Characterization of symptoms after immediate transition from ruxolitinib to momelotinib in patients with myelofibrosis: post hoc analyses of the phase 3 SIMPLIFY-1 and SIMPLIFY-2 trials

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Immediate transition from ruxolitinib to momelotinib in patients with MF is generally well tolerated, with no evidence of severe or acute symptom relapse, and infrequent, low-grade, and transient symptoms

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Introduction

- Ruxolitinib was the first Janus kinase (JAK) inhibitor approved in the US for intermediate- or high-risk myelofibrosis (MF) and in the EU for the treatment of disease-related splenomegaly or symptoms in patients with MF[1-3]
  - Despite its clinical efficacy, ruxolitinib may induce or worsen cytopenias, and up to 89% of patients discontinue treatment within 3 years[4]
- Discontinuation of ruxolitinib in MF carries a risk of ruxolitinib discontinuation syndrome (RDS), characterized by acute flare-up of splenomegaly, symptoms, hematologic abnormalities, hemodynamic decompensation, and, in severe cases, a cytokine storm-like hyperinflammatory response[3,4]
- While manifestations of RDS typically appear within 3 weeks of treatment cessation,[3] a previous post hoc analysis of the phase 3 SIMPLIFY-1 trial demonstrated that patients can immediately cross over from ruxolitinib to momelotinib, a JAK1/JAK2/activin A receptor type 1 inhibitor approved for patients with MF and anemia, without evidence of RDS[4]
- The present analyses were conducted to more thoroughly characterize ruxolitinib dosing and symptom patterns in patients who experienced adverse events (AEs) resembling MF symptoms during the initial weeks post treatment transition to momelotinib

Methods

SIMPLIFY-1: Study Design and Patients

- SIMPLIFY-1 (NCT01969838) was a double-blind, phase 3, randomized trial of momelotinib vs ruxolitinib in JAK inhibitor–naive patients[5]
  - Patients were randomized 1:1 to receive momelotinib or ruxolitinib for 24 weeks, after which all patients could receive open-label momelotinib; there was no tapering or washout of ruxolitinib prior to receiving momelotinib[4,5]
- The current post hoc analyses included patients with AEs in the first 2 weeks post crossover from ruxolitinib-randomized treatment to open-label momelotinib (**Figure 1A**)

SIMPLIFY-1: Assessments

- Ruxolitinib dose before crossover and AEs reported in 2-week intervals post crossover were assessed
  - Because symptoms were not assessed post crossover, AEs resembling commonly reported MF symptoms (ie, fatigue, dizziness, pruritus, and night sweats) were evaluated as surrogate measures
- Data are summarized descriptively as mean and standard deviation, median and range, or frequency count and percentage

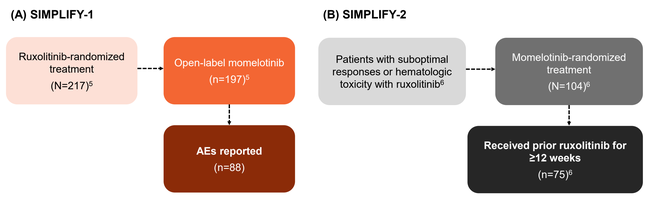
SIMPLIFY-2: Study Design and Patients

- SIMPLIFY-2 (NCT02101268) was an open-label, phase 3, randomized trial of momelotinib vs best available therapy (BAT) in JAK inhibitor–experienced (prior ruxolitinib) patients[6]
  - Patients were randomized 2:1 to receive momelotinib or BAT (88.5% ruxolitinib) for 24 weeks, after which all patients could receive momelotinib[6]
- The current post hoc analyses included momelotinib-randomized patients who transitioned directly after ≥12 weeks of prior ruxolitinib; these patients continued ruxolitinib until the day of randomization to momelotinib (**Figure 1B**)[4]

SIMPLIFY-2: Assessments

- As Total Symptom Score (TSS) was not assessed post crossover in SIMPLIFY-1, TSS from the randomized part of SIMPLIFY-2 was evaluated to supplement the current analyses
  - TSS, including individual symptom items, was assessed at momelotinib initiation (baseline) and at weeks 1-4, 8, 12, and 24
- TSS data are summarized descriptively as mean and standard error or frequency count and percentage

Figure 1: **Post Hoc Patient Populations From (A) SIMPLIFY-1 and (B) SIMPLIFY-2**



AE, adverse event.

Results

SIMPLIFY-1: Patients and Ruxolitinib Dosing Patterns

- A total of 217 patients received ruxolitinib during the 24-week randomized treatment period, after which 197 (90.8%) crossed over to receive open-label momelotinib[5]
  - Of the 197 patients, 88 (44.7%) experienced AEs within 2 weeks post crossover and were included in these analyses; among them, 21 patients had AEs resembling MF symptoms
  - High daily doses of ruxolitinib (>30 mg/day) prior to momelotinib crossover were observed in the 88 patients with AEs, with similarly high doses observed in the 21 patients with AEs resembling MF symptoms (**Table 1**)

Table 1: **Ruxolitinib Daily Dose Prior to Crossover in Patients With AEs in the First 2 Weeks Post Crossover in SIMPLIFY-1**

Daily dose of ruxolitinib prior to momelotinib crossover at week 24, mg/day	Ruxolitinib → momelotinib (n=197)	
	Patients with AEs (n=88)	Patients with AEs resembling MF symptoms (n=21)
Mean (SD)	31.6 (10.0)	32.1 (9.8)
Median (range)	34.5 (10.0-46.2)	37.9 (10.0-40.0)

AE, adverse event; MF, myelofibrosis.

SIMPLIFY-1: AEs in the First 2 Weeks Post Crossover

- AEs that resembled MF symptoms primarily occurred in weeks 1-2 post crossover, and most events were grade 1/2 (**Table 2**)
  - Of patients who had these AEs in the first 2 weeks post crossover to open-label momelotinib, 2 (fatigue), 3 (dizziness), 1 (pruritus), and 1 (night sweats) patients had previously experienced that same AE during the prior 24-week double-blind ruxolitinib-randomized treatment period
  - AEs in the first 2 weeks post crossover related to momelotinib are summarized in **Figure 2**
- The frequency of AEs resembling MF symptoms did not increase over time; incidence rates (new onset) decreased to <5% at weeks 3-4 and then to <3% at weeks 5-6 and thereafter (**Figure 3**)

Table 2: **Severity of AEs Resembling MF Symptoms in the 2 Weeks Post Crossover in SIMPLIFY-1**

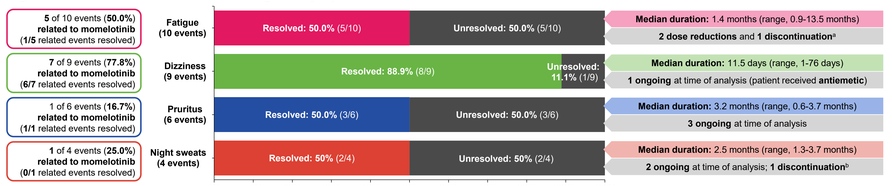
AE, n (%)	Patients (n=88)		
	Any grade	Grade 1/2	Grade 3
Fatigue	10 (11.4)	8 (9.1)	2 (2.3)
Dizziness	9 (10.2)	9 (10.2)	0
Pruritus	6 (6.8)	6 (6.8)	0
Night sweats	4 (4.5)	4 (4.5)	0

AE, adverse event; MF, myelofibrosis.

SIMPLIFY-1: Outcomes in Patients With AEs Resembling MF Symptoms in the First 2 Weeks Post Crossover

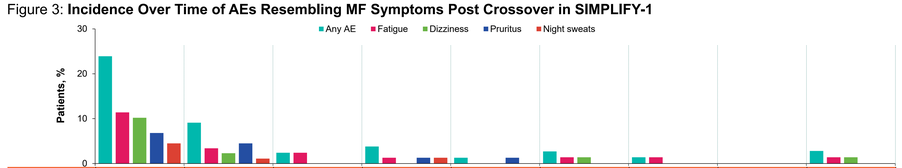
- Outcomes of AEs resembling MF symptoms (ie, fatigue, dizziness, pruritus, and night sweats) are summarized in **Figure 2**
  - At least half of cases for each AE resolved, and all but 1 (dizziness) resolved without intervention after 14 days; this event resolved after electrolyte treatment for syncope
- 3 patients received concomitant medications beyond the first 2 weeks of the open-label momelotinib period: 2 patients for dizziness (1 received potassium chloride and the other received prochlorperazine), and 1 patient received betamethasone butyrate propionate for a subsequent pruritus event

Figure 2: **Outcomes of AEs Resembling MF Symptoms in the 2 Weeks Post Crossover in SIMPLIFY-1**



AE, adverse event; MF, myelofibrosis.
[a] *This patient discontinued treatment after 10 days and is the same patient who discontinued treatment due to night sweats.* [b] *This patient discontinued treatment after 10 days and is the same patient who discontinued treatment due to fatigue.*

Figure 3: **Incidence Over Time of AEs Resembling MF Symptoms Post Crossover in SIMPLIFY-1**



Weeks	1-2 (n=88)	3-4 (n=88)	5-6 (n=84)	7-8 (n=79)	9-10 (n=76)	11-12 (n=73)	13-14 (n=72)	15-16 (n=72)	17-18 (n=71)
Overall, n (%)	21 (23.9)	8 (9.1)	2 (2.4)	3 (3.8)	1 (1.3)	2 (2.7)	1 (1.4)	0	2 (2.8)
Fatigue	10 (11.4)	3 (3.4)	2 (2.4)	1 (1.3)	0	1 (1.4)	1 (1.4)	0	1 (1.4)
Dizziness	9 (10.2)	2 (2.3)	0	0	0	1 (1.4)	0	0	1 (1.4)
Pruritus	6 (6.8)	4 (4.5)	0	1 (1.3)	1 (1.3)	0	0	0	0
Night sweats	4 (4.5)	1 (1.1)	0	1 (1.3)	0	0	0	0	0

AE, adverse event; MF, myelofibrosis.

SIMPLIFY-2: TSS Decreased in Patients Who Received ≥12 Weeks of Ruxolitinib Prior to Momelotinib

- Of the 104 patients who received momelotinib during the 24-week randomized treatment period[6], 75 (72.1%) received prior ruxolitinib for ≥12 weeks until the day of randomization and were included in these analyses
- Among these patients, mean TSS decreased from the first assessment time point (week 1 of momelotinib treatment) and continued to decrease through week 4 (**Figure 4**)
- The percentage of patients with individual symptom score improvement from baseline at weeks 1-4 is shown in **Figure 5**
  - Detailed symptom change distributions for each week are provided in the **Supplement (QR code)**

Figure 4: **Mean TSS (± SE) During Weeks 1-4 in Patients Receiving ≥12 Weeks of Ruxolitinib Prior to Momelotinib in SIMPLIFY-2**

BL, baseline; TSS, Total Symptom Score.

Figure 5: **Percentage of Patients With Improvement in Individual Symptom Scores From BL at Weeks 1-4 With Momelotinib After ≥12 Weeks of Prior Ruxolitinib in SIMPLIFY-2**

Lines show the percentage of patients who improved for each symptom; gray symptoms indicate overlapping symptoms. Improvement is defined as a decrease in individual symptom score of ≥2 points.
BL, baseline.

Discussion

- Safety data from the phase 3 SIMPLIFY-1 trial showed that few patients (<12%) experience AEs resembling MF symptoms in the first 2 weeks post crossover from ruxolitinib to momelotinib
  - Most events were low grade, were transient, and decreased over time, suggesting that this may form part of a short adjustment period post switch from high-dose ruxolitinib rather than true disease worsening or a need for treatment discontinuation
- These safety data from SIMPLIFY-1 also correlate with patient-reported symptom data from SIMPLIFY-2, in which improvement or stabilization in individual symptoms were noted as early as week 1 post crossover, with few patients reporting worsening
- Overall, these clinical data from SIMPLIFY-1 and SIMPLIFY-2 demonstrate that switching from ruxolitinib to momelotinib without a tapering or washout period is not associated with RDS, consistent with a previous analysis[4]

Limitations

- While informative when considering treatment switches for patients with MF, some limitations should be considered in the context of these findings
  - Symptom data were based on a relatively small number of patients and events across trials
  - Patient-reported outcome data were not collected post crossover, and reliance on AE reporting may not fully capture the patient experience
  - These trial-based populations may not represent patients in real-world clinical practice, which may limit the generalizability to other settings

Conclusions

Immediate transition from ruxolitinib to momelotinib appears to be well tolerated in patients with MF

- There was no evidence of severe or acute symptom relapses, and events were infrequent, mostly low grade and transient, and reported primarily in the first few weeks post crossover

Safety findings from SIMPLIFY-1 also aligned with individual symptom data in SIMPLIFY-2, showing early symptom improvement or stabilization post crossover with minimal worsening

These findings may help inform both physician and patient expectations for symptom management during treatment switch from ruxolitinib to momelotinib in patients with MF, supporting informed decision-making and helping to avoid unnecessary tapering and/or overlap of ruxolitinib

Abbreviations

AE, adverse event; BAT, best available therapy; JAK, Janus kinase; MF, myelofibrosis; RDS, ruxolitinib discontinuation syndrome; TSS, Total Symptom Score.

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