Clinical outcomes with momelotinib vs ruxolitinib in patients with myelofibrosis and anemia: subgroup analysis of SIMPLIFY-1

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Introduction

- Anemia is a key hallmark of myelofibrosis (MF); over one-third of patients are anemic at diagnosis, and the majority will become so over time because of advancing disease, treatment-related toxicity, or both[1-3]
- Treatment-related anemia is an adverse event (AE) associated with some approved Janus kinase (JAK) inhibitors such as ruxolitinib and fedratinib and may be managed through dose reductions; however, this approach does not directly address the underlying pathophysiology of anemia in MF and may also compromise clinical efficacy[2,4]
- While hemoglobin (Hb) levels indicative of red blood cell (RBC) transfusion need vary by clinician and institution, current guidelines recommend treatment for anemia at levels <10 g/dL; however, even patients with mild anemia (Hb ≥10 g/dL to less than the lower limit of normal) may benefit from treatment[5-9]
- The JAK1, JAK2, activin A receptor type 1 (ACVR1) inhibitor momelotinib has demonstrated consistent anemia benefits, including increased transfusion independence (TI) rates and reduced transfusion burden at week 24, as well as spleen and symptom benefits across three phase 3 trials in patients with myelofibrosis[10-12]
  - Although the phase 3 MOMENTUM study in JAK inhibitor–experienced patients with MF enrolled only those with baseline Hb levels <10 g/dL,[10] outcomes with momelotinib in JAK inhibitor–naive patients with MF and anemia have not been comprehensively described

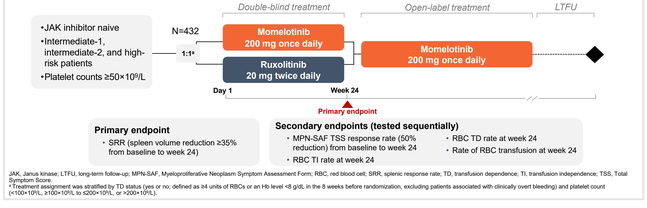
Objective

- To evaluate the efficacy and safety of momelotinib vs ruxolitinib in patients with JAK inhibitor–naive MF and anemia in the phase 3 SIMPLIFY-1 trial

Methods

- SIMPLIFY-1 was a randomized, double-blind, phase 3 trial of momelotinib vs ruxolitinib in adult patients with high-risk, intermediate-2–risk, or symptomatic (splenomegaly, hepatomegaly, or anemia) intermediate-1–risk (per International Prognostic Scoring System criteria) primary, post–polycythemia vera, or post–essential thrombocythemia MF not previously treated with a JAK inhibitor (**Figure 1**)[12]
  - No specific Hb levels were required for study enrollment
- The primary endpoint (noninferiority) was splenic response rate (SRR; defined as spleen volume reduction ≥35% from baseline) at week 24[12]
  - Secondary endpoints at week 24 included modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Total Symptom Score (TSS) response rate (≥50% reduction) and TI rate (zero RBC units transfused and no Hb levels <8 g/dL in the last 12 weeks before week 24)[12]
- Patient subgroups by baseline Hb level were defined post hoc as <10 g/dL or <12 g/dL, and efficacy and safety are summarized descriptively

Figure 1. Study Design (SIMPLIFY-1)[12]



JAK, Janus kinase; LTFU, long-term follow-up; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; RBC, red blood cell; SRR, splenic response rate; TD, transfusion dependence; TI, transfusion independence; TSS, Total Symptom Score.
* Treatment assignment was stratified by TD status (yes or no; defined as ≥4 units of RBCs or an Hb level <8 g/dL in the 8 weeks before randomization, excluding patients associated with clinically overt bleeding) and platelet count (<100×10⁹/L, ≥100×10⁹/L to ≤200×10⁹/L, or >200×10⁹/L).

Results

- The subgroup with Hb levels <10 g/dL at baseline included 180 patients (42%), while the subgroup with Hb levels <12 g/dL at baseline included 322 patients (75%) (**Table 1**)
  - As expected, fewer patients in the anemia subgroups vs the intent-to-treat (ITT) population were transfusion independent at baseline: 68% with momelotinib vs 70% with ruxolitinib in the ITT population,[12] 29% vs 43% in the <10 g/dL subgroup, and 57% vs 60% in the <12 g/dL subgroup
- In the subgroup with baseline Hb levels <10 g/dL, the mean daily dose of momelotinib through week 24 was 186.2 mg (standard deviation [SD], 25.1), 93% of the 200-mg daily starting dose; the mean daily dose of ruxolitinib through week 24 was 26.2 mg (SD, 11.6), 66% of the 20-mg twice-daily maximum starting dose

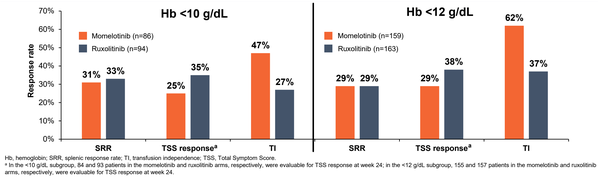
Table 1. Baseline Characteristics in Anemia Subgroups

	Hb <10 g/dL		Hb <12 g/dL	
Key baseline characteristics	**Momelotinib (n=86)**	**Ruxolitinib (n=94)**	**Momelotinib (n=159)**	**Ruxolitinib (n=163)**
Age, mean (SD), years	68.5 (9.0)	65.9 (9.1)	66.5 (10.1)	65.1 (10.3)
Male, n (%)	50 (58)	56 (60)	88 (55)	89 (55)
MF subtype, n (%)				
PMF	59 (69)	54 (57)	103 (65)	94 (58)
PPV-MF	11 (13)	12 (13)	24 (15)	28 (17)
PET-MF	16 (19)	28 (30)	32 (20)	41 (25)
Time since MF diagnosis, mean (SD), years	3.2 (3.9)	3.1 (4.4)	3.6 (4.6)	3.2 (4.2)
IPSS risk category, n (%)				
Intermediate-1	2 (2)	4 (4)	22 (14)	20 (12)
Intermediate-2	26 (30)	20 (21)	57 (36)	45 (28)
High	58 (67)	70 (74)	80 (50)	98 (60)
TSS, mean (SD)	19.0 (13.7)	18.1 (11.9)	19.0 (13.0)	17.8 (11.4)
Hb level, mean (SD), g/dL	8.6 (1.0)	8.7 (1.0)	9.6 (1.4)	9.6 (1.4)
Platelet count, mean (SD), ×10⁹/L	229.3 (155.9)	292.3 (323.2)	268.8 (172.4)	300.1 (277.2)
Platelet count <100×10⁹/L, n (%)	13 (15)	13 (14)	15 (9)	18 (11)
TI, n (%)[a]	25 (29)	41 (44)	91 (57)	98 (60)
TD, n (%)[b]	49 (57)	43 (46)	53 (33)	52 (32)

Hb, hemoglobin; IPSS, International Prognostic Scoring System; MF, myelofibrosis; PET-MF, post–essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis; RBC, red blood cell; SD, standard deviation; TD, transfusion dependence; TI, transfusion independence; TSS, Total Symptom Score.
[a] Defined as zero RBC units transfused and no Hb levels <8 g/dL in the previous 12 weeks. [b] Defined as ≥4 RBC units transfused or an Hb level <8 g/dL in the previous 8 weeks.

- As previously reported in the ITT population, SRRs with momelotinib vs ruxolitinib at week 24 were 27% vs 29%, TSS response rates were 28% vs 42%, and TI rates were 67% vs 49%[12]
  - Spleen and symptom benefits at week 24 in the anemia subgroups were generally consistent with the ITT population (**Figure 2**)
  - As expected, TI rates at week 24 were lower in the anemia subgroups than in the ITT population, but the benefit with momelotinib vs ruxolitinib was numerically higher, particularly for the <12 g/dL subgroup (**Figure 2**)

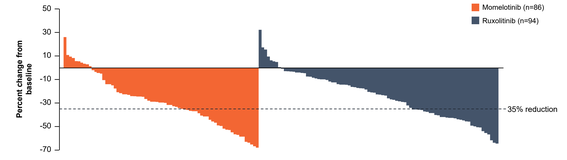
Figure 2. Key Efficacy Endpoints at Week 24



Hb, hemoglobin; SRR, splenic response rate; TI, transfusion independence; TSS, Total Symptom Score.
[a] In the <10 g/dL subgroup, 84 and 93 patients in the momelotinib and ruxolitinib arms, respectively, were evaluable for TSS response at week 24; in the <12 g/dL subgroup, 155 and 157 patients in the momelotinib and ruxolitinib arms, respectively, were evaluable for TSS response at week 24.

- Because the <12 g/dL subgroup included the majority of the ITT population and week 24 response rates were comparable, additional efficacy analyses were conducted to more thoroughly characterize the <10 g/dL subgroup
- Most patients in the <10 g/dL subgroup who were treated with either momelotinib or ruxolitinib had reduction in spleen volume compared with baseline at week 24 (**Figure 3**)

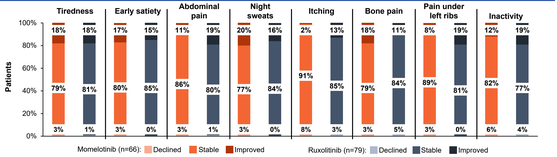
Figure 3. SRR at Week 24 in the Hb <10 g/dL Subgroup



Hb, hemoglobin; SRR, splenic response rate.

- Although TSS response rates were higher with ruxolitinib than momelotinib in both the ITT population[12] and anemia subgroups, previous individual item analyses in the ITT population demonstrated that rates of individual symptom improvement or stability were similar[13]
- In the <10 g/dL subgroup, improvement or stability in individual symptoms was also similar between arms and observed in >90% of patients (**Figure 4**)

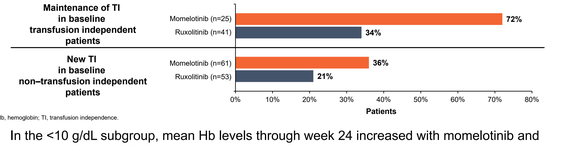
Figure 4. Individual Symptom Improvement in the Hb <10 g/dL Subgroup



The MPN-SAF TSS is an 8-item, patient-reported outcome measure used to assess the worst incidence in the last 24 hours of MPN symptoms. Each item is measured from 0 to 10, with 0 corresponding to "absent" and 10 corresponding to "worst imaginable." "Declined" is defined by an increase of ≥3, "improved" by a decrease of ≥3, and "stable" by a change of ≤2.
Hb, hemoglobin; MPN, myeloproliferative neoplasm; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, Total Symptom Score.

- Among patients who were transfusion independent at week 24 in the <10 g/dL subgroup, momelotinib was associated with numerically higher rates of both maintenance in patients who were transfusion independent at baseline and achievement of new responses in those who were not (**Figure 5**)

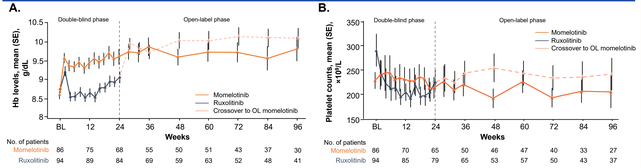
Figure 5. TI at Week 24 in the Hb <10 g/dL Subgroup



Hb, hemoglobin; TI, transfusion independence.

- In the <10 g/dL subgroup, mean Hb levels through week 24 increased with momelotinib and decreased with ruxolitinib before plateauing; during the open-label phase, mean Hb levels improved rapidly in patients who crossed over from the ruxolitinib arm and remained stable with momelotinib (**Figure 6A**)
  - Mean platelet counts remained stable with momelotinib over time but decreased with ruxolitinib (**Figure 6B**)

Figure 6. Mean Hb Levels (A) and Platelet Counts (B) Over Time in the Hb <10 g/dL Subgroup[a]



BL, baseline; Hb, hemoglobin; OL, open label; SE, standard error.
[a] Figure depicts results through week 96 for illustrative purposes, although the study continued beyond this time point.

- During the double-blind treatment period, the safety profile of momelotinib was similar across anemia subgroups and generally consistent with that of the ITT population[12] (**Table 2**)

Table 2. Safety Summary in Anemia Subgroups

	Hb <10 g/dL				Hb <12 g/dL			
	Momelotinib (n=85)		Ruxolitinib (n=95)		Momelotinib (n=159)		Ruxolitinib (n=163)	
TEAEs, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any TEAE	80 (94)	40 (47)	92 (97)	53 (56)	152 (96)	64 (40)	157 (96)	83 (51)
Fatal TEAE	2 (2)	–	4 (4)	–	6 (4)	–	6 (4)	–
Hematologic TEAEs occurring in >5% of patients in the momelotinib arm (Hb <10 g/dL subgroup)								
Thrombocytopenia	18 (21)	9 (11)	32 (34)	6 (6)	34 (21)	13 (8)	53 (33)	9 (6)
Anemia	14 (16)	10 (12)	36 (38)	26 (27)	27 (17)	12 (8)	67 (41)	44 (27)
Neutropenia	4 (5)	3 (4)	9 (9)	7 (7)	8 (5)	6 (4)	10 (6)	8 (5)
Nonhematologic TEAEs occurring in >10% of patients in the momelotinib arm (Hb <10 g/dL subgroup)								
Diarrhea	17 (20)	1 (1)	19 (20)	1 (1)	30 (19)	5 (3)	32 (20)	2 (1)
Nausea	17 (20)	1 (1)	3 (3)	1 (1)	25 (16)	1 (1)	8 (5)	1 (1)
Dizziness	15 (18)	0	10 (11)	1 (1)	28 (18)	0	16 (10)	1 (1)
Fatigue	13 (15)	0	11 (12)	0	23 (14)	1 (1)	20 (12)	2 (1)
Hypotension	12 (14)	2 (2)	0	0	15 (9)	2 (1)	1 (1)	0
Cough	11 (13)	0	9 (9)	0	16 (10)	0	15 (9)	0
Dyspnea	11 (13)	0	8 (8)	1 (1)	16 (10)	0	16 (10)	1 (1)
Abdominal pain	10 (12)	1 (1)	11 (12)	1 (1)	16 (10)	2 (1)	20 (12)	1 (1)
Constipation	10 (12)	0	6 (6)	0	15 (9)	0	13 (8)	0
Pain in extremity	10 (12)	0	5 (5)	0	12 (8)	0	14 (9)	0
Peripheral sensory neuropathy	10 (12)	0	5 (5)	0	16 (10)	0	10 (6)	1 (1)
Headache	9 (11)	0	15 (16)	0	21 (13)	0	34 (21)	0
Pyrexia	9 (11)	0	10 (11)	0	13 (8)	1 (1)	16 (10)	0

Safety analysis set included all patients who received ≥1 dose of treatment. For safety analyses, subgroups were defined by baseline Hb values in the safety data, which may not align with values in the efficacy data, resulting in minor differences in subgroup sizes. TEAEs are sorted based on the momelotinib arm of the <10 g/dL subgroup.
Hb, hemoglobin; TEAE, treatment-emergent adverse event.

Conclusions

- In the phase 3 SIMPLIFY-1 trial, spleen and symptom benefits with momelotinib vs ruxolitinib were generally consistent in patients with anemia (baseline Hb levels <10 or <12 g/dL) compared with the ITT population
- TI rates at week 24 in patients with anemia were nearly doubled with momelotinib vs ruxolitinib (eg, >1.7-times higher in the <10 g/dL subgroup, at 47% vs 27%), including higher rates of both maintenance of TI and achievement of new TI
- No new momelotinib safety signals were identified in patients with anemia, and rates of grade ≥3 hematologic treatment-emergent adverse events during the double-blind period were lower than those observed with ruxolitinib
- Overall, these descriptive analyses highlight the favorable benefit-risk profile of momelotinib in JAK inhibitor–naive patients with myelofibrosis and anemia, thus representing a potential treatment option for this population

Poster MPN-551

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