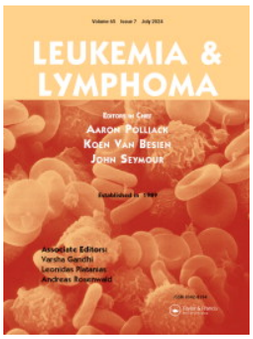

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Momelotinib vs. ruxolitinib in myelofibrosis patient subgroups by baseline hemoglobin levels in the SIMPLIFY-1 trial

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ABSTRACT

A key hallmark of myelofibrosis is anemia, which ranges from mild to severe based on hemoglobin levels. To more clearly define outcomes with the Janus kinase (JAK) 1/JAK2/activin A receptor type 1 inhibitor momelotinib by anemia severity, we performed a descriptive post hoc exploratory analysis of the double-blind, randomized, phase 3 SIMPLIFY-1 study (NCT01969838; *N* = 432, JAK inhibitor naive, momelotinib vs. ruxolitinib); subgroups were defined by baseline hemoglobin: <10 (moderate/severe), ≥10 to <12 (mild), or ≥12 g/dL (nonanemic). Spleen and symptom results were generally consistent with those previously reported for the intent-to-treat population. In anemic subgroups, momelotinib was associated with higher rates of transfusion independence and reduced/stable transfusion intensity vs. ruxolitinib. No new or unexpected safety signals were identified. Overall, momelotinib provides spleen, symptom, and anemia benefits to JAK inhibitor-naive patients with myelofibrosis regardless of baseline hemoglobin level, and greater anemia-related benefits vs. ruxolitinib in patients with hemoglobin <12 g/dL.

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Anemia; hemoglobin; momelotinib; myelofibrosis; ruxolitinib; transfusion independence

Introduction

Anemia is a key hallmark of myelofibrosis, as over one-third of patients are anemic at diagnosis, and the majority will become so over time [1–4]. Hemoglobin levels of <10 g/dL are considered a negative prognostic indicator in myelofibrosis risk assessment, while anemia of any severity may impact quality of life and survival [5–13]. Anemia in myelofibrosis is multifactorial, with contributors including proinflammatory cytokine expression, bone marrow fibrosis, ineffective extramedullary erythropoiesis, red blood cell (RBC) sequestration due to splenomegaly, and upregulation of hepcidin leading to impaired iron metabolism [4]. Anemia can be further exacerbated by Janus kinase (JAK) inhibitors such as ruxolitinib and fedratinib, which have become a mainstay in the treatment of myelofibrosis-related splenomegaly and symptoms but do not directly address anemia and may worsen it over time due to myelosuppressive effects [14–18]. Discontinuation or dose reduction of these JAK inhibitors may in turn reduce clinical efficacy [3]. Thus, optimal management of anemia, without compromising symptom and spleen benefits, represents an area of high medical need in myelofibrosis.

Response rates and durability with supportive agents currently used to address anemia in myelofibrosis, including danazol and other androgens, corticosteroids, immunomodulatory agents, and erythropoiesis-stimulating agents, are suboptimal [4]. Thus, RBC transfusions are a

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frequent component of anemia management [1]. Transfusion requirement, in addition to anemia itself, imparts negative prognostic and quality of life burden in patients with myelofibrosis and is associated with substantial healthcare resource utilization [4,5,8,10,19], highlighting the importance of both achieving transfusion independence in patients who require transfusions and maintaining transfusion independence in those who do not.

Hemoglobin thresholds indicative of transfusion need vary by clinician and institution [20–22] but, consistent with its inclusion in myelofibrosis risk scoring systems [9–11], a hemoglobin level of <10 g/dL is when anemia supportive therapies other than transfusion are generally considered [23]. According to the World Health Organization, hemoglobin levels of <8 g/dL are defined as 'severe' anemia and often require the introduction of transfusion support [24,25]. As hemoglobin levels of ≥8 but <10 g/dL broadly constitute 'moderate' anemia [20,24], patients with moderate/severe anemia collectively are those typically considered for treatment. However, hemoglobin levels of ≥10 g/dL but below the lower limit of normal are also considered 'mild' anemia [20,24] that can have clinical consequences, often continues to progress, and may be negatively associated with survival [6,24], suggesting that treatment may warrant consideration in some patients.

The JAK1/JAK2/activin A receptor type 1 (ACVR1) inhibitor momelotinib received regulatory approvals for the treatment of patients with myelofibrosis and anemia primarily based on data in those with moderate/severe anemia (hemoglobin levels <10 g/dL) [26,27]. Momelotinib directly addresses anemia of inflammation in myelofibrosis through inhibition of ACVR1 [28,29], and has demonstrated consistent anemia benefits – as well as symptom and splenomegaly improvements – across 3 phase 3 trials [30–32]. In MOMENTUM (momelotinib vs. danazol in JAK inhibitor-experienced patients), hemoglobin levels of <10 g/dL were required at enrollment; thus, all patients were moderately/severely anemic [32]. However, SIMPLIFY-1 (momelotinib vs. ruxolitinib in JAK inhibitor-naive patients) and SIMPLIFY-2 (momelotinib vs. best available therapy [88.5% ruxolitinib] in JAK inhibitor-experienced patients) had no hemoglobin requirements for enrollment [30,31]; in particular, mean hemoglobin levels were >10 g/dL in both arms of SIMPLIFY-1 at baseline, suggesting that a substantial number of patients had mild anemia or were nonanemic [30]. Therefore, we performed an exploratory post hoc analysis of SIMPLIFY-1 to characterize the benefits of momelotinib in subgroups defined by baseline hemoglobin levels.

Methods

Study design

SIMPLIFY-1 was a randomized, double-blind, phase 3 trial conducted at multiple study sites; the primary analysis has been reported [30]. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the institutional review board or independent ethics committee at each study site, and all participants provided written informed consent.

Consistent with the primary analysis, the present analysis is based on the 24-week double-blind period, during which patients received either momelotinib 200 mg once daily or ruxolitinib twice daily (dose based on platelet counts, per label) [33]. After the primary endpoint was assessed at week 24 [30], all patients were eligible to receive open-label momelotinib. See Supplemental Methods for assessment details.

Patients

Full inclusion and exclusion criteria have been previously described [30]. Briefly, patients were ≥18 years of age with primary, post-polycythemia vera, or post-essential thrombocythemia myelofibrosis and classified as International Prognostic Scoring System (IPSS) high, intermediate-2, or symptomatic intermediate-1 (defined by splenomegaly, hepatomegaly, or anemia) risk. Patients with prior JAK inhibitor use were excluded. Randomized assignment (1:1) to momelotinib or ruxolitinib was stratified by transfusion dependence (yes or no; defined as ≥4 RBC units transfused or hemoglobin levels of <8 g/dL in the 8 weeks before randomization) and platelet count (<100, ≥100 to ≤200, or >200 × 10^9/L).

Endpoints and statistical analysis

The primary endpoint (noninferiority) was splenic response rate (spleen volume reduction ≥35% from baseline) at week 24. Secondary endpoints included Total Symptom Score (TSS) response rate (≥50% reduction from baseline) at week 24 and transfusion independence rate at week 24 (terminal 12-week criteria: no RBC transfusions and no hemoglobin levels of <8 g/dL in the last 12 weeks before week 24). Transfusion independence by week 24 was also defined post hoc per rolling 12-week criteria: no RBC transfusions and no hemoglobin levels of <8 g/dL during any 12-week period through week 24 [30]. To support the week 24 transfusion independence endpoint, additional efficacy endpoints involving longitudinal assessment of

anemia-related benefits in the present analysis included mean hemoglobin levels over time and post hoc analysis of time-dependent transfusion burden (see Supplemental Methods).

Patient subgroups by baseline hemoglobin level were defined post hoc as <10 g/dL (moderate/severe), ≥10 to <12 g/dL (mild), or ≥12 g/dL (nonanemic). SIMPLIFY-1 enrolled few patients with severe anemia (hemoglobin levels <8 g/dL; *n* = 49); thus, patients with severe and moderate anemia were combined in the <10-g/dL subgroup. Baseline characteristics, safety, and efficacy in the small severely anemic subgroup (<8 g/dL) are described separately in the Supplement. All statistical power was used at the time of the primary analysis [30], and the study was not powered for analysis of these subgroups defined post hoc; thus, efficacy and safety results by subgroup from this exploratory analysis are summarized descriptively.

Results

Patients and demographics

Of 432 patients in SIMPLIFY-1, 180 (41.7%) were moderately/severely anemic (hemoglobin levels of <10 g/dL, including 49 patients [11.3%] with severe anemia [hemoglobin levels of <8 g/dL]; Supplemental Table 1), 142 (32.9%) were mildly anemic (hemoglobin levels of ≥10 to <12 g/dL), and 109 (25.2%) were nonanemic (hemoglobin levels of ≥12 g/dL) at baseline; one patient in the ruxolitinib arm without a baseline hemoglobin level recorded was excluded from the analysis.

The momelotinib and ruxolitinib arms were comparably represented in each subgroup, and baseline characteristics other than mean hemoglobin levels and transfusion status – such as age, TSS, myelofibrosis subtype, and IPSS risk – were generally consistent across subgroups and as previously reported for the intent-to-treat (ITT) population (Table 1) [30]. All patients in the nonanemic subgroup were transfusion independent at baseline, as were most (86.6%) in the mildly anemic subgroup. However, only 36.7% of moderately/severely anemic patients were transfusion independent, while 51.1% met the criteria for transfusion dependence (≥4 units transfused or a hemoglobin level of <8 g/dL in the previous 8 weeks), including all patients with severe anemia. In this moderately/severely anemic subgroup, fewer patients were transfusion independent in the momelotinib arm (29.1%) vs. the ruxolitinib arm (43.6%) at baseline.

Discontinuations and overall safety

The safety profile observed across subgroups was generally consistent with that of the overall safety population [30], and no new or unexpected momelotinib safety signals were detected (Table 2; Supplemental

Table 1. Baseline characteristics in subgroups defined by baseline hemoglobin levels.

	ITT [30]		Hb <10 g/dL		Hb ≥10 to <12 g/dL		Hb ≥12 g/dL	
	Momelotinib (*n* = 215)	Ruxolitinib (*n* = 217)	Momelotinib (*n* = 86)	Ruxolitinib (*n* = 94)	Momelotinib (*n* = 73)	Ruxolitinib (*n* = 69)	Momelotinib (*n* = 56)	Ruxolitinib (*n* = 53)
Age, mean (SD), years	65.0 (10.7)	64.4 (10.6)	68.5 (9.0)	65.9 (9.1)	64.2 (10.9)	64.1 (11.7)	60.6 (11.1)	62.2 (11.4)
Male, *n* (%)	124 (58)	120 (55)	50 (58)	56 (60)	38 (52)	33 (48)	36 (64)	30 (57)
MF subtype, *n* (%)								
Primary	128 (60)	116 (53)	59 (69)	54 (57)	44 (60)	40 (58)	25 (45)	21 (40)
PPV	48 (22)	50 (23)	11 (13)	12 (13)	13 (18)	16 (23)	24 (43)	22 (42)
PET	39 (18)	51 (24)	16 (19)	28 (30)	16 (22)	13 (19)	7 (13)	10 (19)
Time since MF diagnosis, mean (SD), years	3.6 (4.8)	3.1 (4.5)	3.2 (3.9)	3.1 (4.4)	4.0 (5.3)	3.3 (4.0)	3.6 (5.3)	2.8 (5.2)
IPSS, *n* (%)								
Int-1	46 (21)	43 (20)	2 (2)	4 (4)	20 (27)	16 (23)	24 (43)	22 (42)
Int-2	76 (35)	67 (31)	26 (30)	20 (21)	31 (42)	25 (36)	19 (34)	22 (42)
High	93 (43)	107 (49)	58 (67)	70 (74)	22 (30)	28 (41)	13 (23)	9 (17)
TSS, mean (SD)	19.4 (13.2)	17.9 (11.5)	19.0 (13.7)	18.1 (11.9)	19.0 (12.1)	17.3 (10.8)	20.6 (13.7)	18.4 (11.9)
Hb, mean (SD), g/dL[a]	10.6 (2.1)	10.7 (2.4)	8.6 (1.0)	8.7 (1.0)	10.9 (0.6)	10.9 (0.6)	13.3 (1.0)	14.0 (1.7)
TI, *n* (%)[b]	147 (68)	152 (70)	25 (29)	41 (44)	66 (90)	57 (83)	56 (100)	53 (100)
TD, *n* (%)[c]	53 (25)	52 (24)	49 (57)	43 (46)	4 (5)	9 (13)	0	0
TR, *n* (%)[d]	15 (7)	13 (6)	12 (14)	10 (11)	3 (4)	3 (4)	0	0
PLT, mean (SD), $\times 10^9$/L	300.9 (206.9)	301.5 (255.9)	229.3 (155.9)	292.3 (323.2)	315.4 (180.2)	310.8 (200.1)	391.9 (264.0)	306.6 (180.0)
ANC, mean (SD), $\times 10^9$/L	12.0 (13.4)	11.3 (11.0)	7.8 (9.2)	9.7 (11.1)	13.9 (15.9)	12.5 (11.4)	16.0 (13.8)	12.7 (10.2)

ANC: absolute neutrophil count; Hb: hemoglobin; IPSS: International Prognostic Scoring System; int: intermediate; ITT: intent-to-treat; MF: myelofibrosis; PET: post-essential thrombocythemia; PLT: platelet; PPV: post-polycythemia vera; TD: transfusion dependent; TI: transfusion independent; TR: transfusion requiring; TSS: Total Symptom Score.

[a]One patient in the ruxolitinib arm did not have a baseline Hb level recorded.

[b]No RBC transfusions or Hb levels of <8 g/dL in the last 12 weeks before randomization.

[c]≥4 RBC units transfused or an Hb level of <8 g/dL in the 8 weeks before randomization.

[d]Not meeting criteria for TI or TD.

Table 2. Safety summary in subgroups defined by baseline hemoglobin levels[a].

	Overall safety population [30]		Hb <10 g/dL		Hb ≥10 to <12 g/dL		Hb ≥12 g/dL	
n (%)	Momelotinib (*n* = 214)	Ruxolitinib (*n* = 216)	Momelotinib (*n* = 86)	Ruxolitinib (*n* = 94)	Momelotinib (*n* = 73)	Ruxolitinib (*n* = 69)	Momelotinib (*n* = 55)	Ruxolitinib (*n* = 52)
Any TEAE	198 (93)	206 (95)	81 (94)	91 (97)	71 (97)	66 (96)	46 (84)	48 (92)
Any TEAE grade ≥3	77 (36)	94 (44)	42 (49)	52 (55)	22 (30)	31 (45)	13 (24)	11 (21)
Any TEAE leading to discontinuation of active study drug	27 (13)	12 (6)	17 (20)	5 (5)	5 (7)	4 (6)	5 (9)	3 (6)
Any TEAE leading to dose reduction/ interruption of active study drug	39 (18)	79 (37)	19 (22)	34 (36)	9 (12)	29 (42)	11 (20)	16 (31)
Serious TEAEs	49 (23)	39 (18)	26 (30)	23 (24)	13 (18)	12 (17)	10 (18)	4 (8)
Fatal TEAEs	7 (3)	7 (3)	4 (5)	3 (3)	2 (3)	3 (4)	1 (2)	1 (2)

Hb: hemoglobin; TEAE: treatment-emergent adverse event.
[a]Safety analysis set included all patients who received ≥1 dose of treatment. For safety analyses, subgroups were defined by baseline safety Hb values, which may not align with values in the efficacy data, resulting in minor differences in subgroup sizes.

Tables 2 and 3). Discontinuations due to adverse events were more frequent in the moderately/severely anemic subgroup with momelotinib (19.8%) than with ruxolitinib (5.3%), which could reflect per-protocol differences in the approach to dose modifications [34,35], since dose reductions/interruptions of ruxolitinib were more common in this subgroup (36.2% vs. 22.1% with momelotinib); consistently, mean daily doses of momelotinib in this subgroup remained high through week 24, while mean daily doses of ruxolitinib decreased over time despite starting dose dictated by platelet counts (Supplemental Figure 1). Overall, most adverse events leading to discontinuation occurred in one patient each (with the exception of thrombocytopenia, dizziness [*n* = 3 each], malaise, and hypotension [*n* = 2 each] in the momelotinib arm and thrombocytopenia [*n* = 4] and acute myeloid leukemia [*n* = 2] in the ruxolitinib arm). Some expected adverse events for a population with moderate/severe anemia were also more frequent in that subgroup, but rates were generally consistent between treatment arms (e.g. dyspnea, 12.8% vs. 8.5%) (Table 3).

Mean hemoglobin levels and platelet counts over time

Mean hemoglobin levels over time were dependent on the mean level at baseline for each subgroup but followed similar trends per treatment arm. Mean hemoglobin levels increased by weeks 2–4 (anemic subgroups) or remained stable (nonanemic subgroup) with momelotinib. In the ruxolitinib arm, there was an initial decrease in mean hemoglobin levels in all subgroups, including the nonanemic subgroup, which plateaued after weeks 4–6 as patients continued to receive RBC transfusions as deemed clinically necessary per investigators throughout assessment (Figure 1(A–C); Supplemental Figure 2). Following crossover to open-label momelotinib, mean hemoglobin levels increased rapidly in those initially randomized to ruxolitinib before stabilizing.

In all subgroups, mean platelet counts were generally stable over time with momelotinib and declined initially with ruxolitinib before plateauing through week 24; after crossover to momelotinib, mean platelet counts remained stable or increased (Supplemental Figure 3).

Time-dependent transfusion burden

As expected for subgroups defined by baseline hemoglobin levels, time-dependent transfusion burden varied, including the percentages of patients who were transfusion free (no transfusions, regardless of hemoglobin level) at baseline and maintained that status during treatment (Figure 2(A–C); Supplemental Figure 4). In the mildly anemic subgroup, most patients in the momelotinib arm were transfusion free at baseline (66 of 73 [90.4%]); the majority maintained this status during treatment with momelotinib, as 62 of these 66 (93.9%) remained transfusion free and four additional patients who required transfusions at baseline became transfusion free on treatment. While most mildly anemic patients in the ruxolitinib arm were also transfusion free at baseline (60 of 69 [87.0%]), transfusion burden increased on treatment, and 30 of these 60 (50.0%) became transfusion requiring with ruxolitinib. Overall, 68 of 73 (93.2%) mildly anemic patients in the momelotinib arm had stable or reduced transfusion intensity during treatment vs. only 35 of 69 (50.7%) in the ruxolitinib arm (Figure 2(B)).

In the moderately/severely anemic subgroup, only 29 of 85 patients (34.1%) in the momelotinib arm were already transfusion free at baseline before study treatment. However, transfusion burden was reduced in the momelotinib arm on treatment, as the

Table 3. Most common TEAEs in subgroups defined by baseline hemoglobin levels[a].

	Overall safety population [30]				Hb <10 g/dL				Hb ≥10 to <12 g/dL				Hb ≥12 g/dL			
n (%)	Momelotinib (*n* = 214)		Ruxolitinib (*n* = 216)		Momelotinib (*n* = 86)		Ruxolitinib (*n* = 94)		Momelotinib (*n* = 73)		Ruxolitinib (*n* = 69)		Momelotinib (*n* = 55)		Ruxolitinib (*n* = 52)	
Grade:	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3
Any TEAE	198 (93)	77 (36)	206 (95)	94 (44)	81 (94)	42 (49)	91 (97)	52 (55)	71 (97)	22 (30)	66 (96)	31 (45)	46 (84)	13 (24)	48 (92)	11 (21)
Hematologic TEAEs occurring in >5% of patients in a momelotinib arm																
Thrombocytopenia	40 (19)	15 (7)	63 (29)	10 (5)	19 (22)	9 (10)	32 (34)	6 (6)	15 (21)	4 (5)	21 (30)	3 (4)	6 (11)	2 (4)	10 (19)	1 (2)
Anemia	31 (14)	13 (6)	81 (38)	49 (23)	14 (16)	10 (12)	36 (38)	26 (28)	13 (18)	2 (3)	31 (45)	18 (26)	4 (7)	1 (2)	14 (27)	5 (10)
Neutropenia	9 (4)	6 (3)	14 (6)	10 (5)	4 (5)	3 (3)	9 (10)	7 (7)	4 (5)	3 (4)	1 (1)	1 (1)	1 (2)	0	4 (8)	2 (4)
Nonhematologic TEAEs occurring in >10% of patients in a momelotinib arm																
Diarrhea	39 (18)	6 (3)	43 (20)	3 (1)	19 (22)	2 (2)	19 (20)	1 (1)	11 (15)	3 (4)	13 (19)	1 (1)	9 (16)	1 (2)	11 (21)	1 (2)
Nausea	34 (16)	2 (1)	8 (4)	1 (<1)	19 (22)	1 (1)	3 (3)	1 (1)	6 (8)	0	5 (7)	0	9 (16)	1 (2)	0	0
Dizziness	34 (16)	0	25 (12)	1 (<1)	15 (17)	0	10 (11)	1 (1)	13 (18)	0	6 (9)	0	6 (11)	0	8 (15)	0
Fatigue	31 (14)	1 (<1)	26 (12)	2 (1)	13 (15)	0	11 (12)	0	10 (14)	1 (1)	9 (13)	2 (3)	8 (15)	0	6 (12)	0
Hypotension	19 (9)	3 (1)	1 (<1)	0	12 (14)	2 (2)	0	0	3 (4)	0	1 (1)	0	4 (7)	1 (2)	0	0
Cough	18 (8)	0	17 (8)	0	12 (14)	0	9 (10)	0	4 (5)	0	6 (9)	0	2 (4)	0	2 (4)	0
Dyspnea	19 (9)	0	17 (8)	1 (<1)	11 (13)	0	8 (9)	1 (1)	5 (7)	0	8 (12)	0	3 (5)	0	0	0
Abdominal pain	22 (10)	3 (1)	25 (12)	1 (<1)	11 (13)	2 (2)	11 (12)	1 (1)	5 (7)	0	9 (13)	0	6 (11)	1 (2)	5 (10)	0
Constipation	21 (10)	0	15 (7)	0	11 (13)	0	6 (6)	0	4 (5)	0	7 (10)	0	6 (11)	0	2 (4)	0
Peripheral sensory neuropathy	20 (9)	0	12 (6)	1 (<1)	10 (12)	0	5 (5)	0	6 (8)	0	5 (7)	1 (1)	4 (7)	0	2 (4)	0
Pyrexia	14 (7)	1 (<1)	17 (8)	0	10 (12)	1 (1)	10 (11)	0	3 (4)	0	6 (9)	0	1 (2)	0	0	0
Headache	38 (18)	1 (<1)	43 (20)	0	10 (12)	0	15 (16)	0	11 (15)	0	19 (28)	0	17 (31)	1 (2)	9 (17)	0
Pain in extremity	14 (7)	0	18 (8)	0	9 (10)	0	5 (5)	0	3 (4)	0	9 (13)	0	2 (4)	0	4 (8)	0
Abdominal pain upper	10 (5)	0	10 (5)	0	3 (3)	0	2 (2)	0	1 (1)	0	4 (6)	0	6 (11)	0	3 (6)	0
Hypertension	9 (4)	6 (3)	20 (9)	9 (4)	1 (1)	1 (1)	7 (7)	4 (4)	2 (3)	1 (1)	8 (12)	4 (6)	6 (11)	4 (7)	5 (10)	1 (2)

Hb: hemoglobin; TEAE: treatment-emergent adverse event.

TEAEs are sorted based on the Hb <10-g/dL subgroup. Orange shading indicates TEAEs that occurred in >10% in the momelotinib arm in ≥1 subgroup but not the overall safety population.

[a]Safety analysis set included all patients who received ≥1 dose of treatment. For safety analyses, subgroups were defined by baseline safety Hb values, which may not align with values in the efficacy data, resulting in minor differences in subgroup sizes.

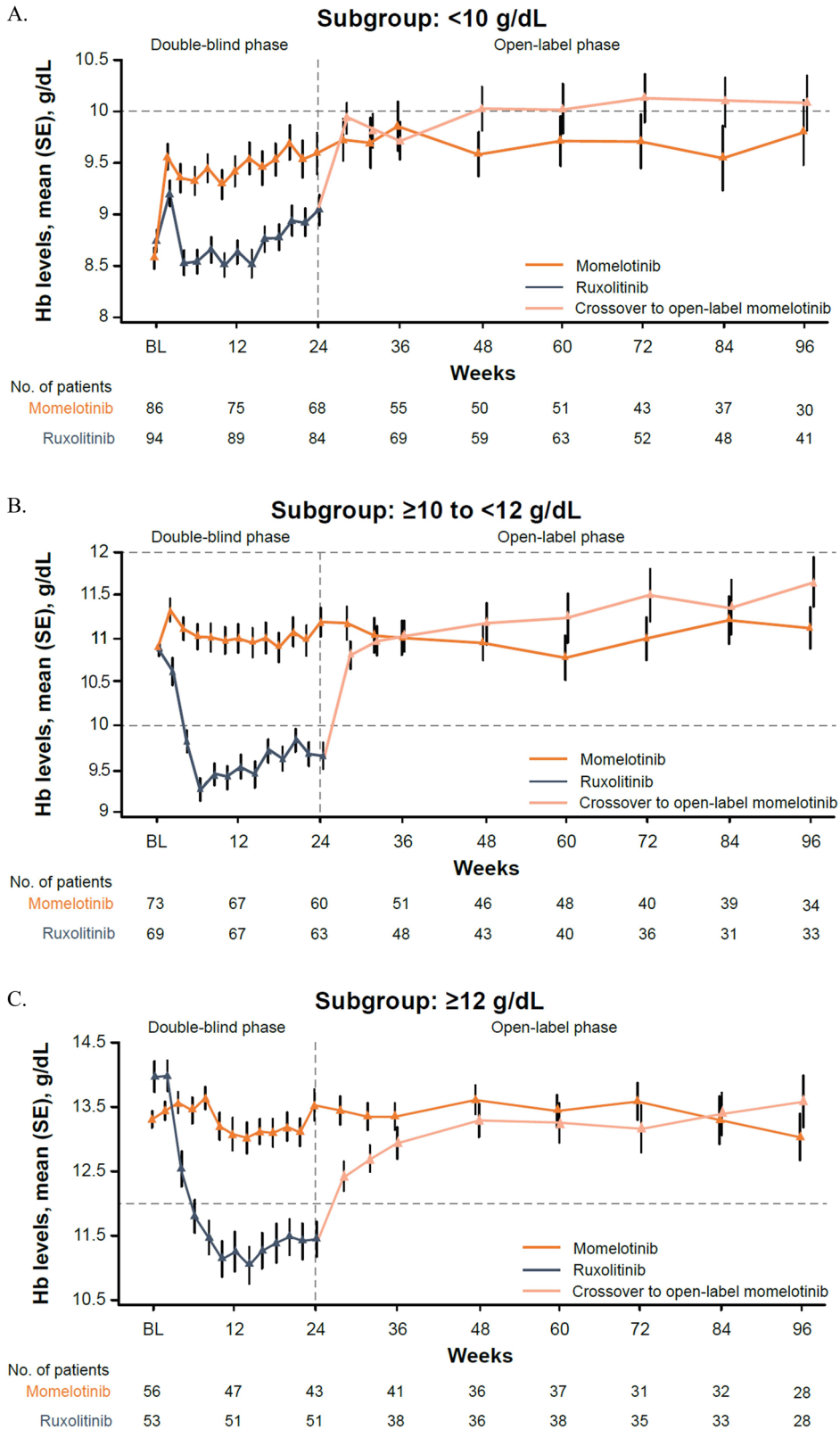

Figure 1. Mean hemoglobin levels over time in subgroups defined by baseline hemoglobin levels (<10 g/dL, A; ≥10 to <12 g/dL, B; ≥12 g/dL, C). Figures depict results through week 96 for illustrative purposes, although the study continued beyond this time point. BL: baseline; Hb: hemoglobin.

majority of baseline transfusion-free patients (25 of 29 [86.2%]) maintained this status, and 14 additional patients who required transfusions at baseline achieved it. Overall, most patients in this subgroup treated with momelotinib (71 of 85 [83.5%]) had stable or reduced transfusion intensity on treatment,

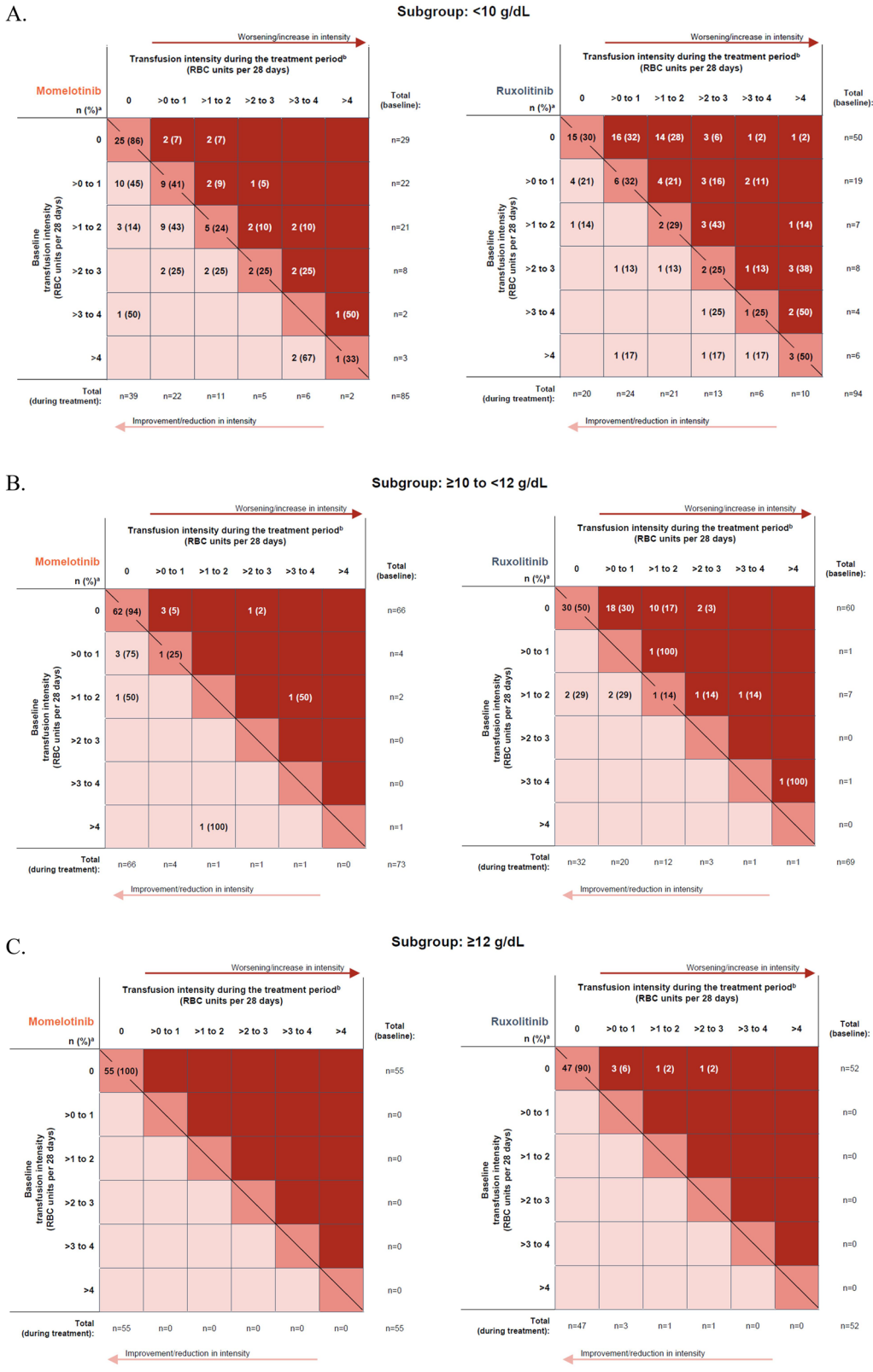

Figure 2. Shift tables of change in RBC transfusion intensity over time from baseline during treatment in subgroups defined by baseline hemoglobin levels (<10 g/dL, A; ≥10 to <12 g/dL, B; ≥12 g/dL, C). Left of diagonal indicates improvement/reduction in transfusion intensity during treatment; right of diagonal indicates worsening/increase in transfusion intensity during treatment. One patient in the momelotinib arm of the <10-g/dL subgroup and two patients (one each in the momelotinib and ruxolitinib arms) in the ≥12-g/dL subgroup were treated for <14 days and excluded from the analyses. [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. RBC: red blood cell.

including 22 of 28 (78.6%) with severe anemia (Supplemental Figure 4). In contrast, although the majority of moderately/severely anemic patients in the ruxolitinib arm (50 of 94 [53.2%]) started out as transfusion free at baseline before study treatment, transfusion burden increased on ruxolitinib, as only 15 of these 50 (30.0%) maintained transfusion-free status during treatment. Fewer patients overall in the ruxolitinib arm (40 of 94 [42.6%]) had stable or reduced transfusion intensity on treatment (Figure 2(A)), including only eight of 21 (38.1%) with severe anemia (Supplemental Figure 4).

In the nonanemic subgroup, all patients in the momelotinib arm were transfusion free at baseline and remained so during treatment; although all patients in the ruxolitinib arm were also transfusion free at baseline, five became transfusion requiring during treatment (Figure 2(C)).

Week 24 transfusion independence

Transfusion independence rates at week 24 (by the prespecified terminal 12-week definition) also varied across hemoglobin subgroups. Consistent with the nominally significant results previously reported in the ITT population [30], momelotinib had numerically greater benefit vs. ruxolitinib in all anemic subgroups, particularly the mildly anemic subgroup (<10 g/dL: 46.5% vs. 26.6%; ≥10 to <12 g/dL: 80.8% vs. 50.7%) (Figure 3(A,B) and Supplemental Figure 5). In the nonanemic subgroup, in which all patients were already transfusion independent at baseline, week 24 transfusion independence rates were comparable with momelotinib and ruxolitinib, with 78.6% vs. 86.8% also transfusion independent at week 24 (Figure 3(C)). Transfusion independence rates by week 24 per the rolling 12-week definition were higher in both arms across subgroups, but trends with momelotinib vs. ruxolitinib were consistent with those observed per the terminal 12-week definition (Figure 3).

In the mildly anemic subgroup, more patients in the momelotinib vs. ruxolitinib arm who were transfusion independent at baseline maintained transfusion independence at week 24 (57 of 66 [86.4%] vs. 33 of 57 [57.9%]). Furthermore, among patients who were non-transfusion independent at baseline in this subgroup (consisting of both those who were transfusion dependent and those who were transfusion requiring, as defined in Table 1), two of seven (28.6%) vs. two of 12 (16.7%) treated with momelotinib vs. ruxolitinib, respectively, achieved transfusion independence at week 24. Similarly, in the moderately/severely anemic subgroup, more patients who were transfusion independent at baseline maintained this status at week 24 with momelotinib (18 of 25 [72.0%]) than with ruxolitinib (14 of 41 [34.1%]), and more who were non-transfusion independent at baseline also achieved transfusion independence with momelotinib at week 24 (22 of 61 [36.1%]) vs. ruxolitinib (11 of 53 [20.8%]) in this subgroup, including eight of 28 (28.6%) vs. three of 21 (14.3%), respectively, with severe anemia (Supplemental Figure 5).

Week 24 spleen and symptom benefits

Consistent with the ITT population, in which momelotinib was noninferior to ruxolitinib with respect to splenic response rate [30], rates of spleen volume reduction of ≥35% at week 24 were comparable across subgroups and generally similar in the momelotinib and ruxolitinib arms, although both anemic subgroups showed numerically greater rates with momelotinib than the nonanemic subgroup; most patients across arms and subgroups had some spleen volume reduction from baseline (Figure 3(A–C) and Supplemental Figure 6). TSS response across subgroups was also consistent with the ITT population [30], with higher response rates at week 24 observed in the ruxolitinib vs. momelotinib arm (Figure 3(A–C)); the proportion of patients with stable or improved scores for individual symptom items was similar between arms and across subgroups (Supplemental Figure 7).

Across subgroups, most patients who were splenic or TSS responders with momelotinib were also transfusion independent at week 24 (Supplemental Figure 8). These dual endpoints were achieved by 19 of 19 (100%) splenic responders and 24 of 25 (96.0%) TSS responders in the mildly anemic subgroup, 23 of 27 (85.2%) and 15 of 21 (71.4%) in the moderately/severely anemic subgroup, and 11 of 11 (100%) and 13 of 14 (92.9%) in the nonanemic subgroup. However, dual endpoint rates were lower with ruxolitinib in the anemic subgroups, as only eight of 17 (47.1%) splenic responders and 17 of 29 (58.6%) TSS responders in the mildly anemic subgroup and seven of 31 (22.6%) and nine of 33 (27.3%) in the moderately/severely anemic subgroup were also transfusion independent at week 24. In contrast, 13 of 16 (81.3%) splenic and 23 of 26 (88.5%) TSS responders in the nonanemic subgroup treated with ruxolitinib were also transfusion independent. Consistently, triple responses (spleen, symptom, and transfusion independence) were also more frequent with momelotinib in anemic subgroups (Supplemental Figure 8).

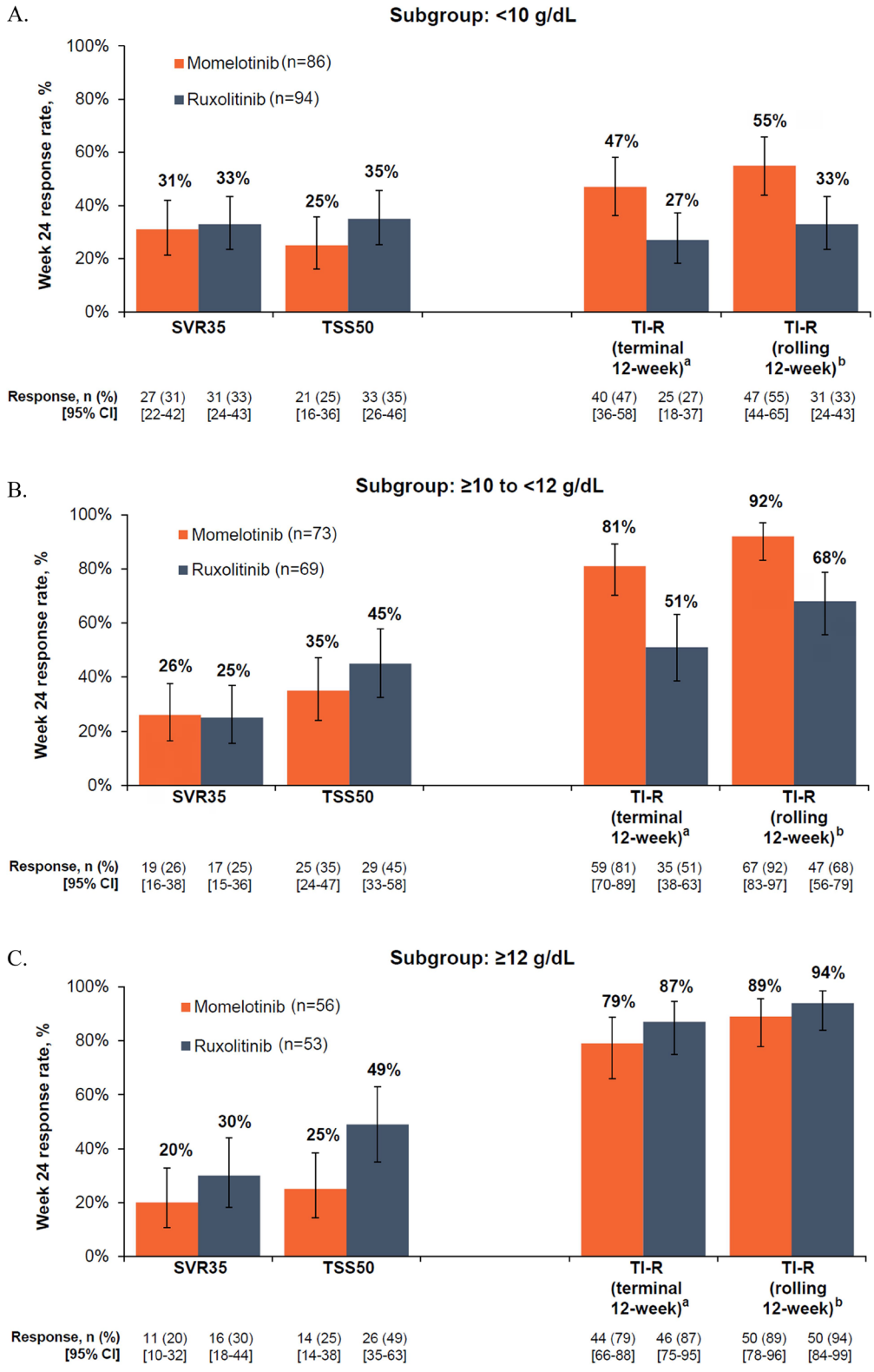

Figure 3. Week 24 efficacy endpoints, including rates of SVR35, TSS50, and TI-R (both terminal 12-week and rolling 12-week definitions) in subgroups defined by baseline hemoglobin levels (<10 g/dL, A; ≥10 to <12 g/dL, B; ≥12 g/dL, C). TSS was assessed in patients with baseline TSS of >0, or baseline TSS of 0 with TSS missing or >0 at week 24; response rates are based on the number of patients evaluable for TSS at week 24 (<10-g/dL subgroup: n = 84 in the momelotinib arm and n = 93 in the ruxolitinib arm; ≥10- to <12-g/dL subgroup: n = 71 in the momelotinib arm and n = 64 in the ruxolitinib arm). For all week 24 endpoints, patients with missing baseline and/or week 24 assessments were counted as nonresponders. [a]Defined as no RBC transfusions and no hemoglobin levels of <8 g/dL in the last 12 weeks before week 24. [b]Defined as no RBC transfusions and no hemoglobin levels of <8 g/dL during any 12-week period through week 24. SVR35: spleen volume reduction ≥35%; TI-R: transfusion independence response; TSS: Total Symptom Score; TSS50: Total Symptom Score reduction ≥50%.

Discussion

This exploratory analysis of subgroups defined by baseline hemoglobin levels in the phase 3 SIMPLIFY-1 study highlights the consistent safety profile and clinical benefits of momelotinib in JAK inhibitor-naive patients with myelofibrosis who have mild, moderate/severe, or no anemia. In particular, momelotinib was associated with increased rates of week 24 transfusion independence and reduced transfusion intensity over time vs. ruxolitinib in both the moderately/severely and mildly anemic subgroups, reflecting both maintenance of transfusion independence and achievement of new transfusion independence responses. While treatment of mild anemia (hemoglobin levels of ≥10 to <12 g/dL) is not always routinely considered [23], our analysis also highlights the potential value of momelotinib in preserving transfusion independence in eligible patients with mild anemia for whom JAK inhibitor treatment is warranted.

Spleen and symptom results with momelotinib vs. ruxolitinib in these subgroup analyses were generally consistent with those previously reported for the ITT population [30]. While study design and statistical considerations in part explain the underperformance of momelotinib with respect to symptoms in SIMPLIFY-1 [34,35], it is notable that both spleen and symptom benefits with ruxolitinib in some patients with anemia may come at the expense of transfusion independence. Our dual endpoint analyses suggest that while more patients achieved TSS responses with ruxolitinib, comparatively few patients in the anemic subgroups also achieved transfusion independence. On the other hand, the majority of splenic and TSS responders, across both anemic and nonanemic subgroups, with momelotinib were also transfusion independent, suggesting that momelotinib can provide comprehensive benefits across symptoms, spleen size, and anemia regardless of baseline hemoglobin levels in some patients.

While momelotinib demonstrated benefits across anemic subgroups, the impact of momelotinib in nonanemic patients is less clear. In this subgroup, transfusion independence was maintained by a similar proportion of patients in both treatment arms at week 24. This may be the result of several factors, including the higher percentages of patients with post-polycythemia vera myelofibrosis in the nonanemic subgroup compared with the anemic subgroups as well those with missing data at week 24, counted as nonresponders per protocol [30]: more patients discontinued momelotinib early due to low-grade adverse events, as the SIMPLIFY-1 protocol included a ruxolitinib dose-modification schema that led to higher rates of dose reductions or interruptions rather than discontinuations [34,35]. Furthermore, the strict prespecified definition of transfusion independence may not fully capture the relative anemia benefits of momelotinib, as even patients who do not meet these criteria may benefit [36]; time-dependent transfusion burden analyses demonstrated that all patients in the nonanemic subgroup maintained their baseline transfusion-free status during momelotinib treatment, while some patients lost this status with ruxolitinib.

Time-dependent transfusion burden analyses further highlighted the relative benefits of momelotinib vs. ruxolitinib in the anemic subgroups, as >80% of patients treated with momelotinib had reduced or stable transfusion intensity during treatment vs. ≤50% with ruxolitinib. Consistently, mean hemoglobin levels increased or remained stable over time with momelotinib but initially decreased with ruxolitinib, trends that were apparent in all subgroups, including those who were nonanemic at baseline and despite inclusion of patients who were receiving transfusions. Thus, baseline hemoglobin levels have a clear impact on the progression of anemia, as although some patients in the nonanemic subgroup also experienced a decrease in mean hemoglobin levels and increased transfusion intensity with ruxolitinib, their starting values may have been sufficient to keep them above the level of transfusion dependence. In contrast, momelotinib was associated with maintenance of transfusion independence and reduction or stabilization in transfusion intensity regardless of baseline hemoglobin levels, including in mildly anemic and nonanemic patients.

Across subgroups, no new momelotinib safety signals were identified. While grade ≥3 and serious treatment-emergent adverse events (TEAEs) were relatively more frequent in the <10-g/dL subgroup, this trend was observed in both treatment arms. Key hematologic TEAEs, including anemia and thrombocytopenia, were less frequent with momelotinib vs. ruxolitinib across all subgroups. As both momelotinib and ruxolitinib prescribing information require dose modification for thrombocytopenia [26,33], the stability of mean platelet counts over time with momelotinib across subgroups may support use at full dose in more patients vs. ruxolitinib, as previously shown for the ITT population [37,38].

SIMPLIFY-1 was not statistically powered to evaluate momelotinib vs. ruxolitinib in these patient subgroups defined by baseline hemoglobin levels; thus, the post hoc and descriptive nature of these analyses is their primary limitation. While sample sizes per subgroup and treatment arm were relatively robust, ranging

from 53 to 94 patients, evaluation in a larger population may be warranted. Furthermore, although the phase 3 SIMPLIFY-2 study also included patients regardless of baseline hemoglobin levels, similar analyses across hemoglobin subgroups could not be conducted in this JAK inhibitor-experienced patient population as comparatively few patients were mildly anemic (21.8%) or nonanemic (10.9%) [31]. However, the phase 3 MOMENTUM study provides robust evidence of the efficacy and safety of momelotinib in JAK inhibitor-experienced patients with myelofibrosis and baseline hemoglobin levels of <10 g/dL [32].

The clinical benefits and safety profile of momelotinib in JAK inhibitor-naive patients with myelofibrosis across mildly to severely anemic and nonanemic subgroups were generally consistent with those observed in the overall SIMPLIFY-1 trial population, thus representing a potential treatment option for patients with myelofibrosis regardless of baseline hemoglobin levels. In addition to the proportion of patients with moderate/severe anemia (hemoglobin levels of <10 g/dL) who become transfusion independent with momelotinib, results in the subgroup with mild anemia (hemoglobin levels of ≥10 to <12 g/dL) suggest that expanding consideration of therapies such as momelotinib to appropriate JAK inhibitor-eligible patients within this population could maintain transfusion independence in the majority who are already transfusion free.

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Data availability statement

Data are available upon reasonable request. Information on GSK's data sharing commitments and requesting access to anonymized individual participant data and associated study documents can be found at https://www.gsk-studyregister.com/en/.

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