Association between hemoglobin improvement and patient-reported outcomes in patients with myelofibrosis and anemia: post hoc pooled analysis of momelotinib phase 3 trials

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Introduction

- Many patients with myelofibrosis (MF) experience debilitating symptoms that substantially impact health-related quality of life (HRQOL), a burden that is compounded in those with cytopenias such as anemia[1-5]
- While red blood cell (RBC) transfusions may improve anemia-related symptoms in MF, their associated burdens and potential complications may further negatively affect HRQOL in patients with anemia[6-8]
- Momelotinib is a Janus kinase (JAK) 1/JAK2/activin A receptor type 1 inhibitor approved for the treatment of patients with myelofibrosis and anemia[9,10]
- A previous exploratory analysis of the phase 3 SIMPLIFY-1 and SIMPLIFY-2 trials of momelotinib found that both baseline transfusion independence, as well as achievement of transfusion independence at week 24 in patients who were transfusion dependent (TD) at baseline, were associated with improved patient-reported outcomes (PROs)[11]
  - However, the association of baseline anemia severity and potential on-treatment improvements—as defined by hemoglobin (Hb) levels—was inconclusive in that analysis[11]
- Here we report a new exploratory post hoc analysis of the association between Hb improvement and PROs, including HRQOL and symptoms, in patients with MF and anemia in the momelotinib phase 3 clinical trial program[12-14]

Results

Baseline Characteristics

- Baseline characteristics of the pooled anemic population are summarized in **Table 1**
- 436 of 480 patients (91%) were evaluable for Hb improvement at week 24 across all 3 trials: 241 of 285 patients with anemia (85%) in SIMPLIFY-1 and SIMPLIFY-2 and all 195 patients in MOMENTUM (**Table 2**)

Table 1: **Baseline Characteristics**[a]

Characteristic	Pooled anemic population (N=480)
Age, median (range), years	70.0 (25-92)
Male sex at birth, n (%)	299 (62)
White, n (%)	390 (81)
Geographic region, n (%)	
Western Europe	228 (48)
Eastern Europe	102 (21)
North America	99 (21)
Asia	32 (7)
Australasia	19 (4)
MF subtype, n (%)	
Primary	305 (64)
PET	98 (20)
PPV	77 (16)
***JAK2* V617F mutation positive, n (%)**	313 (65)
Platelet counts ≤150×10⁹/L, n (%)	250 (52)

JAK, Janus kinase; MF, myelofibrosis; PET, post–essential thrombocythemia; PPV, post–polycythemia vera.
[a]*Characteristics shown are those included in multivariate analyses.*

Table 2: **Hb Improvement at Week 24**

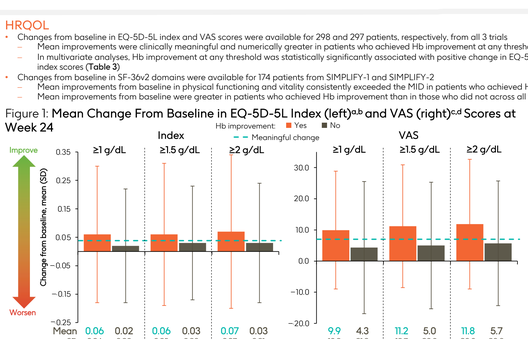
Hb improvement, n (%)[a]	All 3 trials (N=436)	SIMPLIFY-1 + SIMPLIFY-2 (N=241)	MOMENTUM (N=195)
≥1 g/dL			
Yes	193 (44)	102 (42)	91 (47)
No	243 (56)	139 (58)	104 (53)
≥1.5 g/dL			
Yes	134 (31)	67 (28)	67 (34)
No	302 (69)	174 (72)	128 (66)
≥2 g/dL			
Yes	89 (20)	38 (16)	51 (26)
No	347 (80)	203 (84)	144 (74)

Hb, hemoglobin; PRO, patient-reported outcome.
[a]*Sample sizes for each PRO assessment were determined by whether the assessment was administered in all 3 trials, SIMPLIFY-1 and SIMPLIFY-2 only, or MOMENTUM only.*

HRQOL

- Changes from baseline in EQ-5D-5L index and VAS scores were available for 298 and 297 patients, respectively, from all 3 trials
  - Mean improvements were clinically meaningful and numerically greater in patients who achieved Hb improvement at any threshold than in those who did not (**Figure 1**)
  - In multivariate analyses, Hb improvement at any threshold was statistically significantly associated with positive change in EQ-5D-5L VAS scores at week 24; similar but nonsignificant trends were observed for EQ-5D-5L index scores (**Table 3**)
- Changes from baseline in SF-36v2 domains were available for 174 patients from SIMPLIFY-1 and SIMPLIFY-2
  - Mean improvements from baseline in physical functioning and vitality consistently exceeded the MID in patients who achieved Hb improvement at any threshold (**Figure 2**)
  - Mean improvements from baseline were greater in patients who achieved Hb improvement than in those who did not across all domains except role physical

Figure 1: **Mean Change From Baseline in EQ-5D-5L Index (left)[a,b] and VAS (right)[c,d] Scores at Week 24**



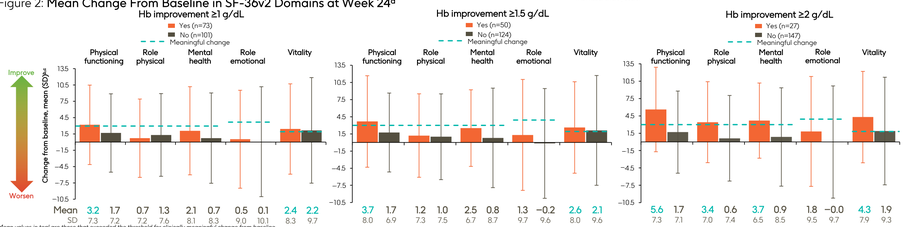
Mean values in teal are those that exceeded the threshold for clinically meaningful change from baseline.
Hb, hemoglobin; VAS, visual analog scale.
[a]*Total N=298.* [b]*Clinically meaningful changes from baseline range from 0.037 to 0.069.*[18] [c]*Total N=297.* [d]*Clinically meaningful change from baseline is 7.*[19]

Table 3: **Multivariate Analyses for Change From Baseline in EQ-5D-5L VAS Scores at Week 24**

	Hb improvement (N=297):	≥1 g/dL (yes, n=141; no, n=156)	≥1.5 g/dL (yes, n=96; no, n=201)	≥2 g/dL (yes, n=61; no, n=236)
Variable	**Value**	**Parameter estimates**		
Intercept	–	**44.96***	**47.82***	**51.75***
Hb improvement (ref: no)	Yes	**5.80***	**5.27***	**6.84***
Age (continuous)	–	0.12	0.11	0.08
Sex (ref: male)	Female	1.37	1.23	1.13
Race (ref: Black)	Asian	−29.37	−30.35	**−32.58***
	Not reported	−12.50	−13.56	−14.38
	Other	−11.47	−11.47	−13.21
	White	−16.73	−17.22	**−18.30***
Region (ref: North America)	Asia	10.84	11.41	12.05
	Australasia	4.70	4.41	3.86
	Eastern Europe	−1.18	−1.18	−1.14
	Western Europe	−2.71	−2.78	−2.77
MF subtype (ref: primary)	PET	**−5.98**	**−6.28**	**−6.85**
	PPV	−4.92	−4.40	−4.66
***JAK2* V617F mutation status (ref: negative)**	Positive	0.07	−0.28	−0.20
	Unknown	−3.65	−5.00	−5.62
Baseline platelet count (ref: ≤150×10⁹/L)	>150×10⁹/L	0.53	0.26	0.37
Baseline VAS score	–	**−0.56***	**−0.55***	**−0.55***

*Bold numbers with * indicate statistical significance (P<.05).*
Hb, hemoglobin; JAK, Janus kinase; MF, myelofibrosis; PET, post–essential thrombocythemia; PPV, post–polycythemia vera; VAS, visual analog scale.

Figure 2: **Mean Change From Baseline in SF-36v2 Domains at Week 24**[a]

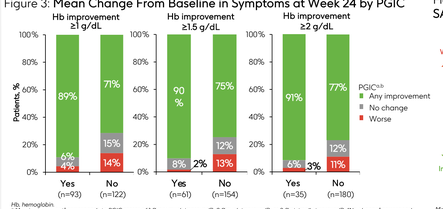


Mean values in teal are those that exceeded the threshold for clinically meaningful change from baseline.
Hb, hemoglobin.
[a]*Shown are SF-36v2 domains hypothesized to have the most potential to be impacted by anemia.* [b]*Total N=174.* [c]*Clinically meaningful changes from baseline are 2 for vitality; 3 for physical functioning, role physical, and mental health; and 4 for role emotional.*[20]

Symptoms

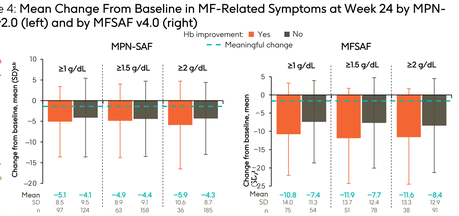
- PGIC at week 24 was available for 215 patients in SIMPLIFY-1 and SIMPLIFY-2; Hb improvement at any threshold was associated with a higher percentage of patients with any symptom improvement and lower percentage with symptom worsening (**Figure 3**)
- 221 patients in SIMPLIFY-1 and SIMPLIFY-2 and 129 patients in MOMENTUM had full MPN-SAF and MFSAF, respectively, TSS data available through week 24
  - Clinically meaningful mean decreases (improvement) in TSS were observed, and were greater in patients who achieved Hb improvement at any threshold than in those who did not, in both SIMPLIFY-1 and SIMPLIFY-2 (MPN-SAF) and MOMENTUM (MFSAF) (**Figure 4**)
  - In multivariate analyses, Hb improvement at any threshold was associated with positive change in TSS at week 24, but these trends generally did not reach the level of statistical significance; only Hb improvement of ≥1 g/dL in MOMENTUM was significantly associated with TSS improvement

Figure 3: **Mean Change From Baseline in Symptoms at Week 24 by PGIC**



Hb, hemoglobin.
[a]*"Any improvement" corresponds to PGIC scores of 1 ("very much improved"), 2 ("much improved"), or 3 ("minimally improved"). "No change" corresponds to a PGIC score of 4. "Worse" corresponds to PGIC scores of 5 ("minimally worse"), 6 ("much worse"), or 7 ("very much worse").* [b]*Patients with missing data were excluded from the analysis and are not reflected in the percentages shown.*

Figure 4: **Mean Change From Baseline in MF-Related Symptoms at Week 24 by MPN-SAF v2.0 (left) and by MFSAF v4.0 (right)**



Mean values in teal are those that exceeded the threshold for clinically meaningful change from baseline.
Hb, hemoglobin; MF, myelofibrosis.
[a]*Total N=221.* [b]*Clinically meaningful absolute change from baseline is 1.5 to 2 points.*[21] [c]*Total N=129.*

Hb Improvement

- Laboratory assessments were performed at baseline and every 2 weeks (Q2W) through week 24 in SIMPLIFY-1 and SIMPLIFY-2; in MOMENTUM, laboratory assessments were performed at baseline, week 2, week 4, and every 4 weeks (Q4W) thereafter through week 24
- In the present analyses, Hb improvement was defined as an increase of ≥1, ≥1.5, or ≥2 g/dL from baseline at week 24

Statistical Analysis

- This descriptive analysis summarized EQ-5D-5L index and VAS scores, SF-36v2 domain scores, MPN-SAF TSS, and MFSAF TSS changes from baseline, as well as the percentages of patients with improved, no change, or worsening in symptoms per PGIC, for subgroups that did vs those that did not achieve each Hb improvement threshold
- Multivariate linear regression models included change in EQ-5D-5L score (either index or VAS), MPN-SAF TSS, or MFSAF TSS from baseline as the dependent variable, and week 24 Hb improvement and key baseline characteristics (age, sex, race, geographic region, MF subtype, *JAK2* V617F status, platelet count, and baseline score) as independent variables
  - Note that these trials were not powered to detect statistically significant differences in subgroups based on Hb improvement, and statistical testing was not controlled for multiplicity

Methods

Study Population

- The pooled treatment-agnostic analysis set included patients with anemia (baseline Hb of <10 g/dL) from three phase 3 trials (N=480):

SIMPLIFY-1[12]
- JAK inhibitor naive
- Momelotinib vs ruxolitinib
- Intent-to-treat population (ITT), N=432
- Hb of <10 g/dL, n=180

SIMPLIFY-2[13]
- JAK inhibitor experienced
- Momelotinib vs best available therapy (BAT; 88.5% ruxolitinib)
- ITT, N=156
- Hb of <10 g/dL, n=105

MOMENTUM[14]
- JAK inhibitor experienced, symptomatic (Total Symptom Score [TSS] ≥10), and anemic (Hb of <10 g/dL)
- Momelotinib vs danazol
- ITT, N=195
- Hb of <10 g/dL, n=195

PRO Assessments

	HRQOL		Symptoms	
Tool	**EQ-5D-5L**[15]	**SF-36v2**[11,20]	**PGIC**	**MPN-SAF v2.0 / MFSAF v4.0**[21,22]
Trial(s) and endpoints	SIMPLIFY-1, SIMPLIFY-2, MOMENTUM (exploratory in all 3 trials)	SIMPLIFY-1, SIMPLIFY-2 (exploratory in both trials)	SIMPLIFY-1, SIMPLIFY-2 (exploratory in both trials)	SIMPLIFY-1, SIMPLIFY-2 (key secondary in both trials) / MOMENTUM (primary)
Assessment schedule through week 24	Baseline and then Q4W in SIMPLIFY-1 and SIMPLIFY-2; baseline, week 12, and week 24 in MOMENTUM	Baseline and then Q4W in both trials	Q2W in both trials	Daily from baseline in all 3 trials
MF specific?	No; generic questionnaire in 2 parts: (1) index score (5 dimensions rated across 5 levels) and (2) visual analog scale (VAS; single question)	No; generic measure across 8 HRQOL and functioning domains	No; single question about general symptom improvement since start of treatment	Yes; items related to 7 MF symptoms (tiredness, early satiety, abdominal discomfort, night sweats, itching, bone pain, and pain under ribs on left side) scored for severity over the past 24 hours
Measurement	Index: dimensions rated from 1 (no problem) to 5 (extreme problem) on the day administered; level for each dimension represents 1 digit of a 5-digit code corresponding to overall health state, weighted against UK (SIMPLIFY-1 and SIMPLIFY-2) or US (MOMENTUM) utility value sets[16,17] to derive a single number (index score) reflecting how good or bad that health state is (higher = better) VAS: general health rated from 0 (worst imaginable) to 100 (best imaginable)	Scores from 0 (worst) to 100 (best); norm-based score ranges vary by domain, but higher scores = better HRQOL	Scores range from 1 (very much improved) to 7 (very much worse); 1, 2, or 3 = improved; 4 = no change; 5, 6, or 7 = worse	Scores for each item range from 0 (absent) to 10 (worst imaginable), for a maximum (worst) TSS of 70
Minimally important difference (MID)	Index: change from baseline of 0.037 to 0.069[18] VAS: change from baseline of 7[19]	Meaningful change from baseline varies by domain from 2.0 to 4.0[20]	N/A	Absolute TSS change from baseline of 1.5 to 2.0 (determined for MFSAF v4.0)[23]

Conclusion

- In this clinical trial population of patients with MF and anemia, Hb improvement of any threshold at week 24 was associated with clinically meaningful improvements in symptoms and some aspects of HRQOL, as measured by multiple generic and MF-specific PRO assessments
  - Multivariate analyses further highlighted Hb improvement at week 24 as a clinically significant variable associated with improvements in HRQOL measured by EQ-5D-5L VAS, even after controlling for other potentially clinically relevant factors
- Overall, these results highlight the potential value of treatments with anemia-related benefits in improving the patient experience in MF
  - While these analyses illustrate a positive impact of anemia-related benefits on HRQOL and symptoms, the lack of statistical significance in some analyses and high degree of uncertainty around the means, as reflected by the SDs, suggest that currently available PRO assessment tools largely do not adequately characterize anemia burden
  - Novel MF-specific PRO measures are needed that are designed to capture the effects of anemia on the patient experience

Discussion/Limitations

- These results are post hoc, exploratory, and descriptive given that these clinical trials were not designed to prospectively evaluate the impact of anemia on HRQOL
  - The small sample size in some subgroups may have impacted the ability of these analyses to reach statistical significance
  - Statistical testing was not controlled for multiplicity
- The strength of conclusions that can be drawn from these analyses is also limited by the fact that the SDs were high, suggesting a high degree of uncertainty around the means
  - Median values (not reported) did not always follow the same trends as the means
- Patients receiving transfusions during the 24-week treatment period were not excluded from these analyses
  - Thus, the impacts of continued or increased transfusion burden on both Hb improvement (likely positive) or HRQOL (likely negative) are not evaluable
- To increase sample size and show the generalizability of associations between Hb improvement and HRQOL, data from all treatment arms of these momelotinib clinical trials were pooled
  - Future analyses may consider the relative impacts of specific MF-directed therapies on Hb improvements and associated HRQOL changes
- Generic PRO assessment instruments (eg, EQ-5D-5L, SF-36v2, PGIC) may not be optimal to capture the experience of patients with MF
  - New tools may be needed to assess meaningful changes in HRQOL associated with anemia improvement
- Although the MPN-SAF and MFSAF are MF-specific tools, even they may not be sensitive enough to fully characterize the impact of anemia on MF-related symptoms, given that patients who did not achieve Hb improvement also showed meaningful TSS change from baseline
  - Future analyses may explore the ability of these tools to show the impact of anemia-related benefits on individual TSS items

Abbreviations

BAT, best available therapy; Hb, hemoglobin; HRQOL, health-related quality of life; ITT, intent to treat; JAK, Janus kinase; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MID, minimally important difference; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; PET, post–essential thrombocythemia; PGIC, Patient Global Impression of Change; PPV, post–polycythemia vera; PRO, patient-reported outcome; Q2W, every 2 weeks; Q4W, every 4 weeks; RBC, red blood cell; SF-36v2, Short Form-36, version 2; TI, transfusion independent; TD, transfusion dependent; TSS, Total Symptom Score; VAS, visual analog scale.

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