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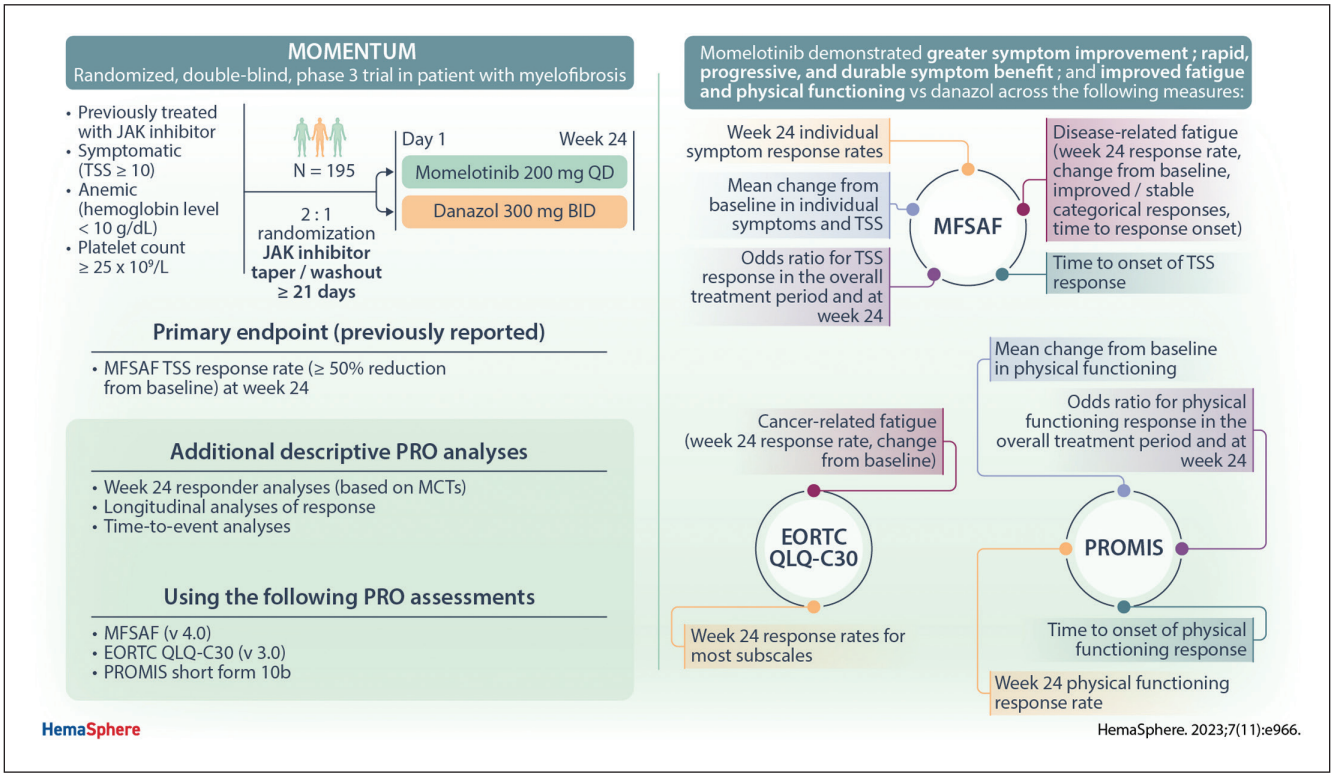
GRAPHICAL ABSTRACT



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Patient-reported Outcomes and Quality of Life in Anemic and Symptomatic Patients With Myelofibrosis: Results From the MOMENTUM Study

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ABSTRACT

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm that typically manifests with debilitating symptoms that progressively worsen, negatively impacting patients' quality of life. Fatigue is a multifactorial and burdensome MF-related symptom due to its severity, persistence, and prevalence, with anemia a contributing factor and major unmet need. Clinical trials of the Janus kinase (JAK)1/JAK2/activin A receptor type 1 inhibitor momelotinib have shown consistent anemia benefits, in addition to improvements in MF-related symptoms. The phase 3 MOMENTUM trial in symptomatic and anemic patients met its primary end point, with a greater proportion having a Myelofibrosis Symptom Assessment Form (MFSAF) Total Symptom Score (TSS) reduction ≥50% at week 24 with momelotinib versus danazol. To support the positive primary end point result, we conducted longitudinal, responder, and time-to-event analyses of patient-reported outcomes from MOMENTUM, as measured by the MFSAF, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and Patient-Reported Outcomes Measurement Information System (PROMIS) assessments. These analyses demonstrated rapid and durable response benefits with momelotinib, with achievement of first TSS response by day 29 and continued improvement over time. Improvements favored momelotinib versus danazol for each MFSAF individual item, and greater improvements were observed for disease- and cancer-related fatigue and physical functioning at week 24, with significant results for multiple items/domains across the 3 assessments. These findings are consistent in demonstrating that momelotinib provides substantial symptom benefit.

INTRODUCTION

Myelofibrosis (MF) is a chronic and progressive myeloproliferative neoplasm largely driven by dysregulated Janus kinase (JAK)-signal transducer and activator of transcription signaling, leading to uncontrolled myeloid proliferation, increased cytokine release, bone marrow fibrosis, and cytopenias (eg, thrombocytopenia and anemia).[1,2] Most patients with MF have high symptom burden due to debilitating constitutional symptoms (night sweats, fever, and weight loss), other systemic symptoms

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(eg, fatigue, bone pain, and pruritus), and symptoms associated with an enlarged spleen (abdominal pain and early satiety), all contributing to a severely compromised quality of life (QOL).[3,4] Symptoms become progressively disabling—as the number of symptoms from diagnosis increases, and emotional well-being, QOL, and ability to work decrease.[5–7] In the international MPN Landmark Survey, 90% of patients reported experiencing symptoms in the past 12 months; the majority reported that their symptoms reduced their QOL, including both activities of daily living (eg, family/social life) and work/productivity (eg, reduced work hours, sick leave, and job termination).[6,7] While high prognostic risk and symptom severity were associated with higher QOL impact, even respondents considered low prognostic risk or with the lowest symptom severity reported reduced QOL, demonstrating the substantial and wide-ranging impact of symptoms on patients.[6]

Fatigue is recognized as a predominant symptom in MF due to its severity, persistence, and high prevalence, resulting in drastically impaired QOL and diminished physical and social functioning.[8] In a survey of 207 patients with MF, 81% reported reduced QOL due to disease-related symptoms, of which fatigue was the most common and severe.[6] Additionally, a study evaluating symptoms in 293 patients with MF revealed that 96% experienced fatigue, which also represented the highest symptom intensity.[9] While drivers of fatigue in MF are diverse, including cytokine dysregulation and deconditioning, anemia may contribute to the weakness and fatigue experienced by patients.[8,10] However, fatigue is complex and multifactorial, and patients' activity levels and patient experience data (timing and duration of fatigue) must also be taken into account to accurately assess fatigue.[11]

Although JAK inhibitors are a mainstay of MF treatment, some approved JAK inhibitors (eg, ruxolitinib and fedratinib) do not address and may even exacerbate anemia, depending on disease phenotype, and none are specifically indicated to treat disease-associated anemia, potentially contributing to fatigue burden.[12,13] Momelotinib is a JAK inhibitor that blocks JAK1, JAK2, and activin A receptor type 1 (ACVR1) and has previously demonstrated clinical activity against anemia, symptoms, and splenomegaly in MF clinical trials.[12,14] Studies have shown that suppression of ACVR1-mediated hepcidin production leads to increased serum iron availability and erythropoiesis, resulting in anemia benefits, including the increased transfusion independence (TI) observed with momelotinib.[15–19]

Anemia benefits with momelotinib have been consistent across trials, but associated symptom improvement results have been more complex to interpret. In SIMPLIFY-1, momelotinib demonstrated symptom improvement in JAK inhibitor–naive patients, as assessed by the percentage of patients achieving a Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Total Symptom Score (TSS) reduction ≥50% at week 24 (secondary end point), but noninferiority of momelotinib to ruxolitinib was not met.[15] Notably, the prespecified noninferiority margin was based on a historical metric that did not include a measure of fatigue, which individual symptom analysis identified as the most prevalent and severe item reported at baseline in SIMPLIFY-1; the margin was also more conservative than the standard application of the fixed-margin method. Post hoc longitudinal mixed-effects model for repeated measures (MMRM) analysis showed similar changes from baseline in TSS on a continuous scale with momelotinib and ruxolitinib in both the intent-to-treat (ITT) and symptomatic (TSS ≥10) populations.[15,20] Meanwhile, in patients previously treated with ruxolitinib (SIMPLIFY-2), there was a nominally significant difference in favor of momelotinib versus best available therapy (88.5% ruxolitinib) in MPN-SAF TSS.[16] Because the threshold for superiority for the primary end point (splenic response rate [SRR]) was not met, symptoms could not be formally assessed. Findings from post hoc MMRM and individual item analyses further supported the TSS results.[16,20] Collectively, these symptom analyses across SIMPLIFY-1 and SIMPLIFY-2 not only highlight the symptom benefits associated with momelotinib but also illustrate the importance of considering patient-reported outcome (PRO) analyses beyond TSS response in assessing the impact of treatment on symptoms.

The effects of momelotinib in symptomatic patients were further explored in MOMENTUM, a randomized, phase 3 trial evaluating momelotinib versus danazol (an androgen) in symptomatic and anemic patients with MF previously treated with JAK inhibitor therapy.[17] Notably, to our knowledge, MOMENTUM is the first phase 3 trial to include Myelofibrosis Symptom Assessment Form (MFSAF) TSS response rate as the primary end point. The study met the primary end point with a significantly greater proportion of patients achieving a ≥50% reduction in MFSAF TSS from baseline with momelotinib versus danazol (25% versus 9%; $P = 0.01$). All key secondary end points were also met, demonstrating statistical noninferiority of momelotinib versus danazol in TI, with a numerically higher rate with momelotinib (30% versus 20%; $P = 0.012$), and statistical superiority in spleen volume reduction ≥25% (39% versus 6%; $P < 0.001$), mean TSS change from baseline (−11.5 versus −3.9; $P = 0.001$), spleen volume reduction ≥35% (22% versus 3%; $P = 0.001$), and rate of zero transfusions to week 24 (35% versus 17%; $P = 0.001$).[17] Several other PRO assessments, such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30),[21] Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form 10b,[22] and EuroQOL Five Dimension 5-Level (EQ-5D-5L),[23] were included as secondary end points to more thoroughly characterize the effects of momelotinib on the most clinically relevant symptoms and other aspects of QOL.[17] Here, we report results from the MOMENTUM study evaluating the effect of momelotinib on patient-reported health status and health-related QOL, including the impact on fatigue and physical function.

MATERIALS AND METHODS

MOMENTUM study design

MOMENTUM (NCT04173494) is a randomized, double-blind, global, phase 3 trial evaluating momelotinib plus placebo versus danazol plus placebo in anemic (hemoglobin <10 g/dL) and symptomatic (TSS ≥10 assessed by a single MFSAF v4.0 assessment at screening) patients who previously received approved JAK inhibitor therapy for MF for ≥90 days (≥28 days if therapy was complicated by ≥4 red blood cell units transfused in 8 weeks or grade 3/4 thrombocytopenia, anemia, or hematoma). Patients were randomized 2:1 to receive momelotinib 200 mg orally once daily plus placebo or danazol 300 mg orally twice daily plus placebo for 24 weeks. The primary end point was MFSAF TSS response rate at week 24 (≥50% reduction in mean TSS over the 28 days immediately before the end of week 24 compared with baseline). Key secondary end points included TI rate, SRR, change from baseline of mean TSS at week 24, and proportion of patients with zero red blood cell units transfused through week 24.[17]

PRO assessments

PRO assessments reported in this analysis included the MFSAF v4.0,[24] EORTC QLQ-C30 v3.0,[21] and PROMIS Short Form 10b.[22] All questionnaires were completed using an electronic device at the time points noted below.

MFSAF v4.0

The MFSAF v4.0 is an MF-specific symptom questionnaire comprising 7 individual item scores (fatigue, early satiety,

abdominal discomfort, night sweats, itching, bone pain, and rib pain assessed on an 11-point numeric rating scale ranging 0–10) and TSS (sum of the 7 individual item scores, representing a range of scores from 0 to 70; higher score corresponds to more severe symptoms). Patients were assessed at screening (≤6 weeks before randomization), baseline (average of the daily TSS for the 7 days before randomization), randomization (daily for week 1), and daily during the randomized phase from weeks 2 to 24. Change from baseline for MFSAF TSS was calculated for every 4-week period based on the average of consecutive 28-day periods for weeks 4, 8, 12, 16, 20, and 24 (at least 20 daily TSS readings in each 28-day period were required; otherwise, the score was reported as missing).

EORTC QLQ-C30

EORTC QLQ-C30 is a questionnaire that assesses the QOL of patients with cancer. It consists of 5 functional scales, 3 symptom scales, 1 Global Health Status (GHS)/QOL scale, and 6 single items, and scores range from 0 to 100; for functional and GHS/QOL scales, higher scores indicate better QOL, and for symptom scales, higher scores indicate more severe symptoms. Assessments were conducted at baseline and at weeks 12 and 24 during the randomized phase.

PROMIS Physical Function Short Form 10b

PROMIS is a bank of 124 items assessing various aspects of physical functioning based on self-reporting, and the Short Form 10b includes 10 of these items. PROMIS Short Form 10b was administered at baseline, at weeks 2 and 4, and then every 4 weeks during the randomized phase.

Statistical methods

Week 24 responder analyses

A data cutoff of December 3, 2021 was used for these analyses (consistent with the main analysis) and they were performed in the ITT population.[17] Descriptive responder analyses were performed for MFSAF individual items and TSS, EORTC QLQ-C30–derived scales and items, and PROMIS Short Form physical function total score for the scheduled visits in the randomized treatment period. The number and percentage of responders for improvement at week 24 by corresponding meaningful change threshold (MCT) were summarized (Suppl. Table S1). The distribution of change from baseline for nonresponders was further summarized as improvement of less than MCT and deterioration. All summaries were performed by the randomized treatment arm. The response rate was compared between treatments with the Cochran-Mantel-Haenszel test using nonresponder imputation (ie, missing response was considered nonresponse) for the primary week 24 responder analysis.

MMRM change from baseline

Longitudinal change from baseline scores were analyzed with MMRM using an unstructured covariance matrix.[20] The distribution of change from baseline was summarized by descriptive statistics.

Longitudinal analyses of response

Longitudinal analyses of response were performed for MFSAF TSS and PROMIS physical function total score by randomized treatment visit. Missing scores were imputed by multiple imputation first and transformed into response status based on the corresponding MCT (Suppl. Table S1). A generalized estimating equation (GEE) model was fitted on the data set, and the model included treatment effect, time point, treatment versus time point interaction, and stratification variables (except study sites). Odds ratio (OR) for response, 95% confidence interval (CI), and *P* value were derived from the GEE model and presented at each time point as the treatment effect (momelotinib versus danazol).

Time-to-event analyses

Time-to-event analysis was conducted for MFSAF TSS and individual items and for PROMIS physical function total score in the 24-week randomized treatment period. For each patient, time to first response was defined as the duration from the first dose to the date of first visit day with response and analyzed using the Kaplan-Meier method. Time to first response for patients without a response was censored at the last visit day with nonmissing response status, and patients without postbaseline measurements were censored at day 1. A stratified log-rank test with randomization stratification factors was performed to compare the treatment arms. Hazard ratio (HR) and its 95% CI were estimated from a stratified Cox regression model.

RESULTS

Study population and baseline characteristics

A total of 195 patients were randomized (130 to the momelotinib arm and 65 to the danazol arm). Of those patients, 94 (72.3%) in the momelotinib arm and 38 (58.5%) in the danazol arm completed randomized treatment; the most common reasons for early treatment discontinuation were adverse events and patient decision. Baseline characteristics and demographics were similar between the treatment arms. Full study population details and baseline characteristics have been previously published (Suppl. Table S2).[17]

MFSAF TSS and individual items

Responder analysis, TSS, and individual items

Data for MFSAF TSS and individual items at week 24 were available for 92 patients (70.8%) in the momelotinib arm and 37 patients (56.9%) in the danazol arm. As previously reported, the MFSAF TSS response rate based on percentage change (MCT ≥50%) was significantly higher with momelotinib (24.6% [32/130 patients]) versus danazol (9.2% [6/65 patients]; P = 0.01).[17] Similarly, TSS response rate by absolute change (MCT ≥19-point change) was also significantly higher with momelotinib versus danazol (16.2% versus 6.2%; P = 0.046).

Median improvements from baseline at week 24 were greater with momelotinib versus danazol in all individual items, with the greatest treatment difference with momelotinib versus danazol seen in night sweats, abdominal discomfort, bone pain, and rib pain (Figure 1A). Responder analyses also favored momelotinib versus danazol for all individual items, with significant differences in the same 4 items (Figure 1B). The proportion of patients who declined (defined as an increase/worsening in a score of >0 compared with baseline) was lower for all items in the momelotinib versus danazol arm, except for early satiety (itching was equivalent for both arms) (Suppl. Figure S1).

Least-squares mean change from baseline and MMRM

At week 4, mean (SD) change from baseline for MFSAF TSS was −5.67 (8.15) and −2.34 (6.02) with momelotinib and danazol, respectively. As previously reported, mean (SD) change from baseline was −11.5 (12.9) with momelotinib and −3.9 (11.9) with danazol at week 24.[17] Mean change from baseline for each of the individual MFSAF items showed improvement at every 4-week period in the momelotinib arm, and a greater magnitude of improvement was observed for each item at every time point in the momelotinib versus danazol arm, demonstrating superiority of momelotinib (Suppl. Table S3). MMRM analyses further showed that the least-squares (LS) mean difference, momelotinib versus danazol, for change from baseline in each individual item favored momelotinib (Table 1).

Longitudinal analysis of response

Longitudinal analysis of response (defined as ≥50% reduction) was performed for the MFSAF TSS after imputing

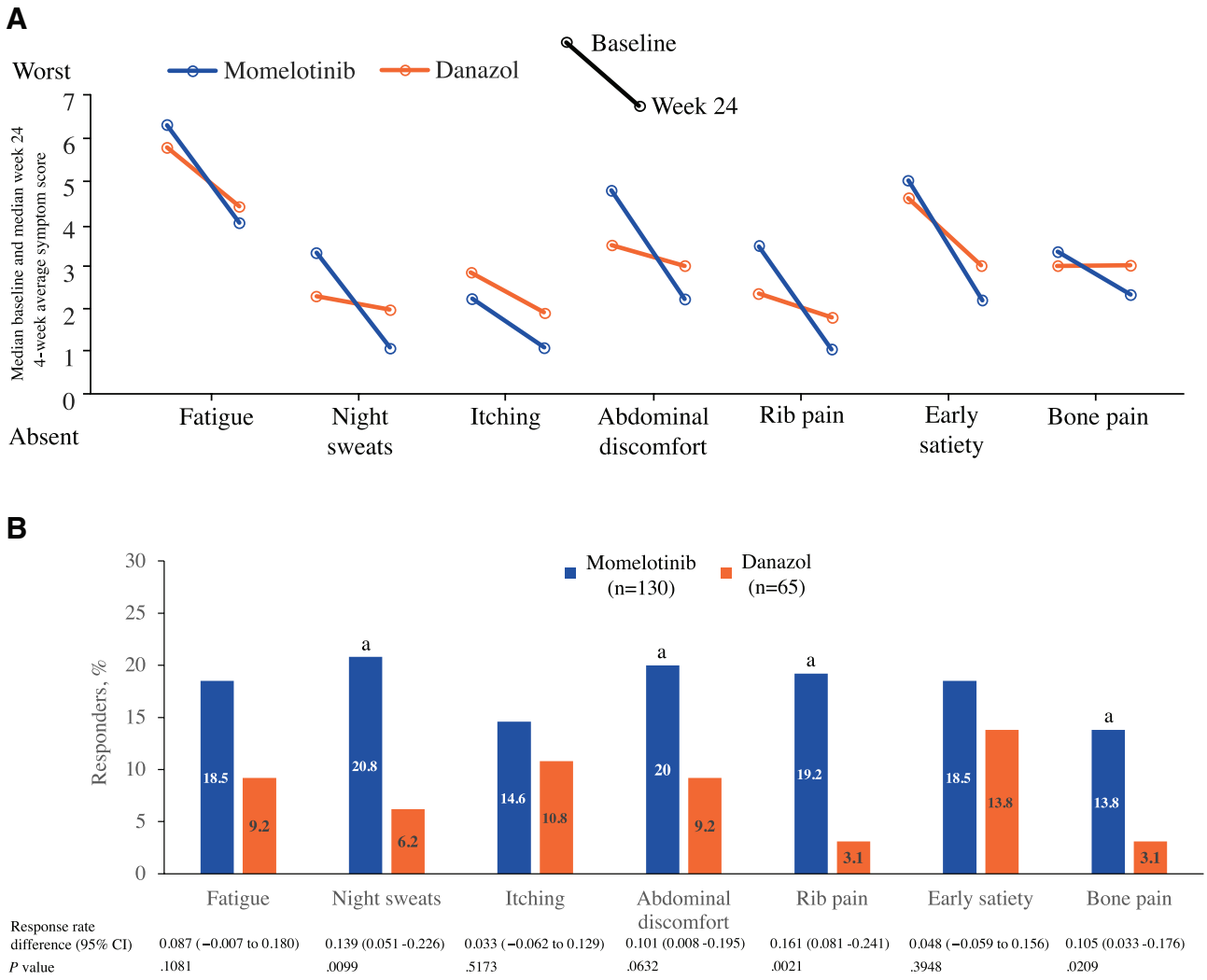


Figure 1. MFSAF individual item scores and descriptive responder analysis by corresponding MCTs. (A) MFSAF individual item scores at baseline and week 24 in the momelotinib and danazol arms. (B) Descriptive responder analysis for MFSAF at week 24; response was defined as a reduction from baseline ≥ MCT (≥3-point score reduction). Response rate difference and *P* values were stratified by Cochran-Mantel-Haenszel with missing week 24 results as nonresponders. [a]*P* < 0.05. MCT = meaningful change threshold; MFSAF = Myelofibrosis Symptom Assessment Form.

missing TSS raw scores with multiple imputation. Throughout the 24-week randomized period, the likelihood of improvement in MFSAF TSS based on percent change favored the momelotinib versus danazol arm. The OR for response in the overall treatment period was 2.5 (95% CI, 1.2-5.1), and the treatment effect favoring momelotinib was observed as early as week 8 and onward; at week 24, the OR (derived by a GEE model) was 2.3 (95% CI, 1.0-5.4).

Time-to-event analysis

The median time to first response, represented on the first day of the averaged 28-day period during which the MCT was achieved, was not reached for TSS with either momelotinib or danazol. First TSS response (≥50% reduction) by percent change for 25% of patients was achieved by day 29 (first day of the week 8 assessment) in the momelotinib arm and by day 57 (first day of the week 12 assessment) in the danazol arm (Figure 2). First TSS ≥−19-point change response by absolute change for 25% of patients was achieved by day 141 (first day of the week 24 assessment) with momelotinib and was not achieved with danazol (Suppl. Figure S2). For MFSAF TSS percent change (≥50%) and absolute change (≥−19 points), the proportion of patients with a response by any time point during randomized treatment was higher with momelotinib versus danazol.

Fatigue

Disease-related fatigue

Data on disease-related fatigue (one of the individual items in the MFSAF) were available for 92 patients (70.8%) in the momelotinib arm and 37 patients (56.9%) in the danazol arm at week 24. As shown in Figure 1B, responder analysis of the individual MFSAF fatigue item favored momelotinib versus danazol, with a higher proportion of patients demonstrating improvement (MCT defined as ≥3-point reduction from baseline) in MFSAF disease-related fatigue at week 24 ($P = 0.108$). Categorical response analysis for the MFSAF disease-related fatigue item showed a greater proportion of patients who improved or remained stable with momelotinib (56.2%) versus danazol (36.9%) (Suppl. Figure S1). Mean (SD) change from baseline for the MFSAF fatigue item was −1.79 (2.20) and −0.81 (2.36) at week 24 in the momelotinib and danazol arms, respectively. The proportion of patients with MFSAF fatigue response at week 24 was higher in the momelotinib versus danazol arm, with an HR for time to first response at any time in the randomized period demonstrating a trend in favor of momelotinib (Figure 3). MMRM analysis showed that the LS mean difference, momelotinib versus danazol (SE), for disease-related fatigue by MFSAF was −0.71 (0.36; $P = 0.051$; Table 2).

Of the 38 patients in the momelotinib arm who were transfusion independent (TI) at week 24 (no red blood cell or whole blood transfusions and all hemoglobin levels ≥8 g/dL in the last 12 weeks of the 24-week randomized treatment period) and also had fatigue data, 13 (34.2%) showed an MFSAF fatigue response (≥3-point score reduction), and 33 (86.8%) had some improvement in fatigue (>0-point score reduction). Of the 13 patients in the danazol arm who were TI and also had fatigue data at week 24, two (15.4%) were fatigue responders, and 8 (61.5%) had some improvement in fatigue. Of patients with baseline and week 24 data, 11 of 54 (20.4%) who were not TI at week 24 in the momelotinib arm and 4 of 24 (16.7%) who were not TI at week 24 in the danazol arm were fatigue responders. Similarly, hemoglobin improvements of ≥1 g/dL from baseline at week 24 were noted in both fatigue responders and nonresponders. Among 83 patients in the momelotinib arm evaluable for hemoglobin response, 14 of 43 hemoglobin responders (32.6%) were also fatigue responders, while 29 of 43 (67.4%) were not. Among 29 evaluable patients in the danazol arm, 4 of 16 hemoglobin responders (25.0%) were also fatigue responders, while 12 of 16 (75.0%) were not.

Table 1

Treatment Differences Using MMRM in MFSAF Individual Item Change From Baseline Score at Week 24

MFSAF Individual Item Score	LS Mean Difference (95% CI)[a,b]
Fatigue	–0.71 (–1.42 to 0)
Night sweats	–1.27 (–2.00 to –0.53)[c]
Itching	–0.31 (–1.14 to 0.51)
Abdominal discomfort	–1.11 (–1.91 to –0.31)[c]
Rib pain	–0.80 (–1.54 to –0.05)[c]
Early satiety	–0.78 (–1.58 to 0.01)
Bone pain	–1.19 (–1.92 to –0.46)[c]

[a]Based on MMRM adjusted for baseline MFSAF TSS (≥22 vs <22), baseline palpable spleen length below the LCM (≥12 vs <12 cm), and baseline RBC or whole blood units transfused in the 8-wk period before randomization (0, 1–4, ≥5 units).
[b]Negative LS mean difference values indicate that the treatment benefit in the momelotinib arm was greater than treatment benefit in the danazol arm.
[c]95% CI does not cross zero.
CI = confidence interval; LCM = left costal margin; LS = least squares; MFSAF = Myelofibrosis Symptom Assessment Form; MMRM = mixed-effects model for repeated measures; RBC = red blood cell; TSS = Total Symptom Score.

Cancer-related fatigue

Data for the EORTC QLQ-C30 cancer-related fatigue subscale were available for 89 of 130 patients (68.5%) in the momelotinib arm and 35 of 65 patients (53.8%) in the danazol arm at week 24. Momelotinib was superior to danazol, with a significant proportion difference of 20% between momelotinib and danazol and a response rate difference of 0.21 (95% CI, 0.07-0.33; $P = 0.005$). Change from baseline analysis using MMRM showed that the LS mean difference (SE) for cancer-related fatigue by EORTC QLQ-C30 was –10.82 (4.21; $P = 0.011$; Table 2).

EORTC QLQ-C30 domains

Responder analysis

Similar to the availability of data for the cancer-related fatigue subscale, data for all other EORTC QLQ-C30 domains were available for 89 of 130 patients (68.5%) in the momelotinib arm and 35 of 65 patients (53.8%) in the danazol arm at week 24, except for the constipation domain in the momelotinib arm (completed by 88 patients [67.7%]) and the insomnia, appetite loss, and constipation domains in the danazol arm (completed by 34 patients [52.3%]) (Figure 4). The proportion of patients who met the response rate definition (based on corresponding MCTs) was higher in the momelotinib versus danazol arm for most subscales (similar for nausea and vomiting and constipation, equivalent for dyspnea, and lower for diarrhea). For the GHS/QOL scale, a significant difference was observed, with a higher proportion of patients experiencing improvement with momelotinib versus danazol (36.2% versus 21.5%). The proportion of patients who reported an improvement in pain, fatigue, insomnia, social functioning (ability to fulfill one's role within various environments, including work, social activities, and relationships with partners and family), and role functioning (ability to perform daily activities, leisure time activities, and work) subscales were significantly higher with momelotinib versus danazol ($P < 0.05$).

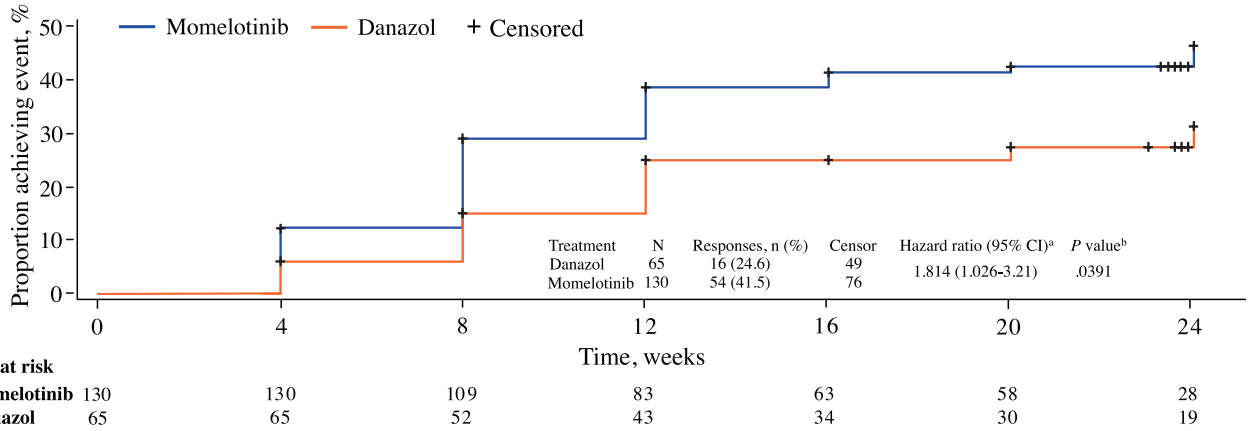


Figure 2. Time to first MFSAF total symptom score percent change response in randomized treatment period. [a]Hazard ratio (momelotinib divided by danazol) is from stratified Cox proportional hazards model with a single factor of treatment group, stratified by baseline MFSAF TSS (≥22 vs <22), baseline palpable spleen length below the LCM (≥12 vs <12 cm), and baseline RBC or whole blood units transfused in the 8-wk period before randomization (0, 1–4, and ≥5). [b]*P* value is from log-rank test stratified by baseline MFSAF TSS (≥22 vs <22), baseline palpable spleen length below the LCM (≥12 vs <12 cm), and baseline RBC or whole blood units transfused in the 8-wk period before randomization (0, 1–4, and ≥5). LCM = left costal margin; MFSAF = Myelofibrosis Symptom Assessment Form; RBC = red blood cell; TSS = Total Symptom Score.

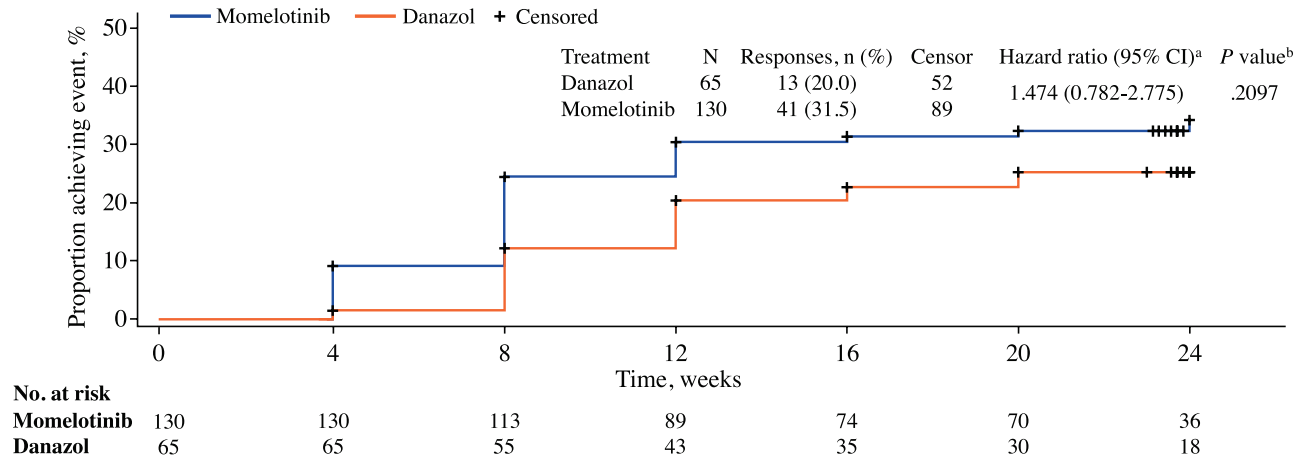


Figure 3. Time to first MFSAF fatigue response in randomized treatment period. [a]Hazard ratio (momelotinib divided by danazol) is from stratified Cox proportional hazards model with a single factor of treatment group, stratified by baseline MFSAF TSS (≥22 vs <22), baseline palpable spleen length below the LCM (≥12 vs <12 cm), and baseline RBC or whole blood units transfused in the 8-wk period before randomization (0, 1–4, and ≥5). [b]*P* value is from log-rank test stratified by baseline MFSAF TSS (≥22 vs <22), baseline palpable spleen length below the LCM (≥12 vs <12 cm), and baseline RBC or whole blood units transfused in the 8-wk period before randomization (0, 1–4, and ≥5). LCM = left costal margin; MFSAF = Myelofibrosis Symptom Assessment Form; RBC = red blood cell; TSS = Total Symptom Score.

Table 2

Treatment Differences Using MMRM in Disease-Related Fatigue (MFSAF), Cancer-Related Fatigue (EORTC QLQ-C30), and Physical Function (PROMIS) by Change From Baseline Score at Week 24

Change From Baseline at week 24	Momelotinib (n = 130)	Danazol (n = 65)
Disease-related fatigue by MFSAF		
LS mean (SE)[a]	−1.53 (0.20)	−0.82 (0.31)
LS mean difference (SE)[a]	−0.71 (0.36)	
95% CI[a]	−1.42 to 0	
P value[b]	0.051	
Cancer-related fatigue by EORTC QLQ-C30		
LS mean (SE)[a]	−14.34 (2.35)	−3.52 (3.65)
LS mean difference (SE)[a]	−10.82 (4.21)	
95% CI[a]	−19.15 to −2.48	
P value[b]	0.011	
Physical function by PROMIS		
LS mean (SE)[a]	1.19 (0.77)	−0.11 (1.21)
LS mean difference (SE)[a]	1.31 (1.42)	
95% CI[a]	−1.49 to 4.11	
P value[b]	0.357	

[a]Based on MMRM adjusted for baseline MFSAF TSS (≥22 vs <22), baseline palpable spleen length below the LCM (≥12 vs <12 cm), and baseline RBC or whole blood units transfused in the 8-wk period before randomization (0, 1–4, and ≥5 units).

[b]*P* value for LS mean difference between the 2 arms from the MMRM.

CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; LCM = left costal margin; LS = least squares; MFSAF = Myelofibrosis Symptom Assessment Form; MMRM = mixed-effects model for repeated measures; PROMIS = Patient-Reported Outcomes Measure Information System; RBC = red blood cell; TSS = Total Symptom Score.

Physical function

Responder analysis and MMRM

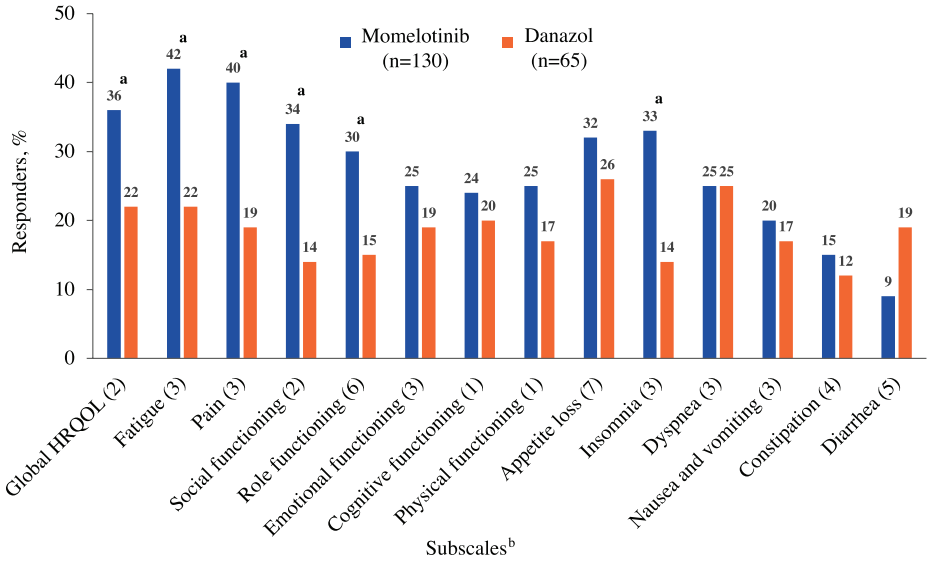
Data for the PROMIS physical function assessments were available for 89 of 130 patients (68.5%) in the momelotinib arm and 32 of 65 patients (49.2%) in the danazol arm at week 24. Momelotinib was associated with a significantly greater response rate (defined as a reduction of ≥6 points) versus danazol for physical function based on the Short Form 10b (*P* = 0.014) (Figure 5). Mean (SD) change from baseline in physical function based on the Short Form 10b was 1.94 (8.74) with momelotinib versus 0.22 (5.79) with danazol, and the LS mean difference per MMRM analysis was 1.31 (SE, 1.42; [95% CI, −1.49 to 4.11]; *P* = 0.357) (Table 2). Longitudinal analysis of response showed that the likelihood of improvement in the Short Form 10b raw score trended in favor of the momelotinib arm for every time point in the randomized treatment period. The OR for response was 1.7 (95% CI, 0.8-3.6) in the overall treatment period and 1.7 (95% CI, 0.6-4.8) at week 24.

Time-to-event analysis

Time to first response was assessed for PROMIS physical function 10b total score (Figure 6). Median time to first response was 24.6 weeks with momelotinib and not estimable with danazol. For 25% of patients, first response for the PROMIS physical function 10b total score was achieved by day 84 (week 12) in the momelotinib arm and not estimable in the danazol arm. The proportion of PROMIS physical function 10b total score response events was higher in the momelotinib versus danazol arm. The proportion of patients with a response at any time point during the randomized treatment was also higher with momelotinib versus danazol, and the HR favored momelotinib for each additional PROMIS question.

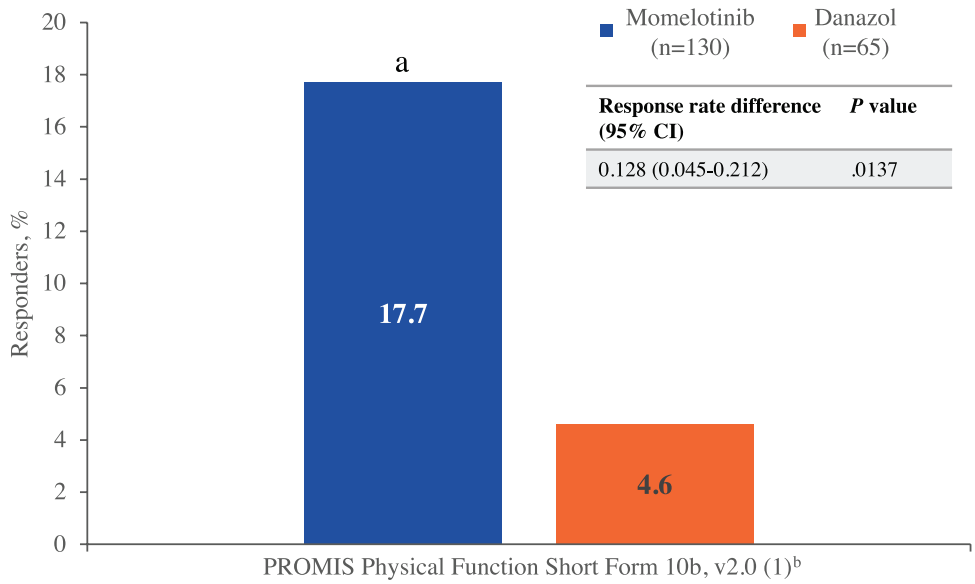
DISCUSSION

The descriptive responder, longitudinal responder, and time-to-event analyses described in this study support the primary end point of MOMENTUM in demonstrating that patients who received momelotinib derived proportionally greater and consistent improvement in symptoms compared with those who received danazol across multiple PRO assessments based on their corresponding MCTs at week 24. The increasing magnitude of response and results from time-to-event analyses showed rapid, progressive, and durable symptom benefit of momelotinib in patients with MF, as evidenced by achievement of first TSS reduction ≥50% by day 29 and continued improvement of MFSAF TSS at every 4-week period. Improvements favored momelotinib for each MFSAF individual item, including significantly increased proportions of responders for night sweats, abdominal discomfort, rib pain, and bone pain. Notably, patients treated with momelotinib also experienced greater



	Response rate difference (95% CI)	*P* value
Global HRQOL	0.146 (0.015-0.277)	.0401
Fatigue	0.206 (0.073-0.339)	.0053
Pain	0.209 (0.083-0.336)	.0030
Social functioning	0.209 (0.092-0.326)	.0020
Role functioning	0.144 (0.020-0.267)	.0314
Emotional functioning	0.071 (–0.050 to 0.192)	.2683
Cognitive functioning	0.051 (–0.073 to 0.174)	.4375
Physical functioning	0.067 (–0.051 to 0.186)	.2888
Appetite loss	0.074 (–0.067 to 0.215)	.2983
Insomnia	0.205 (0.088-0.322)	.0028
Dyspnea	0.001 (–0.129 to 0.132)	.9833
Nausea and vomiting	0.033 (–0.080 to 0.146)	.5875
Constipation	0.026 (–0.04 to 0.126)	.6251
Diarrhea	–0.087 (–0.193 to 0.020)	.0945

Figure 4. Descriptive responder analysis for EORTC QLQ-C30 at week 24 by corresponding MCTs. Response rate difference and *P* values were stratified by Cochran-Mantel-Haenszel with missing week 24 results as nonresponders. [a]*P* < 0.05; [b]Response was defined as a reduction from baseline ≥MCT; MCT defined as >(1) 7-, (2) 8-, (3) 9-, (4) 10-, (5) 11-, (6) 12-, and (7) 13-point improvement from baseline. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HRQOL = health-related quality of life; MCT = meaningful change threshold.



Response rate difference (95% CI)	*P* value
0.128 (0.045-0.212)	.0137

Figure 5. Descriptive responder analysis for PROMIS at week 24 by corresponding MCTs. Response rate and *P* values were stratified by Cochran-Mantel-Haenszel with missing week 24 results as nonresponders. [a]*P* < 0.05; [b]Response was defined as a reduction from baseline ≥MCT; MCT defined as >(1) 6-point score reduction from baseline. MCT = meaningful change threshold; PROMIS = Patient-Reported Outcomes Measure Information System.

improvement in both disease-related (MFSAF) and cancer-related (EORTC QLQ-C30) fatigue, and a higher proportion of patients demonstrated improvement in physical functioning (PROMIS, EORTC QLQ-C30) at week 24 versus those treated with danazol.

Consistent with the individual item analysis results from SIMPLIFY-1,[15,20] the baseline scores for fatigue were higher (patients experienced more fatigue) than those of other symptoms in this current analysis. Nevertheless, a higher proportion of patients experienced an improvement in MFSAF disease-related fatigue with momelotinib versus danazol at week 24, and more patients who were TI at week 24 with momelotinib versus danazol showed improvement in fatigue. Additionally, the cancer-specific EORTC QLQ-C30 fatigue subscale showed a significant proportion difference favoring momelotinib versus danazol ($P = 0.005$). The MFSAF v4.0 includes 1 question asking patients how severe their worst MF-related fatigue was during the past 24 hours, which is averaged over a 28-day period, whereas the EORTC QLQ-C30 evaluates general fatigue over the past week via 3 questions. Differences in assessment may contribute to variance in fatigue outcomes, although trends between the 2 tests both favored improvement with momelotinib. For physical function, a significantly greater response was observed with momelotinib versus danazol, and a higher proportion of PROMIS physical function 10b total score response events occurred with momelotinib versus danazol. These results

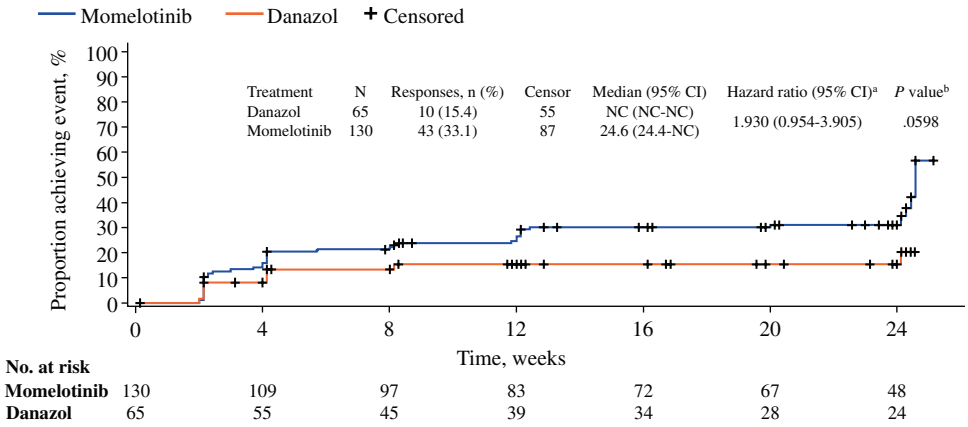


Figure 6. Time to first PROMIS physical function short form 10b response. [a]Hazard ratio (momelotinib divided by danazol) is from stratified Cox proportional hazards model with a single factor of treatment group, stratified by baseline MFSAF TSS (≥22 vs <22), baseline palpable spleen length below the LCM (≥12 vs <12 cm), and baseline RBC or whole blood units transfused in the 8-wk period before randomization (0, 1–4, and ≥5). [b]*P* value is from log-rank test stratified by baseline MFSAF TSS (≥22 vs <22), baseline palpable spleen length below the LCM (≥12 vs <12 cm), and baseline RBC or whole blood units transfused in the 8-wk period before randomization (0, 1–4, and ≥5). LCM = left costal margin; MFSAF = Myelofibrosis Symptom Assessment Form; NC = not calculable; PROMIS = Patient-Reported Outcomes Measure Information System; RBC = red blood cell; TSS = Total Symptom Score.

collectively demonstrate the positive impact of momelotinib on MF-associated symptoms, particularly fatigue and physical function, which may be driven in part by its effects on anemia, meeting a key unmet need and improving the QOL of patients with MF.

Anemia is a negative prognostic factor for survival in patients with MF, and ≥50% present with symptomatic anemia at the time of diagnosis.[25] Additionally, anemia has consistently been correlated with inferior QOL.[25,26] In a survey of 1179 patients with myeloproliferative neoplasms, 81% reported fatigue, which was a substantially higher rate than that of any other symptom, and the presence of anemia correlated with a stepwise increase in fatigue. Fatigue was reported as the main barrier to partaking in physical activity.[10] Therefore, effective treatment options for MF-related anemia and associated symptoms represent a substantial medical need. Momelotinib's mechanism of action, through the inhibition of JAK1, JAK2, and ACVR1, has been associated with improvement in anemia end points, including TI.[18] Thus, MOMENTUM was designed to evaluate momelotinib versus danazol in symptomatic patients with moderate-to-severe anemia. Although momelotinib demonstrated both symptom and anemia benefits, and a greater proportion of TI patients also showed fatigue improvement, some patients who did not achieve TI also showed fatigue improvement, demonstrating both that fatigue in MF is not attributable to anemia alone and that anemia benefits do not fully account for the symptom benefits of momelotinib. Potential alternative mechanisms of fatigue improvement may include reduced cytokine production leading to reduced inflammation, or reduction in spleen volume improving overall patient well-being. This is consistent with previous literature on JAK inhibitors such as ruxolitinib, which is not associated with anemia benefit but was shown to reduce fatigue in the COMFORT trials.[5,27,28] It is also possible that some patients experienced an anemia benefit with momelotinib that was not captured by the strict TI end point, such as reduced transfusion burden over time[29] that nevertheless may have contributed to fatigue improvement.

Momelotinib enhances patient global QOL by not only treating MF (ie, reducing spleen size and improving disease symptoms), but also by reducing inflammation associated with MF, decreasing hematologic toxicity, and improving anemia,[30] as evidenced by the results in this analysis. Most EORTC QLQ-C30 scales showed greater improvement with momelotinib versus danazol, including significant differences in the GHS/QOL, pain, fatigue, insomnia, social functioning, and role functioning subscales. Collectively, achieving significance on these diverse subscales suggests that momelotinib comprehensively improves patients' symptoms (eg, pain, fatigue, and insomnia), role functioning (ability to perform activities of daily living, including chores, leisure time activities, and work), and social functioning (ability to fulfill one's roles within various environments), ultimately enhancing multiple aspects of QOL.

Despite the extensive results obtained by using multiple assessment tools (MFSAF, EORTC QLQ-C30, and PROMIS Short Form 10b), the methods of evaluating and scoring—including differences in frequency of assessments—vary for each tool and therefore any changes that occurred during the times between assessments may have been missed and potential correlations between assessments could not be determined, representing a limitation of the present analysis. Furthermore, although patient-reported fatigue (EORTC QLQ-C30 domain) was a secondary end point of MOMENTUM, the trial was not designed to investigate the relationship between anemia and symptoms, including fatigue; thus, this likely multifactorial relationship cannot be further evaluated or formally defined based on the present study. Finally, treatment with danazol was not necessarily expected to improve symptoms,[25,31] as TSS data had never been formally captured and reported in the literature; however, danazol was chosen as the comparator arm in MOMENTUM based on the guidelines for the management of MF-associated anemia—9% of patients randomized to danazol did achieve a TSS response, and modest improvements were observed for the other PRO measures captured in this study.[17] The phase 3 SIMPLIFY-1 and SIMPLIFY-2 studies provide some evidence of the symptom benefits of momelotinib versus ruxolitinib, an active comparator expected to improve symptoms; while statistical significance varied across trials and analyses, these studies collectively suggest that symptom benefits are comparable.[15,16,20]

Nevertheless, consistent with the positive primary end point result of MOMENTUM (≥50% reduction in mean TSS at week 24 from baseline), these responder, longitudinal, and time-to-event analyses demonstrate that momelotinib provides comprehensive improvements in disease-related symptoms with associated improvement in physical function and overall health-related QOL compared with danazol in patients with MF.[17] Momelotinib showed significantly greater symptom and QOL improvement compared with danazol at week 24

for fatigue, abdominal discomfort, night sweats, pain, physical function, social functioning, role functioning, insomnia, and global health-related QOL as measured by the MFSAF, EORTC QLQ-C30, and PROMIS assessments. Taken together, the MOMENTUM results demonstrated superior symptom response with momelotinib compared with danazol in patients with MF who were symptomatic, anemic, and previously treated with an approved JAK inhibitor.

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AUTHOR CONTRIBUTIONS

RAM contributed to the study design and collected and analyzed the data. CH, JMP, VG, DPM, LF, MLF, DMR, STO, and ACP collected and interpreted the data. MFM, J-JK, UP, AJM, and MFL contributed to data interpretation. JK and SD contributed to the study design and analyzed and interpreted the data. SR and RD contributed to the study design, data acquisition, and data analysis. BG analyzed and interpreted the data. SV contributed to the study design and data interpretation. All authors participated in writing, reviewing, and editing the article, and approved the final version for submission.

DATA AVAILABILITY

Sierra Oncology, a GSK company, commits to sharing clinical study data with qualified researchers to enable enhancement of public health. As such, Sierra will share anonymized patient-level data on request or if required by law or regulation. Qualified scientific and medical researchers can request patient-level data for studies of Sierra pharmaceutical substances listed on ClinicalTrials.gov and approved by health authorities in the USA and the EU. Patient-level data for studies of newly approved pharmaceutical substances or indications can be requested 9 months after US Food and Drug Administration and European Medicines Agency approvals. Such requests are assessed at Sierra's discretion, and the decisions depend on the scientific merit of the proposed request, data availability, and the purpose of the proposal. If Sierra agrees to share clinical data for research purposes, the applicant is required to sign an agreement for data sharing before data release, to ensure that the patient data are deidentified. In case of any risk of reidentification of anonymized data despite measures to protect patient confidentiality, the data will not be shared. The patients' informed consent will always be respected. If the anonymization process will provide futile data, Sierra will have the right to refuse the request. Sierra will provide access to patient-level clinical trial analysis datasets in a secured environment upon execution of the data sharing agreement. Sierra will also provide the protocol, statistical analysis plan, and the clinical study report synopsis if needed. For additional information or requests for access to Sierra clinical trial data for research purposes, please contact us at GSKClinicalSupportHD@ gsk.com.

DISCLOSURES

RAM has consulted and received honoraria from Novartis, Sierra Oncology, Gentech, Blueprint, Geron, Telios, CTI, Incyte, BMS, AbbVie, GSK and Morphosys. CH has consulted for Galecto DISC and Keros and received compensation; received honoraria from Novartis, CTI, BMS, Sierra, and GSK; participated on an Ad Board for AOP, Telios, Sumitomo, and Keros; and had a leadership role in EHA, HemaSphere, and MPN Voice. VG has consulted for Novartis, BMS Celgene, Sierra Oncology, AbbVie, Constellation Biopharma, Pfizer, GSK Pharma, and CTI Biopharma and received compensation; received honoraria from Novartis and BMS Celgene; and received compensation for participation on an Ad Board for BMS Celgene, Roche, AbbVie, Pfizer, Sierra Oncology, and CTI Biopharma. DPM received a research grant from Imago Biosciences; received honoraria from JAZZ Pharma, AbbVie, and Novartis; participated in the UK ALL RIC TRIAL – DSM board and is an EBMT Scientific Council Member Chair of the EBMT CMWP. MFM received honoraria from Novartis, Abbvie, and AOP; and received compensation for participation on an Ad Board from Novartis, BMS, AbbVie, CTI, Sierra Oncology, and GSK. J-JK received compensation and participated in Ad Boards for Novartis, AbbVie, BMS, GSK, Incyte, and AOP Health. LF received honoraria from Novartis and BMS and participated in Ad Boards for Incyte and GS. MLF has consulted for Novartis, GSK, AbbVie, and Sierra Oncology and received compensation; and received honoraria from Novartis and BMS and attended meetings for AbbVie. DMR has consulted for Keros, and the institution received compensation; received honoraria from Novartis personally and to the institution; received compensation from Novartis to attend a meeting; received compensation to the institution for participation on an Ad Board from Novartis, Menarini, and Takeda. STO has consulted for AbbVie, Constellation, CTI BioPharma, BMS, Geron, Sierra Oncology, Cogent, Protagonist, and Incyte and received compensation. JK owned stock in Sierra Oncology and owns stock in Gilead. SR and RD owned stock in Sierra Oncology. SD is an employee at Sierra Oncology. BG received compensation from GSK for attending meetings and owns stock in GSK. SV received compensation for participation on an Ad Board. UP received honoraria and research support from Geron, GSK, Novartis, Abbvie, and Curis. JMP received honoraria to the institution from CTI; and received compensation to the institution for participation in an Ad Board for Morphosys. AJM received support from Abbvie for the present article; received grants or contracts from Celgene/BMS; received royalties or licenses from Alethiomics; received consulting fees from Celgene/BMS paid to the Sierra Oncology, Novartis paid to Karyopharm, Abbvie paid to Sensyn, and CTI paid to Incyte, Galecto, Pfizer, and Gilead; received honoraria from Celgene/BMS, Novartis, and Abbvie; received support to attend meetings from Celgene/BMS and Novartis; and participated on an Ad Board for Celgene/BMS and Abbvie. All authors received medical writing support for this article funded by Sierra Oncology, a GSK company. All the other authors have no conflicts of interest to disclose.

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