Indirect treatment comparison (ITC) of momelotinib (MMB) vs fedratinib (FED) safety in patients (pts) with myelofibrosis (MF)

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Introduction

- Janus kinase (JAK) inhibitors are a mainstay of myelofibrosis (MF) treatment, with proven ability to improve symptoms and reduce spleen volume for most patients[1-3]
- Safety profiles can vary, however, and some approved JAK inhibitors such as ruxolitinib and fedratinib have been associated with hematologic toxicity and may induce or exacerbate anemia[1,2]
- The JAK1/JAK2/activin A receptor type 1 (ACVR1) inhibitor momelotinib has shown consistent benefit in terms of spleen response, symptom response, and transfusion-independent rates across 3 phase 3 trials (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM)[4-6]
- Head-to-head comparisons of momelotinib and ruxolitinib in the SIMPLIFY-1 and SIMPLIFY-2 trials demonstrated that momelotinib had a more favorable hematologic adverse event (AE) profile vs ruxolitinib[4,5]
- Because data comparing momelotinib vs other JAK inhibitors are limited to ruxolitinib, we performed an indirect treatment comparison (ITC) of safety outcomes between momelotinib and fedratinib in JAK inhibitor–experienced and –naive patients with MF

Objective

- To compare safety outcomes between momelotinib and fedratinib separately in JAK inhibitor–experienced and JAK inhibitor–naive patient populations

Methods

- A matching-adjusted indirect comparison (MAIC)[7,8] was undertaken to compare safety outcomes from phase 2 and/or 3 momelotinib and fedratinib trials
- Treatment-emergent adverse events (TEAEs) occurring in ≥10% of a treatment arm over 24 weeks were evaluated; evaluable outcomes were those reported in peer-reviewed manuscripts[9-11] and/or regulatory documents for fedratinib[12,13]
  - Primary outcomes were grade 3/4 anemia and thrombocytopenia; other outcomes occurring in ≥10% of a treatment arm were considered secondary outcomes
- Separate analyses were performed in both patient populations using data from momelotinib and 400-mg fedratinib trial arms:
  - JAK inhibitor experienced: SIMPLIFY-2[5]/MOMENTUM[6] vs JAKARTA2[9]
  - JAK inhibitor naive: SIMPLIFY-1[4] vs JAKARTA[10]
- MAIC involved reweighting momelotinib patient data to match baseline characteristics of fedratinib trial arms
  - Adjustment for transfusion status was explored but resulted in a substantial decrease in effective sample size (ESS). Thus, adjustment for Hb levels was instead used as a proxy for transfusion status
- Risk differences were estimated to compare TEAEs for the reweighted momelotinib populations vs fedratinib
- For the JAK inhibitor–naive population, sensitivity analyses were conducted to assess the impact of potential differences in TEAE definitions and/or assessment periods when reporting of these factors was unclear or differed across different sources of fedratinib safety data

Results

- After adjustment, patient populations were well balanced, with an acceptable ESS (**Table 1**)
  - In JAK inhibitor–experienced patients, adjustment for DIPSS, TSS, platelet counts, spleen volume, Hb levels, and spleen length resulted in removal of significant imbalances between the momelotinib and fedratinib groups in all identified potential adjustment factors except for transfusion status
  - In JAK inhibitor–naive patients, adjustment for IPSS, TSS, platelet counts, spleen volume, and Hb levels resulted in removal of significant imbalances between the momelotinib and fedratinib groups in all identified potential adjustment factors except for transfusion status

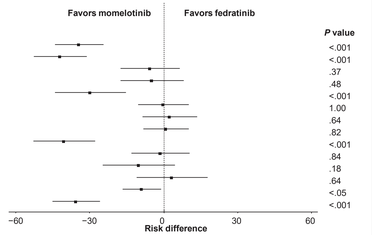
Table 1. Demographics and Baseline Characteristics Before and After Adjustment

	JAK inhibitor experienced			JAK inhibitor naive		
	Before adjustment		After adjustment	Before adjustment		After adjustment
	Fedratinib (JAKARTA2; N=97)	Momelotinib (SIMPLIFY-2 and MOMENTUM; N=215)	Momelotinib (ESS=79.4)	Fedratinib (JAKARTA; N=96)	Momelotinib (SIMPLIFY-1; N=212)	Momelotinib (ESS=151.1)
Age, mean (SD), y	66.5 (8.1)	67.9 (8.2)	68.0 (8.7)	62.9 (9.6)	64.8 (10.7)	64.6 (9.9)
Male, %	54.6	60.5	53.7	56.3	58.5	63.8
Race, %						
White	94.8	82.3	80.4	89.6	83.0	85.5
Baseline TSS (MFSAF v2.0), mean (SD)[a]	20.7 (12.1)	18.4 (12.6)	20.7 (13.5)	17.5 (13.5)	15.3 (11.4)	17.5 (12.3)
MF subtype, %						
Primary MF	54.6	60.5	60.6	64.6	59.0	57.3
PPV	25.8	19.1	20.0	25.0	22.6	26.3
PET	19.6	20.5	19.4	10.4	18.4	16.5
DIPSS/IPSS risk category, %[b]						
Intermediate-1	16.5	14.0	16.5	0	21.7	20.0
Intermediate-2	48.5	56.7	48.5	59.4	34.9	39.3
High	35.1	29.3	35.1	40.6	43.4	40.6
ECOG PS, %						
0-1	73.2	82.8	84.6	91.7	92.4	91.6
2	23.7	17.2	15.5	8.3	7.5	8.4
RBC transfusion dependent, %[c]	14.4	67.0	56.8	8.3	27.8	30.3
Spleen volume ≥ median (JAKARTA-2), %	50.0	34.9	50.0	50.0	27.8	50.0
Spleen length ≥ median (JAKARTA-2), %	50.0	23.3	50.0	50.0	30.3	44.7
Hemoglobin, %						
<10 g/dL	52.6	81.4	52.6	50.0[d]	52.4[d]	50.0[d]
≥10 g/dL	47.4	18.6	47.4	50.0[e]	47.6[e]	50.0[e]
Platelet count, %						
<100 × 10^9/L	34.0	48.8	34.0	14.6	8.0	14.6
≥100 × 10^9/L	66.0	51.2	66.0	85.4	92.0	85.4

DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; PET, post–essential thrombocytopenia; PPV, post–polycythemia vera; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independent; TSS, Total Symptom Score.
[a] TSS definitions varied between SIMPLIFY-1/SIMPLIFY-2/MOMENTUM and JAKARTA/JAKARTA-2. Definitions were harmonized to use the MFSAF v2.0 criteria. Estimates were reestimated for momelotinib trials using individual patient data. [b] JAKARTA excluded patients with IPSS scores of intermediate-1. Matching was performed using an aggregate categorization of intermediate-1 and intermediate-2 scores. [c] Transfusion status definitions varied between SIMPLIFY-1/SIMPLIFY-2/MOMENTUM and JAKARTA/JAKARTA-2. Definitions were harmonized to use definitions reported in JAKARTA-2. TI/TD status was reestimated for momelotinib trials using individual patient data. [d] < Median (JAKARTA); estimated using a threshold of 10.7 g/dL. [e] ≥ Median (JAKARTA); estimated using a threshold of 10.7 g/dL.

Figure 1. Comparison of Safety Outcomes in JAK Inhibitor–Experienced Patients

Outcome	RD (95% CI)	*P* value
Anemia (grades 3/4)	−34.13 (−44.02 to −24.24)	<.001
Anemia (all grades)	−41.85 (−52.57 to −31.13)	<.001
Thrombocytopenia (grades 3/4)	−5.44 (−17.33 to 6.45)	.37
Thrombocytopenia (all grades)	−4.63 (−17.46 to 8.19)	.48
Diarrhea (all grades)	−29.65 (−44.04 to −15.26)	<.001
Headache (all grades)	0.01 (−10.27 to 10.28)	1.00
Dizziness (all grades)	2.61 (−8.47 to 13.68)	.64
Abdominal pain (all grades)	1.05 (−8.20 to 10.31)	.82
Nausea (all grades)	−40.22 (−52.81 to −27.63)	<.001
Fatigue (all grades)	−1.23 (−13.03 to 10.56)	.84
All AEs (grades 3/4)	−10.00 (−24.65 to 4.66)	.18
Serious AEs	3.45 (−10.86 to 17.76)	.64
TEAEs (discontinuation)	−8.79 (−16.61 to −0.96)	<.05
TEAEs (dose reduction)	−35.33 (−44.97 to −25.69)	<.001

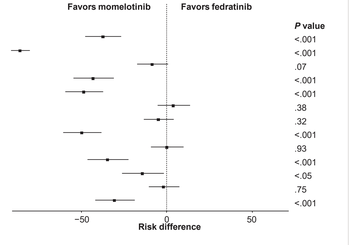


AE, adverse event; JAK, Janus kinase; RD, risk difference; TEAE, treatment-emergent adverse event.

- In JAK inhibitor–experienced patients, momelotinib was associated with a significantly lower risk of grade 3/4 anemia, any-grade anemia, any-grade diarrhea, any-grade nausea, TEAEs leading to treatment discontinuation, and TEAEs leading to dose reduction (**Figure 1**)
  - No identified outcomes were statistically less likely with fedratinib
  - Median exposure duration was 24 weeks for momelotinib and 24.4 weeks for fedratinib

Figure 2. Comparison of Safety Outcomes in JAK Inhibitor–Naive Patients

Outcome	RD (95% CI)	*P* value
Anemia (grades 3/4)	−36.98 (−47.54 to −26.43)	<.001
Anemia (all grades)	−85.34 (−90.94 to −79.74)	<.001
Thrombocytopenia (grades 3/4)	−8.23 (−17.22 to 0.75)	.07
Thrombocytopenia (all grades)	−42.70 (−54.44 to −30.96)	<.001
Diarrhea (all grades)	−48.16 (−59.38 to −36.95)	<.001
Headache (all grades)	4.21 (−5.25 to 13.67)	.38
Abdominal pain (all grades)	−4.41 (−13.11 to 4.29)	.32
Nausea (all grades)	−49.25 (−60.41 to −38.09)	<.001
Fatigue (all grades)	0.42 (−9.13 to 9.96)	.93
All AEs (grades 3/4)	−34.22 (−46.15 to −22.28)	<.001
Serious AEs	−13.89 (−26.01 to −1.76)	<.05
TEAEs (discontinuation)	−1.46 (−10.36 to 7.44)	.75
TEAEs (dose reduction)	−30.23 (−41.80 to −18.65)	<.001

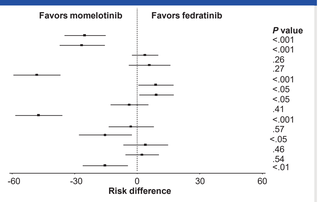


AE, adverse event; JAK, Janus kinase; RD, risk difference; TEAE, treatment-emergent adverse event.

- In JAK inhibitor–naive patients, momelotinib was associated with a significantly lower risk of grade 3/4 anemia, any-grade anemia, any-grade thrombocytopenia, any-grade diarrhea, any-grade nausea, grade 3/4 TEAEs, and TEAEs leading to dose reduction (**Figure 2**)
  - No identified outcomes were statistically less likely with fedratinib
  - Median exposure duration was 24 weeks for momelotinib and 30 weeks for fedratinib

Figure 3. Sensitivity Analyses in JAK Inhibitor–Naive Patients

Outcome	RD (95% CI)	*P* value
Anemia (grades 3/4)	−24.98 (−34.93 to −15.04)	<.001
Anemia (all grades)	−26.34 (−37.45 to −15.23)	<.001
Thrombocytopenia (grades 3/4)	3.77 (−2.81 to 10.34)	.26
Thrombocytopenia (all grades)	5.75 (−4.49 to 15.98)	.27
Diarrhea (all grades)	−48.16 (−59.38 to −36.95)	<.001
Headache (all grades)	9.21 (0.61 to 17.82)	<.05
Dizziness (all grades)	9.39 (1.16 to 17.62)	<.05
Abdominal pain (all grades)	−3.80 (−12.81 to 5.20)	.41
Nausea (all grades)	−47.25 (−58.51 to −36.00)	<.001
Fatigue (all grades)	−3.19 (−14.20 to 7.81)	.57
All AEs (grades 3/4)	−15.22 (−27.86 to −2.57)	<.05
Serious AEs	4.11 (−6.67 to 14.99)	.46
TEAEs (discontinuation)	2.54 (−5.65 to 10.73)	.54
TEAEs (dose reduction)	−15.23 (−28.14 to −4.32)	<.01



AE, adverse event; JAK, Janus kinase; RD, risk difference; TEAE, treatment-emergent adverse event.

- Sensitivity analyses were performed due to discrepancies noted between peer-reviewed manuscripts[10] and regulatory documents[12,13] in the JAK inhibitor–naive population data for fedratinib (**Figure 3**)
  - Comparisons were over 24 weeks for all outcomes except any-grade thrombocytopenia, abdominal pain, and fatigue, for which median exposure was 82 weeks for momelotinib and 62 weeks for fedratinib

Limitations

- Evaluable outcomes were limited by published aggregate data so not all were feasible to compare; comparison of lower frequency events (<10%) was not feasible due to small sample sizes
- Comparison of nonrandomized groups may result in bias due to unmeasured/residual confounding, despite adjusting for prognostic factors/effect modifiers
- Imbalances in transfusion status between the momelotinib and fedratinib arms remained after adjustment of other prognostic variables, although other known prognostic/effect modifiers were well balanced
- While definitions and criteria for AEs were similar across trials, reporting of AEs may still differ based on differences in investigators' judgment, especially for less severe events

Conclusions

- Momelotinib showed a favorable safety profile vs fedratinib in both JAK inhibitor–experienced and –naive patients during a 24-week treatment window from phase 2/3 trials of momelotinib and fedratinib
- There was a significantly lower risk of key hematologic AEs, including any-grade and grade 3/4 anemia in both populations
- The risk of key gastrointestinal AEs such as nausea and diarrhea was significantly reduced with momelotinib vs fedratinib
- The favorable safety profile is consistent with what has been observed vs ruxolitinib in SIMPLIFY-1 and SIMPLIFY-2, particularly with respect to rates of anemia and thrombocytopenia[4,5]
- These data support the use of momelotinib as a safe and tolerable treatment option for JAK inhibitor–experienced and JAK inhibitor–naive patients with MF

Poster MPN-091

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