

Patient-reported Effects of Fedratinib, an Oral, Selective Inhibitor of Janus Kinase 2, on Myelofibrosis-related Symptoms and Health-related Quality of Life in the Randomized, Placebo-controlled, Phase III JAKARTA Trial

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Abstract

Patients with myelofibrosis (MF) experience an array of symptoms that impair health-related quality of life (HRQoL). Fedratinib, an oral, selective Janus-kinase 2 (JAK2) inhibitor, was investigated in the randomized, placebo-controlled, phase III JAKARTA study in adult patients with intermediate- or high-risk JAK-inhibitor-naïve MF. The effect of fedratinib 400 mg/d on patient-reported MF symptoms and HRQoL in JAKARTA was assessed. Participants completed the modified Myelofibrosis Symptom Assessment Form (MFSAF v2.0), which evaluates 6 key MF symptoms (night sweats, early satiety, pruritus, pain under ribs on the left side, abdominal discomfort, bone/muscle pain). The modified MFSAF v2.0 was completed during the first 6 treatment cycles and at end of cycle 6 (EOC6). Symptom response was a $\geq 50\%$ improvement from baseline in total symptom score (TSS). Overall HRQoL was assessed by EQ-5D-3L health utility index (HUI) score. The MFSAF-evaluable population comprised 91/96 patients randomized to fedratinib 400 mg and 85/96 patients randomized to placebo. Mean baseline TSS was 17.6 and 14.7 for fedratinib and placebo, respectively, and mean EQ-5D-3L HUI was 0.70 and 0.72. Fedratinib elicited statistically significant and clinically meaningful improvements in TSS from baseline versus placebo at all postbaseline visits. Symptom response rates at EOC6 were 40.4% with fedratinib and 8.6% with placebo (OR 7.0 [95% CI, 2.9-16.9]; $P < 0.001$), and a significantly higher proportion of fedratinib-treated patients achieved clinically meaningful improvement from baseline on the EQ-5D-3L HUI at EOC6 (23.2% versus 6.5%; $P = 0.002$). Fedratinib provided clinically meaningful improvements in MF symptoms and overall HRQoL versus placebo in patients with JAK-inhibitor-naïve MF.

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Data requests may be submitted to Celgene, A Bristol-Myers Squibb Company, at <https://vivli.org/ourmember/celgene/> and must include a description of the research proposal.

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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) because of disease-related constitutional symptoms (fatigue, weight loss, night sweats), symptoms associated with hepatosplenomegaly (early satiety, pain under ribs on the left side, abdominal discomfort), and the need for blood transfusions.^{2,3} Patients with MF report worse HRQoL compared with control subjects without MF, and even compared with patients with other *BCR-ABL*-negative MPNs (polycythemia vera [PV], essential thrombocythemia [ET]).⁴

Fedratinib is an oral, selective inhibitor of Janus kinase 2 (JAK2) approved in the United States for treatment of adult patients with intermediate-2 or high-risk MF. The recommended starting dose of fedratinib is 400 mg/d, taken in continuous 28-day treatment cycles.⁵ The randomized, placebo-controlled, phase III JAKARTA study (NCT01437787) assessed fedratinib

in adult patients with intermediate-2 or high-risk, JAK-inhibitor-naïve MF. In JAKARTA, fedratinib was associated with significant improvements in spleen volume by the end of 6 treatment cycles compared with placebo: the spleen volume response rate ($\geq 35\%$ spleen volume reduction [SVR] from baseline) with fedratinib 400 mg/d at the end of cycle 6 (EOC6), with a follow-up scan 4 weeks later, was 36%, compared with 1% in the placebo arm ($P < 0.0001$).^{5,6}

Objective measures of MF disease control, such as reduced splenomegaly, do not always correlate with improvements in patient-reported HRQoL. These analyses were performed to thoroughly evaluate patient-reported outcomes with fedratinib 400 mg/d versus placebo during the first 6 treatment cycles (~24 wks) in the JAKARTA trial.

Methods

Study design, eligibility criteria, clinical efficacy, and safety outcomes have been reported elsewhere.^{6,7} Briefly, eligible patients were aged ≥ 18 years, with intermediate-2 or high-risk primary or secondary (post-PV or post-ET) MF, palpable splenomegaly (≥ 5 cm below the left costal margin), platelet counts $\geq 50 \times 10^9/L$, and Eastern Cooperative Oncology Group performance status (ECOG PS) scores of ≤ 2 . Prior therapy with JAK inhibitors was not allowed. Patients were randomized 1:1:1 to fedratinib 400 mg, fedratinib 500 mg, or placebo, self-administered orally once-daily for at least 6 continuous 28-day treatment cycles. At EOC6 (or earlier in cases of disease progression), patients randomized to placebo could crossover to fedratinib. As noted, this report details outcomes among patients randomized to fedratinib 400 mg (the approved starting dose) or placebo; the 500 mg daily fedratinib dose evaluated in JAKARTA was not more effective than the 400 mg dose and was associated with a less favorable safety profile.⁶ Due to the prospectively planned crossover, comparative endpoints are limited to the initial 6-cycle double-blind randomized treatment period.

Symptom responses were assessed using the modified Myelofibrosis Symptom Assessment Form (MFSAF, version 2.0),³ which measures patient-reported severity of 6 key MF symptoms: night sweats, early satiety, pruritus, pain under the ribs on the left side, abdominal discomfort, and bone or muscle pain, each scored from 0 (absent) to 10 (worst imaginable). Patients reported modified MFSAF v2.0 scores in an e-diary on each of the 7 days before day 1 of each treatment cycle, and during the 7 days before EOC6. A daily total symptom score (TSS) was calculated by summing the 6 individual symptom scores and was considered missing if any individual symptom score was missing on that day. The weekly TSS was the average of the daily scores for patients with nonmissing daily TSS for ≥ 5 days from that week. The weekly TSS score ranged between 0 and 60, with a higher score indicating a higher level of symptomatology. Modified MFSAF compliance rate at each assessment was the number of patients with nonmissing scores divided by the number of patients eligible for assessment at that visit. Completion rates were calculated by dividing the number of patients with nonmissing TSS at a given visit by the intent-to-treat (ITT) population at baseline.

The following modified MFSAF v2.0 endpoints were assessed: mean changes from baseline in TSS and individual symptom scores, symptom response rate, durability of symptom response, time to first symptom response, and time to definitive symptom improvement. The MFSAF-evaluable population included all patients with a valid TSS at baseline, defined as available daily TSS for ≥ 5 of the 7 days in the week before cycle 1 day 1 (C1D1).

Within each treatment arm, changes from baseline TSS and individual symptom scores were assessed at each postbaseline visit by paired 1-sample, 2-sided *t*-test. Differences between fedratinib and placebo in mean score changes from baseline were

compared using 2-sample *t*-tests with pooled variances. Effect sizes for between-group differences in mean modified MFSAF v2.0 score changes from baseline were estimated using Hedges' *g*.⁸ An effect size of ≥ 0.5 is a commonly used threshold to determine whether between-group differences are clinically meaningful, but others have advocated for a threshold of ≥ 0.2 .⁹ For these analyses, small, medium, and large treatment effects were defined as effect sizes of 0.20 to < 0.50 , 0.50 to < 0.80 , and ≥ 0.80 , respectively.¹⁰

Symptom response, defined as a reduction of $\geq 50\%$ in weekly TSS from baseline, was assessed at each postbaseline visit among patients with a baseline TSS > 0 . A logistic regression model was used to compare symptom response rates in the fedratinib 400 mg and placebo arms at each postbaseline visit. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) and *P* values were estimated controlling for baseline scores. Durability of symptom response was measured by the number of the postbaseline assessment visits in which patients achieved a symptom response. Time to response was estimated using Kaplan-Meier methods, and compared between treatment arms using Cox proportional hazards regression analyses including treatment arm and baseline scores as covariates.

Overall HRQoL during treatment was assessed by EQ-5D-3L,¹¹ a nondisease specific, self-administered instrument that includes a descriptive questionnaire and a visual analogue scale (VAS). The descriptive questionnaire measures level of impairment in 5 key dimensions—mobility, self-care, usual activities, pain, and anxiety/depression—as rated on a 3-level severity scale (*no problems, some problems, extreme problems*). Weighted scores from the 5 are used to determine a composite “health utility index,” with higher scores representing a better health state. For these analyses, health utility index scores were derived using published guidance from United Kingdom population preferences,¹² with a range from -0.594 to 1.0. The EQ-5D VAS is a single-item visual scale for patient-rated health on a vertical scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

In JAKARTA, patients completed the EQ-5D-3L at baseline (C1D1) and EOC6. Baseline EQ-5D-3L completion rate was calculated as the number of patients with nonmissing health utility (ie, all 5 items completed) and VAS assessments, divided by the total number of patients in the ITT population. Compliance rate was the number of patients with nonmissing scores divided by the number of patients eligible for assessment at a given visit.

EQ-5D-3L endpoints included changes in health utility index and VAS scores from baseline at EOC6, and proportions of patients in each arm who experienced clinically meaningful improvement or deterioration from baseline. There is as yet no consensus definition of response based on changes in EQ-5D-3L health utility scores for patients with MF. Data regarding clinically meaningful change in health utility scores for patients with other hematological or oncological illnesses¹³ were the basis for the “minimally important differences” (MIDs) used in this study to interpret changes from baseline at the individual and group levels. Accordingly, clinically meaningful improvement from baseline on the health utility index was defined as a ≥ 0.08 -point increase, and clinically meaningful deterioration was defined as a ≥ 0.10 -point reduction.¹³ For the EQ-5D VAS, an MID of ± 7 points was used to determine clinically meaningful improvement ($+7$) or deterioration (-7 points) from baseline.¹⁴ EQ-5D-3L-evaluable patients had nonmissing health utility and VAS scores at baseline (ie, C1D1).

Other assessments included comparisons of within-group and between-group least-square (LS) mean score changes from baseline at each postbaseline timepoint estimated using analysis of covariance (ANCOVA) models controlling for baseline instrument score. Within- and between-group differences in LS mean changes from baseline were also assessed by mixed model repeated measures (MMRM) analysis, with changes from

baseline scores as the dependent variable. The MMRM model had the intercept and time as the random effects and the following covariates as fixed effects: baseline domain score, treatment group, time, and a treatment-by-time interaction. Responder analyses compared the proportion of patients in each arm who achieved clinically meaningful improvement (modified MFSAF and EQ-5D-3L) or deterioration (EQ-5D-3L only) at each visit, defined as a $\geq 50\%$ reduction from baseline in TSS or individual symptom scores on the modified MFSAF v2.0 and using the MIDs described above on the EQ-5D-3L. Responder analyses were performed with logistic regression methods; adjusted ORs, 95% CIs, and *P* values were estimated controlling for baseline scores. To assess potential heterogeneity in treatment effects, modified MFSAF v2.0 symptom response rates at EOC6 were assessed among patient subgroups defined by baseline characteristics. Finally, to evaluate potential associations between patient-reported outcomes and objective spleen volume changes with fedratinib, changes in MFSAF and EQ-5D-3L scores among patients randomized to fedratinib 400mg were stratified by degree of SVR from baseline at EOC6: $<10\%$ (including spleen volume increases), 10% to $<35\%$, or $\geq 35\%$. Analysis of variance (ANOVA) methods were used for pairwise comparisons of changes from baseline in each fedratinib SVR subgroup versus the overall placebo arm for patients with available TSS and spleen volume data at both baseline and EOC6.

All analyses were performed using SAS version 9.4 or higher. *P* values were not adjusted to control for type I error rate for multiplicity.

Results

Patients

Overall, 96 patients were randomized to fedratinib 400mg and 96 were randomized to placebo. The MFSAF-evaluable population comprised 91 patients (95%) in the fedratinib 400mg arm and 85 patients (89%) in the placebo arm. The EQ-5D-3L health utility and VAS evaluable populations comprised 95 (99%) and 91 (95%) fedratinib-randomized patients, respectively, and 92 (96%) and 88 (92%) placebo-randomized patients. Baseline demographic and disease characteristics in the MFSAF-evaluable populations (Supplemental Digital Table 1; <http://links.lww.com/HS/A157>) were consistent with the ITT population⁶ and were mostly comparable between treatment arms. Compared with the placebo arm, the fedratinib 400mg arm included a lower proportion of patients aged ≥ 65 years (35% in the fedratinib 400mg arm versus 56% in the placebo arm) and fewer patients with high-risk MF (40% versus 56%, respectively), and had a longer median time from MF diagnosis to study entry (3.6 versus 2.4 yrs). In all, 72 patients (75%) in the fedratinib arm and 50 patients (52%) in the placebo arm had nonmissing TSS scores at baseline and EOC6.

Modified MFSAF v2.0

Compliance rates were high ($>80\%$ of eligible patients at each time-point) in both treatment groups at C2D1 through C6D1. At EOC6, compliance rate was significantly greater in the fedratinib arm than in the placebo arm (96% versus 79%, respectively; $P=0.002$) (Supplemental Digital Figure 1; <http://links.lww.com/HS/A157>). Completion rate declined over time in both treatment groups but was significantly higher in the fedratinib 400mg arm (78%) than in the placebo arm (58%) at EOC6 ($P=0.005$).

At baseline, mean weekly TSS and individual symptom scores on the modified MFSAF v2.0 were slightly higher in the fedratinib arm than in the placebo arm (Table 1), although overall mean symptom scores (which ranged from 2.1 to 3.3) suggested

that MF symptoms were generally mild in severity at study entry. Patients reported early satiety as the most problematic symptom at baseline.

During treatment, mean TSS changes from baseline indicated significant improvement with fedratinib 400mg compared with placebo at all postbaseline visits through EOC6, with generally medium effect sizes (Figure 1). At EOC6, the mean [\pm SD] change from baseline in TSS among evaluable patients was -8.0 [13.0] in the fedratinib arm ($n=72$) and $+0.6$ [7.7] in the placebo arm ($n=50$) (effect size -0.67 [95% CI -0.97 to -0.36]), and the majority of evaluable patients in the fedratinib 400mg arm achieved a reduction in TSS from baseline (Figure 2A). These findings were confirmed by supporting ANCOVA analyses: fedratinib was associated with significant improvements in LS mean changes from baseline at all assessment time points through EOC6, and LS mean changes at each time point were significantly greater with fedratinib 400mg compared with placebo (Supplemental Digital Table 2; <http://links.lww.com/HS/A157>). Between-group results were further confirmed in the MMRM analysis (Supplemental Digital Table 3; <http://links.lww.com/HS/A157>). Statistically significant between-group differences in mean changes from baseline favoring fedratinib were also observed for all 6 modified MFSAF v2.0 symptoms across all visits except for pruritus scores at 1 assessment (EOC6) (Figure 3). Fedratinib was associated with clinically meaningful medium effect sizes relative to placebo starting at C3D1 for night sweats, early satiety, and pain under ribs on the left side; small, medium, and large effect sizes were seen for abdominal discomfort; and differences in pruritus and bone or muscle pain scores were associated with small effect sizes (0.20 to <0.50) at almost all postbaseline assessments. Symptom scores in the placebo arm generally remained at or above baseline levels across postbaseline visits.

The symptom response rate (ie, $\geq 50\%$ reduction in TSS from baseline) at EOC6 was significantly greater with fedratinib versus placebo: 40% versus 9%, respectively (Supplemental Digital Figure 2; <http://links.lww.com/HS/A157>), with an OR for response with fedratinib of 7.0 (95% CI, 2.9-16.9; $P<0.001$). Median time to first symptom response was 11.9 weeks in the fedratinib arm and was not reached (NR) in the placebo arm (hazard ratio [HR] 2.8 [95% CI, 1.7-4.7]; $P<0.0001$). The difference between fedratinib and placebo in time to definitive symptom improvement was also statistically significant: 16.1

Table 1.

Baseline Scores on the Modified MFSAF and EQ-5D-3L Instruments

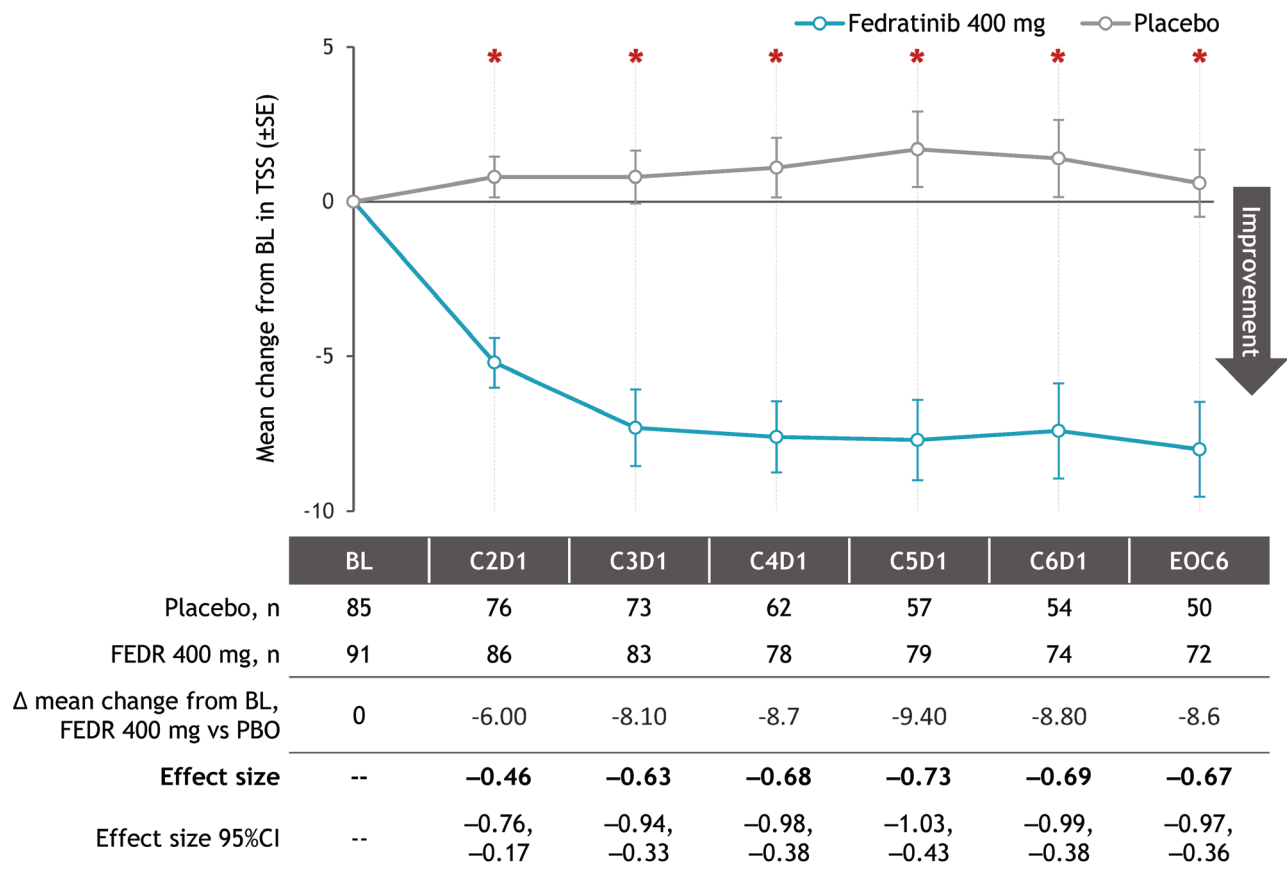
	Fedratinib 400 mg	Placebo	Total
	Mean [SD]		
MFSAF^a	N=91	N=85	N=176
Total symptom score	17.6 [13.5]	14.7 [12.0]	16.2 [12.8]
Night sweats	3.0 [3.0]	2.4 [2.9]	2.7 [2.9]
Pruritus	2.3 [2.7]	1.9 [2.3]	2.1 [2.5]
Abdominal discomfort	3.1 [2.6]	2.6 [2.5]	2.9 [2.5]
Early satiety	3.5 [2.6]	3.1 [2.6]	3.3 [2.6]
Pain under ribs on left side	2.6 [2.7]	2.0 [2.5]	2.3 [2.6]
Bone or muscle pain	3.2 [2.9]	2.6 [2.5]	2.9 [2.7]
EQ-5D-3L			
Health utility index^b	N=95	N=92	N=187
	0.70 [0.25]	0.72 [0.26]	0.71 [0.25]
Visual analogue scale^c	N=91	N=88	N=179
	61.3 [22.2]	62.5 [21.2]	61.9 [21.7]

^aTotal symptom scores range from 0 to 60; individual symptom scores range from 0 to 10 (higher scores = worse symptomatology).

^bScores range from -0.594 to 1.0 (higher scores = better health state).

^cScores range from 0 to 100 (higher scores = better health state).

MFSAF = Myelofibrosis Symptom Assessment Form; SD = standard deviation.



* $P < 0.05$, fedratinib 400 mg vs. placebo.

Effect sizes and 95% CIs for difference in observed mean change from baseline between fedratinib 400 mg vs placebo were estimated using Hodges' g .

95%CI, 95% confidence interval; BL, baseline; CxD1, Cycle x Day 1; Δ , difference; EOC6, end of cycle 6; FEDR, fedratinib; SE, standard error; TSS, total symptom score.

Figure 1. Mean change from baseline in MFSAF TSS by visit, and effect sizes for differences between fedratinib 400mg vs placebo. MFSAF = Myelofibrosis Symptom Assessment Form.

weeks versus NR, respectively (HR 4.2 [95% CI, 2.2-8.2]; $P < 0.0001$) (Figure 4). Nearly one-half (49%) of all MFSAF-evaluable patients in the fedratinib 400mg arm achieved a symptom response for ≥ 3 of the first 6 treatment cycles, compared with 9% in the placebo arm.

At EOC6, response rate ($\geq 50\%$ reduction from baseline score) for each modified MFSAF v2.0 symptom was significantly higher with fedratinib versus placebo, with the greatest magnitudes of treatment effect observed in night sweats, early satiety, and abdominal discomfort (all $P \leq 0.001$) (Supplemental Digital Figure 2; <http://links.lww.com/HS/A157>).

EQ-5D-3L

Compliance rates at EOC6 were significantly higher in the fedratinib arm on both the descriptive questionnaire (96%, versus 82% in the placebo arm; $P = 0.007$) and VAS (95% versus 77%; $P = 0.003$). Completion rates for the descriptive questionnaire in the fedratinib and placebo arms at EOC6 were 77% versus 60%, respectively ($P = 0.019$), and for the VAS were 76% versus 57% ($P = 0.009$).

At baseline, patients in the fedratinib 400mg and placebo arms reported similar mean EQ-5D-3L health utility index and VAS scores (Table 1). Baseline EQ-5D-3L scores in this study were worse than reference values from a general population

aged 55–64 years in the United Kingdom¹⁵; when applying the prespecified MIDs for clinically meaningful deterioration (-0.10 in health utility score and -7 in VAS score^{13,14}), the overall health utility index at baseline in this trial was borderline meaningfully worse compared with the reference value (mean 0.71 versus 0.80, respectively), and baseline mean EQ-5D VAS score was substantially lower (61.9 versus 81.7), indicating that the HRQoL of study patients was considerably impaired at baseline relative to that of healthy individuals.

At EOC6, fedratinib was associated with a significantly greater improvement in mean health utility score compared with placebo (0.045 versus -0.048 , respectively; $P = 0.01$), with a clinically meaningful small effect size of 0.37 (95% CI, 0.08-0.66). On the VAS, the mean change from baseline at EOC6 was $+6.2$ in the fedratinib 400mg arm, compared with -0.9 in the placebo arm ($P = 0.068$). These findings were supported by ANCOVA analyses: fedratinib was associated with significantly better changes from baseline compared with placebo in LS mean health utility score (fedratinib $+0.039$, placebo -0.040 ; $P = 0.008$) and VAS score ($+5.94$ versus -0.65 ; $P = 0.035$) at EOC6, after adjusting for baseline score for each assessment. Similarly, a significantly higher proportion of individual patients in the fedratinib arm reported clinically meaningful improvement in EQ-5D-3L health utility at EOC6 (23%, versus 7% in the placebo arm; OR 5.12 [95% CI, 1.81-14.48];

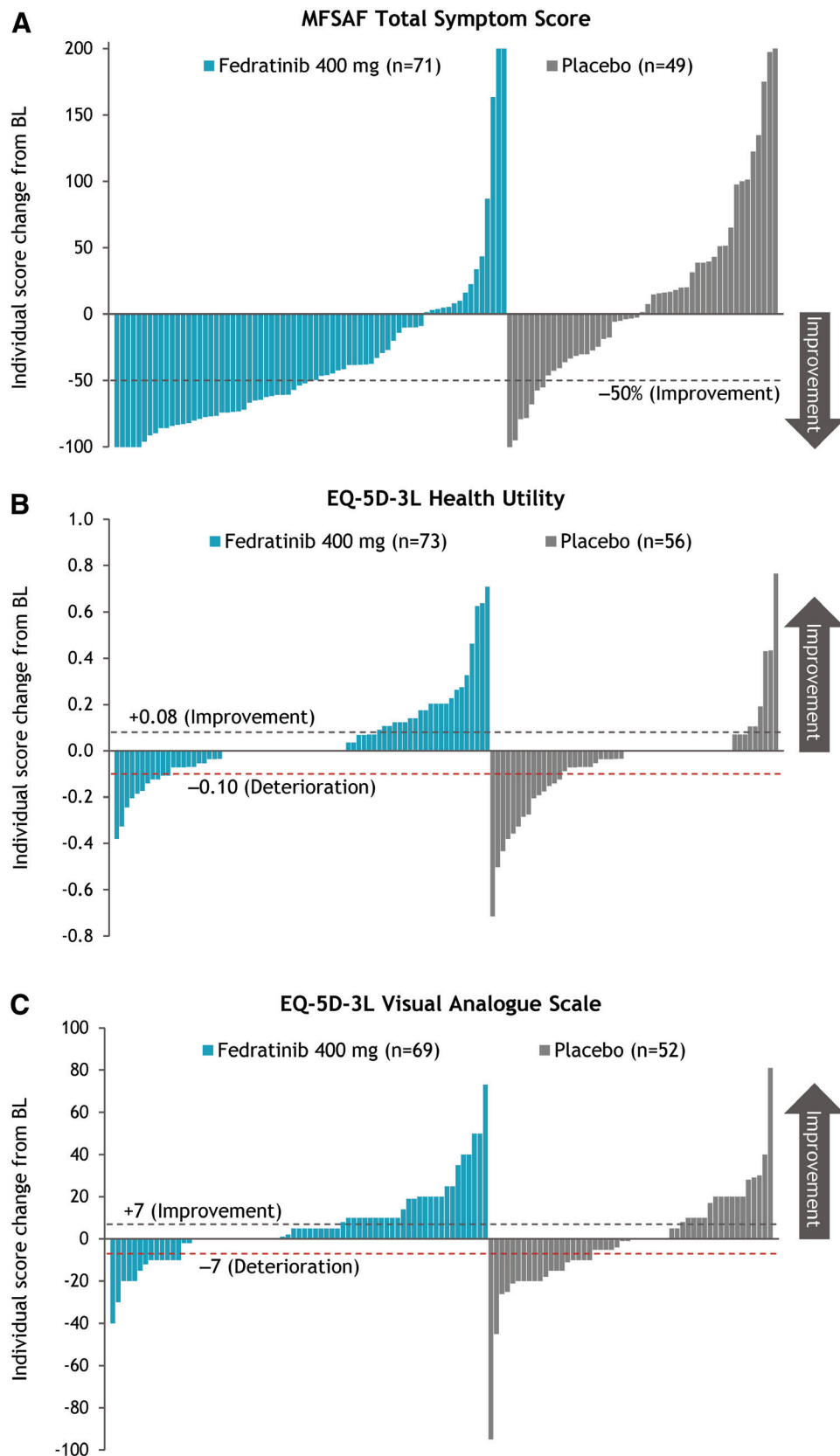
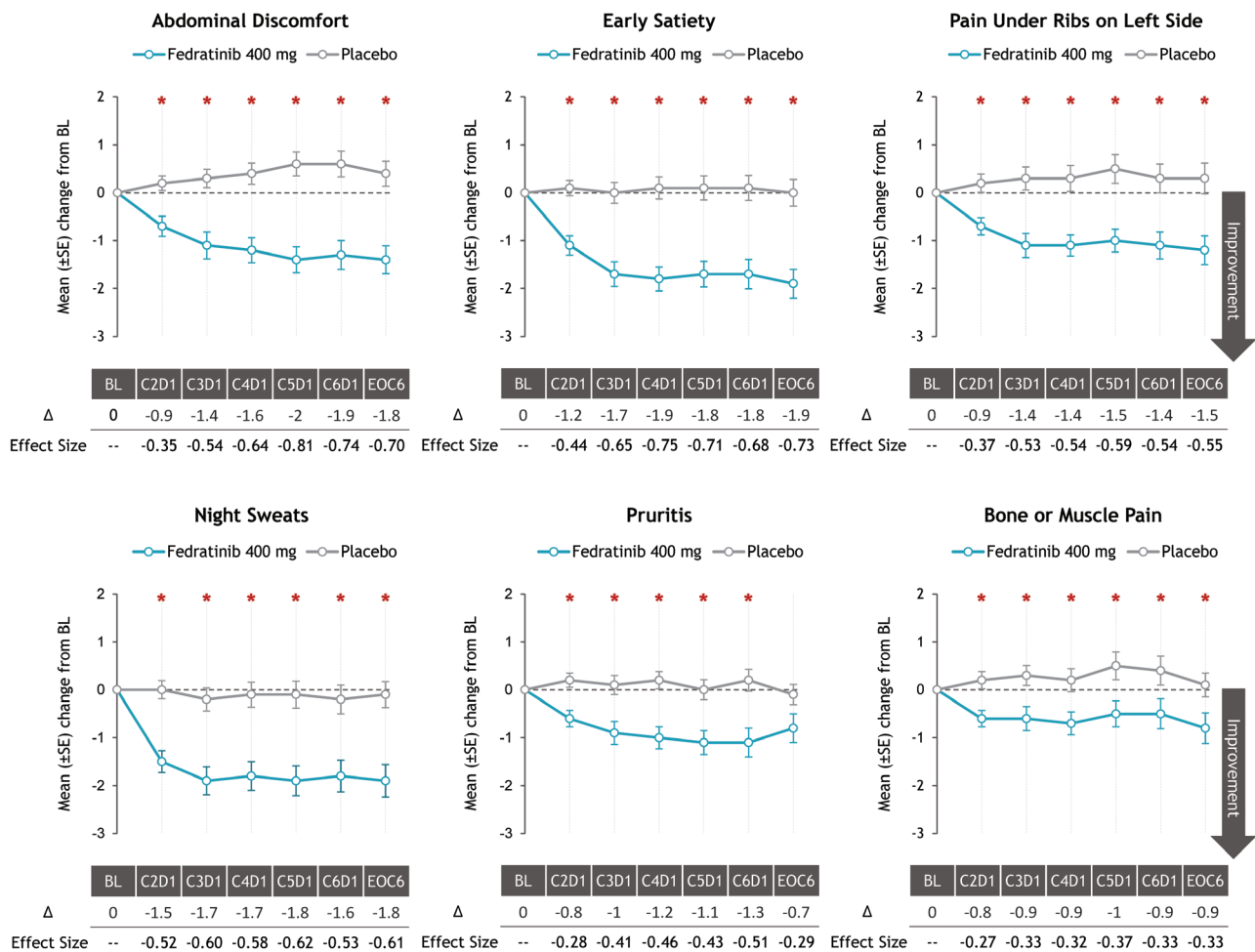


Figure 2. Mean changes from baseline at end of cycle 6 for patients randomized to fedratinib 400mg and placebo: (A) MFSAF TSS; (B) EQ-5D-3L health utility score; and (C) EQ-5D visual analogue scale. MFSAF = Myelofibrosis Symptom Assessment Form; TSS = total symptom score.

$P=0.002$), and 30% and 19% of evaluable patients in the fedratinib and placebo arms, respectively, experienced clinically meaningful improvement in VAS scores (OR 1.80 [95% CI,

0.85-3.78]; $P=0.122$). Figure 2B and 2C show changes from baseline in EQ-5D-3L health utility and VAS scores for individual patients at EOC6.



*P < 0.05, fedratinib 400 mg vs. placebo.

BL, baseline; Cx2D1, Cycle x Day 1; Δ, mean change from BL, FEDR 400 mg vs PBO; EOC6, end of cycle 6; SE, standard error.

Figure 3. Mean changes in individual MFSAF symptom scores and effect sizes across visits with fedratinib 400mg versus placebo. MFSAF = Myelofibrosis Symptom Assessment Form.

Associations With Spleen Volume Reductions

At EOC6, a clear correlation was observed between degree of SVR from baseline with fedratinib and improvements in modified MFSAF v2.0 TSS and EQ-5D-3L health utility and VAS (Figure 5). For fedratinib-treated patients who achieved SVRs of ≥35%, or SVRs between 10% and <35%, mean TSS improvements and MFSAF symptom response rates at EOC6 were significantly greater than those for the overall placebo arm. The mean TSS reduction from baseline in patients who received fedratinib 400mg and attained <10% SVR was -3.2 (95% CI, 11.1-4.7), which was not significantly different from the overall TSS change in patients receiving placebo (+0.9; P=0.34). Improvements in health utility and VAS scores at EOC6 were both significantly greater for fedratinib-treated patients who achieved ≥35% SVR from baseline compared with the placebo arm (Figure 5).

Subgroup Analyses

Symptom response rates at EOC6 were nominally greater with fedratinib 400mg versus placebo across patient subgroups defined by baseline demographic and disease characteristics (Figure 6). Moreover, TSS improvements with fedratinib within patient subgroups were relatively consistent. Fedratinib was also associated with higher rates of clinically meaningful improvement and lower rates of clinically meaningful deterioration

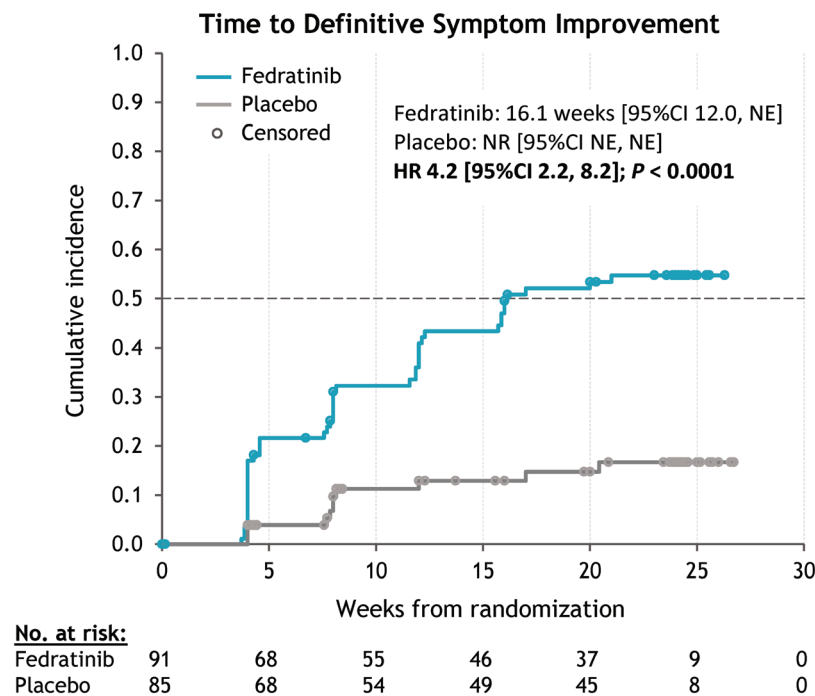
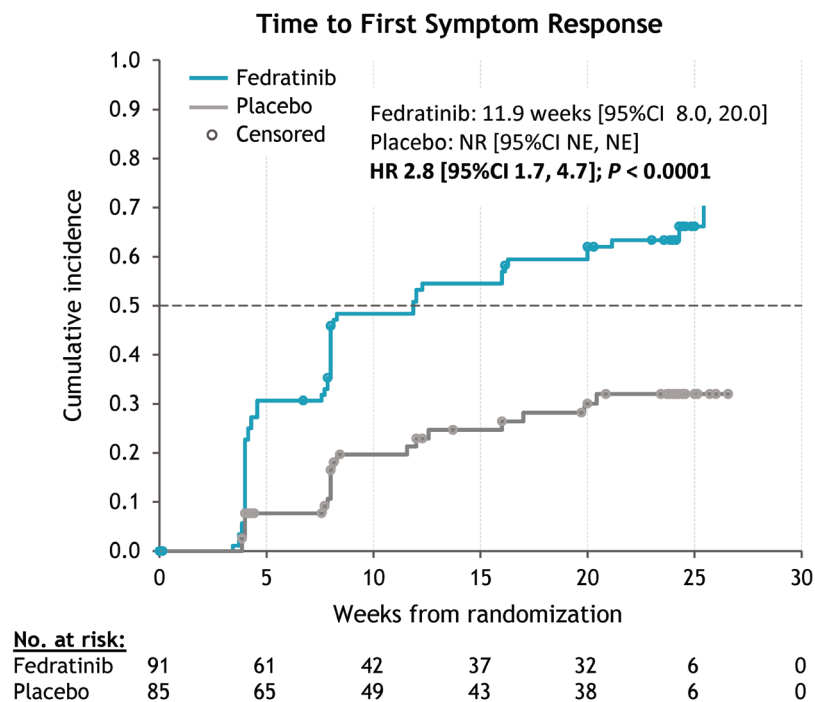
compared with placebo in both EQ-5D-3L health utility and EQ-5D VAS scores at EOC6 across all subgroups defined by baseline characteristics.

Discussion

At entry to the JAKARTA trial, these patients with intermediate-2 or high-risk, JAK-inhibitor-naïve MF reported generally mild MF-related symptoms on the modified MFSAF v2.0 at baseline in both treatment groups. Despite this, EQ-5D-3L health utility and VAS scores indicated patients in this study had considerably impaired HRQoL at baseline relative to an age-matched general population.¹³⁻¹⁵

By EOC6, patients treated with fedratinib 400mg/d were 7 times more likely to achieve a symptom response than those who received placebo. Dampening MF-related inflammation may contribute to the effect of fedratinib on ameliorating MF symptoms. Abnormal cytokine expression is thought to contribute to the pathogenesis of MF and related constitutional symptoms.¹⁶ In a phase II dose-finding study in patients with MF, fedratinib treatment was shown to regulate cytokine expression, including upregulation of anti-inflammatory adiponectin and downregulation of proinflammatory TNF-α.¹⁷

Rapid improvement of debilitating symptoms that have a negative impact on patients' quality of life is an important goal of MF treatment. The JAK1/2 inhibitor, ruxolitinib, which until

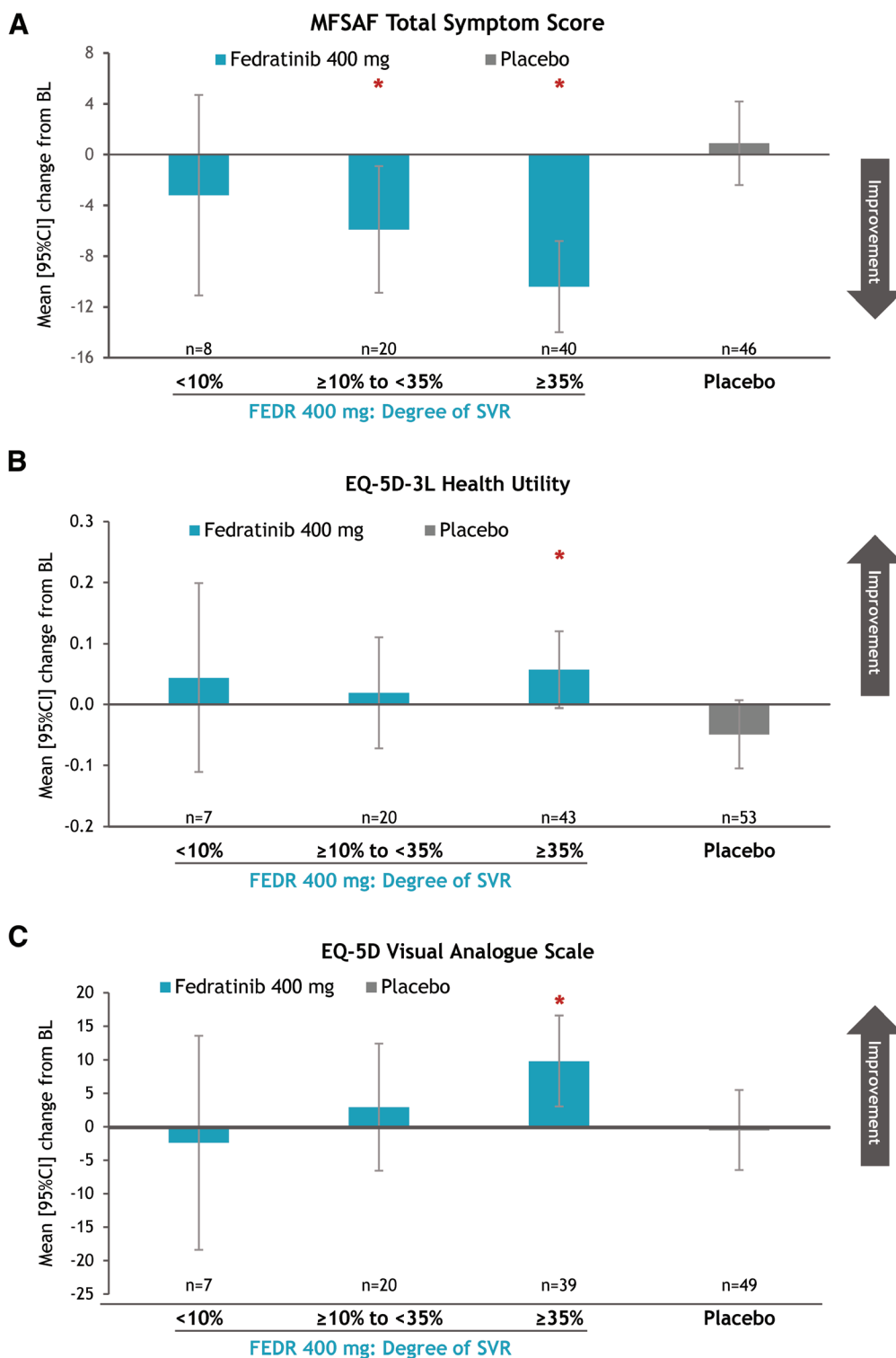


Effect sizes and 95% CIs for difference in observed mean change from baseline between fedratinib 400 mg vs placebo were estimated using Hedges' g. 95%CI, 95% confidence interval; HR, hazard ratio; NE, not estimable; No, number; NR, not reached.

Figure 4. Time to first response and time to definitive improvement in MFSAF TSS with fedratinib 400 mg and placebo. MFSAF = Myelofibrosis Symptom Assessment Form; TSS = total symptom score.

recently was the only JAK inhibitor approved for MF treatment, was shown to induce symptom responses in 46% of patients with JAK-inhibitor-naïve intermediate-2 or high-risk MF in the phase III, placebo-controlled COMFORT-I study,¹⁸ similar to the rate of symptom response with fedratinib 400 mg daily (40%) in this study. Thus, the choice of front-line JAK inhibitor

therapy—now that there is a choice—may depend more on clinical factors such as pretreatment platelet counts and anemia severity than differential effects on HRQoL.^{5,19} While the efficacy of ruxolitinib therapy after fedratinib failure is currently unknown, fedratinib treatment after ruxolitinib failure has been shown to induce spleen responses in 31% of patients who discontinued



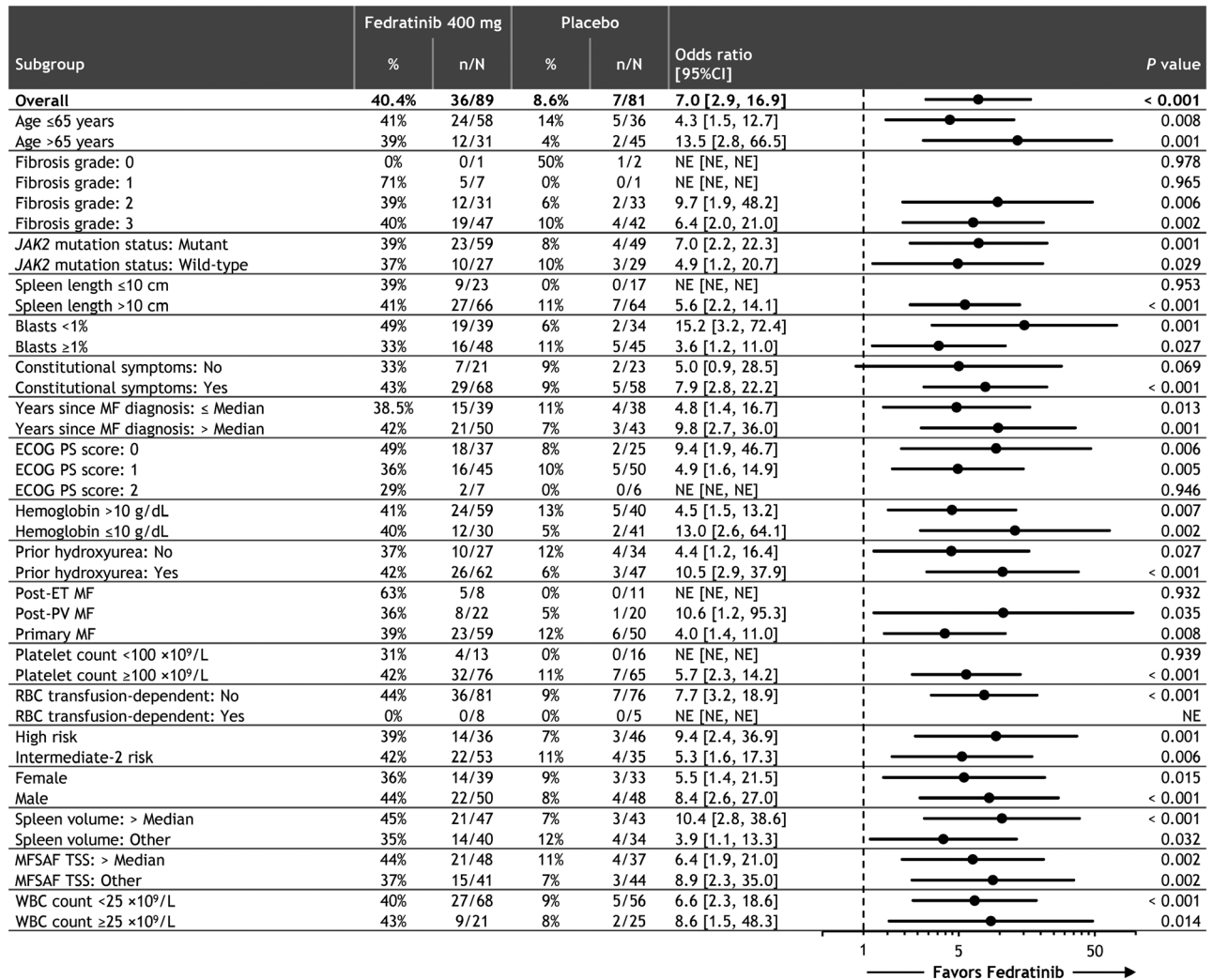
*Indicates significant *P* value (< 0.05) calculated from pairwise comparisons using ANOVA contrasts to compare each spleen volume reduction subgroup vs. placebo.
 95%CI, 95% confidence interval; BL, baseline; FEDR, fedratinib; SVR, spleen volume reduction; TSS, total symptom score.

Figure 5. Relationships between level of spleen volume reduction in the fedratinib 400mg arm and changes from baseline in (A) MFSAF TSS, (B) EQ-5D-3L health utility index, and (C) EQ-5D visual analogue scale. MFSAF = Myelofibrosis Symptom Assessment Form.

roxolitinib due failure to attain a response, loss of response, or intolerance.²⁰

As early as the first postbaseline assessment (ie, C2D1), treatment with fedratinib was associated with clinically meaningful and statistically significant improvements from baseline in

individual MFSAF symptom scores and TSS compared with placebo that were sustained through EOC6. Differences between fedratinib and placebo were generally of medium effect size (≥ 0.50) except for pruritus and bone/muscle pain, which had small but clinically meaningful effect sizes of ≥ 0.30 . Time to



95%CI, 95% confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythemia; JAK2, Janus kinase 2; MF, myelofibrosis; MFSAF, MF Symptom Assessment Form; NE, not estimable; PV, polycythemia vera; RBC, red blood cell; TSS, total symptom score; WBC, white blood cell.

Figure 6. Forest plot of MFSAF symptom response with fedratinib 400mg and placebo at the end of cycle 6 in patient subgroups defined by clinically meaningful baseline characteristics.

definitive symptom improvement was significantly more rapid in the fedratinib arm and symptom responses with fedratinib were durable, with approximately one-half of patients in that arm achieving ≥50% TSS reductions from baseline at 3 or more of the 6 postbaseline visits.

Patients receiving fedratinib 400mg were also about 5 times more likely than patients in the placebo arm to experience clinically meaningful improvement in general HRQoL by EOC6, as measured by EQ-5D-3L health utility scores. Although a greater proportion of patients in the fedratinib arm showed clinically meaningful improvement from baseline at EOC6 in EQ-5D VAS scores, the difference between treatment arms was not statistically significant. Nevertheless, LS mean changes from baseline in health utility and VAS at EOC6 were both significantly greater with fedratinib versus placebo after adjusting for baseline scores. Treatment benefits in favor of fedratinib were observed across all patient subgroups defined by baseline demographic and disease characteristics, and the beneficial effects of fedratinib on MF symptoms and HRQoL were similar within these subgroups, suggesting minimal heterogeneity of treatment effect. It is worth noting that fewer patients in the fedratinib arm were aged >65

years and a smaller proportion of patients receiving fedratinib had high-risk MF at study entry, which may have influenced relative HRQoL outcomes, although to what extent is unknown.

Overall, there was a clear association at EOC6 between extent of SVR and symptom response for patients treated with fedratinib: the greater the SVR, the better the symptom response. Similar associations between degree of SVR and symptom improvements have been observed with front-line ruxolitinib in a relatively comparable patient population in the COMFORT-I study.² Notably, in this study, some patients who had a SVR of ≥35% from baseline did not attain a symptom response, and conversely, some patients with a ≥50% reduction from baseline TSS from baseline at EOC6 did not have an accompanying spleen response. When asked, MF-related symptoms are reported by a majority of patients with the disease, regardless of the presence of palpable splenomegaly.²¹

In summary, in addition to significantly improving spleen volume response compared with placebo, patients treated with fedratinib 400mg/d experienced rapid and sustained clinically meaningful and statistically significant improvements in MF-related symptoms and overall HRQoL compared with placebo.

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Author contributions

RAM directed content for the first draft. NS, AMV, J-JK, FP, SZ, MT, CNH, and SV participated in the development of each draft. SR, PA, JLB, and DT participated in the performance of the research and assisted in manuscript development. SG and XY performed data analysis and assisted in manuscript development. All authors approved the final draft for publication and take responsibility for the integrity of the data and the accuracy of the analysis.

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