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Fedratinib Improves Myelofibrosis-related Symptoms and Health-related Quality of Life in Patients with Myelofibrosis Previously Treated with Ruxolitinib: Patient-reported Outcomes from the Phase II JAKARTA2 Trial

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Abstract

Myelofibrosis symptoms compromise health-related quality of life (HRQoL). Ruxolitinib can reduce myelofibrosis symptom severity, but many patients discontinue ruxolitinib due to loss of response or unacceptable toxicity. Fedratinib is an oral, selective JAK2 inhibitor approved in the United States for treatment of patients with intermediate-2 or high-risk myelofibrosis. The single-arm, phase II JAKARTA2 trial assessed fedratinib 400 mg/d (starting dose) in patients with myelofibrosis previously treated with ruxolitinib. Patient-reported changes in myelofibrosis symptom severity using the modified Myelofibrosis Symptom Assessment Form (MFSAF), and overall HRQoL and functional status using the EORTC QLQ-C30, were evaluated at each cycle. Clinically meaningful changes from baseline HRQoL scores were based on effect sizes. Ninety patients were MFSAF-evaluable. Myelofibrosis symptoms were mild-to-moderate at baseline. Patients showed statistically significant and clinically meaningful improvements in total symptom scores from baseline on the MFSAF at all post baseline visits through the end of cycle 6 (EOC6). Baseline global health status/QoL and functional domain scores on the EORTC QLQ-C30 were meaningfully worse than in the general population. At EOC6, 44% of patients reported clinically meaningful improvements in global health status/QoL, and 30%–53% of patients experienced clinically meaningful improvement in QLQ-C30 functional domains across post baseline timepoints. Over 80% of ongoing patients perceived fedratinib as beneficial on the Patient's Global Impression of Change questionnaire. Fedratinib effects were consistent among prognostically relevant patient subgroups. Patients with myelofibrosis previously treated with ruxolitinib experienced clinically meaningful improvements in myelofibrosis symptom burden, overall HRQoL, and functional status in the first 6 months of fedratinib treatment.

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Introduction

Myelofibrosis (MF) is a serious, life-threatening myeloproliferative neoplasm (MPN) characterized by stem cell-derived clonal myeloproliferation, abnormal cytokine expression, bone marrow fibrosis, splenomegaly, extramedullary hematopoiesis, constitutional symptoms, cachexia, leukemic progression, and shortened survival.[1] Patients with MF can experience substantially compromised health-related quality of life (HRQoL) as a result of disease-related constitutional symptoms (night sweats, fatigue, and weight loss), symptoms resulting from hepatosplenomegaly (early satiety, pain under the ribs on the left side, and abdominal discomfort), treatment-related toxicities, and the need for blood transfusions.[2,3] Patients with MF report worse HRQoL than those with other *BCR-ABL*-negative MPNs (polycythemia vera [PV] and essential thrombocythemia [ET]).[4] Until recently, ruxolitinib, a JAK1/JAK2 inhibitor, was the only approved treatment for intermediate- or high-risk MF. Ruxolitinib treatment has been shown to induce improvements in spleen volume and severity of MF symptoms, but some patients may discontinue ruxolitinib within a few years due to loss of response or tolerability concerns.[5,6] In the phase III COMFORT-I and COMFORT-II clinical trials, ruxolitinib discontinuation rates in patients with MF were approximately

50% at 3 years and ~75% at 5 years.[7–10] Prognosis after ruxolitinib failure is generally poor; median survival after treatment discontinuation can range from 6 months to 2 years.[6,11,12]

Fedratinib (INREBIC) is an oral, selective inhibitor with activity against wild-type and mutationally activated *JAK2* and *FLT3*.[13] The National Comprehensive Cancer Network Clinical Practice Guidelines for MPNs currently recommend fedratinib (400 mg/d QD) and ruxolitinib (5–20 mg/d BID, depending on pretreatment platelet count) as initial MF treatment for patients with platelet counts of ≥ 50 × 10^9/L, and fedratinib is recommended as the second-line therapy for patients previously treated with ruxolitinib.[14] The single-arm, phase II JAKARTA2 trial assessed the safety and efficacy of fedratinib 400 mg/d (starting dose) in patients with intermediate- or high-risk MF previously exposed to ruxolitinib.[15] Patients in JAKARTA2 generally had advanced MF disease features, including low platelet counts and hemoglobin levels and substantial splenomegaly, and had received multiple prior MF-directed therapies. The primary endpoint of the JAKARTA2 study was the spleen volume response rate after 6 cycles of fedratinib therapy, defined as the proportion of patients achieving a spleen volume reduction of ≥ 35% from baseline at the end of treatment cycle 6 (EOC6). Despite prior treatment with ruxolitinib, 31% of patients enrolled in JAKARTA2 achieved a spleen volume response at EOC6, which is similar to the spleen volume response rate in JAK-inhibitor-naïve patients receiving fedratinib in the placebo-controlled phase III JAKARTA trial.[15,16] Patient-reported changes in MF symptom severity and HRQoL were secondary and exploratory endpoints of JAKARTA2. Described here are results of three patient-reported assessments of: (1) the impact of fedratinib on MF-related symptom burden, (2) overall HRQoL and functional status, and (3) perceptions of the overall benefit of treatment, during the first 6 fedratinib treatment cycles in the JAKARTA2 trial.

Methods

Study design and eligibility criteria

The phase II, international, multicenter, open-label, single-arm JAKARTA2 study was conducted at 40 sites in 10 countries. The study protocol was approved by relevant independent ethics committees or institutional review boards at each site. All patients provided written informed consent before study participation. The study is registered on ClinicalTrials.gov (NCT01523171).

Detailed study design and eligibility criteria have been described previously.[15,17] Briefly, eligible patients were adults with primary, post-PV or post-ET MF; Dynamic International Prognostic Scoring System (DIPSS)[18] defined intermediate-1 (with symptoms), intermediate-2, or high risk disease; palpable splenomegaly ≥ 5 cm below the left costal margin; Eastern Cooperative Oncology Group (ECOG) performance status scores ≤ 2; and platelet counts ≥ 50 ×10^9/L. Although no formal criteria for ruxolitinib failure existed at the time of study initiation, all patients must have been considered by their treating investigator to be resistant to ruxolitinib following ≥ 14 days of therapy, or intolerant to ruxolitinib following any duration treatment (Supplemental Digital Figure 1, http://links.lww.com/HS/A145). All patients were to receive oral fedratinib at a starting dose of 400 mg/d for at least 6 continuous 28-day treatment cycles. Fedratinib dose escalation to 600 mg/d was permitted for patients who showed a < 50% reduction in spleen size by palpation from baseline at the end of cycle 2 or cycle 4.

Myelofibrosis symptom assessment form

The myelofibrosis symptom assessment form (MFSAF)[3] is an evidence-based brief inventory used to measure symptomatic response to treatment from the patient's perspective. The JAKARTA2 study employed a modified version of the MFSAF (version 2.0) comprising 6 key MF symptoms: night sweats, pruritus, early satiety, pain under ribs on the left side, abdominal discomfort, and bone or muscle pain, each scored from 0 (absent) to 10 (worst imaginable). During the 6-cycle treatment period, patients were to complete the MFSAF by electronic diary once-daily for 7 days before the beginning of each cycle, beginning 7 days before cycle 1, day 1 (C1D1; "baseline"), and prior to the EOC6. The weekly total symptom score (TSS) was the average of the nonmissing daily TSS during the 7 days preceding each post baseline visit. Scores were nonmissing if the daily TSS was reported in ≥ 5 of those 7 days. Weekly TSS ranged from 0 to 60, with a higher score indicating a worse level of symptomology.

The modified MFSAF endpoints in JAKARTA2 included mean symptom score changes from baseline and symptom response rate (defined as the proportion of patients with a TSS reduction of ≥ 50% from baseline) at each post baseline visit, time to first symptom response, and durability of symptom responses. These endpoints were assessed among patients in the modified MFSAF-evaluable population; that is, patients who had an evaluable assessment at baseline and received at least 1 full cycle of fedratinib therapy. The magnitude of changes from baseline in symptom scores at each post baseline visit was evaluated using effect sizes, calculated using Hedges' *g*[19]; a medium effect size of ≥ 0.5, which represents one-half of the SD, is a commonly used threshold to indicate a "clinically meaningful" change from baseline at a given visit when a threshold is not well-established.[20] Modified MFSAF score changes from baseline were also assessed for statistical significance using a 1-sample, 2-sided t-test. In responder analyses, the proportions of patients achieving reductions (improvements) from baseline scores of ≥ 50% in TSS or in individual symptom scores at each visit were assessed among MFSAF-evaluable patients with a baseline TSS > 0. An MFSAF-evaluable patient with a missing score at a post baseline assessment was deemed a nonresponder at that timepoint. The 95% confidence intervals (95% CIs) for symptom responses were estimated using Clopper–Pearson methods. Time to first symptom response was defined as the time from baseline to the first visit at which a patient achieved a TSS reduction of ≥ 50% from baseline, and was estimated using Kaplan–Meier methods. Definitive symptom improvement was defined as ≥ 2 consecutive visits at which a patient achieved a symptom response. Durability of the symptom response was measured by the number of cycles at which individual patients achieved a symptom response through EOC6.

Compliance rate at each visit was calculated as the number of patients who had received at least 1 full cycle of fedratinib treatment and had a nonmissing weekly TSS, divided by the number of patients on-study at that visit. Completion rates were calculated by dividing the number of patients with nonmissing TSS at a given visit by the number of patients in the intent-to-treat (ITT) population at baseline.

European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30

Overall HRQoL and functional status were evaluated using the Quality of Life Questionnaire Core 30 (QLQ-C30), a self-administered questionnaire that measures HRQoL in patients with cancer.[21] The QLQ-C30 consists of 30 items in 15 HRQoL domains, including a 2-item global health status/QoL domain, 5 multiitem functional domains (physical, role, emotional, cognitive, and social functioning), 3 multiitem symptom domains (fatigue, nausea/vomiting, and pain), and 6 single-item domains assessing various symptoms and perceived financial impact of

disease. The primary QLQ-C30 domain of interest was global health status/QoL. Each domain score ranged from 0 to 100; higher scores on the global health status/QoL domain and the 5 functional domains indicate better overall HRQoL and level of functioning, whereas higher symptom domain scores represent worse symptomatology. During the 6-cycle treatment phase in these analyses, patients completed the QLQ-C30 on day 1 of each treatment cycle and at EOC6. A QLQ-C30 domain score was included in analyses if responses were available for ≥ 50% of items in that domain; otherwise, it was considered missing. The QLQ-C30–evaluable population included patients with nonmissing QLQ-C30 scores at baseline (C1D1) who had received ≥ 1 dose of fedratinib on-study. The QLQ-C30 compliance rate was calculated at each visit by dividing the number of patients who received at least 1 dose of fedratinib and had an evaluable QLQ-C30 assessment by the number of ongoing patients at that visit, and the completion rate was the number of patients with nonmissing scores at a given visit divided by the number of patients in the ITT population.

QLQ-C30 endpoints included observed mean changes from baseline in domain scores and the rate of clinically meaningful improvement in QLQ-C30 domain scores at each post baseline visit. Changes from baseline in QLQ-C30 domain scores at each post baseline visit were assessed by effect sizes, calculated using Hedges' *g*,[19] and *P* values were calculated using a 1-sample, 2-sided t-test. A change from baseline of ≥ 10 points on any QLQ-C30 domain has been considered clinically meaningful.[22] In responder analyses, rates of clinically meaningful changes from baseline in domain scores were assessed among patients with nonmissing domain scores at each visit, and corresponding 95% CIs were estimated using Clopper–Pearson methods.

Patient's global impression of change

The patient's global impression of change (PGIC) comprises 1 item from the clinical global impressions scale[23] that assesses patients' perceptions of changes in MF symptom severity over time to provide an overall sense of whether treatment is beneficial. Global impression of change during treatment is measured using a 7-point Likert scale associated with responses to the statement, "Since the start of the treatment you have received in this study, your MF symptoms are…" Response options are: *very much improved* (level 1), *much improved*, *minimally improved*, *no change*, *minimally worse*, *much worse*, and *very much worse* (level 7). The PGIC questionnaire was administered at C4D1, C6D1, and EOC6. Because the PGIC was not assessed at baseline, PGIC outcomes were assessed at each timepoint among patients in the ITT population who were still ongoing at each timepoint. PGIC scores were summarized into 3 categories representing perceived change from start of treatment at each visit: *improved* (levels 1–3); *no change* (level 4); and *worsened* (levels 5–7). The 95% CIs for the proportion of patients in each category at each timepoint were estimated using Clopper–Pearson methods.

Subgroup analyses

To understand the potential impact of patient- and disease-related characteristics at baseline on patient-reported outcomes during fedratinib therapy, subgroup analyses were conducted assessing the proportions of patients who achieved a ≥ 50% reduction from baseline in TSS on the modified MFSAF, and proportions of patients who had meaningful improvement from baseline in QLQ-C30 global health status/QoL domain score (≥ 10-point increase), at EOC6. Rates of clinically meaningful improvement in TSS and global health status/QoL were compared between subgroups using Fisher's exact test.

Results

Patients

In all, 97 patients were enrolled in JAKARTA2 and received fedratinib 400 mg/d (starting dose). The MFSAF-evaluable population comprised 90 patients (93%) with an evaluable weekly TSS at baseline. Compliance rate on the modified MFSAF remained high (> 90%) at all post baseline visits through EOC6 (Supplemental Digital Figure 2, http://links.lww.com/HS/A146), with an overall rate of 98%. At EOC6, the MFSAF compliance rate was 93% (51/55) and the completion rate was 57% (51/90). The QLQ-C30–evaluable population included 94 patients (97%), and compliance rates were also high (≥ 90%) at all post baseline assessments through EOC6 (Supplemental Digital Figure 2, http://links.lww.com/HS/A146). At EOC6, 94% (50/53) of eligible patients were QLQ-C30 compliant and the completion rate was 52% (50/97).

Baseline demographic and disease characteristics for the modified MFSAF-evaluable population (Supplemental Digital Table 1, http://links.lww.com/HS/A144) were generally comparable to those for all enrolled patients (ITT population). At study entry, median age was 67 years, over one-half of modified MFSAF-evaluable patients had a diagnosis of primary MF (53%), and most had intermediate-2 risk MF (51%). Median time from MF diagnosis was 4.0 years (range 0.3–21.0), median spleen volume was 2894 mL (784–7815), and median duration of prior ruxolitinib exposure was 11.1 months (0.1–62.4). All patients in the modified MFSAF-evaluable cohort reported experiencing constitutional MF symptoms at baseline.

Table 1.

Baseline Scores on the Modified MFSAF and QLQ-C30 Instruments

	JAKARTA2	Reference Value From General Population
Instrument Measure	**Mean [SD]**	**Mean**
Modified MFSAF	N = 90*	
Total symptom score	20.7 [12.1]	NR
Night sweats	3.4 [2.6]	NR
Pruritus	2.3 [2.5]	NR
Abdominal discomfort	4.1 [2.8]	NR
Early satiety	4.4 [2.6]	NR
Pain under ribs on left side	2.9 [2.7]	NR
Bone or muscle pain	3.6 [2.8]	NR
EORTC QLQ-C30	N = 97	N = 11,343[24]
Global health/QoL	44.6 [22.2]	66.2
Physical functioning	60.5 [22.6]	82.9
Role functioning	51.3 [30.7]	83.6
Emotional functioning	70.8 [23.7]	79.7
Cognitive functioning	76.3 [23.0]	86.9
Social functioning	62.2 [31.1]	88.4
Fatigue	59.1 [26.5]	25.9
Nausea/vomiting	11.6 [17.3]	3.0
Pain	43.4 [32.4]	24.2
Dyspnea	41.9 [32.6]	17.0
Insomnia	47.7 [35.2]	25.8
Appetite loss	41.9 [31.1]	7.3
Constipation	18.9 [25.5]	10.9
Diarrhea	20.7 [26.2]	6.8
Financial difficulties	18.5 [27.9]	8.5

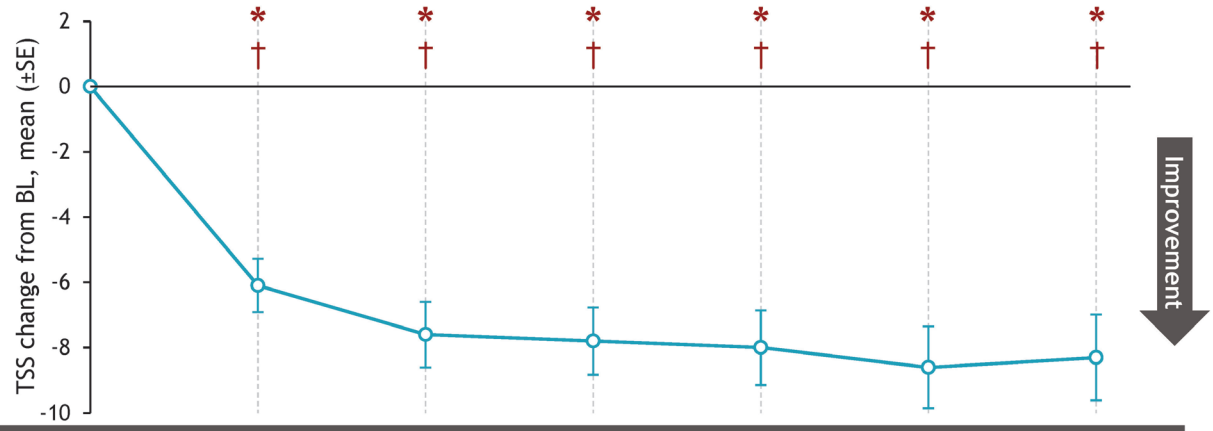
*The modified MFSAF HRQoL-evaluable population comprised patients with at least 1 full cycle of fedratinib treatment who had a non-missing TSS score at baseline (ie, ≥ 5 of the 7 daily TSS were not missing).

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30; HRQoL = health-related quality of life; MFSAF = myelofibrosis symptom assessment form; NR = not reported; QoL = quality of life; TSS = total symptom score.

Myelofibrosis symptom assessment form

Baseline mean [±SD] TSS on the modified MFSAF was 20.7 [12.1]. Mean scores for the 6 individual MFSAF symptoms at baseline ranged from 2.3 to 4.4, indicating mild to moderate MF symptom severity (Table 1), with the highest scores reported for early satiety (4.4 [2.6]) and abdominal discomfort (4.1 [2.8]).

During the first 6 cycles of fedratinib treatment, patients reported significant ($P < 0.05$) mean TSS improvements from baseline beginning at the cycle 2 assessment followed by all subsequent scheduled post baseline visits through EOC6, with clinically meaningful medium effect sizes (at least –0.5) at each timepoint (Figure 1). At EOC6, mean [±SD] TSS was 11.8 [8.2], representing a clinically meaningful (effect size –0.68) mean change from baseline of –8.3 [1.3] points for the 51 patients with data at both baseline and EOC6. Significant ($P < 0.05$) improvements from baseline were also reported for all 6 individual MFSAF symptoms at all time points through EOC6. Changes from baseline were clinically meaningful for most individual symptoms, with medium effect sizes at every visit for night sweats and early satiety, at all but C2D1 for pain under the ribs on left side, and at one-half of all visits for abdominal discomfort. Effect sizes for pruritis and bone or muscle pain were at least –0.20 at almost all post baseline assessments. At EOC6, mean symptom scores were clinically meaningfully improved from baseline for early satiety (effect size –0.69), night sweats



	C2D1	C3D1	C4D1	C5D1	C6D1	EOC6
N	88	88	84	73	62	51
Mean change [SE]	-6.1 [0.8]	-7.6 [1.0]	-7.8 [1.0]	-8.0 [1.1]	-8.6 [1.2]	-8.3 [1.3]
Effect size [95%CI]	**-0.50** [-0.72, -0.28]	**-0.62** [-0.84, -0.39]	**-0.64** [-0.87, -0.40]	**-0.66** [-0.91, -0.41]	**-0.70** [-0.98, -0.43]	**-0.68** [-0.98, -0.38]

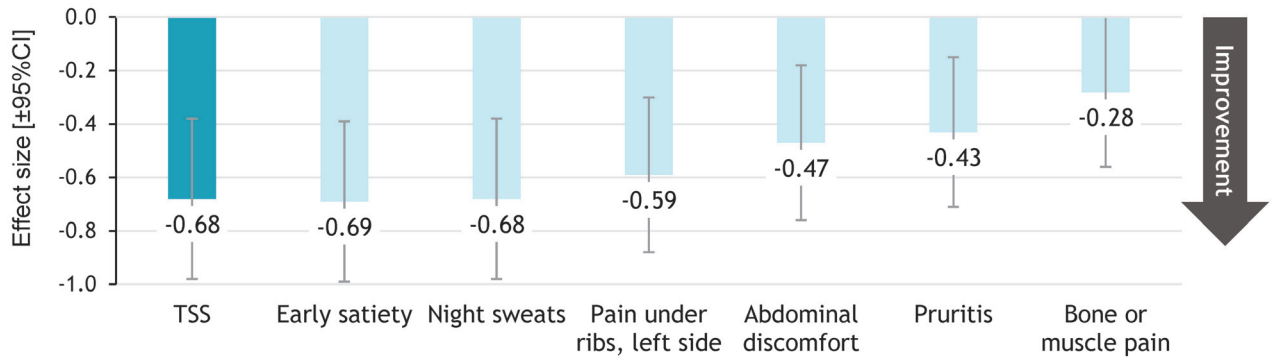
*Clinically meaningful effect size for change from baseline (≥ –0.50).

†Statistically significant ($P < 0.001$) change from baseline (1-sample, 2-sided t-test).

An effect size of 0.50 was considered clinically meaningful.

95%CI, 95% confidence interval; BL, baseline; CxD1, Cycle x Day 1; EOC6, end of cycle 6; MFSAF, Myelofibrosis Symptom Assessment Form; N, number; SE, standard error; TSS, total symptom score.

Figure 1. Changes from baseline in MFSAF total symptom score and corresponding effect sizes.



Effect sizes of at least -0.50 were considered clinically meaningful.

95%CI, 95% confidence interval; MFSAF, Myelofibrosis Symptom Assessment Form; TSS, total symptom score.

Figure 2. Effect sizes for changes from baseline in MFSAF total symptom score and the 6 individual MFSAF symptoms at the end of cycle 6.

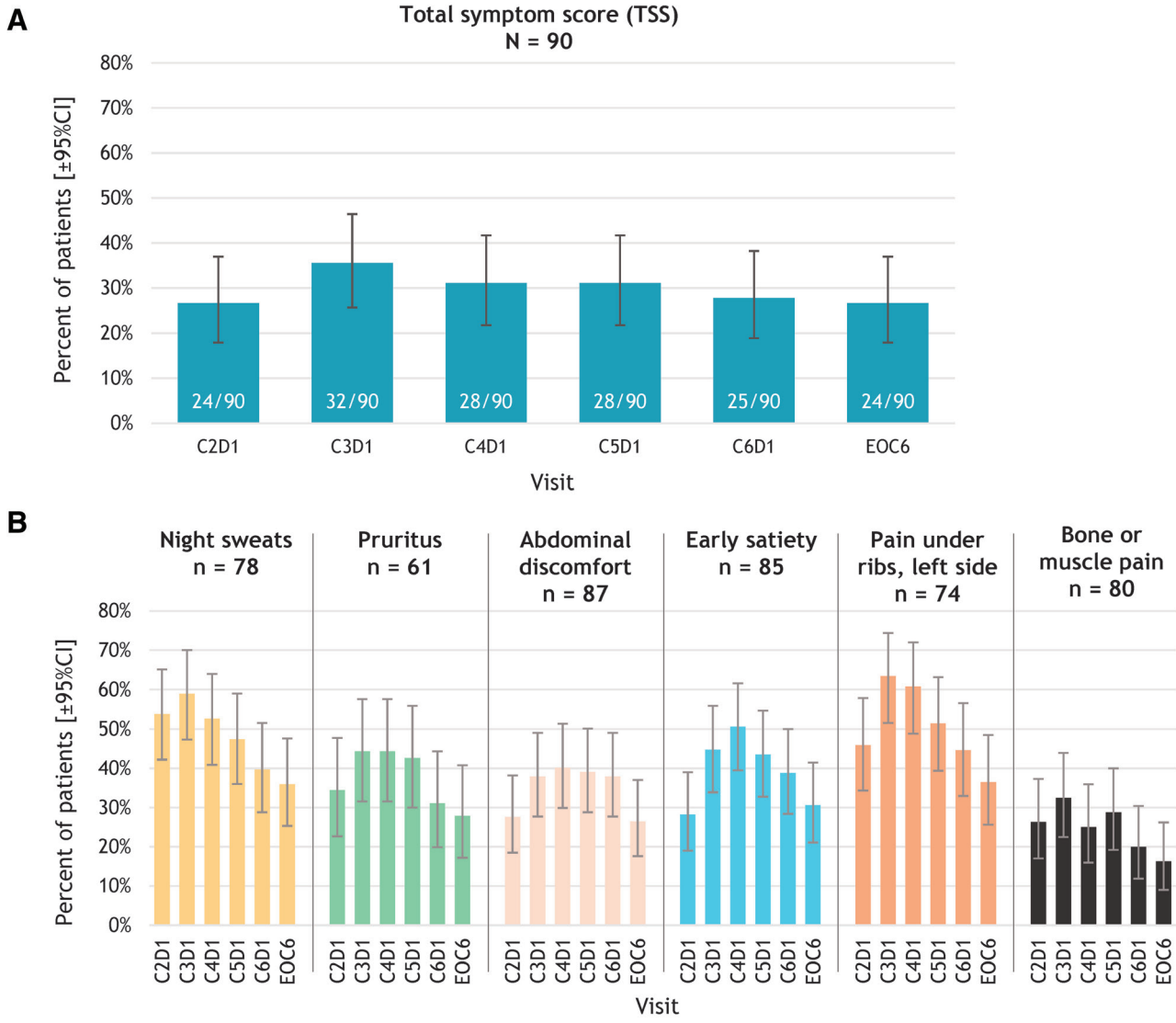
(–0.68), and pain under the ribs on left side (–0.59), and effect sizes trended toward clinically meaningful for abdominal discomfort (–0.47) and pruritus (–0.43) (Figure 2).

In responder analyses, 27%–36% of MFSAF-evaluable patients had TSS reductions of ≥ 50% from baseline across post baseline visits through EOC6 (Figure 3A). Of all modified MFSAF-evaluable patients, durable responses were attained by 38% of patients who achieved ≥ 50% reductions in TSS score from baseline at ≥ 2 post baseline timepoints. Median time to ≥ 50% reduction in TSS was 20 weeks (95% CI 12, 24) (Figure 4) and approximately 40% of patients achieved definitive symptom improvement by EOC6. As previously reported, the overall (TSS) symptom response rate at EOC6 was 27% (24/90) (95% CI 18%, 37%).[15] Response rates for individual symptoms at EOC6 were 36% for pain under ribs on the left side, 36% for night sweats, 31% for early satiety, 28% for pruritus, 26% for abdominal discomfort, and 16% for bone or muscle pain (Figure 3B).

The overall symptom response rate at EOC6 was generally consistent across patient subgroups defined by clinically relevant baseline demographic and disease characteristics, suggesting minimal heterogeneity of treatment effect (Figure 5). Patient age at study entry was the only baseline characteristic significantly associated with symptom response in subgroup analyses, with patients aged ≤ 65 years at baseline more likely to achieve a symptom response than those aged > 65 years ($P = 0.033$).

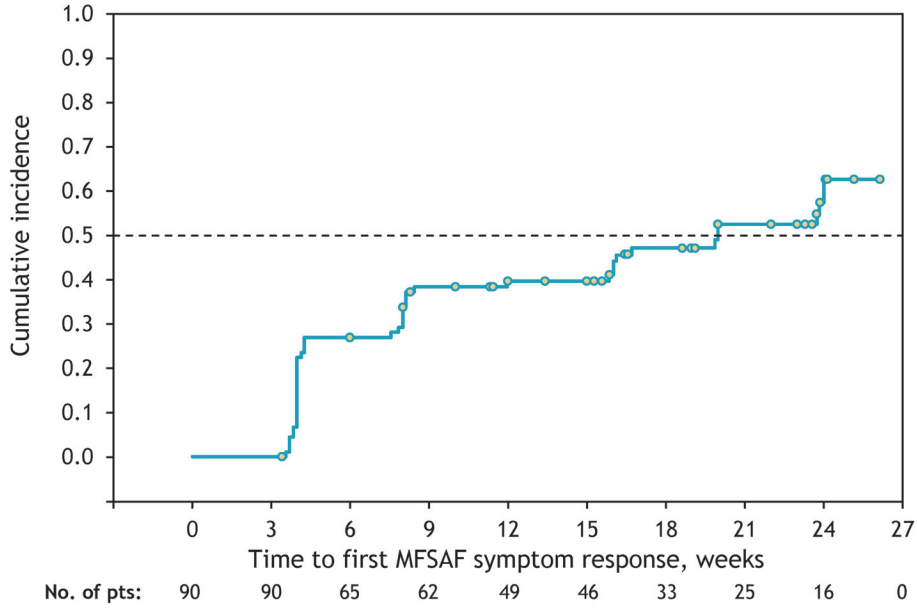
Quality of Life Core 30

At baseline, mean scores for QLQ-C30 domains were worse than reference values from the general population when mean scores were reweighted with an age-by-gender distribution (Table 1).[24] Based on the preestablished 10-point threshold, scores were clinically meaningfully worse than in the general population in the domains of global health status/QoL, physical



Symptom response was defined as a reduction of ≥ 50% from baseline in TSS or any individual symptom score.
95% confidence intervals were estimated by Clopper-Pearson method.
95%CI, 95% confidence interval; CxD1, Cycle x, Day 1; EOC6, end of cycle 6; MFSAF, Myelofibrosis Symptom Assessment Form; TSS, total symptom score.

Figure 3. Proportions of patients with ≥ 50% reduction from baseline score in (A) total symptom score; and (B) individual symptom scores, on the modified MFSAF through the end of cycle 6.



Times to response estimated using Kaplan-Meier methods.
MFSAF, Myelofibrosis Symptom Assessment Form.

Figure 4. Time to ≥ 50% reduction from baseline in total symptom score on the modified MFSAF.

functioning, role functioning, cognitive functioning, social functioning, fatigue, pain, dyspnea, insomnia, appetite loss, and diarrhea. Notably, the mean [±SD] baseline global health status/QoL score in JAKARTA2 was 44.6 [20.1], > 20 points lower than the mean score of 66.1 [21.7] in the age- and gender-matched general population.[24]

Mean global health status/QoL domain score was significantly ($P < 0.01$) improved from baseline at all visits through EOC6, exceeding the +10-point threshold for clinically meaningful improvement at three timepoints (Figure 6). At EOC6, mean QLQ-C30 global health status/QoL domain score had increased by 11.1 points from baseline (mean 57.5 points) for patients with scores available at both visits. Effect sizes for changes from baseline in global health status/QoL scores ranged from 0.34 to 0.49, with an approximately medium effect size at EOC6 (0.49). Similar trends for improvement were observed for most other QLQ-C30 domains. Statistically significant and clinically meaningful improvements were reported at EOC6 in mean scores for physical functioning (+10.8 points), social functioning (+9.4 points), and role functioning (+9.2 points); and for the symptom domains of appetite loss (–20.4 points), insomnia (–18.1 points), fatigue (–14.5 points), dyspnea (–13.2 points), and pain (–10.9 points). In contrast, the mean nausea and vomiting domain score was clinically meaningfully worsened (mean +10.2 points) from baseline at EOC6.

In responder analyses, 48% of patients reported clinically meaningful improvements from baseline in global health status/QoL scores as early as C2D1 (Figure 7). At EOC6, 44% of patients reported clinically meaningful improvements from baseline in global health status/QoL scores, 40% reported no meaningful change (ie, < 10-point change from baseline score), and 17% reported meaningful deterioration (ie, decrease of ≥ 10 points). In subgroup analysis, no baseline demographic or disease characteristic was significantly associated with achieving clinically meaningful improvement from baseline in the QLQ-C30 global health status/QoL score at EOC6 (Figure 8).

For the 5 QLQ-C30 functional domains, proportions of patients experiencing clinically meaningful improvement from baseline at EOC6 ranged from 29% to 53%, with highest improvement rates in the physical functioning (53%) and social functioning (40%) domains, and lowest rates in the emotional functioning domain (29%). Among the symptom domains, the rate of clinically meaningful improvement at EOC6 was highest for fatigue (67%), and was generally low for nausea/vomiting, constipation, and diarrhea domains (12%, 19%, and 17%, respectively).

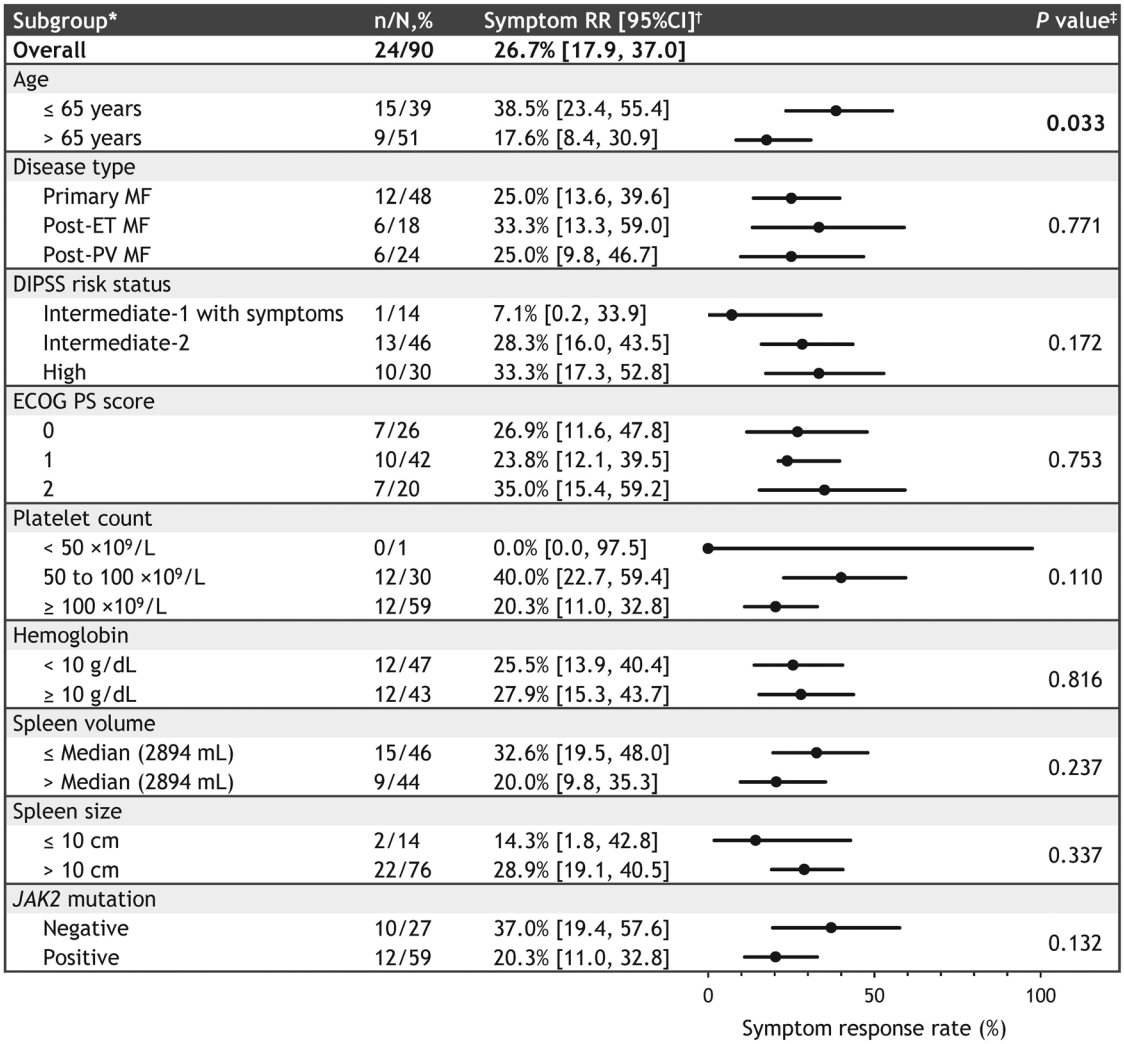
Rates of clinically meaningful deterioration in the global health status/QoL score at each assessment ranged from 11% to 19% (Figure 7). At EOC6, clinically meaningful deterioration rates were < 20% in all 5 functional domains, and in all symptom domains except diarrhea (25%) and nausea and vomiting (49%) (Supplemental Digital Figure 3, http://links.lww.com/HS/A147).

Patient's global impression of change

The PGIC-evaluable population included 76 patients at C4D1, 56 patients at C6D1, and 44 patients at EOC6. Over 80% of patients reported some improvement in MF symptoms (PGIC levels 1–3) at each time point, and fewer than 10% of patients reported worsened MF symptoms (PGIC levels 5–7) at any time (Supplemental Digital Figure 4, http://links.lww.com/HS/A148). At EOC6, 84% of patients reported improvements in MF symptoms, 11% reported "no change," and 4.5% reported worsened symptoms.

Discussion

During fedratinib treatment, patients with MF who were resistant or intolerant to prior ruxolitinib therapy experienced clinically meaningful improvements from baseline in MF symptom burden, overall HRQoL, and functional status. By EOC6, 27% of all randomized patients achieved a symptom response on the modified MFSAF. Of patients who were evaluable at EOC6, 44% experienced clinically meaningful improvement



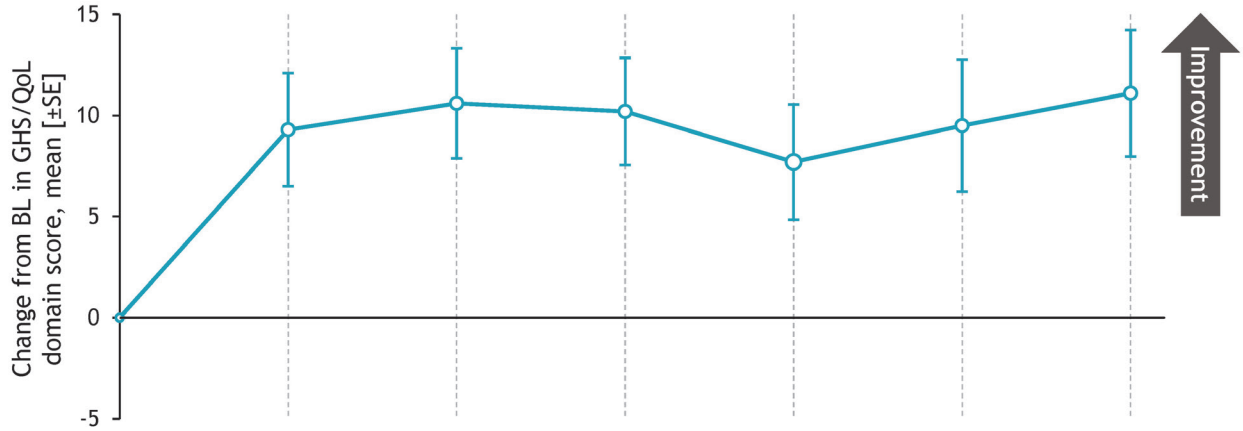
Symptom response was defined as a reduction of ≥ 50% from baseline in MFSAF total symptom score (TSS).
*Each category includes only non-missing data.
†95%CIs estimated by Clopper-Pearson method.
‡*P* values estimated by Fisher's exact test.
95%CI, 95% confidence interval; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythemia; JAK2, Janus kinase 2; MF, myelofibrosis; MFSAF, MF Symptom Assessment Form; PV, polycythemia vera; RR, response rate.

Figure 5. Symptom response rates at the end of cycle 6 in patient subgroups defined by baseline demographic and disease characteristics.

on the QLQ-C30 Global health status/QoL domain, and 84% reported improvements in MF symptoms on the PGIC questionnaire. Although the study required only ≥ 14 days of prior ruxolitinib therapy for patients who were deemed resistant to ruxolitinib, and allowed for any duration of prior ruxolitinib therapy in patients who discontinued the drug due to tolerability problems, the actual median exposure to ruxolitinib prior to JAKARTA2 in HRQoL-evaluable patients was 11.1 months,[25] indicating relatively substantial ruxolitinib exposure before receiving fedratinib. At study entry, patients in the JAKARTA2 MFSAF-evaluable population had clinical features consistent with advanced MF disease: median spleen volume (2894 mL) was ~14 times the normal volume,[26] all patients reported experiencing MF-related constitutional symptoms, and one-third of patients had DIPSS-defined high-risk MF. Accordingly, patients in JAKARTA2 reported clinically meaningfully worse baseline scores on most EORTC QLQ-C30 domains relative to an age- and gender-matched general population, and a higher total symptom score on the MFSAF compared with fedratinib-treated patients with JAK-inhibitor-naïve MF from the phase III JAKARTA trial (mean 20.7 versus 17.6, respectively).[27]

Patients reported significant and clinically meaningful improvements in MF symptoms on the modified MFSAF at all timepoints while receiving fedratinib, with more than one-fourth of all patients achieving a ≥ 50% reduction in TSS by the end of the first treatment cycle. Responses were generally durable, with 38% of all patients achieving symptom responses at ≥ 2 post baseline timepoints. The overall symptom response rate at EOC6 among all enrolled patients was 27%,[15] with similar or slightly higher response rates for 5 of the 6 individual symptoms on the modified MFSAF, suggesting that TSS improvements were likely attributable to broad improvements in both spleen-related and constitutional symptoms.

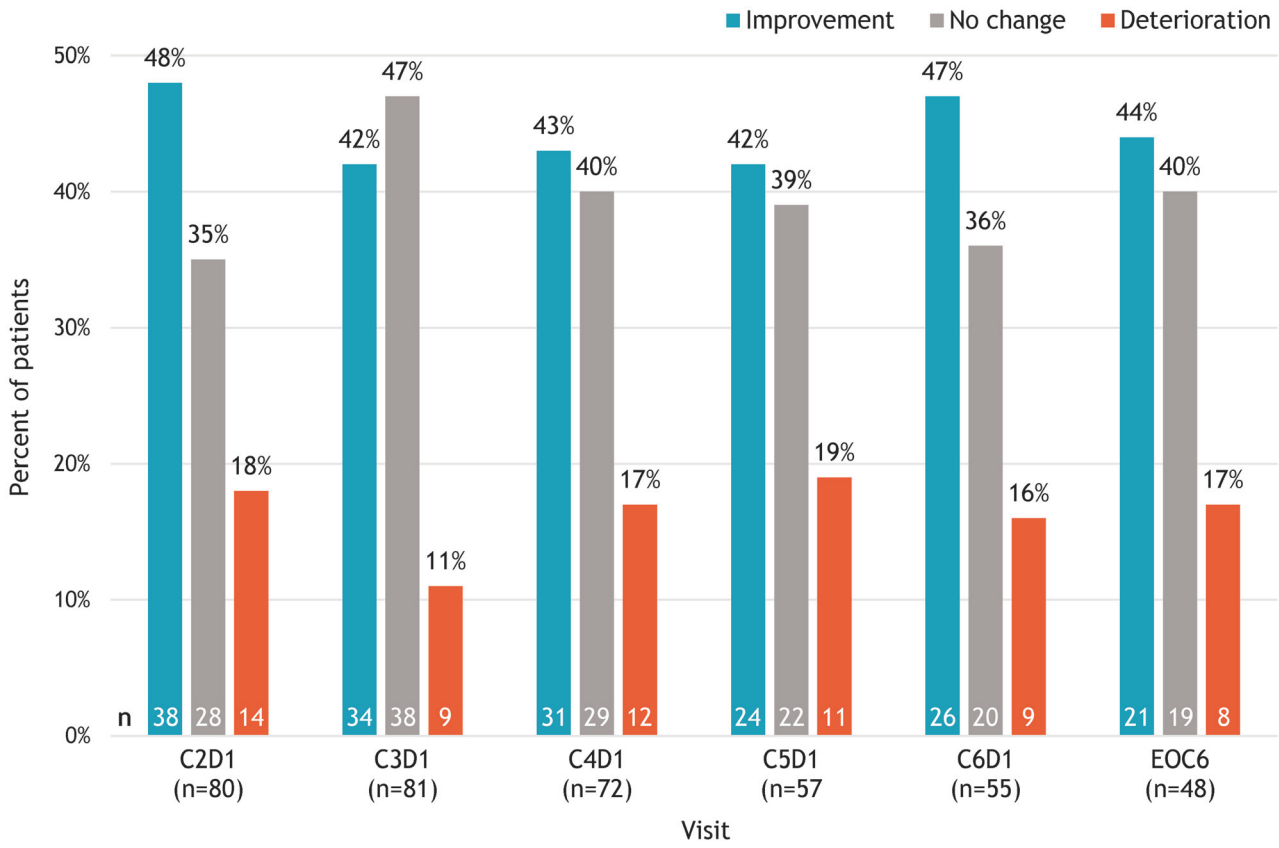
Mean QLQ-C30 global health status/QoL domain score was also significantly and clinically meaningfully improved from baseline at each post baseline assessment with approximately medium effect sizes. Whereas the baseline mean global health



	C2D1	C3D1	C4D1	C5D1	C6D1	EOC6
N	80	81	72	57	55	48
Mean change [SE]	+9.3 [2.8]	+10.6 [2.7]	+10.2 [2.7]	+7.7 [2.9]	+9.5 [3.3]	+11.1 [3.1]
Effect Size [95%CI]	0.41 [0.19, 0.64]	0.47 [0.24, 0.70]	0.45 [0.21, 0.69]	0.34 [0.08, 0.61]	0.42 [0.15, 0.70]	0.49 [0.20, 0.79]

95%CI, 95% confidence interval; BL, baseline; CxD1, Cycle x Day 1; EOC6, end of cycle 6; GHS/QoL, global health status/QoL; N, number; SE, standard error.

Figure 6. Mean changes from baseline in QLQ-C30 Global Health Status/QoL domain scores and corresponding effect sizes.

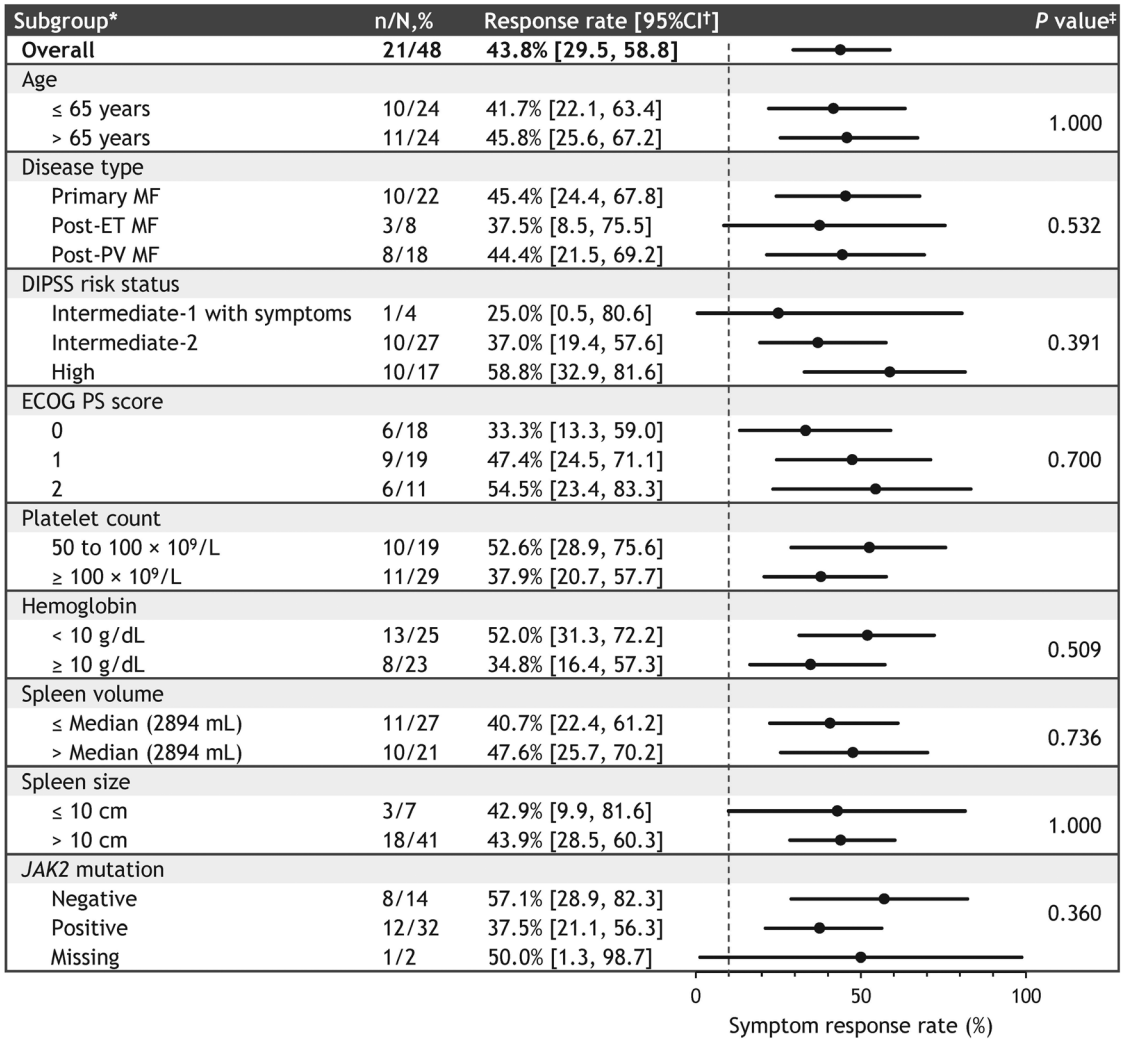


Clinically meaningful improvement and deterioration were defined as a ≥ 10-point increase and decrease, respectively, from baseline in global health status/QoL score. A change from baseline of < 10 points was considered no change.
CxD1, Cycle x, Day 1; EOC6, end of cycle 6; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30; QoL, quality of life.

Figure 7. Clinically meaningful changes from baseline scores in EORTC QLQ-C30 Global Health Status/QoL scores by cycle.

status/QoL score for patients in JAKARTA2 was 22 points lower than that for patients from an age- and gender-matched general population—a difference 2 times higher than the 10-point threshold used to define clinically meaningful differences—patients who completed 6 fedratinib treatment cycles reported a mean global health status/QoL score at EOC6 of 57.5, which was within the clinically meaningful threshold (ie, 10 points) compared with the mean reference value from the general population (66.1).[24] Significant and clinically meaningful improvements were also observed at EOC6 in the physical, role, and social functioning domains, and for the symptom domains of fatigue, pain, dyspnea, insomnia, and appetite loss. Improvements in overall HRQoL during fedratinib therapy were achieved despite clinically meaningfully worsening from baseline scores in the nausea/vomiting domain. Gastrointestinal adverse events are known side effects of fedratinib therapy, and are the most common events reported in fedratinib clinical trials.[15,16,28] The ongoing phase IIIb FREEDOM (NCT03755518) and phase III FREEDOM2 (NCT03952039) studies of fedratinib in patients previously treated with JAK inhibitors include mitigation strategies to ameliorate or prevent adverse gastrointestinal events associated with fedratinib, which if successful, could improve patient-reported outcomes related to these events.

Improvements in MF symptoms and overall HRQoL in JAKARTA2 were observed across clinically relevant patient subgroups, with consistent rates of MFSAF symptom response across all baseline characteristic subgroups except patient



Clinically meaningful improvement was defined as an improvement of ≥ 10 points from baseline in global health status/QoL score.
*Each category includes only non-missing data.
†95%CIs estimated by Clopper-Pearson method.
‡*P* values estimated by Fisher's exact test.
95%CI, 95% confidence interval; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30; ET, essential thrombocythemia; *JAK2*, Janus kinase 2; MF, myelofibrosis; PV, polycythemia vera; QoL, quality of life.

Figure 8. Rate of clinically meaningful improvement from baseline in EORTC QLQ-C30 Global Health Status/QoL scores at the end of cycle 6 in patient subgroups defined by baseline demographic and disease characteristics.

age (patients aged ≤ 65 years at study entry were significantly more likely to achieve a symptom response than those aged > 65 years), and no significant differences in rates of clinically meaningful improvement from baseline in global health status/QoL, indicating an overall benefit of fedratinib therapy regardless of MF subtype (primary or secondary), DIPSS MF risk status, ECOG PS score, hemoglobin levels, platelet counts, *JAK2* mutation status (wild-type or mutant), or extent of splenomegaly at study entry. Similar outcomes among patient subgroups are supported by results of the PGIC questionnaire, which showed that the majority (> 80%) of ongoing patients self-reported improvements in symptom severity and perceived fedratinib treatment as beneficial. It should be noted that patients knew they were receiving active treatment in this open-label study; therefore, with no control arm, there is the possibility that such knowledge could influence patient-reported perceptions.

Results from this study show that treatment with fedratinib resulted in clinically meaningful improvements in MF symptom burden and severity, functional status, and overall HRQoL in patients with intermediate or high risk MF who were previously treated with ruxolitinib, with generally consistent treatment effects among patient subgroups defined by demographic and disease characteristics at baseline. Patient-reported outcomes associated with prolonged fedratinib treatment are being evaluated in the ongoing FREEDOM and FREEDOM2 studies in patients with MF for whom ruxolitinib is no longer a therapeutic option.

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References

1. Tefferi A. Primary myelofibrosis: 2017 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2016;91:1262–1271.
2. Mesa RA, Gotlib J, Gupta V, et al. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-I: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2013;31:1285–1292.
3. Mesa RA, Schwager S, Radia D, et al. The myelofibrosis symptom assessment form (MFSAF): an evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis. *Leuk Res*. 2009;33:1199–1203.
4. Anderson LA, James G, Duncombe AS, et al. Myeloproliferative neoplasm patient symptom burden and quality of life: evidence of significant impairment compared to controls. *Am J Hematol*. 2015;90:864–870.
5. Fonseca E, Silver RT, Kazis LE, et al. Ruxolitinib discontinuation in patients with myelofibrosis: an analysis from clinical practice. *Blood* 2013;122:Abstract 2833.
6. Kuykendall AT, Shah S, Talati C, et al. Between a rux and a hard place: evaluating salvage treatment and outcomes in myelofibrosis after ruxolitinib discontinuation. *Ann Hematol*. 2018;97:435–441.
7. Verstovsek S, Mesa RA, Gotlib J, et al; COMFORT-I investigators. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. *Haematologica*. 2015;100:479–488.
8. Verstovsek S, Mesa RA, Gotlib J, et al; COMFORT-I investigators. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. *J Hematol Oncol*. 2017;10:55.
9. Harrison CN, Vannucchi AM, Kiladjian JJ, et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. *Leukemia*. 2016;30:1701–1707.
10. Cervantes F, Vannucchi AM, Kiladjian JJ, et al; COMFORT-II investigators. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. *Blood*. 2013;122:4047–4053.
11. Palandri F, Elli EM, Polverelli N, et al. Outcome of patients with myelofibrosis after ruxolitinib failure: role of disease status and treatment strategies in 214 patients. *Blood*. 2018;132(suppl 1):Abstract 4277.
12. Newberry KJ, Patel K, Masarova L, et al. Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation. *Blood*. 2017;130:1125–1131.
13. INREBIC® (Fedratinib) Prescribing Information. Impact Biomedicines, Inc., Summit, NJ; Rev 08/2019. Available at: https://packageinserts.bms.com/pi/pi_inrebic.pdf. Accessed March 25, 2021.
14. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology—Myeloproliferative neoplasms v1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Accessed March 30, 2021.
15. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: an updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. *Am J Hematol*. 2020;95:594–603.
16. Pardanani A, Harrison C, Cortes JE, et al. Safety and efficacy of fedratinib in patients with primary or secondary myelofibrosis: a randomized clinical trial. *JAMA Oncol*. 2015;1:643–651.
17. Harrison CN, Schaap N, Vannucchi AM, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. *Lancet Haematol*. 2017;4:e317–e324.
18. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115:1703–1708.
19. Hedges LV, Olkin I. *Statistical Methods for Meta-analysis*. San Diego, CA: Academic Press; 1985.
20. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003;41:582–592.
21. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a

quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365–376.
22. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16:139–144.
23. Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised*. In: US Department of Health E, and Welfare Publication (ADM) ed. Rockville, MD: National Institute of Mental Health; 1976:76–338.
24. Nolte S, Liegl G, Petersen MA, et al; EORTC Quality of Life Group. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. *Eur J Cancer*. 2019;107:153–163.
25. Harrison C, Schaap N, Vannucchi A, et al. Fedratinib induces spleen responses in patients with myeloproliferative neoplasm (MPN)-associated intermediate- or high-risk myelofibrosis (MF) resistant or intolerant to ruxolitinib: an updated analysis of the phase II JAKARTA2 study. *Clin Lymphoma Myeloma Leuk*. 2019;19(Suppl 1):S356.
26. Caglar V, Kumral B, Uygur R, et al. Study of volume, weight and size of normal pancreas, spleen and kidney in adults autopsies. *Forensic Med Anatomy Res*. 2014;2:63–69.
27. Mesa RA, Schaap N, Vannucchi AM, et al. Health-related quality of life (HRQoL) in patients with myelofibrosis treated with fedratinib, an oral, selective inhibitor of janus kinase 2 (JAK2), in the randomized, placebo-controlled, phase III JAKARTA study. *Blood*. 2019;134(suppl_1):704–704.
28. Pardanani A, Tefferi A, Jamieson C, et al. A phase 2 randomized dose-ranging study of the JAK2-selective inhibitor fedratinib (SAR302503) in patients with myelofibrosis. *Blood Cancer J*. 2015;5:e335.