Longitudinal Assessment of Transfusion Intensity in Patients With JAK Inhibitor–Naive or –Experienced Myelofibrosis Treated With Momelotinib in the Phase 3 SIMPLIFY-1 and MOMENTUM Trials

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Introduction

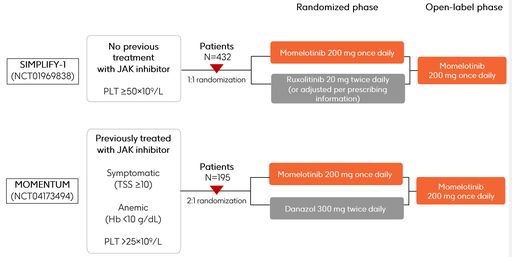
- Anemia is a cardinal feature of myelofibrosis (MF), along with splenomegaly and constitutional symptoms[1,2]
- Red blood cell (RBC) transfusions, which are often used to manage anemia in patients with MF, are a negative prognostic factor for overall survival and are associated with diminished quality of life and increased health care–related economic burden[2-7]
- Momelotinib is a Janus kinase (JAK) 1/JAK2/activin A receptor type 1 inhibitor recently approved by the US Food and Drug Administration for the treatment of patients with MF and anemia[8]
  - Momelotinib has demonstrated clinically meaningful and durable improvements from baseline in anemia, splenomegaly, and symptoms across 3 phase 3 trials[9-12]
  - Prespecified anemia endpoints in momelotinib phase 3 studies prioritized achievement of a strict transfusion independence response, defined as no transfusions for ≥12 weeks immediately before the end of week 24, with all hemoglobin (Hb) levels ≥8 g/dL[9-11]
- Longitudinal analysis of transfusion intensity (units per 28 days) in a phase 2 trial of momelotinib in patients with transfusion-dependent MF demonstrated a reduction in transfusion burden in most (85%) patients despite a transfusion independence response rate of 34% at week 24 in the trial, highlighting that the binary endpoint may not fully characterize the treatment effect on overall RBC transfusion burden in patients with MF[13,14]

Objective

- The aim of the current study was to characterize the impact of momelotinib and comparators on transfusion burden in JAK inhibitor–naive or –experienced patients with MF from the phase 3 SIMPLIFY-1 and MOMENTUM trials (**Figure 1**)

Methods

Figure 1. SIMPLIFY-1[9] and MOMENTUM[11] Study Designs



Transfusion Intensity Analyses

- Time-dependent transfusion burden (number of RBC units administered per 28 days) was tracked for every patient, with corresponding mean baseline-period (84 days prior to enrollment) and treatment-period (up to ≈168 days on study treatment for most patients) intensities per patient
  - Patients who received <14 days of study treatment were excluded from these analyses
- For visualization of shifts in RBC transfusion burden on treatment, patients were grouped jointly based on baseline- and treatment-period intensities per 28 days into ordinal bins based on number of RBC units transfused: exactly 0 units, >0 to 1 unit, >1 to 2 units, >2 to 3 units, >3 to 4 units, and >4 units
- Summary measures for the total study patient population, including mean change in RBC transfusion intensity from baseline, were also calculated

Results

- Baseline characteristics in SIMPLIFY-1 and MOMENTUM are summarized in **Table 1**[9,11]

Table 1. Baseline Characteristics[9,11]

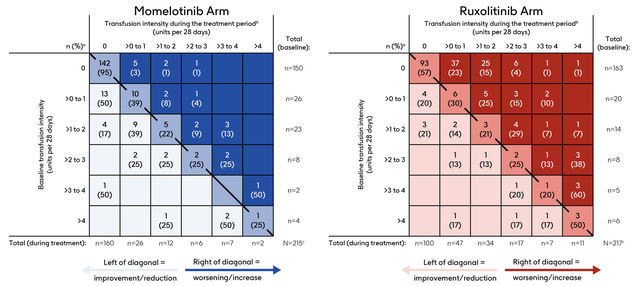
	SIMPLIFY-1		MOMENTUM	
	Momelotinib n=215	Ruxolitinib n=217	Momelotinib n=130	Danazol n=65
Age, mean (SD), y	65.0 (10.7)	64.4 (10.6)	69.9 (8.2)	71.5 (7.0)
Male, n (%)	124 (58)	120 (55)	79 (61)	44 (68)
White, n (%)	179 (83)	178 (82)	107 (82)	50 (77)
MF subtype, n (%)				
PMF	128 (60)	116 (53)	78 (60)	46 (71)
PPV-MF	48 (22)	50 (23)	27 (21)	11 (17)
PET-MF	39 (18)	51 (24)	25 (19)	8 (12)
IPSS/DIPSS risk category, n (%)[a]				
Intermediate-1	46 (21)	43 (20)	7 (5)	3 (5)
Intermediate-2	76 (35)	67 (31)	72 (55)	40 (62)
High	93 (43)	107 (49)	50 (38)	19 (29)
Missing	0	0	1 (1)	3 (5)
***JAK2 V617F* mutation positive, n (%)**	125 (58)[b]	141 (65)[b]	97 (75)[c]	51 (78)[c]
Previous JAK inhibitor duration, mean (SD), wk	NA	NA	138.5 (123.0)	124.8 (120.0)
TSS, mean (SD)	19.4 (13.2)	17.9 (11.5)	28.0 (13.8)	25.7 (12.8)
Hb level, mean (SD), g/dL	10.6 (2.1)	10.7 (2.4)	8.1 (1.1)	7.9 (0.8)
Hb level ≥8 g/dL, n (%)	187 (87)	195 (90)	67 (52)	33 (51)
Transfusion independent, n (%)	147 (68)	152 (70)	17 (13)	10 (15)
Transfusion dependent, n (%)	53 (25)	52 (24)	63 (48)	34 (52)

[a] IPSS and DIPSS were used in SIMPLIFY-1 and MOMENTUM, respectively. [b] In total, 29 patients (13%) randomized to momelotinib and 23 patients (11%) randomized to ruxolitinib had unknown JAK mutation status. [c] In total, 5 patients (4%) randomized to momelotinib and 2 patients (3%) randomized to danazol had unknown JAK mutation status.

SIMPLIFY-1

- 150 of 213 evaluable patients (70%) in the momelotinib arm and 163 of 216 evaluable patients (75%) in the ruxolitinib arm required zero units of RBC transfusion per 28 days at baseline (**Figure 2**)
  - Momelotinib led to better maintenance of zero RBC transfusion requirement, with nearly all these patients maintaining zero RBC transfusion requirement (142 of 150 [95%]), when compared with ruxolitinib (93 of 163 [57%])
- Using ordinal bins, 87% of patients in the momelotinib arm maintained (144 [67%]) or experienced improved (41 [19%]) RBC transfusion intensity during randomized treatment compared with baseline vs 54% in the ruxolitinib arm (maintained, 94 [44%]; improved, 23 [11%]; **Figure 2**; **Table 2**)
  - In the open-label treatment phase, the majority of patients (81%) switching from ruxolitinib to momelotinib experienced improved or maintained RBC transfusion intensity vs baseline
- Mean RBC transfusion burden per 28 days decreased by 0.10 units (SD, 0.7) from baseline to randomized treatment in the momelotinib arm and increased by 0.39 units (SD, 1.0) in the ruxolitinib arm (**Table 2**)
  - Similar trends were observed in RBC transfusion burden when assessed in the subset of patients who were not transfusion independent at baseline
- Analysis of change from baseline in mean RBC transfusion burden by month was consistent with increased RBC transfusion burden at each time point in the ruxolitinib arm and a decrease in transfusion burden at each time point in the momelotinib arm (**Figure 3**)

Figure 2. SIMPLIFY-1: Shift From Baseline in Transfusion Intensity During the Randomized Phase by Treatment



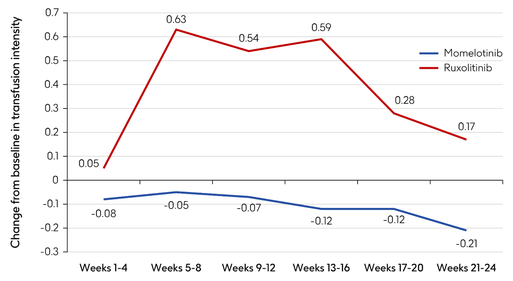
[a] Percentage of baseline transfusion intensity category. [b] Rounding was applied to place patients in each ordinal bin/category; as a result, changes in intensity during treatment that did not result in a change in ordinal bin from baseline may not be apparent. [c] Two patients in the momelotinib arm and 1 patient in the ruxolitinib arm were not evaluable for transfusion intensity (evaluable populations, n=213 and n=216, respectively).

Table 2. SIMPLIFY-1: Change From Baseline in Transfusion Intensity

	Momelotinib n=215	Ruxolitinib n=217
Randomized phase (ITT)		
Transfusion intensity status, n (%)[a,b]	n=214[c]	n=216[c]
Improved from baseline	41 (19)	23 (11)
No change from baseline	144 (67)	94 (44)
Worsened from baseline	28 (13)	99 (46)
Change from baseline in transfusion intensity, mean (SD)	−0.10 (0.7)	0.39 (1.0)
Non–transfusion independent at baseline		
Transfusion intensity status, n (%)[a]	n=68	n=65
Improved from baseline	41 (60)	23 (35)
No change from baseline	5 (7)	4 (6)
Worsened from baseline	22 (32)	38 (58)
Change from baseline in transfusion intensity, mean (SD)	−0.37 (1.2)	0.29 (1.5)
Open-label phase (ITT)	**Momelotinib→momelotinib**	**Ruxolitinib→momelotinib**
Transfusion intensity status, n (%)[a,b]	n=171	n=197
Improved from baseline	34 (20)	35 (18)
No change from baseline	109 (64)	125 (63)
Worsened from baseline	27 (16)	37 (19)
Change from baseline in transfusion intensity, mean (SD)	−0.07 (0.8)	−0.03 (1.0)

[a] Transfusion intensity is calculated as the number of RBC units transfused divided by the number of days in an observation period and multiplied by 28. Improved means any decrease from the baseline RBC units transfused, and worsened means any increase from the baseline RBC units transfused; no change means neither improved nor worsened. [b] One patient in the momelotinib arm had insufficient transfusion intensity information. [c] One patient in each arm did not receive any treatment at all and are excluded from descriptive analysis of transfusion intensity status.

Figure 3. SIMPLIFY-1: Mean Change From Baseline in Transfusion Intensity by Month During Randomized Treatment (ITT)



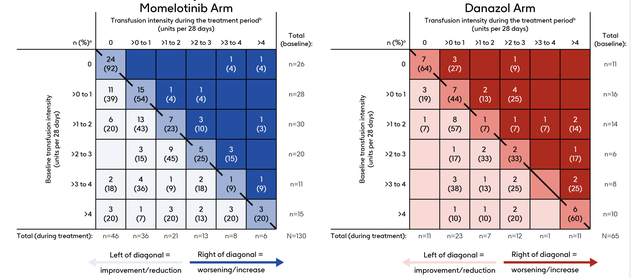
MOMENTUM

- In MOMENTUM, most patients had some transfusion requirement at baseline, with 26 of 130 (20%) in the momelotinib arm and 11 of 65 (17%) in the danazol arm requiring zero units of RBC transfusion per 28 days (**Figure 4**)
  - During randomized treatment, a higher proportion of patients in the momelotinib arm (46 of 130 [35%]) required zero units of RBC transfusion vs the danazol arm (11 of 65 [17%]), including a higher proportion of those who had zero RBC transfusion requirement at baseline and maintained the requirement during randomized treatment (92% vs 64%)
- When assessed using ordinal bins, 85% of patients in the momelotinib arm maintained (25 [19%]) or experienced improved (85 [65%]) RBC transfusion intensity compared with baseline vs 63% in the danazol arm (maintained, 7 [11%]; improved, 34 [52%]; **Figure 4**; **Table 3**)
- The mean RBC transfusion burden per 28 days decreased by 0.86 units (SD, 1.8) from baseline to randomized treatment in the momelotinib arm and decreased by 0.28 units (SD, 1.6) in the danazol arm (**Table 3**)
  - Similar changes were observed for RBC transfusion burden when assessed in the subset of patients who were not transfusion independent at baseline

Conclusion

- Momelotinib was associated with improvements in RBC transfusion intensity and zero RBC transfusion status vs ruxolitinib in JAK inhibitor–naive patients with MF (SIMPLIFY-1)
  - Momelotinib treatment was associated with a reduction in mean RBC transfusion burden, while ruxolitinib was associated with increased mean RBC transfusion burden
  - Most patients who crossed over from ruxolitinib to momelotinib during the open-label phase experienced improved or maintained RBC transfusion burden vs baseline
  - These data suggest that increases in transfusion burden were delayed or prevented in patients treated with momelotinib compared with those treated with ruxolitinib
- In JAK inhibitor–experienced patients with MF (MOMENTUM), momelotinib showed greater reduction in RBC transfusion burden from baseline vs danazol, which is a standard anemia therapy
- Across both trials, ≥85% of patients treated with momelotinib either maintained or experienced improved transfusion intensity compared with baseline, highlighting that momelotinib provides consistent anemia benefit for the majority of patients

Figure 4. MOMENTUM: Shift From Baseline in Transfusion Intensity During the Randomized Phase by Treatment



[a] Percentage of baseline transfusion intensity category. [b] Rounding was applied to place patients in each ordinal bin/category; as a result, changes in intensity during treatment that did not result in a change in ordinal bin from baseline may not be apparent.

Table 3. MOMENTUM: Change From Baseline in Transfusion Intensity

	Momelotinib n=130	Danazol n=65
Randomized phase (ITT)		
Transfusion intensity status, n (%)[a]	n=130	n=65
Improved from baseline	85 (65)	34 (52)
No change from baseline	25 (19)	7 (11)
Worsened from baseline	20 (15)	24 (37)
Change from baseline in transfusion intensity, mean (SD)	−0.86 (1.8)	−0.28 (1.6)
Non–transfusion independent at baseline		
Transfusion intensity status, n (%)[a]	n=113	n=55
Improved from baseline	85 (75)	34 (62)
No change from baseline	9 (8)	0
Worsened from baseline	19 (17)	21 (38)
Change from baseline in transfusion intensity, mean (SD)	−1.03 (1.8)	−0.39 (1.7)
Open-label phase (ITT)	**Momelotinib→momelotinib**	**Danazol→momelotinib**
Transfusion intensity status, n (%)	n=93	n=41
Improved from baseline	51 (55)	20 (49)
No change from baseline	19 (20)	8 (20)
Worsened from baseline	23 (25)	13 (32)
Change from baseline in transfusion intensity, mean (SD)	−0.73 (1.6)	−0.44 (1.7)

[a] Transfusion intensity is calculated as the number of RBC units transfused divided by the number of days in an observation period and multiplied by 28. Improved means any decrease from the baseline RBC units transfused, and worsened means any increase from the baseline RBC units transfused; no change means neither improved nor worsened.

Abbreviations

DIPSS, Dynamic International Prognostic Scoring System; Hb, hemoglobin; ITT, intent to treat; JAK, Janus kinase; MF, myelofibrosis; PET-MF, post–essential thrombocythemia myelofibrosis; PLT, platelet; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis; RBC, red blood cell; TSS, Total Symptom Score.

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