#TBD

Clinical Outcomes With Momelotinib vs Ruxolitinib in Patients With Myelofibrosis and Moderate Anemia: Subgroup Analysis of SIMPLIFY-1

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Introduction

- Anemia is a common and progressive clinical manifestation of myelofibrosis (MF), ranging in severity from mild to severe based on hemoglobin (Hb) levels[1-3]
- Hb levels of <10 g/dL are a negative prognostic indicator in MF risk assessments, and anemia of any severity is associated with negative impacts on survival, quality of life, and healthcare resource utilization; these burdens are compounded in patients who become red blood cell (RBC) transfusion dependent (TD)[4-9]
- Although dose reduction of myelosuppressive Janus kinase (JAK) inhibitors such as ruxolitinib and the addition of anemia supportive care may mitigate treatment-related cytopenias, these approaches do not address the underlying mechanism of cytopenias in MF and may lead to suboptimal outcomes[4,10]
- Momelotinib is a JAK1, JAK2, and activin A receptor type 1 inhibitor approved in several regions for the treatment of patients with MF and anemia[11,12]
- Clinical benefits with momelotinib vs ruxolitinib have been previously characterized only in patients with moderate (Hb ≥8 to <10 g/dL) and severe (Hb <8 g/dL) anemia collectively[3]; thus, results specific to patients with moderate anemia have not been reported
- Here we describe the efficacy and safety of momelotinib vs ruxolitinib in JAK inhibitor–naive patients with MF and moderate anemia in the phase 3 SIMPLIFY-1 trial

Methods

Efficacy

- SIMPLIFY-1 was a randomized, double-blind, phase 3 trial of momelotinib vs ruxolitinib in adult JAK inhibitor–naive patients with intermediate- or high-risk primary or secondary MF[3,13]
  - Patients were randomized to either momelotinib 200 mg once daily or ruxolitinib 20 mg twice daily (or modified as per label)
  - The randomized period was 24 weeks, after which patients in the ruxolitinib arm could cross over to receive open-label momelotinib
- The focus of this analysis was the moderate anemia subgroup from SIMPLIFY-1, defined post hoc as patients with baseline Hb levels of ≥8 to <10 g/dL[3]

Severe anemia	Moderate anemia
n=49 (11.3%) (Hb <8 g/dL)	n=131 (30.3%) (Hb ≥8 to <10 g/dL)
Mild anemia	**No anemia**
n=142 (32.9%) (Hb ≥10 to <12 g/dL)	n=109 (25.2%) (Hb ≥12 g/dL)

Efficacy and Safety Analyses

- Efficacy and safety were summarized descriptively, including:
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  - Splenic response rate (SRR): defined as spleen volume reduction of ≥35% from baseline at week 24
  - Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Total Symptom Score (TSS) response rate: defined as a ≥50% reduction from baseline at week 24
  - Transfusion-independent (TI) rate (prespecified terminal 12-week definition): defined as no transfusions and no Hb levels of <8 g/dL in the last 12 weeks before week 24
    - TI rate by week 24 was also assessed via a rolling 12-week definition: no transfusions and no Hb levels of <8 g/dL during any 12-week period through week 24

Results

Baseline Characteristics

- The moderate anemia subgroup included 58 of 215 patients (27%) in the momelotinib arm and 73 of 217 (34%) in the ruxolitinib arm (**Table 1**)
  - At baseline before treatment, fewer patients in the momelotinib arm (43%) vs ruxolitinib arm (56%) were TI (**Table 1**)

Table 1: **Baseline characteristics in the moderate anemia subgroup**

Characteristic	Momelotinib (n=58)	Ruxolitinib (n=73)
Age, mean (SD), years	68.3 (9.2)	65.7 (9.7)
Male, n (%)	31 (53)	42 (58)
MF subtype, n (%)		
PMF	40 (69)	44 (60)
PPV-MF	5 (9)	8 (11)
PET-MF	13 (22)	21 (29)
Time since MF diagnosis, mean (SD), years	3.2 (4.3)	3.3 (4.8)
IPSS risk category, n (%)		
Intermediate-1	2 (3)	3 (4)
Intermediate-2	20 (34)	17 (23)
High	36 (62)	53 (73)
TSS, mean (SD)	19.4 (14.2)	17.4 (11.5)
Hb level, mean (SD), g/dL	9.1 (0.6)	9.2 (0.6)
Platelet count, mean (SD), ×10⁹/L	249.4 (174.6)	285.2 (188.1)
Platelet count <100×10⁹/L, n (%)	7 (12)	8 (11)
TI, n (%)[a]	25 (43)	41 (56)
TD, n (%)[b]	21 (36)	22 (30)

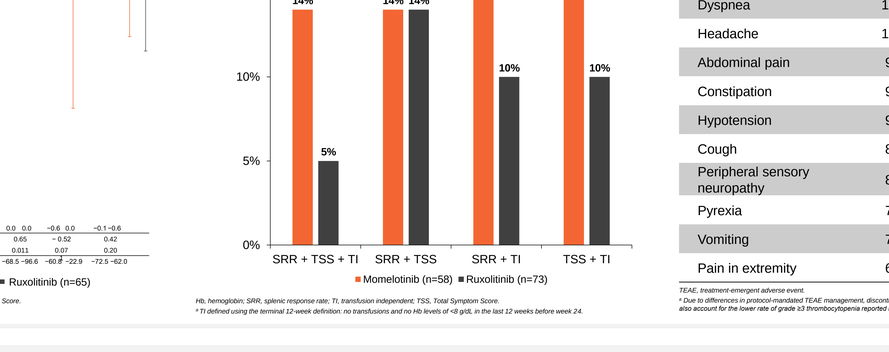
Hb, hemoglobin; IPSS, International Prognostic Scoring System; MF, myelofibrosis; PET, post–essential thrombocythemia; PMF, primary myelofibrosis; PPV, post–polycythemia vera; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independent; TSS, Total Symptom Score.

[a] TI was defined as no transfusions and no Hb levels of <8 g/dL in the 12 weeks before randomization. [b] TD was defined as ≥4 units of RBC transfusions or an Hb level of <8 g/dL in the 8 weeks before randomization.

Dosing

- Most patients initiated momelotinib at the full daily dose (200 mg), and >80% remained on full or near-full dose through week 24 (**Figure 1A**); the mean (SD) daily dose at week 24 was 187.3 (36.3) mg, 95% of the mean starting dose (197.5 mg)
- In contrast, while 84% of patients initiated ruxolitinib at >20 mg daily, including approximately 50% at >30 mg daily, the percentage of patients receiving lower doses increased over time, which may reflect dose reductions due to anemia and/or thrombocytopenia per prescribing information; by week 24, 43% of patients were receiving ≤20 mg daily (**Figure 1B**), and the mean (SD) daily dose was 27.6 (13.0) mg, 86% of the mean starting dose (32.1 mg)

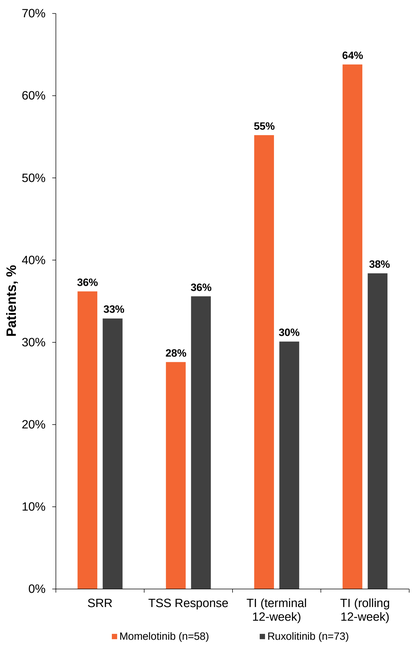
Figure 1: **Dose intensity of momelotinib (A) and ruxolitinib (B) in the moderate anemia subgroup**



Efficacy

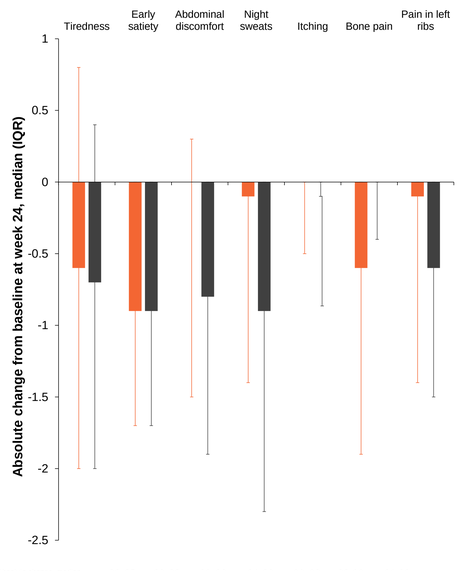
- Similar to results previously reported for the moderate and severe anemia subgroup (Hb <10-g/dL),[3] spleen and symptom results in the moderate anemia subgroup were consistent with the intent-to-treat (ITT) analysis (Figure 2)[13]
  - Improvements in individual symptom items at week 24 were similar between the momelotinib and ruxolitinib arms (**Figure 3**)
  - A longitudinal mixed-effects model for repeated measures found no significant least-squares mean difference in absolute change from baseline between arms for all items except itching, which was the least prevalent symptom at baseline[14]
- Week 24 TI rates were numerically higher, nearly doubling, with momelotinib vs ruxolitinib (**Figure 2**), and dual or triple responses involving TI were also more common with momelotinib (**Figure 4** for terminal 12-week TI; **QR code** for rolling 12-week TI)

Figure 2: **Key efficacy endpoints in patients with moderate anemia**



SRR, splenic response rate; TI, transfusion-independent; TSS, Total Symptom Score.

Figure 3: **Individual item analyses of TSS in patients with moderate anemia**

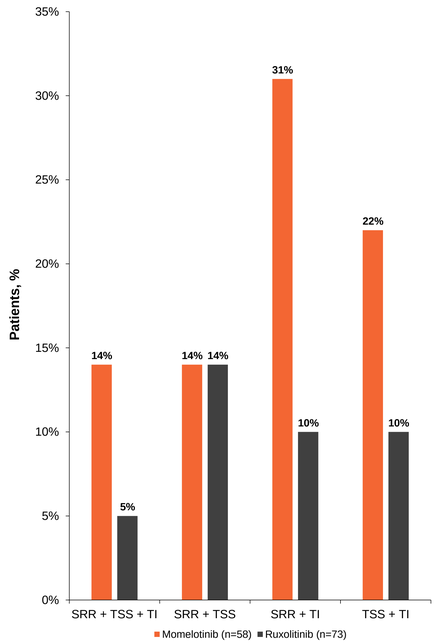


	Tiredness	Early satiety	Abdominal discomfort	Night sweats	Itching	Bone pain	Pain in left ribs
Absolute change, median	−0.6	−0.7	−0.9	−0.9	0.0	−0.8	−0.1	−0.9	0.0	0.0	−0.6	0.0	−0.1	−0.6
LS mean difference[a]	0.43		0.25		0.50		0.50		0.65		−0.52		0.42	
P value	0.20		0.49		0.11		0.065		0.011		0.07		0.20	
Percent change, median	−23.0	−27.2	−52.2	−46.2	−40.3	−47.1	−66.6	−86.3	−68.5	−96.6	−60.8	−22.9	−72.5	−62.0

LS, least squares; MMRM, mixed-effects model for repeated measures; TSS, Total Symptom Score.

[a] LS mean difference from an MMRM for absolute change from baseline at week 24.

Figure 4: **Dual/triple endpoint responder analyses in the moderate anemia subgroup: terminal 12-weeka**



Hb, hemoglobin; SRR, splenic response rate; TI, transfusion independent; TSS, Total Symptom Score.

[a] TI defined using the terminal 12-week definition: no transfusions and no Hb levels of <8 g/dL in the last 12 weeks before week 24.

Safety

- The safety profiles of both momelotinib and ruxolitinib were consistent with that observed in the overall safety population, and no new momelotinib safety signals were identified in the moderate anemia subgroup (**Table 2**)

Table 2: **Safety in patients with moderate anemia**

TEAEs, n (%)	Momelotinib (n=58) Any grade	Momelotinib (n=58) Grade ≥3	Ruxolitinib (n=73) Any grade	Ruxolitinib (n=73) Grade ≥3
Any TEAE	55 (95)	25 (43)	71 (97)	39 (53)
Serious TEAEs	15 (26)		17 (23)	
TEAE leading to discontinuation[a]	10 (17)		1 (1)	
TEAE leading to dose reduction[a]	12 (21)		27 (37)	
Hematologic TEAEs (occurring in ≥5% of momelotinib-treated patients)				
Thrombocytopenia	13 (22)	6 (10)	22 (30)	3 (4)[a]
Anemia	9 (16)	5 (9)	29 (40)	21 (29)
Neutropenia	3 (5)	2 (3)	8 (11)	6 (8)
Nonhematologic TEAEs (occurring in ≥10% of momelotinib-treated patients)				
Diarrhea	16 (28)	2 (3)	14 (19)	1 (1)
Nausea	14 (24)	1 (2)	3 (4)	1 (1)
Dizziness	11 (19)	0	7 (10)	1 (1)
Fatigue	11 (19)	0	10 (14)	0
Dyspnea	10 (17)	0	7 (10)	0
Headache	10 (17)	0	13 (18)	0
Abdominal pain	9 (16)	2 (3)	8 (11)	1 (1)
Constipation	9 (16)	0	5 (7)	0
Hypotension	9 (16)	1 (2)	0	0
Cough	8 (14)	0	7 (10)	0
Peripheral sensory neuropathy	8 (14)	0	5 (7)	0
Pyrexia	7 (12)	1 (2)	8 (11)	0
Vomiting	7 (12)	1 (2)	4 (5)	0
Pain in extremity	6 (10)	0	4 (5)	0

TEAE, treatment-emergent adverse event.

[a] Due to differences in protocol-mandated TEAE management, discontinuations of momelotinib and dose reductions of ruxolitinib were more common. Ruxolitinib dose reduction may also account for the lower rate of grade ≥3 thrombocytopenia reported in patients treated with ruxolitinib vs momelotinib (3% vs 10%).

Conclusions

- In the phase 3 SIMPLIFY-1 trial, spleen and symptom benefits with momelotinib vs ruxolitinib in patients with moderate anemia were generally consistent with the ITT population
- Anemia-related benefits, including week 24 TI rates, were greater with momelotinib vs ruxolitinib in the moderate anemia subgroup, including nearly double the percentage of patients who achieved TI at week 24 by the prespecified definition
- These results confirm and expand upon previous analyses in patients with moderate to severe anemia, demonstrating that momelotinib's benefits are not limited to patients with severe anemia or transfusion dependence and that it should be considered earlier in patients with anemia
- Overall, these descriptive analyses highlight how momelotinib offers a favorable benefit-risk profile in JAK inhibitor–naive patients with MF and moderate anemia and may provide more comprehensive efficacy vs ruxolitinib in this subpopulation

Abbreviations

Hb, hemoglobin; IPSS, International Prognostic Scoring System; ITT, intent to treat; JAK, Janus kinase; LS, least squares; MF, myelofibrosis; MMRM, mixed-effects model for repeated measures; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; PET, post–essential thrombocythemia; PMF, primary myelofibrosis; PPV, post–polycythemia vera; RBC, red blood cell; SRR, splenic response rate; TD, transfusion dependent; TEAE, treatment-emergent adverse event; TI, transfusion independent; TR, transfusion requiring; TSS, Total Symptom Score.

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