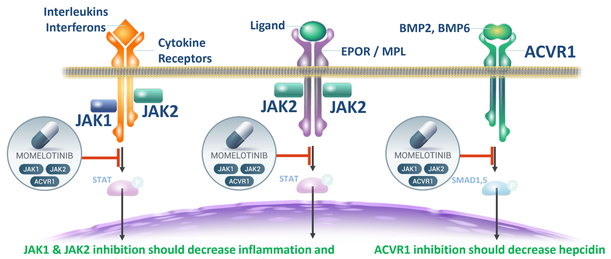
MOMENTUM: A Phase 3 Study of Momelotinib vs Danazol in Patients with Myelofibrosis Previously Treated with a JAKi who are Symptomatic and Anemic

Srdan Verstovsek[1], Chih-Cheng Chen[2], Martin Ellis[3], Laura Fox[4], Yeow Tee Goh[5], Vikas Gupta[6], Claire Harrison[7], Jean-Jacques Kiladjian[8], Mihaela Cornelia Lazaroiu[9], Adam Mead[10], Donal McLornan[11], Mary F. McMullin[12], Stephen T. Oh[13], Andrew Perkins[14], Uwe Platzbecker[15], Christof Scheid[16], Alessandro Vannucchi[17], Sung-Soo Yoon[18], Mark Kowalski[19], Ruben A Mesa[20]

[1]Department of Leukemia at The University of Texas MD Anderson Cancer Center, Houston, TX, [2]Division of Hematology, Chiayi Chang Gung Memorial Hospital, Taiwan , [3]Hematology Institute and Blood Bank, Meir Medical Center, Kfar Saba and Sackler School of Medicine, Tel Aviv University, Israel, [4]Hospital Universitario Vall d'Hebrón, Spain, [5]Singapore General Hospital, Singapore, [6]Cancer Clinical Research Unit, Princess Margaret Cancer Centre, Toronto, ON, Canada, [7]Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom, [8]Centre d'Investigations Cliniques (INSERM CIC 1427), AP-HP, Hopital Saint-Louis, Université de Paris, Paris, France, [9]Policlinica de Diagnostic Rapid Brasov, Romania, [10]Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom, [11]Guy's and Saint Thomas' NHS Foundation Trust, London, United Kingdom, [12]Queen's University Belfast, Belfast, N Ireland, [13]Hematology Division, Washington University, St. Louis, MO, [14]The Alfred Hospital and Monash University, Melbourne, Australia, [15]Leipzig University Hospital, Leipzig, Germany, [16]Department I of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University of Cologne, Germany, [17]Center Research and Innovation of Myeloproliferative Neoplasms, AOU Careggi, Florence, Italy, [18]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea, [19]Sierra Oncology, Vancouver, BC, Canada, [20]Mays Cancer Center, UT Health San Antonio Cancer Center, San Antonio, TX**

Background

- Currently marketed JAK inhibitors (JAKi; ruxolitinib [RUX] and fedratinib) provide symptomatic and splenic benefit in myelofibrosis (MF) patients; however, these agents exacerbate cytopenia in an already markedly myelosuppressed patient population. Importantly, anemia is amongst the most important negative prognostic indicators of MF patient survival.
- Momelotinib (MMB) is a potent and selective small-molecule inhibitor of JAK1, JAK2 and uniquely, ACVR1. This differentiated profile may result in a restoration of iron homeostasis and erythropoiesis, an array of anemia benefits and low hematological toxicity, in concert with symptomatic and splenic activity.
- Exploratory analyses from a prior double-blind study of MMB vs RUX in JAKi–naïve patients (SIMPLIFY-1), demonstrate that MMB patients received half as many RBC units transfused at any time and had a 9.3-fold higher odds of receiving no transfusions during the 24-week study period versus RUX patients.
- Long-term safety data from > 820 Phase 2 and 3 MF patients, some of whom have received MMB for > 10 years, suggest a favorable risk/benefit profile.



HYPOTHESIS: MMB should improve constitutional symptoms and splenomegaly whilst maintaining or improving hemoglobin

Study Rationale and Design

MOMENTUM (NCT04173494) is a Phase 3 study designed to confirm and augment the existing data from the SIMPLIFY and extended access (XAP) studies. The benefits of MMB for all three hallmarks of MF are key study outcomes: constitutional symptom improvement, transfusion independence, and control of splenomegaly.

- **SIMPLIFY-1 (S1)** was a Phase 3, 1:1 randomized, double blind, head-to-head, non-inferiority comparison of MMB to RUX in JAKi-naive subjects with MF (N=432).
  - MMB demonstrated a statistically non-inferior splenic response rate to RUX with a similar proportion between treatment groups having splenic response (26.5% for MMB vs 29.0% for RUX).
  - Robust symptomatic benefit with MMB was observed but did not demonstrate formal non-inferiority to RUX based on the predefined endpoint.
  - MOMENTUM is stratified for baseline TSS, as confounding between baseline TSS level and treatment was observed in S1.

- **SIMPLIFY-2 (S2)** was a Phase 3, 2:1 randomized second-line study comparing MMB to best available therapy (BAT which was ~90% RUX) in anemic or thrombocytopenic subjects with MF previously treated with RUX (N=156).
  - MMB demonstrated a nominally statistically superior symptom response to BAT (26.2% for MMB vs 5.6% for BAT (p=0.001)).
  - Superiority was not demonstrated for splenic response, however washout from prior RUX therapy was prohibited per protocol confounding the baseline spleen assessment since RUX is effective in reducing spleen volume.
  - MOMENTUM requires absence of active anti-MF therapy, including JAKi, for ≥ 2 weeks prior to study randomization to mitigate against confounding baseline splenomegaly assessment.

MOMENTUM is a randomized, double-blind study of MMB vs danazol (DAN) in symptomatic, anemic patients previously treated with an approved JAKi.

- The study population represents patients previously treated with JAKi with unmet medical need due to anemia and inadequate control of symptoms.
- Randomization MMB:DAN (n=180, 2:1) is stratified by baseline MFSAF Total Symptom Score (TSS), palpable spleen length, and baseline RBC units transfused in the 8–week period prior to randomization.
- DAN was selected as the comparator given its use to ameliorate anemia in patients with MF (NCCN and ESMO guidelines).
- During the double-blind treatment period of 24 weeks, subjects orally self-administer their blinded, randomized treatment. Thereafter, subjects have the option to receive MMB in the open-label extended treatment period. Early crossover to MMB is available in the event of confirmed symptomatic splenic progression (Figure 1).
- The primary endpoint of the study is the MFSAF TSS response rate at Week 24. The sample size provides a power of 99% to detect a clinically significant difference in TSS response.
- Secondary endpoints include Transfusion Independence rate and Splenic Response Rate (SRR).
- Key eligibility criteria are shown in Table 1, and key study endpoints in Table 2.

Eligibility Criteria and Study Endpoints

Table 1: Key eligibility criteria for MOMENTUM

Key inclusion criteria:	Key exclusion criteria:
• Age ≥ 18 years • Confirmed diagnosis of PMF in accordance with the WHO 2016 criteria, or Post-PV/ET MF in accordance with the IWG-MRT criteria • Symptomatic, defined as a MFSAF TSS of ≥ 10 units • Anemic, defined as Hgb < 10 g/dL • Previously treated with an approved JAKi for PMF or Post-PV/ET MF for ≥ 90 days, or ≥ 28 days if JAKi therapy is complicated by RBC transfusion requirement of ≥ 4 units in 8 weeks, or Grade 3/4 AEs of thrombocytopenia, anemia, or hematoma • Baseline splenomegaly, defined as having a palpable spleen at ≥ 5 cm, or with volume ≥ 450 cm3 • High risk, intermediate-2, or intermediate-1 risk as defined by DIPSS, or DIPSS-plus • No allogeneic stem cell transplant planned • Acceptable laboratory assessments: – ANC ≥ 0.75 × 10^9/L, PLT ≥ 25 × 10^9/L – Peripheral blast count < 10% – AST/SGOT and ALT/SGPT ≤ 3 × ULN (≤ 5 × ULN if liver is involved by extramedullary hematopoiesis as judged by the investigator or if related to iron chelator therapy that was started within the prior 60 days) – CrCl ≥ 30 mL/min according to Cockcroft-Gault – Direct bilirubin ≤ 2.0 × ULN	• Use of the following treatments within the time periods noted, relative to randomization: – Prior momelotinib treatment at any time – JAKi therapy within 2 weeks – Active anti-MF therapy within 2 weeks – Potent CYP3A4 inducers within 1 week – Investigational agent within 4 weeks – ESA within 4 weeks – DAN within 3 months – Splenic irradiation within 3 months – Current treatment with simvastatin, atorvastatin, lovastatin or rosuvastatin • History of prostate cancer (except localized and presumed cured) • PSA > 4 ng/mL • Unsuitable for spleen volume measurement • Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection • Any of the following within the time periods noted, relative to randomization: – Significant active or chronic bleeding event ≥ Grade 2, within 4 weeks – Unstable angina pectoris within 6 months – Symptomatic congestive heart failure within 6 months – Uncontrolled cardiac arrhythmia within 6 months • QTcF interval > 500 msec, unless attributed to bundle branch block • Current progressive thrombosis despite treatment • History of porphyria • Child-Pugh score ≥ 10 • Presence of peripheral neuropathy ≥ Grade 2

Abbreviations: ANC = absolute neutrophil count, ALT/SGPT = alanine aminotransferase/ serum glutamic-pyruvic transaminase, AST/SGOT = aspartate aminotransferase/ glutamic-oxaloacetic transaminase, CrCl = calculated creatinine clearance, CTCAE = Common Terminology Criteria for Adverse Events, DAN = danazol, ECOG = Eastern Cooperative Oncology Group, ESA = erythropoiesis stimulating agent, ICF = informed consent form, IWG MRT = International Working Group-Myeloproliferative Neoplasms Research and Treatment, MMB = momelotinib, PLT = platelet count, PRO = patient reported outcome, PSA = prostate specific antigen, ULN = upper limit of normal, WHO = World Health Organization, WOCBP = women of childbearing potential.

Table 2: Key Endpoints

Primary Endpoint:

- MFSAF TSS response rate at Week 24; TSS response defined as the proportion of subjects who achieve a ≥ 50% reduction in TSS over the 28 days immediately prior to the end of Week 24 compared to baseline.

Key Secondary Endpoints:

- Proportion of subjects with transfusion independence status at the end of Week 24; defined as not requiring RBC transfusion (except in the case of clinically overt bleeding) for ≥ 12 weeks immediately prior to the end of Week 24, with Hgb level ≥ 8 g/dL.
- Splenic Response Rate (SRR); defined as the proportion of subjects who have splenic response (reduction in spleen volume of ≥ 35% from baseline) at the end of Week 24.
- Other secondary endpoints include: measures of anemia benefit and duration of response, mean change from baseline MFSAF TSS, safety assessments, survival analyses, change from baseline in PROs, and plasma concentration of MMB.

Key Exploratory Endpoints:

- Measures of rate and duration of MFSAF TSS response
- Time to splenic progression
- Correlates of response and exploratory analysis (including mutational analysis)
- Health resource utilization

Abbreviations: MFSAF TSS = Myelofibrosis Symptom Assessment Form v4.0 Total Symptom Score, MMB = momelotinib, RBC = red blood cell count, SRR = splenic response rate.

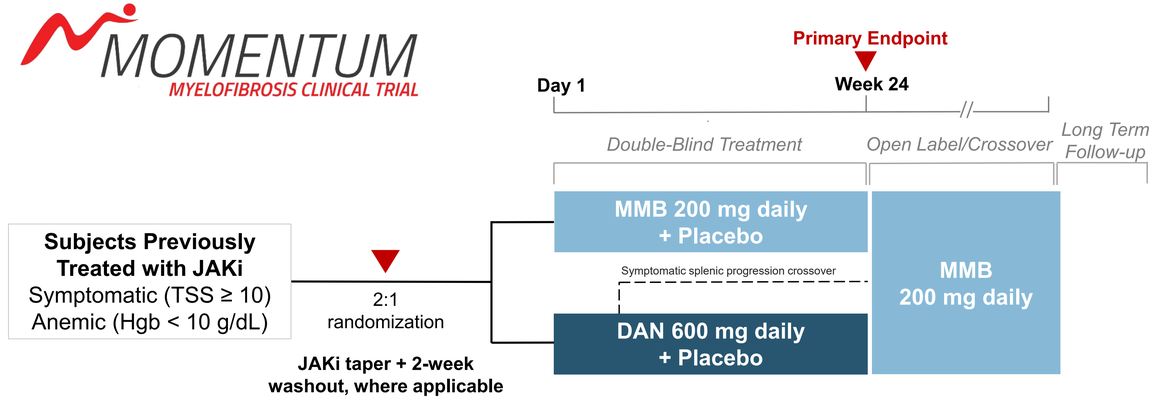


Figure 1: MOMENTUM Study Design Schematic

Summary

- Momelotinib has been investigated in over 820 patients with myelofibrosis, including in two Phase 3 studies, and possesses a pharmacological and clinical profile differentiated from other JAKi via inhibition of JAK1, JAK2 and ACVR1.
- Momelotinib addresses the complex drivers of iron-restricted anemia and chronic inflammation in myelofibrosis and should improve constitutional symptoms and splenomegaly whilst maintaining or improving hemoglobin across the continuum of JAKi-naïve and previously JAKi-treated patients.
- The global MOMENTUM Phase 3 study is designed to confirm and extend preliminary observations of the symptom benefit of MMB made in the SIMPLIFY studies, and to further evaluate splenic benefit, transfusion burden, and other metrics including patient reported outcome measures.