Momelotinib Long-Term Safety: Pooled Data from Three Phase 3 Randomized-Controlled Trials (RCTs)

Poster 4348

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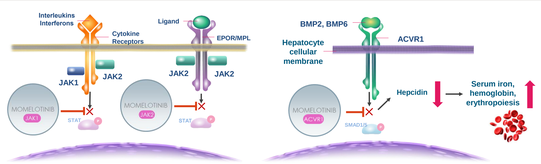
Introduction

- Janus kinase inhibitors (JAKi) approved for treatment of myelofibrosis have demonstrated clinical benefit in splenomegaly and symptoms but do not improve anemia and have limitations that can lead to dose reductions/interruptions and reduced efficacy[1-3]
  - Ruxolitinib (RUX) and fedratinib are associated with worsened anemia and thrombocytopenia
  - Fedratinib is associated with gastrointestinal toxicity and risk of Wernicke's encephalopathy
  - Pacritinib has safety concerns of bleeding and cardiovascular events and is currently only indicated for patients with severe thrombocytopenia
- Momelotinib, the first inhibitor of Janus kinase 1/2 to also inhibit activin A receptor type 1, a key regulator of iron homeostasis, was evaluated in 3 RCTs (SIMPLIFY-1 [S-1], SIMPLIFY-2 [S-2], and MOMENTUM) in patients with high- and intermediate-risk myelofibrosis,[4-6] and has demonstrated clinical activity against anemia, constitutional symptoms, and splenomegaly[4-8]
  - S-1: 432 JAKi-naïve patients randomized 1:1 to momelotinib versus RUX
  - S-2: 156 RUX-treated patients randomized 2:1 to momelotinib versus best available therapy (BAT)
  - MOMENTUM: 195 JAKi-treated patients randomized 2:1 momelotinib versus danazol (DAN)



Dysregulated **JAK-STAT signaling** in myelofibrosis drives overproduction of inflammatory cytokines, **bone marrow fibrosis, systemic symptoms,** and clonal proliferation resulting in extramedullary hematopoiesis and **splenomegaly**[8,10]

Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of myelofibrosis[11,12]

ACVR1, activin A receptor type 1; BMP, bone morphogenetic protein; EPOR, erythropoietin receptor; JAK1/2, Janus kinase 1/2; MPL, myeloproliferative leukemia protein; SMAD1,5, mothers against decapentaplegic homolog 1,5; STAT, signal transducer and activator of transcription.

Objective

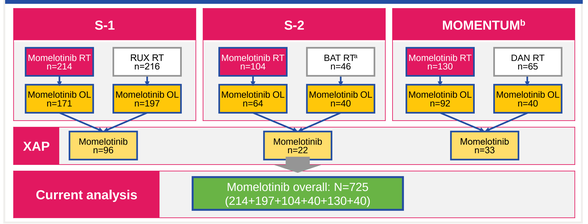
To characterize momelotinib long-term safety from pooled RCTs and extended access study (XAP) data, which included both JAK inhibitor-naive and JAK inhibitor-experienced, transfusion dependent and independent patients, as well as those with and without thrombocytopenia

Methods

- Patients were randomized to momelotinib or RUX (S-1; NCT01969838), momelotinib or BAT, which included RUX in 89% of patients (S-2; NCT02101268), and momelotinib or DAN (MOMENTUM; NCT04173494)
- At the end of the 24-week randomized treatment (RT) period, patients in the momelotinib arms could continue treatment with open-label (OL) momelotinib, and patients in the control arms could cross over to receive OL momelotinib
- Patients from all 3 RCTs continued to receive long-term extended access to momelotinib in the XAP study (NCT03441113)

Results

Figure 1. The Pooled Patient Population Represents the Largest Clinical Trial Safety Database to Date for a JAKi in Myelofibrosis



[a]Forty-six patients received at least 1 dose of RUX. [b]Rollover to XAP was not complete at time of data cut.
BAT, best available therapy; DAN, danazol; JAK, Janus kinase; JAKi, Janus kinase inhibitor; OL, open-label; RT, randomized treatment; RUX, ruxolitinib; S-1, SIMPLIFY-1; S-2, SIMPLIFY-2; XAP, extended access protocol.

- Median follow-up time was 20 months in S-1, 10 months in S-2, and 7 months in MOMENTUM
- The total follow-up time was 1261 patient-years in the 725 patients

Table 1. Demographics and Baseline Characteristics of the Pooled Patient Population Were Similar Across Studies

	Pooled momelotinib-treated patients (N=725)	MOMENTUM momelotinib RT (N=130)	S-1 momelotinib RT (N=214)	S-2 momelotinib RT (N=104)
Age, mean (range), y	66.4 (25-92)	69.8 (38-86)	65.0 (28-85)	66.4 (41-92)
≥65 y, n (%)	459 (63.3)	101 (77.7)	125 (58.4)	63 (60.6)
Male, n (%)	423 (58.3)	79 (60.8)	123 (57.5)	69 (66.3)
Ethnic origin, n (%)	592 (81.7)	107 (82.3)	178 (83.2)	83 (79.8)
White				
DIPSS risk category, n (%)[a]				
Intermediate-1	123 (17.0)	2 (1.5)	45 (21.0)	23 (22.1)
Intermediate-2	300 (41.4)	63 (48.5)	76 (35.5)	62 (59.6)
High	301 (41.5)	65 (50.0)	93 (43.5)	19 (18.3)
Hemoglobin, mean (SD), g/dL	9.9 (2.2)	8.1 (1.1)	10.6 (2.0)	9.6 (1.8)
Hemoglobin <10 g/dL, n (%)	429 (59.2)	126 (96.9)	85 (39.7)	64 (61.5)
Prior JAKi treatment, n (%)	314 (43.3)	130 (100)	0	104 (100)
Transfusion independent, n (%)	359 (49.5)	17 (13.1)	146 (68.2)	32 (30.8)
Transfusion dependent, n (%)	253 (34.9)	63 (48.5)	53 (24.8)	58 (55.8)
Transfusion required but not dependent, n (%)	113 (15.6)	50 (38.5)	15 (7.0)	14 (13.5)
Platelet count, mean (SD), ×10⁹ platelets/L	238.9 (211.1)	151.7 (130.9)	298.5 (206.4)	173.2 (148.2)

[a]Patients enrolled in S-1 were categorized using the IPSS, while patients enrolled in S-2 and MOMENTUM were categorized using the DIPSS.
DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System; JAKi, Janus kinase inhibitor; RT, randomized treatment; S-1, SIMPLIFY-1; S-2, SIMPLIFY-2.

Table 2. Dose Intensity of Momelotinib Was Maintained at a High Level Throughout the Duration of Treatment

	Momelotinib overall (N=725)
Duration of exposure, median (range), mo[a]	11.3 (0.1-90.4)
Duration of exposure for ≥60 mo, n (%)	88 (12.1)
Relative dose intensity, median (range), %	97.3 (0-247)

[a]The mean duration of exposure was 20.3 months; the maximum duration of exposure was approximately 7.5 years.

- Patients in XAP from earlier trials have been treated with momelotinib for up to 12 years

Table 3. Severe Nonhematologic TEAEs Were Infrequent

	Momelotinib overall (N=725)		
	Any-grade TEAE		Grade ≥3 TEAE
	n (%)	E	n (%)
Nonhematologic AEs			
Diarrhea	194 (26.8)	23.0	19 (2.6)
Nausea	141 (19.4)	15.6	14 (1.1)
Fatigue	127 (17.5)	12.8	18 (2.5)
Cough	126 (17.4)	13.9	5 (0.7)
Dizziness	112 (15.4)	11.5	4 (0.6)
Abdominal pain	102 (14.1)	11.1	13 (1.8)
Pyrexia	102 (14.1)	12.0	9 (1.2)
Headache	101 (13.9)	12.0	6 (0.8)
Asthenia	96 (13.2)	12.1	18 (1.4)
Pruritus	90 (12.4)	9.6	5 (0.7)
Dyspnea	89 (12.3)	9.0	15 (2.1)
Peripheral sensory neuropathy	89 (12.3)	9.5	5 (0.7)
Urinary tract infection	88 (12.1)	11.4	18 (2.5)
Pneumonia	83 (11.4)	8.9	61 (8.4)
Constipation	81 (11.2)	7.6	1 (0.1)
Edema peripheral	75 (10.3)	7.7	5 (0.7)
Arthralgia	73 (10.1)	7.7	2 (0.3)
Upper respiratory tract infection	73 (10.1)	7.3	3 (0.4)
Hematologic AEs			
Thrombocytopenia	181 (25.0)	35.4	119 (16.4)
Anemia	170 (23.4)	34.2	107 (14.8)
Neutropenia	49 (6.8)	9.4	35 (5.2)

AE, adverse event; E, exposure-adjusted event rate in 100 person years; TEAE, treatment-emergent adverse event.

- After adjusting for exposure, event rates decreased from the RT phase to the OL treatment phase
- Infections occurred in 55.4% of patients; opportunistic infections were rare (1.5% of all fatal infections)
- Fatal adverse events (AE) were reported in 102 (14.1%) patients, with pneumonia being the most common (n=9), followed by acute myeloid leukemia (AML) (n=6) and sepsis (n=5); only 1 was hematologic (anemia). All were reported as unrelated

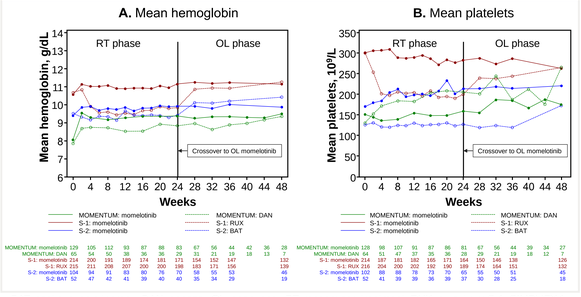
Table 4. Frequent and Clinically Important AEs Did Not Increase in Incidence Over Time

n (%)	24 weeks (n=725)	25-48 weeks (n=510)	49-96 weeks (n=367)	97-144 weeks (n=213)	145-192 weeks (n=150)	193-240 weeks (n=109)	241-288 weeks (n=93)	≥289 weeks (n=64)
Any AE	663 (91.4)	371 (72.7)	280 (76.3)	159 (74.6)	99 (66.0)	60 (55.0)	51 (54.8)	20 (31.3)
All infections	263 (36.3)	134 (26.3)	121 (33.0)	64 (30.0)	38 (25.3)	22 (20.2)	20 (21.5)	8 (12.5)
Opportunistic infections	13 (1.8)	7 (1.4)	9 (2.5)	8 (3.8)	3 (2.0)	0	4 (4.3)	1 (1.6)
Malignancies	38 (5.2)	21 (4.1)	23 (6.3)	13 (6.1)	12 (8.0)	3 (2.8)	7 (7.5)	3 (4.7)
AML/leukemic transformation	12 (1.7)	1 (0.2)	6 (1.6)	1 (0.5)	2 (1.3)	0	0	0
NMSC	9 (1.2)	14 (2.7)	10 (2.7)	5 (2.3)	3 (2.0)	1 (0.9)	3 (3.2)	3 (4.7)
MACE	20 (2.8)	9 (1.8)	18 (4.9)	8 (3.8)	4 (2.7)	1 (0.9)	2 (2.2)	1 (1.6)
Thromboembolism	25 (3.4)	12 (2.4)	19 (5.2)	8 (3.8)	6 (4.0)	2 (1.8)	3 (3.2)	2 (3.1)
Peripheral neuropathy	55 (7.6)	28 (5.5)	20 (5.4)	13 (6.1)	5 (3.3)	3 (2.8)	0	0

AE, adverse event; AML, acute myeloid leukemia; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer.

- No cumulative toxicity was evident; occurrence of AEs was stabilized after 24 weeks of momelotinib treatment
- The frequency of second primary malignancies was within the expected range for the patient age group
  - All nonmelanoma skin cancer events were nonserious, and none lead to discontinuation
  - Malignancies occurring, on average, in less than 1 percent include myelofibrosis, malignant melanoma, uterine leiomyoma, and metastatic squamous cell carcinoma
- AML/malignant transformation led to discontinuation in 2.1% of patients
  - Event rates decreased from the RT phase to the OL phase from 4.3 to 1.4 events per 100 patient-years
- Serious opportunistic infections were rare, and none were life-threatening
- Nonhematologic AEs, including peripheral neuropathy, were mainly grade 1/2 and did not increase over time
  - Two events were considered serious (both grade 3), and 1 resolved after discontinuation

Figure 2. Momelotinib Maintains Mean Platelet Levels and Improves Hemoglobin Over Time



BAT, best available therapy; DAN, danazol; OL, open-label; RT, randomized treatment; RUX, ruxolitinib; S-1, SIMPLIFY-1; S-2, SIMPLIFY-2.

Conclusions

- This study reports the largest clinical trial safety database to date in patients with JAKi-naive or -experienced myelofibrosis
- Most patients tolerated continuous treatment with momelotinib without cumulative toxicity
- Consistent with the lack of increasing hematologic AEs over time, hemoglobin and platelet values improved or remained consistent, respectively
- Peripheral neuropathy was mostly mild/moderate and noncumulative
- The risk of second primary malignancies and AML were not increased for a myelofibrosis population
- This integrated analysis demonstrated the long-term safety of momelotinib in patients with myelofibrosis from early to late stages, and with varying degrees of anemia

Acknowledgments

This study was funded by Sierra Oncology, Inc., a GSK company.

The sponsor thanks all participating patients and their families as well as participating study sites.

Writing support was provided by Timothy Zumwalt, PhD, and Ekaterina Taneva, PhD, of The Lockwood Group (Stamford, CT, USA), and was supported by funding from Sierra Oncology, Inc. (San Mateo, CA, USA), a GSK company.

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Further analyses of momelotinib can be accessed in poster presentations **1729** (burden of myelofibrosis and transfusion dependence) and **1733** (transition to momelotinib from RUX).

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Presented at the 64th American Society of Hematology Annual Meeting & Exposition, New Orleans, LA, USA | December 10-13, 2022