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Assessment of Minimal Clinically Important Difference in Patient-Reported Myelofibrosis-Associated Symptoms Using an Anchor-Based Analysis Based on MANIFEST Arm 3 Data

Ruben Mesa,[1] Vikas Gupta,[2] John Mascarenhas,[3] Gabriela Hobbs,[4] Jean-Jacques Kiladjian,[5] Giacomo Coltro,[6] Vincenzo Bagnardi,[7] Chiara Oriecuia,[8] Lennart Kann,[9] Gozde Colak,[10] Claire Harrison,[11] Debarshi Dey[9]

[1]Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC, USA
[2]Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada
[3]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[4]Division of Hematology/Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[5]Clinical Investigation Center, Hôpital Saint-Louis, Université de Paris, Paris, France
[6]Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy
[7]Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy
[8]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[9]MorphoSys AG, Planegg, Germany
[10]Constellation Pharmaceuticals, a MorphoSys Company, Boston, MA, USA
[11]Department of Haematology, Guy's and St Thomas' NHS Foundation Trust, London, UK

SUMMARY AND CONCLUSION

Assuming a one-category change in the seven-category PGIC represents a clinically meaningful difference, the analyses suggest that the MCID in TSS for JAKi treatment-naïve patients with MF could be approximately 11–12% for percentage change from baseline and approximately 1.5–2 points for absolute change from baseline.

These findings could provide valuable guidance in contextualizing treatment outcomes in terms of symptom benefits that are clinically meaningful and relevant for patients with JAKi treatment-naïve MF.

Further exploration of these findings requires larger datasets, which will be addressed in the forthcoming Phase 3 MANIFEST-2 study evaluating pelabresib and ruxolitinib versus placebo and ruxolitinib in JAKi treatment-naïve patients with MF.

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Abbreviations: BET, bromodomain and extraterminal domain; CI, confidence interval; JAKi, Janus kinase inhibitor; MCID, minimal clinically important difference; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; PGIC, Patient Global Impression of Change; PRO, patient-reported outcome; QR, quick response; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline.

Pelabresib (CPI-0610) is an investigational, selective, small-molecule therapy designed to promote antitumor activity by inhibiting the function of bromodomain and extraterminal domain (BET) proteins to decrease the expression of abnormally expressed genes in cancer. Pelabresib is being investigated as a treatment for myelofibrosis and has not yet been evaluated or approved by any regulatory authorities.

OBJECTIVE

To determine the minimal clinically important difference (MCID) for changes in the total symptom score (TSS) between two treatment groups with Janus kinase inhibitor (JAKi) treatment-naïve patients with myelofibrosis (MF). The MCID is determined based on patients treated with pelabresib and ruxolitinib from Arm 3 of the Phase 2 MANIFEST study using an anchor-based analysis to facilitate a more precise assessment of treatment effects and the clinical significance of symptom improvement.

INTRODUCTION

- MF is a myeloproliferative neoplasm that can arise as a primary condition (primary MF) or as a progression from polycythemia vera or essential thrombocythemia (secondary MF)[1]
- The MFSAF v4.0 is a seven-symptom questionnaire that assesses symptom severity from the patients' perspective[2]
  - Each symptom is rated on a scale from 0 (absent) to 10 (worst imaginable). The MFSAF TSS ranges from 0 to 70, with higher scores indicating worse symptoms[2]
- A ≥50% reduction in TSS from baseline (TSS50) is a commonly used binary endpoint in clinical trials[3,4]
- However, the clinical interpretation of the dichotomization of response at the 50% cutoff across the spectrum of responses is limited, especially when assessing the benefit of combination treatments
- The Patient's Global Impression of Change (PGIC) questionnaire is an established seven-point patient reported outcome (PRO) scale reflecting overall improvement compared with baseline, in which patients rate their change in symptoms from 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse' to 'very much worse'[5]
- Pelabresib (CPI-0610) is an investigational, oral, small-molecule BET inhibitor being investigated as a treatment for MF.[3,4] Currently, the JAKis ruxolitinib and fedratinib are the standard of care for intermediate- or high-risk patients with MF[6,7]
  - In Arm 3 of the Phase 2 MANIFEST trial of JAKi treatment-naïve patients with MF treated with pelabresib and ruxolitinib, 56% achieved TSS50 response at Week 24[3]

METHODS: ANCHOR-BASED ANALYSIS

- Data from Arm 3 of the Phase 2 MANIFEST study of JAKi treatment-naïve patients with MF treated with pelabresib combined with ruxolitinib were used (data cutoff July 29, 2022) (Figure 1 and Table 1)
- Anchor-based methods compare the change in a scale-based outcome measure with that of an established PRO[8]
  - These methods are commonly used to establish the MCID, defined as the smallest difference in score that patients consider beneficial[8]
- In this analysis, the PGIC questionnaire was used as the anchor PRO
- The relationship between TSS changes (percentage and absolute) at Week 24 and PGIC categories was examined using correlation and regression analyses
- The impact of a one-category difference in PGIC score on TSS change at Week 24 was assessed
  - TSS change was adjusted for baseline TSS score. Only patients with available TSS and PGIC data at Week 24 were included, with no imputation for missing values

RESULTS

Figure 1. Baseline TSS distribution

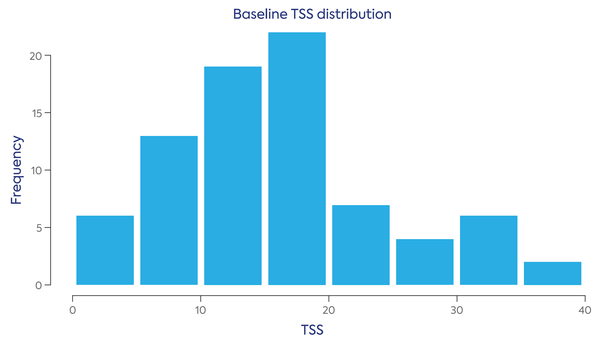

Table 1. Baseline TSS and reduction at 24 weeks

	N=78*
Mean (SD) TSS at baseline	16.4 (8.4)
Median (range) TSS at baseline	15.5 (2.0–38.3)
Median % reduction in TSS at Week 24	-58.8%
Median absolute reduction in TSS at Week 24	-7.7

*In Arm 3 of the MANIFEST trial, 78 of 84 patients treated with pelabresib and ruxolitinib had complete TSS and PGIC data at Week 24.
PGIC, Patient Global Impression of Change; SD, standard deviation; TSS, total symptom score.

Figure 2. Relationship between absolute change in TSS at Week 24 and PGIC categories

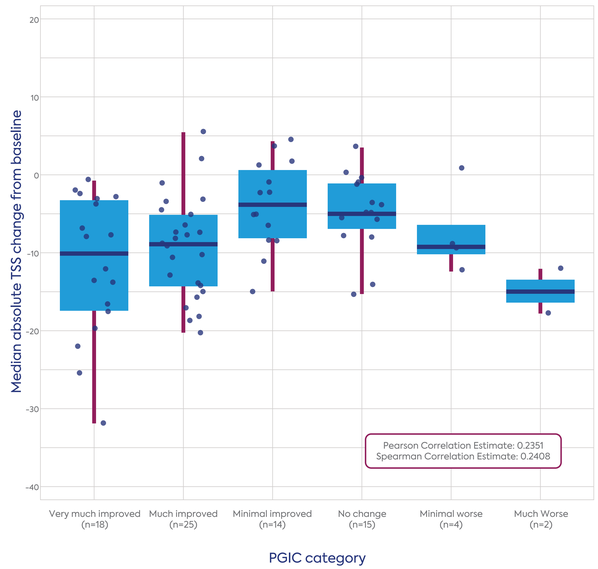

Table 2. Change in TSS at Week 24 for each PGIC category

PGIC at Week 24	N (%)	Mean (%) Change in TSS From Baseline	Median (%) Change in TSS From Baseline	Mean (Abs) Change in TSS From Baseline	Median (Abs) Change in TSS From Baseline	TSS50 Responders (% in PGIC Category)
Very much improved	18 (23.1)	-78.1	-78.5	-12.0	-11.4	16 (88.9)
Much improved	25 (32.1)	-53.0	-59.2	-9.2	-8.9	16 (64.0)
Minimally improved	14 (17.9)	-16.9	-26.0	-4.0	-3.8	5 (35.7)
No change	15 (19.2)	-25.7	-30.0	-4.9	-4.9	5 (33.3)
Minimally worse	4 (5.1)	-46.9	-53.3	-7.1	-8.6	2 (50.0)
Much worse	2 (2.6)	-58.4	-58.4	-14.9	-14.9	1 (50.0)
Very much worse	0	-	-	-	-	0

Abs, absolute; PGIC, Patient Global Impression of Change; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline.

- For PGIC at Week 24, no patients scored in the 'very much worse' PGIC category, and only six patients (7.7%) scored in the 'minimally' and 'much worse' categories (Table 2)
- Linear regression suggests that a one-category change in PGIC corresponds to an 11.89% change (95% confidence interval [CI] 3.12–20.65) in TSS at Week 24
- The quantile regression estimate for this relationship was 11.36% (95% CI 3.53–19.19)
- For absolute change at Week 24, a one-category change in PGIC was associated with a 1.67 (range 0.74–2.60) change in mean TSS, with a 1.87 (range 0.62–3.12) increase in median TSS (Figure 2) ($r = 0.2351$; $\rho = 0.2408$)

STUDY LIMITATIONS

- The data used for this analysis (Arm 3 of the Phase 2 MANIFEST study of JAKi treatment-naïve patients with MF treated with pelabresib combined with ruxolitinib) is limited in sample size from an open-label single-arm study
- Potential recall bias for PGIC at Week 24
- Very few patients in worsening PGIC categories adds to the complexity in the interpretation of the strength of the relationship between PGIC and TSS (absolute or percentage)
- Potential for missing data from patients who withdrew from the study due to severity of their symptoms
- MCID for absolute change in TSS can be potentially influenced by absolute baseline TSS scores