Impact of transfusion burden on health-related quality of life (HRQOL) and functioning in patients (pts) with myelofibrosis (MF): post hoc analysis of SIMPLIFY-1 (S1) and -2 (S2)

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Introduction

- Myelofibrosis (MF) is associated with a substantial symptom burden that can negatively impact patients' health-related quality of life (HRQOL) and functioning[1-3]
- Red blood cell (RBC) transfusions are commonly used to address anemia in MF and may improve anemia-related symptoms as a result; however, they are burdensome and may be associated with complications that could negatively impact social, emotional, and general health status[4-6]
  - Thus, HRQOL may be further compromised in patients with MF who are transfusion dependent (TD) or transfusion requiring (TR)
  - However, the relationship between transfusion status and HRQOL in MF has not been comprehensively characterized to date
- Here we report an exploratory post hoc analysis of the association between transfusion status, hemoglobin (Hb) levels, and patient-reported outcomes (PROs) in phase 3 trials of the Janus kinase (JAK) 1/JAK2/activin A receptor type 1 inhibitor momelotinib in patients with MF[7]

Objective

- To evaluate the impact of transfusion burden and anemia, using PROs to capture concepts such as HRQOL and functioning, on patients with MF in phase 3 trials of momelotinib

Methods

Clinical Trials

- SIMPLIFY-1 and SIMPLIFY-2 were phase 3 trials of momelotinib vs ruxolitinib in JAK inhibitor–naive patients with MF (SIMPLIFY-1; N=432) or vs best available therapy (88.5% ruxolitinib) in JAK inhibitor–experienced patients with MF (SIMPLIFY-2; N=156)[7,8]
  - The treatment-agnostic pooled analysis set for these post hoc analyses comprised both arms of the intent-to-treat populations of SIMPLIFY-1 and SIMPLIFY-2
- To confirm and expand on results observed in the SIMPLIFY trials, a PRO analysis in the treatment-agnostic pooled analysis set of the phase 3 MOMENTUM trial (momelotinib vs danazol in JAK inhibitor–experienced patients with MF; N=195)[9] was also performed

Subgroups

- Across trials, transfusion status at baseline and at week 24 on study was defined as follows[7-9]:
  - **Transfusion independent (TI)**: no transfusions and all Hb levels ≥8 g/dL in the previous 12 weeks
  - **TD**: ≥4 RBC units transfused or an Hb level <8 g/dL in the previous 8 weeks
  - **TR**: not meeting the criteria for either TI or TD
- Hb levels at baseline and at week 24 were defined according to corresponding severity of anemia as follows (subgroups at each time point were based on the level at the given visit)[10]:
  - <8 g/dL
  - ≥8 to <10 g/dL
  - ≥10 to <12 g/dL
  - ≥12 g/dL

PRO Assessment

- Short Form-36 version 2 (SF-36v2) was an exploratory endpoint in both SIMPLIFY trials
  - Completed at baseline and then every 4 weeks on study to week 24
  - Generic measure of patients' self-reported health, well-being, and functioning across 8 HRQOL domains, with high scores indicating better HRQOL and/or functioning; norm-based score ranges and minimally important differences (MIDs) vary by domain (**Table 1**), with a norm-based score of 50 corresponding to the mean value of the general population (SD, 10)[11,12]
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) was a secondary endpoint (assessment of cancer-related fatigue) in MOMENTUM
  - Completed at baseline, week 12, and week 24
  - Self-report assessment of HRQOL in patients with cancer, with 30 items spanning 15 domains covering global health status, symptoms, and functioning; scores are transformed on a scale from 0 to 100, with high scores indicating either better global health status/functioning or worse symptoms, and MIDs vary by domain (**Table 1**)[13,14]
- The current descriptive analyses are focused on domains of the SF-36v2 and EORTC QLQ-C30 that were hypothesized to have the most potential to be impacted by transfusions, such as those related to physical and social functioning[15]

Table 1. Reported SF-36v2 and EORTC QLQ-C30 Score Ranges and MIDs

		Range of possible scores		
	Domain	Lowest	Highest	MID
SF-36v2[12,a]	Physical functioning	19.3	57.5	≥3.0
	Role-physical	21.2	57.2	≥3.0
	Bodily pain	21.7	62.0	≥3.0
	General health	19.0	66.5	≥2.0
	Vitality	22.9	70.4	≥2.0
	Social functioning	17.2	57.3	≥3.0
	Role-emotional	14.4	56.2	≥4.0
	Mental health	11.6	64.00	≥3.0
EORTC QLQ-C30[14,15,b]	Cognitive functioning, physical functioning	–	–	>7.0
	Global quality of life, social functioning	–	–	>8.0
	Emotional functioning, nausea and vomiting, dyspnea, fatigue, insomnia, pain	–	–	>9.0
	Constipation	–	–	>10.0
	Diarrhea	–	–	>11.0
	Role functioning	–	–	>12.0
	Appetite loss	–	–	>13.0

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; MID, minimally important difference; SF-36v2, Short Form-36 version 2.
[a]Highest and lowest observed scores in 2009 general population normative sample, per reference 12. [b]All domains are scored on a scale from 1 to 100, per reference 14.

Results

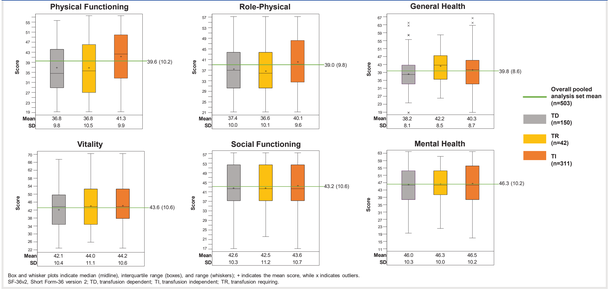
- Baseline characteristics of the pooled analysis sets are shown in **Table 2**; more patients were TI in SIMPLIFY-1 (69.2%) than in SIMPLIFY-2 (32.7%) or MOMENTUM (13.8%)
- SF-36v2 results were available from 503 patients (85.5%) in the pooled SIMPLIFY trials at baseline; across all domains, mean scores in this clinical trial population with MF were lower than the reported general population mean (**Figure 1**)
  - Patients who were TD or TR at baseline had lower mean scores than those who were TI across most domains (all domains for TD vs TI, all domains but general health for TR vs TI; **Figure 1**)
  - Trends at week 24 were similar to those observed at baseline, with patients who were TD (n=142) or TR (n=42) having lower mean SF-36v2 scores than those who were TI (n=289) across all domains
- In analyses of the impact of baseline transfusion status on PROs by study, differences were observed in the physical functioning, role-physical, and general health SF-36v2 domains in the JAK inhibitor–naive population of SIMPLIFY-1, with higher mean scores in patients who were TI vs those who were TD (**Figure 2A**); similar trends were observed to a lesser extent in SIMPLIFY-2 (**Figure 2B**)
  - Associations between transfusion status and PROs in the JAK inhibitor–experienced population of MOMENTUM were also observed in some domains of the EORTC QLQ-C30, including better physical functioning and improved fatigue in patients who were TI vs those who were TD (**Figure 2C**)
- Among patients in the pooled SIMPLIFY trials who were TD and had SF-36v2 results at baseline, 75 remained TD (50.0%), 21 became TR (14.0%), 40 became TI (26.7%), and 14 had no data (9.3%) at week 24
- Patients who were TD at baseline but became TI at week 24 experienced substantially greater improvement (positive mean change from baseline) in most SF-36v2 domains vs those who remained TD (all domains except vitality); mean changes from baseline in patients who became TI exceeded the MID for all domains except role-physical (**Figure 3**)
- At both baseline and week 24 in the SIMPLIFY trials, a modest incremental effect of Hb level on the SF-36v2 physical functioning domain was observed (**Figure 4**); no clear association was found between Hb levels and other SF-36v2 domains

Table 2. Baseline Characteristics in the Pooled Analysis Sets

Baseline characteristics[a]	SIMPLIFY-1 (N=432)	SIMPLIFY-2 (N=156)	Pooled SIMPLIFY-1 + SIMPLIFY-2 (N=588)	MOMENTUM (N=195)
Age, median (range), years	66 (25-86)	68 (41-92)	67 (25-92)	71 (38-86)
Male sex, n (%)	244 (56.5)	93 (59.6)	337 (57.3)	123 (63.1)
White, n (%)	357 (82.6)	127 (81.4)	484 (82.3)	157 (80.5)
MF subtype, n (%)				
PMF	244 (56.5)	94 (60.3)	338 (57.5)	124 (63.6)
PET-MF	90 (20.8)	32 (20.5)	122 (20.7)	33 (16.9)
PPV-MF	98 (22.7)	30 (19.2)	128 (21.8)	38 (19.5)
Risk level, n (%)[b]				
Int-1	89 (20.6)	39 (25.0)	128 (21.8)	10 (5.1)
Int-2	143 (33.1)	90 (57.7)	233 (39.6)	112 (57.4)
High	200 (46.3)	27 (17.3)	227 (38.6)	69 (35.4)
Palpable spleen size, median (range), cm	12 (5-31)	12 (5-30)	NA	11 (2-39)
Platelet count, n (%)				
<100×10⁹/L	41 (9.5)	60 (44.2)	101 (17.2)	100 (51.3)
≥100 to ≤200×10⁹/L	129 (29.9)	49 (31.4)	178 (30.3)	50 (25.6)
>200×10⁹/L	262 (60.6)	36 (23.1)	298 (76.8)	42 (21.5)
Hb level, n (%)				
<8 g/dL	49 (11.3)	33 (21.2)	82 (13.9)	94 (48.2)
≥8 g/dL	382 (88.4)	123 (78.8)	505 (85.9)	100 (51.3)
Transfusion status, n (%)				
TI	299 (69.2)	51 (32.7)	350 (59.5)	27 (13.8)
TD	105 (24.3)	85 (54.5)	190 (32.3)	97 (49.7)
TR	28 (6.5)	20 (12.8)	48 (8.2)	71 (36.4)
JAK2V617F mutation status, n (%)				
Positive	266 (61.6)	107 (68.6)	373 (63.4)	148 (75.9)
Negative	114 (26.4)	43 (27.6)	157 (26.7)	40 (20.5)

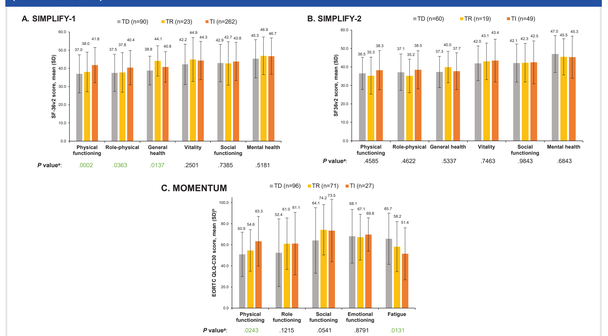
DIPSS, Dynamic International Prognostic Scoring System; Hb, hemoglobin; Int, intermediate; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; NA, not available; PET-MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera myelofibrosis; TD, transfusion dependent; TI, transfusion independent; TR, transfusion requiring.
[a]Some categories may not total 100% due to patients with missing data. [b]Per IPSS in SIMPLIFY-1 and SIMPLIFY-2 and per DIPSS in MOMENTUM.

Figure 1. SF-36v2 Scores at Baseline by Transfusion Status in SIMPLIFY-1 and SIMPLIFY-2



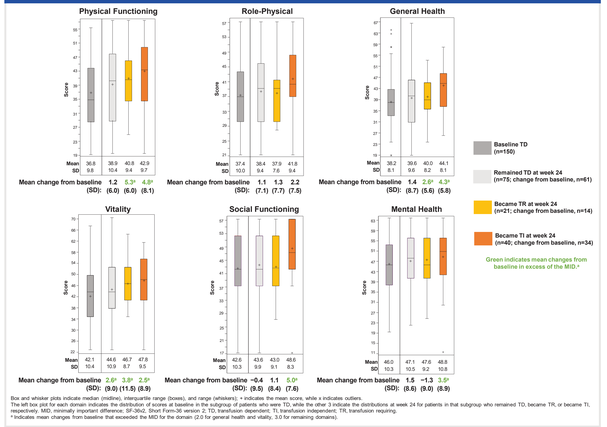
Box and whisker plots indicate median (midline), interquartile range (boxes), and range (whiskers); + indicates the mean score, while x indicates outliers.
SF-36v2, Short Form-36 version 2; TD, transfusion dependent; TI, transfusion independent; TR, transfusion requiring.

Figure 2. Scores at Baseline by Transfusion Status in SIMPLIFY-1 (SF-36v2), SIMPLIFY-2 (SF-36v2), and MOMENTUM (EORTC QLQ-C30)



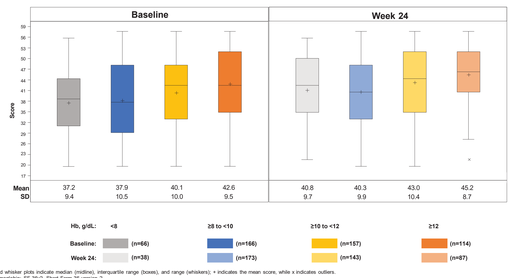
Values above each bar denote the mean.
ANOVA, analysis of variance; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; SF-36v2, Short Form-36 version 2; TD, transfusion dependent; TI, transfusion independent; TR, transfusion requiring.
*Parametric *P* value for between-group comparisons by ANOVA for continuous variables. † Higher scores indicate improvement for all 4 functioning domains but worsening for the fatigue domain.

Figure 3. SF-36v2 Scores at Baseline and Week 24 in the Baseline TD Patient Subgroup in SIMPLIFY-1 and SIMPLIFY-2



Box and whisker plots indicate median (midline), interquartile range (boxes), and range (whiskers); + indicates the mean score, while x indicates outliers.
The left box plot for each domain indicates the distribution of scores at baseline in the subgroup of patients who were TD, while the other 3 indicate the distributions at week 24 for patients in that subgroup who remained TD, became TR, or became TI, respectively. MID, minimally important difference; SF-36v2, Short Form-36 version 2; TD, transfusion dependent; TI, transfusion independent; TR, transfusion requiring.
*Indicates mean changes from baseline that exceeded the MID for the domain (2.0 for general health and vitality; 3.0 for remaining domains).

Figure 4. SF-36v2 Physical Functioning Domain Scores by Baseline Hb Levels in SIMPLIFY-1 and SIMPLIFY-2



Box and whisker plots indicate median (midline), interquartile range (boxes), and range (whiskers); + indicates the mean score, while x indicates outliers.
Hb, hemoglobin; SF-36v2, Short Form-36 version 2.

Limitations

- SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM were not designed to prospectively evaluate the impact of transfusion burden on quality of life; these analyses are post hoc, exploratory, and descriptive
  - These studies were not powered for statistical comparison between groups defined by transfusion status. No formal hypothesis testing was prespecified, and the analyses were not controlled for multiplicity
- The SF-36v2 and EORTC QLQ-C30 are generic PRO assessment instruments and do not specifically characterize the experience of patients with MF and/or those receiving transfusions; thus, changes specific to this disease state may not be captured
- A PRO assessment every 4 or 12 weeks may not be granular enough to fully capture changes in patient experience due to changes in transfusion status

Conclusions

- Lower HRQOL and functioning at baseline were reported in patients with MF in the phase 3 SIMPLIFY trials of momelotinib compared with the general population, highlighting the detrimental impact of MF on PROs regardless of transfusion status
- Lower mean scores across all SF-36v2 domains were reported in patients who were TD than in those who were TI, either at baseline or at week 24 in the SIMPLIFY trials, suggesting that transfusion dependence in MF has a further negative impact on multiple aspects of patient quality of life
- Associations between baseline transfusion status and PROs were observed in the physical functioning, role-physical, and general health SF-36v2 domains in SIMPLIFY-1
  - These results were supported by associations between transfusion status and the physical functioning and fatigue domains of the EORTC QLQ-C30 in MOMENTUM
- Greater improvement across the SF-36v2 physical functioning, role-physical, general health, social functioning, and mental health domains was reported in patients who were TD at baseline in the SIMPLIFY trials but became TI at week 24 compared with those who remained TD, supporting the importance of transfusion independent status for physical functioning, general health, mental health, and overall quality of life
  - Mean changes for patients who became TI exceeded the MID for groups with low baseline scores in all domains except role-physical (MID, 3.0; mean change, 2.2)[12]
- Hb levels at both baseline and week 24 in the SIMPLIFY trials may be incrementally associated with SF-36v2 physical functioning score, although the association was modest
- These analyses highlight the detrimental impact of transfusion dependence on several HRQOL domains, most notably those related to physical functioning and fatigue, and the benefits of achieving transfusion independence at week 24, supporting further research into the effects of transfusions and anemia on quality of life in MF

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