trend toward greater reduction in *JAK2* V617F VAF was observed with pelabresib + ruxolitinib versus placebo + ruxolitinib (**Figure 7**). Independent of treatment, SVR35 responders had a greater reduction in *JAK2* V617F VAF versus non-responders (**Figure 8**)

Figure 7. *JAK2* V617F VAF at Week 48

Early trend toward greater reduction in *JAK2* V617F VAF in patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib

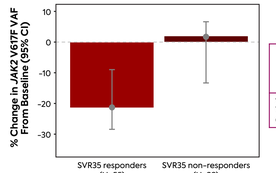


	Pelabresib + ruxolitinib (N=46)	Placebo + ruxolitinib (N=37)
≥50% VAF reduction from baseline at Week 48	13.0%	8.1%
Mean % change from baseline at Week 48	-23.9	-16.8
Difference (95% CI)	-9.5 (-23.6, 2.9)	

Data cutoff date: August 31, 2023. Mutational analyses were conducted from peripheral whole blood samples obtained by targeted NGS.

Figure 8. SVR35 Response and *JAK2* V617F VAF

Independent of treatment, SVR35 responders at Week 24 had a significantly greater reduction from baseline in *JAK2* V617F VAF compared with non-responders



	SVR35 responders (N=55)	SVR35 non-responders (N=28)	Nominal p-value mean difference
% Change in *JAK2* V617F VAF from baseline (mean, 95% CI)	-21.2 (-28.0, -9.1)	1.7 (-13.1, 6.3)	<0.001

Data cutoff date: August 31, 2023.