Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): results from an international, double-blind, randomised, controlled, phase 3 study

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Summary

Background Janus kinase (JAK) inhibitors approved for myelofibrosis provide spleen and symptom improvements but do not meaningfully improve anaemia. Momelotinib, a first-in-class inhibitor of activin A receptor type 1 as well as JAK1 and JAK2, has shown symptom, spleen, and anaemia benefits in myelofibrosis. We aimed to confirm the differentiated clinical benefits of momelotinib versus the active comparator danazol in JAK-inhibitor-exposed, symptomatic patients with anaemia and intermediate-risk or high-risk myelofibrosis.

Methods MOMENTUM is an international, double-blind, randomised, controlled, phase 3 study that enrolled patients at 107 sites across 21 countries worldwide. Eligible patients were 18 years or older with a confirmed diagnosis of primary myelofibrosis or post-polycythaemia vera or post-essential thrombocythaemia myelofibrosis. Patients were randomly assigned (2:1) to receive momelotinib (200 mg orally once per day) plus danazol placebo (ie, the momelotinib group) or danazol (300 mg orally twice per day) plus momelotinib placebo (ie, the danazol group), stratified by total symptom score (TSS; <22 *vs* ≥22), spleen size (<12 cm *vs* ≥12 cm), red blood cell or whole blood units transfused in the 8 weeks before randomisation (0 units *vs* 1–4 units *vs* ≥5 units), and study site. The primary endpoint was the Myelofibrosis Symptom Assessment Form (MFSAF) TSS response rate at week 24 (defined as ≥50% reduction in mean MFSAF TSS over the 28 days immediately before the end of week 24 compared with baseline). MOMENTUM is registered with ClinicalTrials.gov, number NCT04173494, and is active but not recruiting.

Findings 195 patients were randomly assigned to either the momelotinib group (130 [67%]) or danazol group (65 [33%]) and received study treatment in the 24-week randomised treatment period between April 24, 2020, and Dec 3, 2021. A significantly greater proportion of patients in the momelotinib group reported a 50% or more reduction in TSS than in the danazol group (32 [25%] of 130 *vs* six [9%] of 65; proportion difference 16% [95% CI 6–26], p=0·0095). The most frequent grade 3 or higher treatment-emergent adverse events with momelotinib and danazol were haematological abnormalities by laboratory values: anaemia (79 [61%] of 130 *vs* 49 [75%] of 65) and thrombocytopenia (36 [28%] *vs* 17 [26%]). The most frequent non-haematological grade 3 or higher treatment-emergent adverse events with momelotinib and danazol were acute kidney injury (four [3%] of 130 *vs* six [9%] of 65) and pneumonia (three [2%] *vs* six [9%]).

Interpretation Treatment with momelotinib, compared with danazol, resulted in clinically significant improvements in myelofibrosis-associated symptoms, anaemia measures, and spleen response, with favourable safety. These findings support the future use of momelotinib as an effective treatment in patients with myelofibrosis, especially in those with anaemia.

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Introduction

Myelofibrosis is a chronic, progressive myeloproliferative neoplasm that might present de novo (ie, primary) or develop from essential thrombocythaemia or polycythaemia vera (ie, secondary).[1] Dysregulated Janus kinase (JAK)-mediated signalling, leading to uncontrolled myeloproliferation and elevated inflammatory cytokine production, is characteristic of myelofibrosis and typically manifests as bone marrow fibrosis, anaemia, splenomegaly, and debilitating symptoms (ie, fatigue, cachexia, fever, night sweats).[2] Patients with mild myelofibrosis-associated anaemia (defined as haemoglobin ≥10 g/dL but below sex-adjusted lower limit of normal) have a median survival of 4·9 years, those with moderate myelofibrosis-associated

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*A complete list of principal investigators for the MOMENTUM study is provided in the appendix (pp 2–3)

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See **Online** for appendix

Research in context

Evidence before this study

Dysregulated Janus kinase (JAK)-mediated signalling leading to uncontrolled clonal proliferation and elevated inflammatory cytokine production is characteristic of myelofibrosis and typically manifests as bone marrow fibrosis, anaemia, splenomegaly, and debilitating symptoms. JAK inhibitors approved for the treatment of myelofibrosis provide spleen and symptom improvements but fail to address—and might induce or worsen—anaemia. The investigational agent momelotinib has a unique mechanism of action in that it inhibits not only disease drivers JAK1 and JAK2, but also activin A receptor type 1 (ACVR1), a key regulator of iron metabolism. In the phase 3 SIMPLIFY-1 trial in patients who are naive to JAK inhibitors, momelotinib was non-inferior to ruxolitinib in reducing spleen volume by 35% at week 24 from baseline, and patients who received momelotinib had improvements in transfusion independence rates, haemoglobin concentrations, and roughly half the transfusion burden compared with patients who received ruxolitinib. Preclinical and translational data showed a significant impact on anaemia benefits. Momelotinib did not show non-inferiority to ruxolitinib in reducing total symptom score by at least 50% at week 24 compared with baseline in SIMPLIFY-1, although patients treated with momelotinib reported a 28% symptom response rate. In the phase 3 SIMPLIFY-2 trial in patients previously treated with ruxolitinib, additional symptom responses were observed with momelotinib treatment compared with best available therapy, which was ruxolitinib in 89% of patients. However, superiority of momelotinib in providing additional spleen volume reductions of at least 35% immediately following ruxolitinib treatment without washout was not achieved in SIMPLIFY-2, necessitating a third, redesigned phase 3 study to fully understand the clinical profile of momelotinib in myelofibrosis.

Added value of this study

MOMENTUM is the first randomised, phase 3 study to assess an inhibitor of JAK1, JAK2, and ACVR1 in patients with myelofibrosis and anaemia. The study demonstrated clinically significant benefits in myelofibrosis-associated symptoms, anaemia measures, and spleen responses in symptomatic patients with myelofibrosis and anaemia and previous JAK inhibitor exposure. Furthermore, momelotinib was safe and well tolerated in this advanced patient population, with the overall safety profile of momelotinib consistent with that in previous reports.

Implications of all the available evidence

Anaemia is common in patients with myelofibrosis and is associated with poor survival. Currently approved JAK inhibitors do not meaningfully improve anaemia and can exacerbate anaemia, often requiring attenuated dosing or treatment discontinuation. The clinical benefit seen with momelotinib in patients with myelofibrosis and anaemia, including the reduction of transfusion burden for patients, underscores the potential for momelotinib as a treatment option for this population with high medical need. Given also the favourable safety profile of momelotinib, future research will explore momelotinib in combination with other agents for the treatment of patients with myelofibrosis.

anaemia (haemoglobin between 8 g/dL and <10 g/dL) have a median survival of 3·4 years, and patients with severe myelofibrosis-associated anaemia (haemoglobin <8 g/dL or transfusion dependent) have a median survival of 2·1 years.[3] Approved JAK inhibitors provide spleen and symptom improvements but do not address—and might induce or worsen—anaemia.[4–9] Disease-associated or treatment-exacerbated cytopenias might necessitate attenuated JAK inhibitor dosing or discontinuation, which limit treatment efficacy and are associated with poor survival.[10–12]

Approaches to managing myelofibrosis-associated anaemia include red blood cell transfusions, erythropoiesis stimulating agents, corticosteroids, androgens such as danazol, immunomodulatory drugs, and splenectomy.[10,13–17] These strategies have shown modest and transient clinical benefit, and none directly target chronic inflammation and iron restriction within erythroid progenitors, which are key mechanistic contributors to myelofibrosis-associated anaemia.[18,19]

Momelotinib is a first-in-class oral inhibitor of activin A receptor type 1 (ACVR1), also known as activin receptor-like kinase 2, as well as an inhibitor of JAK1 and JAK2 that has been previously studied in phase 1–3 clinical trials in myelofibrosis.[20–23] In the head-to-head comparison of momelotinib with ruxolitinib in JAK inhibitor-naive patients in SIMPLIFY-1, the primary endpoint of non-inferiority in reducing spleen volume by 35% at week 24 from baseline was met.[20] Further, patients who received momelotinib had a higher week 24 transfusion independence rate, increased haemoglobin concentrations, and roughly half the transfusion burden compared with patients who received ruxolitinib.[20,22] Preclinical and translational studies showed that momelotinib's observed anaemia and transfusion benefits are linked to its suppression of ACVR1-mediated hepcidin production, which leads to increased serum iron availability and stimulation of erythropoiesis.[24,25] Notably, elevated hepcidin concentration is significantly associated with shortened overall survival in patients with myelofibrosis.[26] Nonetheless, momelotinib did not show non-inferiority to ruxolitinib in reducing total symptom score (TSS) by at least 50% at week 24 compared with baseline in SIMPLIFY-1, although patients treated with momelotinib had a 28% symptom response rate.[20] In patients previously treated with ruxolitinib in SIMPLIFY-2, additional symptom responses were observed with momelotinib treatment despite an absence of a ruxolitinib

washout period.[21] However, superiority of momelotinib in providing additional spleen volume reductions of at least 35% immediately following ruxolitinib treatment without washout was not achieved in SIMPLIFY-2,[21] necessitating a third, redesigned phase 3 study to fully understand the clinical profile of momelotinib in myelofibrosis.

We report in this Article results from the MOMENTUM trial of momelotinib versus danazol in symptomatic patients with anaemia and primary, post-essential thrombocythaemia, or post-polycythaemia vera myelofibrosis who previously received JAK inhibitor therapy.

Methods

Study design and patients

MOMENTUM is an international, double-blind, randomised, controlled, phase 3 study. Patients were enrolled at 107 sites (78 in Europe, 14 in North America, ten in Asia, and five in Australia) in 21 countries. Eligible patients were 18 years or older with a confirmed diagnosis of primary myelofibrosis (per WHO 2016 criteria) or post-polycythaemia vera or post-essential thrombocythaemia myelofibrosis (per International Working Group for Myelofibrosis Research and Treatment criteria) who were previously treated with an approved JAK inhibitor for 90 days or more or 28 days or more if therapy was complicated by four units or more of red blood cells transfused in 8 weeks, or grade 3 or 4 adverse events of thrombocytopenia, anaemia, or haematoma; were symptomatic, defined as a TSS of 10 or more assessed by a single Myelofibrosis Symptom Assessment Form (MFSAF; version 4.0) at screening; were anaemic, defined as haemoglobin of less than 10 g/dL; had platelets of more than 25×10^9 cells per L without requirement for platelet transfusion;[27] had baseline splenomegaly, defined as a palpable spleen of 5 cm or more below the left costal margin or volume of 450 cm³ or more on imaging; were high risk, intermediate-2 risk, or intermediate-1 risk (per Dynamic International Prognostic Scoring System criteria); and had an Eastern Cooperative Oncology Group performance status of 0–2. Discontinuation of previous JAK inhibitor was not required for study enrolment, and reasons for discontinuation were not collected. The trial protocol, which describes the full inclusion and exclusion criteria and other trial design details, as well as the statistical analysis plan, is available in the appendix (pp 14–207).

This study was done in accordance with the Declaration of Helsinki and the International Council for Harmonisation guidelines on Good Clinical Practice. Institutional review boards or independent ethics committees at each site approved the protocol (appendix pp 14–152). All participants provided written consent. A data monitoring committee reviewed study progress, safety data, and critical efficacy endpoints every 6 months.

Randomisation and masking

Patients receiving JAK inhibitor therapy at screening tapered therapy over more than 1 week, then completed a non-treatment interval of at least 2 weeks, beginning at least 7 days before the first day of baseline assessments. Eligible patients completed a baseline period of 7 consecutive days before randomisation. Patients were randomly assigned (2:1) to receive either momelotinib plus danazol placebo (ie, the momelotinib group) or danazol plus momelotinib placebo (ie, the danazol group). Danazol was selected as an appropriate active comparator because of its use in treating patients with anaemia and myelofibrosis, as recommended by the National Comprehensive Cancer Network and European Society for Medical Oncology clinical treatment guidelines.[10,17] Randomisation was done via a non-deterministic biased coin minimisation procedure to reduce imbalance between the two groups for MFSAF TSS (<22 *vs* ≥22), baseline palpable spleen length below the left costal margin (<12 cm *vs* ≥12 cm), baseline red blood cell or whole blood units transfused in the 8 weeks before randomisation (0 units *vs* 1–4 units *vs* ≥5 units), and investigational sites. The allocation probability of randomisation to the momelotinib group was 0·9 and to the danazol group was 0·8 when selected per the imbalance score, defined as the weighted sum of the marginal imbalance across the four aforementioned baseline factors. Patients, site personnel, and project teams were masked to the treatment assignment. Concealment was enabled through use of an interactive voice or web response system, into which site personnel entered patient allocation parameters to receive assigned medication bottles to dispense to the patient. Patients received blinded treatment from day one to the end of week 24. Patients in either treatment group who completed the 24-week randomised treatment period could receive open-label momelotinib in the extended treatment period to the end of week 24, as could patients in the danazol group who discontinued treatment early because of splenic progression, or discontinued treatment early for other reasons but completed scheduled assessments through week 24. Patients in the danazol group could opt to continue danazol as open-label treatment through week 48.

Procedures

During the 24-week randomised treatment period, patients assigned to the momelotinib group received momelotinib 200 mg orally once per day plus danazol placebo, whereas patients assigned to the danazol group received danazol 300 mg orally twice per day plus momelotinib placebo. Danazol placebo capsules were visually identical to the danazol capsules but contained only microcrystalline cellulose, and momelotinib placebo tablets were visually identical to momelotinib tablets but did not contain the active ingredient. Patients orally

self-administered randomised study drugs every day. Dose interruptions or reductions, or both, due to thrombocytopenia, neutropenia, or other toxic effects were permitted during the blinded randomised treatment and open-label treatment periods. During the randomised treatment period, doses of both components of the study treatment were reduced in a stepwise manner, with the momelotinib total daily dose reduced in 50 mg decrements and the danazol total daily dose reduced by 200 mg for the first dose reduction step (from 600 mg to 400 mg) and 100 mg decrements thereafter. The lowest dose of momelotinib allowed was 50 mg; the lowest dose of danazol allowed was 200 mg (appendix pp 4–5).

Clinical visits were at screening, baseline, randomisation, every 2 weeks during the first 4 weeks of treatment, every 4 weeks until week 48, and every 12 weeks thereafter. Patients completed the MFSAF TSS every day beginning 7 days before randomisation until week 24 of the randomised treatment period, and for 7 consecutive days every 4 weeks thereafter. Spleen MRI or CT scans were done at baseline, on weeks 24 and 48, and to confirm splenic progression. Transfusions received 12 weeks before randomisation, during screening, and through study week 96 were recorded.

Patients had to discontinue study treatment for confirmed symptomatic splenic progression, leukaemic transformation, disease progression, or adverse event deemed by the investigator to compromise the patient's ability to continue therapy or the study safely.

Outcomes

The primary endpoint was MFSAF TSS response rate at week 24, defined as the proportion of patients with a 50% or more reduction in mean MFSAF TSS over the 28 days immediately before the end of week 24 compared with baseline. Key secondary endpoints included in the study-wide type I error control by hierarchical testing following the primary endpoint comprised the following: transfusion independence rate at week 24, defined as the proportion of patients with no red blood cell or whole blood transfusions and all haemoglobin values of 8 g/dL or more in the last 12 weeks of the 24-week randomised treatment period; 25% splenic response rate at week 24, defined as the proportion of patients who had 25% or more reduction in spleen volume from baseline as measured by MRI or CT; change in MFSAF TSS from baseline at week 24, defined as the change from baseline in mean MFSAF TSS over the 28 days immediately before the end of week 24; 35% splenic response rate at week 24, defined as the proportion of patients who had 35% or more reduction in spleen volume from baseline; and rate of zero transfusions at week 24, defined as the proportion of patients with no red blood cell or whole blood units transfused during the 24-week randomised treatment period. Additional secondary endpoints related to anaemia, transfusions, and survival are detailed in the appendix (p 5). Secondary endpoint outcomes that require longer follow-up (ie, duration of responses) and those focused on patient-reported outcomes will be published in future reports.

Safety assessments included the type, frequency, severity, timing of onset, duration, and relationship to study drug of any adverse events or abnormalities of laboratory tests, and adverse events leading to discontinuation of study drug.

Statistical analysis

MOMENTUM was designed to enrol at least 180 patients, including approximately 120 in the momelotinib group and 60 in the danazol group, providing 90% power to detect a true difference of 15% (17% *vs* 2%) in the primary endpoint of TSS response rate and 14% (15% *vs* 1%) in the proportion of patients with splenic response for superiority with a two-sided alpha of 0·05.[16,21] Under the assumption of a true difference of 20% (41% *vs* 21%), the power to show non-inferiority in transfusion independence at the non-inferiority margin of 0·8 in response ratio scale exceeds 90%.[16,21]

Efficacy analyses were done according to the intention-to-treat principle, with data from all randomly assigned patients, although the intention-to-treat and safety populations were identical. To control study-wide type I error, the five key secondary endpoints were to be evaluated in hierarchical order only if the primary endpoint showed significance (two-sided p≤0·05) in favour of momelotinib. For the endpoint of transfusion independence rate at week 24, non-inferiority was the hypothesis test included within the hierarchy, whereas superiority was tested within the hierarchy for all other endpoints. A one-sided p value was generated for the non-inferiority test. Evaluating a treatment effect with non-inferiority with an acceptable prespecified margin when superiority over the active control group is actually expected, but with its magnitude of benefit uncertain, has been recommended as a practical approach in comparison to designing a much larger study to assure enough power for superiority (ie, hybrid design).[28] If a stratum-adjusted difference between the proportion of transfusion-independent patients in the momelotinib group and 80% of the proportion of transfusion-independent patients in the danazol group was significantly larger than 0, non-inferiority was to be declared. Superiority was to be evaluated descriptively outside the hierarchy if non-inferiority was demonstrated. Overall survival and leukaemia-free survival were analysed using the Kaplan-Meier method and compared between groups with stratified log-rank tests and proportional hazard Cox regression models stratified by randomisation stratification factors. Analysis of overall survival up to week 24 was post hoc. Additionally, a post-hoc analysis of cumulative incidence of non-COVID-19 deaths, in which Gray's test for non-parametric cumulative incidence comparison by competing risk analysis was used and the Fine and Gray method

stratified by randomisation stratification factors was used to estimate the hazard ratio (HR) for non-COVID-19 deaths in which COVID-19 deaths were considered as competing events. The follow-up for time-to-event endpoint was summarised by the reverse Kaplan-Meier method. Efficacy and overall survival were also analysed by subgroups based on baseline platelet counts that were pre-planned ($<50\times10^9$ cells per L) and defined post hoc ($<100\times10^9$ cells per L). The appendix (pp 5–6) provides additional details about the statistical analyses done. MOMENTUM is registered with ClinicalTrials.gov, number NCT04173494, and is active but not recruiting.

Role of the funding source

The funder of the study had a role in study design, study administration, and study conduct. Study data were collected by site staff and study investigators, followed by verification and analysis by the study sponsor.

Results

From April 24, 2020, to Dec 3, 2021, 195 patients were enrolled and received blinded study treatment in the 24-week randomised treatment period (130 [67%] in the momelotinib group and 65 [33%] in the danazol group; figure 1). 94 (72%) of 130 patients in the momelotinib group and 38 (58%) of 65 in the danazol group completed randomised treatment; the most common reasons for early treatment discontinuation were adverse events (16 [12%] patients in the momelotinib group and 11 [17%] in the danazol group) and patient decision (six [5%] in the momelotinib group and five [8%] in the danazol group). Of the 195 patients, a total of 132 (68%;

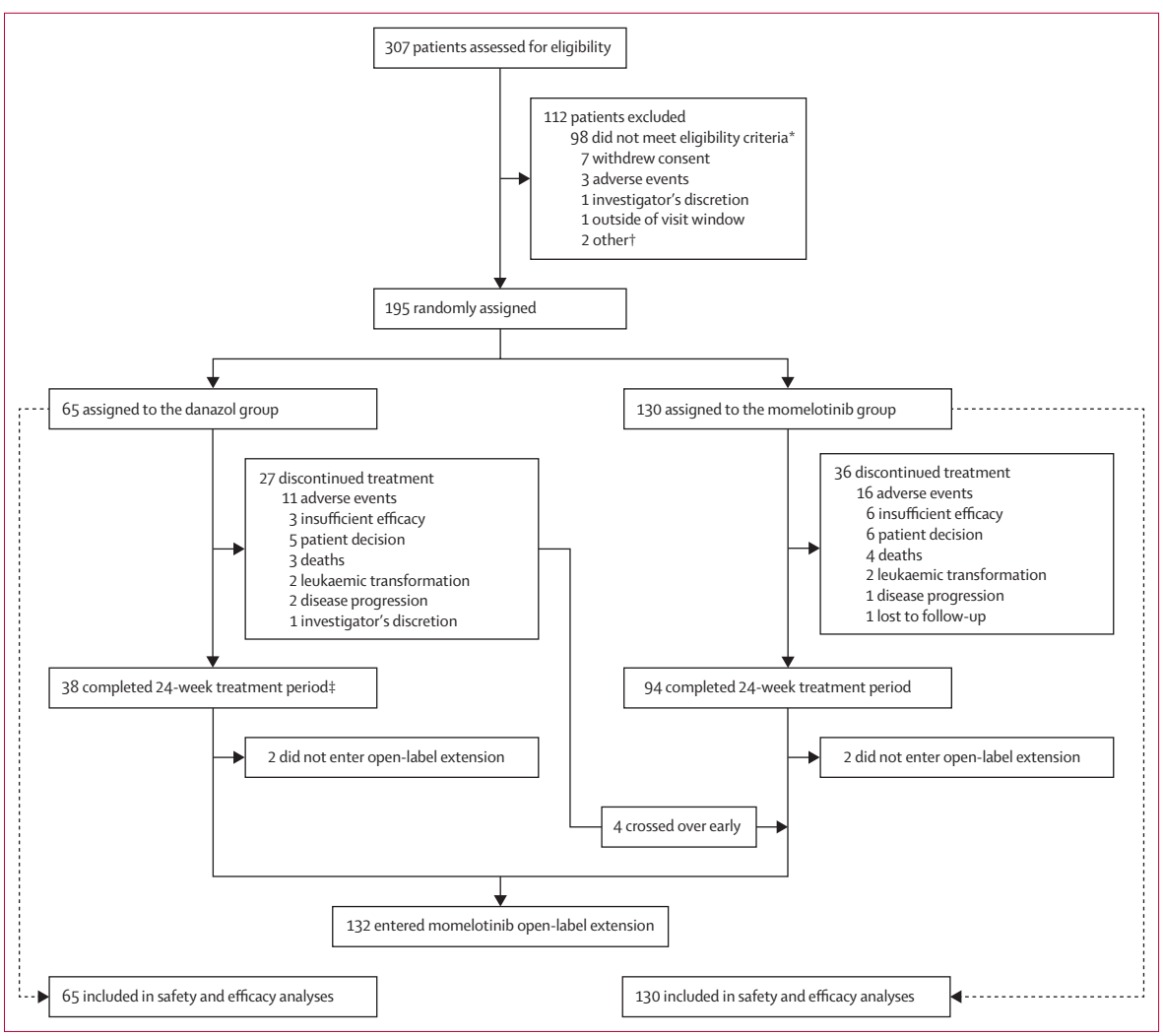

Figure 1: **Study profile**

*Most common reasons for not meeting eligibility criteria were having laboratory values outside of the required parameters (n=37) or having a total symptom score of less than 10 (n=15). †Other reasons for exclusion included improved haemoglobin concentrations (n=1) and death (n=1). ‡Of the 38 patients who were randomised to the danazol group (masked treatment) and completed therapy during the 24-week randomised treatment period, none chose to continue to open-label danazol treatment.

	Momelotinib group (n=130)	Danazol group (n=65)
Median age (years)	71 (65–75)	72 (67–78)
Sex		
Male	79 (61%)	44 (68%)
Female	51 (39%)	21 (32%)
Mean BMI (kg/m²)	25·2 (3·7)	25·7 (6·0)
Race		
White	107 (82%)	50 (77%)
Asian	12 (9%)	6 (9%)
Black	2 (2%)	2 (3%)
Hispanic or Latino	5 (4%)	6 (9%)
Myelofibrosis subtype		
Primary	78 (60%)	46 (71%)
After polycythaemia vera	27 (21%)	11 (17%)
After essential thrombocythaemia	25 (19%)	8 (12%)
DIPSS risk category		
Intermediate-1	7 (5%)	3 (5%)
Intermediate-2	72 (55%)	40 (62%)
High	50 (38%)	19 (29%)
Missing	1 (1%)	3 (5%)
JAK2 Val617Phe mutation		
Positive	97 (75%)	51 (78%)
Negative	28 (22%)	12 (18%)
Unknown or missing	5 (4%)	2 (3%)
ECOG performance status		
0	16 (12%)	15 (23%)
1	83 (64%)	34 (52%)
2	31 (24%)	16 (25%)
Mean previous JAK inhibitor duration (weeks)	138·5 (123·0)	124·8 (120·0)
TSS		
Mean	28·0 (13·8)	25·7 (12·8)
Median	26·4 (16·7–38·0)	23·6 (15·3–36·1)
≥22	77 (59%)	39 (60%)

(Table 1 continues on next column)

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	Momelotinib group (n=130)	Danazol group (n=65)
Haemoglobin		
Mean (g/dL)	8·1 (1·1)	7·9 (0·8)
Median (g/dL)	8·0 (7·5–8·8)	8·0 (7·3–8·4)
≥8 g/dL	67 (52%)	33 (51%)
Transfusion independent	17 (13%)	10 (15%)
Transfusion dependent	63 (48%)	34 (52%)
Red blood cell units transfused ≤8 weeks before randomisation		
0	28 (22%)	13 (20%)
1–4	58 (45%)	27 (42%)
≥5	44 (34%)	25 (38%)
Central spleen volume (cm³)		
Mean	2367 (1302)	2288 (1155)
Median	2112 (1445–2955)	2059 (1446–2817)
Palpable spleen length below the left costal margin ≥12 cm	55 (42%)	28 (43%)
Platelet count (× 10⁹ cells per L)		
Mean	151·7 (130·9)	130·7 (101·0)
Median	97 (60–196)	94 (54–175)
Neutrophil count (× 10⁹ cells per L)		
Mean	8·6 (11·3)	6·9 (8·3)
Median	4·7 (2·3–8·8)	3·6 (1·9–7·7)
Peripheral blasts (%)		
Mean	2·1 (2·9)	1·9 (2·0)
Median	1 (0–3)	1 (1–2)

Data are median (IQR), n (%), or mean (SD). BMI=body-mass index. DIPSS=Dynamic International Prognostic Scoring System. ECOG=Eastern Cooperative Oncology Group. JAK=Janus kinase. TSS=total symptom score.

Table 1: **Baseline patient and disease characteristics in the intention-to-treat population**

92 [71%] of 130 in the momelotinib group and 40 [62%] of 65 in the danazol group), including 128 who completed randomised treatment and four who prematurely discontinued randomised danazol treatment, started open-label momelotinib treatment. No patient chose to continue open-label treatment with danazol. The database cutoff date for these analyses was Dec 3, 2021, which was 24 weeks after the last patient was randomly assigned to a treatment group.

Baseline characteristics, demographics, and disease history were similar between treatment groups (table 1; appendix pp 7–9). For the overall population (n=195), the median age at baseline was 71 years (IQR 66–76) and 123 (63%) patients were men and 157 (81%) were white. Most patients had a diagnosis of primary myelofibrosis (124 [64%] of 195), intermediate-2 risk (112 [57%]), and positive JAK2 mutation status (148 [76%]). 27 (14%) of 195 patients were transfusion independent and 97 (50%) were transfusion dependent, with the remainder requiring transfusions but not enough to meet the definition of transfusion dependency. Mean duration of previous JAK inhibitor therapy for the overall population was 2·6 years (SD 2·3). Previous JAK inhibitor use with ruxolitinib was reported in all 195 patients; nine (5%) of 195 also received fedratinib. For the overall population, mean baseline TSS was 27·2, mean haemoglobin concentration was 8·0 g/dL, and mean platelet count was 144·7×10⁹ cells per L.

The proportion of patients reporting a 50% or more reduction in MFSAF TSS from baseline at week 24 was significantly greater in the momelotinib group than in the danazol group (32 [25%] of 130 patients *vs* six [9%] of 65; proportion difference 16% [95% CI 6–26], p=0·0095), demonstrating superiority of momelotinib for the primary endpoint (table 2; figure 2A). Transfusion independence at week 24 was achieved by 40 (31% [95% CI 23–39]) of 130 patients in the momelotinib group and 13 (20% [11–32]) of 65 in the danazol group, with a

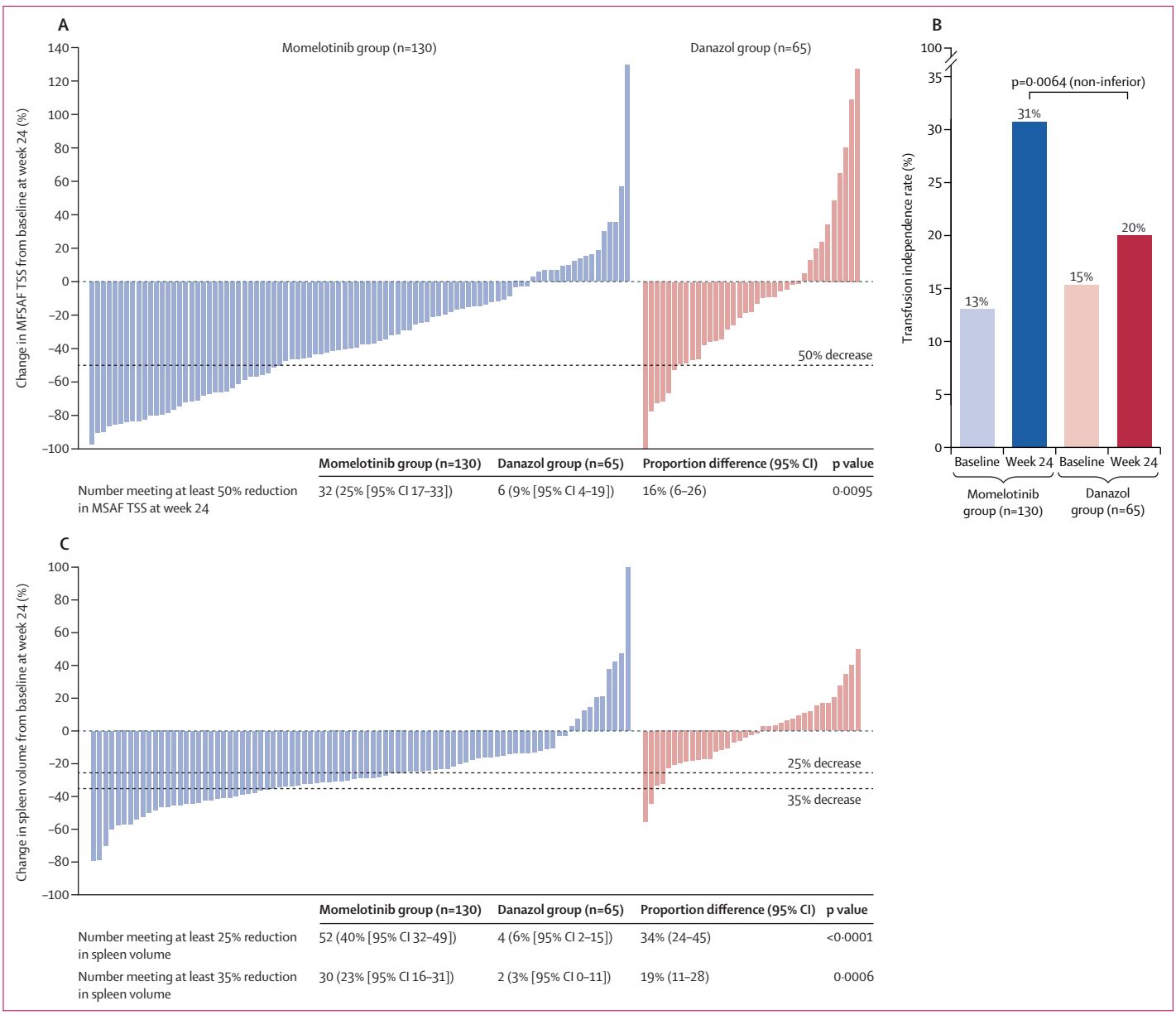
	Test order	Criterion for significance	Momelotinib group (n=130)	Danazol group (n=65)	p value
TSS response rate*	1	Superiority (p≤0·05)	32 (25%)	6 (9%)	Two-sided 0·0095 (superior)
Transfusion independence rate†	2	Non-inferiority	40 (31%)	13 (20%)	One-sided 0·0064 (non-inferior)‡
Splenic response rate (≥25% reduction)	3	Superiority (p≤0·05)	52 (40%)	4 (6%)	Two-sided <0·0001 (superior)
Absolute TSS change from baseline§	4	Superiority (p≤0·05)	−11·5	−3·9	Two-sided 0·0014 (superior)¶
Splenic response rate (≥35% reduction)	5	Superiority (p≤0·05)	30 (23%)	2 (3%)	Two-sided 0·0006 (superior)
Rate of zero transfusions to week 24	6	Superiority (p≤0·05)	46 (35%)	11 (17%)	Two-sided 0·0012 (superior)

Data are n (%), unless otherwise specified. TSS=total symptom score. *Primary endpoint was TSS response, defined as a 50% or more reduction in mean TSS over the 28 days immediately before the end of week 24 compared with baseline. †Proportion of patients with transfusion-independent status defined as not requiring red blood cell transfusion for the last 12 weeks of the 24-week randomised period, with all haemoglobin concentrations during the 12-week interval of 8 g/dL or more. ‡Non-inferior if p (momelotinib) − 0·8 × p (danazol) >0 with significance. Transfusion independence tested for superiority with a p value (two-sided) of 0·086. §Mean change from baseline in TSS at week 24. ¶p value for the least squares mean difference between the two groups from the mixed effect repeated measures model.

Table 2: **Summary of primary and key secondary efficacy endpoint analyses at week 24**

non-inferiority difference of 15% (95% CI 3–26; one-sided p=0·0064; table 2). Because momelotinib was non-inferior to danazol, a superiority test was done, and the treatment difference was 11% (95% CI −1 to 23; p=0·086). Transfusion independence rates from baseline to week 24 increased by 18% in the momelotinib group versus 5% in the danazol group (figure 2B). The transfusion independence rate at week 24 was higher in patients with baseline haemoglobin of 8 g/dL or more versus less than 8 g/dL in both the momelotinib (27 [40%] of 67 *vs* 12 [19%] of 62) and danazol (nine [27%] of 33 *vs* four [13%] of 32) groups. Among those who did not become transfusion independent at week 24, patients receiving momelotinib required fewer transfused units during randomised treatment than those receiving danazol (appendix p 11), as was also observed in each stratified patient subgroup based on the number of units transfused in the 8 weeks before randomisation (0 units, 1–4 units, ≥5 units; appendix p 11). Among the 168 patients who were not transfusion independent at baseline, 30 (27%) of 113 patients in the momelotinib group and eight (15%) of 55 in the danazol group became transfusion independent at week 24. Among the 27 patients who were transfusion independent at baseline, seven (41%) of 17 patients in the momelotinib group and three (30%) of ten patients in the danazol group had a 2 g/dL or more increase in haemoglobin concentration as measured over a rolling period of at least 12 consecutive weeks occurring entirely before the end of week 24. Momelotinib was superior to danazol in observed splenic response rates at week 24, on the basis of both a 25% reduction or more (52 [40%] of 103 patients in the momelotinib group *vs* four [6%] of 65 patients in the danazol group; p<0·0001) and 35% or more reduction (30 [23%] in the momelotinib group and two [3%] in the danazol group; p=0·0006) in spleen volume from baseline at week 24 (table 2; figure 2C). Momelotinib-randomised splenic responders had higher rates of transfusion independence at week 24 (25% reduction, transfusion independence in 23 [44%] of 52; 35% reduction, transfusion independence in 15 [50%] of 30) compared with splenic non-responders (25% reduction, transfusion independence in 17 [22%] of 78; 35% reduction, transfusion independence in 25 [28%] of 90). Superiority of momelotinib over danazol was also shown for mean TSS change from baseline at week 24 (−11·5 *vs* −3·9; least squares mean difference −6·2 [95% CI −10·0 to −2·4]; p=0·0014) and rate of zero transfusions to week 24 (46 [35%; 95% CI 27–44] of 130 in the momelotinib group and 11 [17%; 9–28] of 65 in the danazol group; p=0·0012; table 2). The rate of zero transfusions at week 24 was higher in patients with baseline haemoglobin of 8 g/dL or more versus less than 8 g/dL in both the momelotinib (33 [49%] of 67 *vs* 13 [21%] of 62) and danazol (eight [24%] of 33 *vs* three [9%] of 32) groups.

The mean duration of randomised treatment was 20·6 weeks (SD 6·2) in the momelotinib group and 17·3 weeks (8·0) in the danazol group. The maximum exposure to momelotinib was 60·7 weeks at the time of data cutoff. The overall safety profile of momelotinib was consistent with previous clinical studies and compared favourably with danazol (table 3; appendix p 10). Most common all grade, non-haematological treatment-emergent adverse events during the randomised treatment phase with momelotinib were diarrhoea (29 [22%] of 130), nausea (21 [16%]), and asthenia (17 [13%]), and with danazol were increased blood creatinine (ten [15%] of 65), dyspnoea (nine [14%]), and peripheral oedema (nine [14%]). The most frequent non-haematological grade 3 or higher treatment-emergent adverse events with momelotinib and danazol were acute kidney injury (four [3%] of 130 *vs* six [9%] of 65) and pneumonia (three [2%] *vs* six [9%]). Anaemia was the most frequent grade 3 or higher haematological abnormality based on laboratory values and occurred more frequently with danazol than with momelotinib (49 [75%] of 65 *vs* 79 [61%] of 130; table 3). Although momelotinib and danazol each induced a rapid increase in mean haemoglobin concentrations, patients in the momelotinib group reported a greater increase in haemoglobin that was maintained over time than those



	Momelotinib group (n=130)	Danazol group (n=65)	Proportion difference (95% CI)	p value
Number meeting at least 50% reduction in MSAF TSS at week 24	32 (25% [95% CI 17–33])	6 (9% [95% CI 4–19])	16% (6–26)	0·0095

	Momelotinib group (n=130)	Danazol group (n=65)	Proportion difference (95% CI)	p value
Number meeting at least 25% reduction in spleen volume	52 (40% [95% CI 32–49])	4 (6% [95% CI 2–15])	34% (24–45)	<0·0001
Number meeting at least 35% reduction in spleen volume	30 (23% [95% CI 16–31])	2 (3% [95% CI 0–11])	19% (11–28)	0·0006

Figure 2: **Change in symptom scores, transfusion independence, and spleen volume**
(A) Percentage change of TSS from baseline to week 24 for each patient. (B) Change in transfusion independence rate from baseline to week 24. (C) Percentage change of spleen volume from baseline to week 24 for each patient. MFSAF=Myelofibrosis Symptom Assessment Form. TSS=total symptom score.

in the danazol group (appendix p 12). Haemoglobin concentrations increased further in patients in the danazol group upon crossing over to momelotinib treatment in the open-label period (appendix p 12). Grade 3 or higher thrombocytopenia based on laboratory values was similar between groups (36 [28%] of 130 in the momelotinib group *vs* 17 [26%] of 65 in the danazol group). Mean platelet concentrations remained stable over time in the momelotinib group and increased in the danazol group during randomised treatment but were similar in both groups during open-label treatment (appendix p 12). Among patients with baseline platelet counts of less than 50×10^9 cells per L, nine (50%) of 18 with momelotinib and six (46%) of 13 with danazol received platelet transfusions in the randomised treatment phase. The most reported serious adverse events were infections (20 [15%] of 130 patients with momelotinib and 11 [17%] of 65 patients with danazol). Peripheral neuropathy (all grade ≤2) occurred in five (4%) of 130 patients with momelotinib and one (2%) of 65 patients with danazol, and none discontinued the study drug. Treatment-emergent adverse event rates for increased alanine

aminotransferase (nine [7%] patients with momelotinib and five [8%] with danazol) and aspartate aminotransferase (seven [5%] with momelotinib and three [5%] with danazol) were similar between groups. Overall, adverse events led to study drug discontinuation in 23 (18%) of 130 patients receiving momelotinib and 15 (23%) of 65 patients receiving danazol in the randomised treatment phase.

As of the data cutoff date, 41 deaths (21%) were reported from the 195 patients (25 [19%] of 130 in the momelotinib group and 16 [25%] of 65 in the danazol group). Fatal adverse events were reported in 16 (12%) of 130 patients in the momelotinib group and 11 (17%) of 65 in the danazol group during the randomised treatment period; infections and infestations were the most commonly reported fatal events with momelotinib (eight [6%]) and anaemia was the most reported fatal event with danazol (three [5%]). The primary causes of death were mostly consistent with known principal causes of death in patients with myelofibrosis and no other pattern was apparent, although seven (4%) of 195 patients died of complications of COVID-19 (six [5%] of 130 in the momelotinib group during randomised treatment, contributing to the eight total fatal events due to infections and infestations, and one [2%] of 65 in the danazol group more th30 days after the last dose of study drug; none were vaccinated against COVID-19). The other two fatal events due to infections and infestations in the momelotinib group were septic shock and pneumonia.

In secondary endpoint analyses of overall survival and leukaemia-free survival over the entire study period, the HR for overall survival was 0·73 (95% CI 0·38–1·41; p=0·35; figure 3) and for leukaemia-free survival was 0·65 (0·35–1·21; p=0·17), favouring momelotinib versus danazol. Three (2%) of 130 patients in the momelotinib group and four (6%) of 65 in the danazol group had a leukaemic transformation event. Median follow-up time for overall survival was 275 days (95% CI 238–314; range 41–476) with 105 (81%) of 130 patients censored in the momelotinib group, and 295 days (95% CI 233–333; range 26–523) with 49 (75%) of 65 censored in the danazol group. For leukaemia-free survival, the median follow-up times were 281 days (95% CI 238–316; range 41–476) with 103 (79%) of 130 patients censored in the momelotinib group, and 275 days (95% CI 228–324; range 26–509) with 47 (72%) of 65 censored in the danazol group. Patients were censored at the last known date to be absent of the event; no other reason for censoring existed. A non-significant survival advantage for momelotinib relative to danazol was also observed in the exploratory analyses of overall survival during the randomised treatment period only, which included data up to week 24 (15 [54%] of 28 total events; HR 0·51 [95% CI 0·24–1·08]; log-rank p=0·072). Based on analysis of cumulative incidence of non-COVID-19 deaths up to week 24, treating COVID-19 deaths as competing events, survival was significantly improved with momelotinib (HR 0·33 [95% CI 0·14–0·76]; p=0·010; appendix p 13).

	Momelotinib group (n=130)		Danazol group (n=65)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Non-haematological abnormalities (preferred term)				
Diarrhoea	29 (22%)	0	6 (9%)	1 (2%)
Nausea	21 (16%)	3 (2%)	6 (9%)	2 (3%)
Asthenia	17 (13%)	1 (1%)	6 (9%)	1 (2%)
Pruritus	14 (11%)	2 (2%)	7 (11%)	0
Weight decreased	14 (11%)	0	4 (6%)	0
Blood creatinine increased	10 (8%)	1 (1%)	10 (15%)	2 (3%)
Dyspnoea	10 (8%)	3 (2%)	9 (14%)	1 (2%)
Peripheral oedema	10 (8%)	2 (2%)	9 (14%)	0
Fatigue	8 (6%)	1 (1%)	7 (11%)	2 (3%)
Acute kidney injury	6 (5%)	4 (3%)	8 (12%)	6 (9%)
Haematological abnormalities*				
Anaemia	129 (99%)	79 (61%)	65 (100%)	49 (75%)
Thrombocytopenia	99 (76%)	36 (28%)	40 (62%)	17 (26%)
Neutropenia	38 (29%)	16 (12%)	17 (26%)	6 (9%)

Data are n (%). *Haematological abnormalities are based on laboratory values. The data shown are for events of the worst grade during the 24-week randomised treatment phase of the study, regardless of whether this grade was a change from baseline.

Table 3: **Treatment-emergent adverse events observed in at least 10% of patients in either treatment group during the 24-week randomised treatment period**

In secondary endpoint and additional pre-planned and exploratory post-hoc analyses in thrombocytopenic groups, patients with baseline platelet counts of less than 100×10^9 cells per L who received momelotinib (n=66) had higher week 24 TSS response rates (19 [29%] *vs* five [15%]), transfusion independence rates (18 [27%] *vs* seven [21%]), and splenic response rates based on 35% reduction or more (13 [20%] *vs* two [6%]) than those in the danazol group (n=34). Patients with baseline platelet counts of less than 50×10^9 cells per L who received momelotinib (n=18) had higher week 24 TSS response rates (four [22%] *vs* one [8%]) and splenic response rates based on 35% reduction or more (four [22%] *vs* none) than those in the danazol group (n=13), but similar transfusion independence rates (three [17%] *vs* two [15%]). The safety profile of momelotinib, even in patients with platelet counts of less than 50×10^9 cells per L, was consistent with the overall patient population; grade 3 or higher thrombocytopenia was reported in eight (44%) of 18 patients with momelotinib and two (15%) of 13 with danazol; grade 3 or higher haemorrhage was reported in one (6%) with momelotinib and no patients with danazol; and week 24 event-free rates for overall survival were reported in 17 (94%) with momelotinib and eight (62%) with danazol (appendix p 13).

Discussion

The randomised, phase 3 MOMENTUM study met all prespecified primary and key secondary efficacy

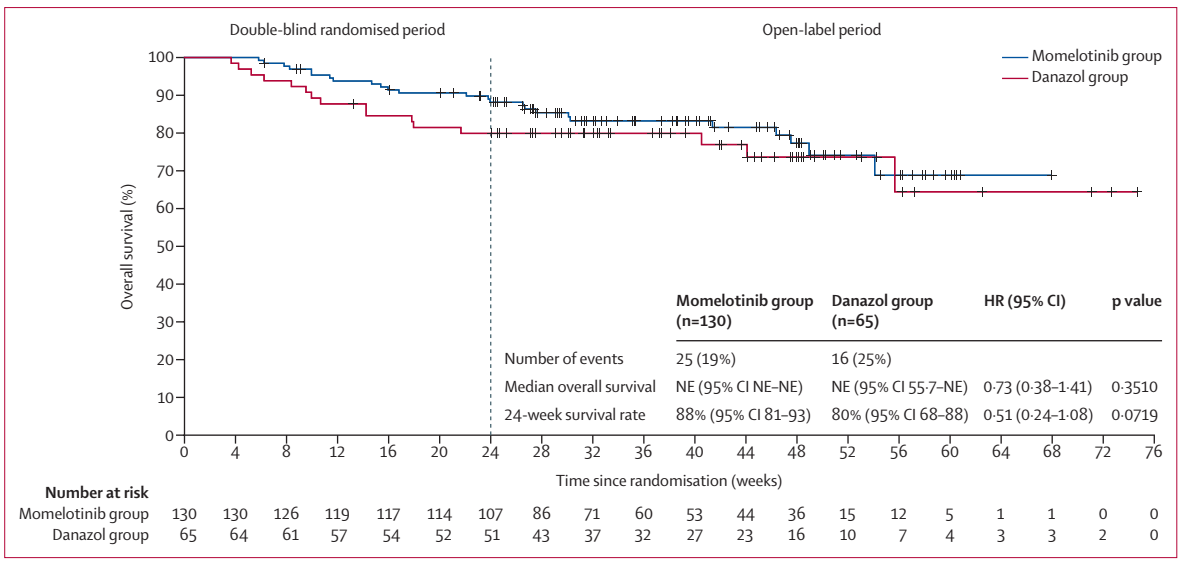


Figure 3: **Overall survival in the intention-to-treat population**
Kaplan-Meier estimates of overall survival in the intention-to-treat population from the time of randomisation to the data cutoff date (Dec 3, 2021). The vertical line at week 24 indicates the transition between the double-blind randomised period and the open-label period when patients ongoing in the study started receiving open-label momelotinib treatment. p value from a stratified log-rank test; HR (momelotinib group *vs* danazol group) from a stratified Cox proportional hazards model with a single factor of treatment group and stratified by baseline stratification factors. HR=hazard ratio. NE=not estimable.

endpoints as demonstrated by clinically meaningful and statistically significant improvements in myelofibrosis-associated symptoms, anaemia measures, and spleen size in patients treated with momelotinib compared with danazol. The overall safety profile, including the pattern of adverse events, is consistent with completed clinical studies of momelotinib.[20,21]

Current treatment of myelofibrosis is limited by myelosuppressive effects of approved JAK inhibitors. Through a distinct mechanism of action, momelotinib can improve anaemia, and also provide symptom and spleen benefits, ultimately addressing an essential unmet need.[29] Momelotinib uniquely inhibits ACVR1, an important modulator of iron homoeostasis, which results in decreased expression of hepcidin in the liver and increased iron availability for erythropoiesis, in addition to inhibiting drivers of myelofibrosis, JAK1 and JAK2.[24,25] In this study, rapid and sustained improvements in haemoglobin concentrations were observed with momelotinib treatment, as well as non-inferior transfusion-independent rates, a superior rate of zero transfusions, and fewer transfusions among all patients, including those who did not achieve transfusion independence at week 24, relative to danazol. Patients in the danazol group who crossed over to momelotinib treatment at week 24 had further increases in haemoglobin concentrations in the open-label period. These findings augment previous phase 3 studies in which momelotinib showed clinical activity against splenomegaly and constitutional symptoms, as well as clinically meaningful anaemia benefits including conversion to and maintenance of durable transfusion independence, reductions in transfusion burden including in those who do not achieve transfusion independence, increased haemoglobin concentrations, and fewer adverse events of anaemia.[20–22]

A key benefit of treatment with momelotinib compared with other JAK inhibitors such as ruxolitinib is the ability to maintain higher doses of momelotinib because of reduced myelosuppressive activity.[20,30,31] In this study of patients with advanced myelofibrosis, including those with platelet counts as low as 25×10^9 cells per L, dose interruptions and discontinuation rates were lower for momelotinib than for danazol; few serious adverse events of bleeding were reported; and haematological toxicity was manageable for the momelotinib group as evidenced by clinically meaningful efficacy outcomes. Observed safety profiles and efficacy of momelotinib in subgroups of patients with moderate and severe thrombocytopenia were consistent with findings from the overall population, supporting the safe and effective use of momelotinib in patients with low platelet counts.

MOMENTUM was done during the COVID-19 pandemic before the widespread availability of vaccines. Despite the unprecedented challenges presented, this international, multicentre study was successfully completed within the planned timeframe. Of note, the safety of JAK inhibitor use in the setting of COVID-19 has since been demonstrated.[32] Although only a modest number of survival events were documented during the first 24 weeks, a trend towards improved overall survival was observed for the momelotinib group versus the danazol group for this interim period, in which the treatment group comparison is not affected by

the planned crossover at week 24 for the danazol group. Patient follow-up is ongoing and long-term survival analyses will be forthcoming.

As mentioned, limitations inherent to the week 24 crossover design of the MOMENTUM study exist—most notably, a direct, long-term comparison of survival between treatment groups was not possible. Also, despite the double-blinded study design, patients and investigators might have tried to predict their treatment assignment based on previous JAK inhibitor experience, but patients randomised to danazol treatment demonstrated benefits across all key efficacy endpoints, minimising the risk of potential bias. Early study discontinuation in this population with advanced, symptomatic, anaemic myelofibrosis was also a potential concern; however, most patients in both treatment groups were able to complete the randomised treatment phase. The finding that momelotinib-randomised splenic responders had a higher rate of transfusion independence at week 24 than splenic non-responders is confounded by the fact that proportionally more splenic responders were available for assessment at week 24, as patients who discontinued early were considered non-responders.

In conclusion, treatment with momelotinib was associated with clinically significant improvements in myelofibrosis-associated symptoms, anaemia measures, and spleen size, with favourable safety compared with danazol in symptomatic patients with anaemia and previous JAK inhibitor exposure. These findings support the future use of momelotinib as an effective treatment in patients with myelofibrosis, especially in those with anaemia.

Contributors

CNH, VG, RM, AMV, and SV contributed to the study design as members of a clinical advisory board for Sierra Oncology, a GSK company. All authors had access to the data and contributed to its interpretation, participated in writing and reviewing the manuscript, approved the final version, and agreed to be accountable for the accuracy and integrity of the data.

Declaration of interests

SV reports consulting fees from Bristol Myers Squibb/Celgene, Incyte, Novartis, and Sierra Oncology. ATG reports consulting fees from AbbVie, Bristol Myers Squibb, Constellation/MorphoSys, CTI Biopharma, Novartis, Pharma Essentia, and Sierra Oncology. ATK reports grants from AbbVie, Bristol Myers Squibb, Prelude, and Sierra; consulting fees from AbbVie and Prelude; honoraria from Bristol Myers Squibb, Incyte, and Novartis; and participation on a data safety monitoring board or advisory board for AbbVie, Bristol Myers Squibb, CTI Biopharma, Geron, Imago, and Incyte. MLF reports payment for expert testimony from OncLive; meeting attendance or travel support from Novartis; and participation on a data safety monitoring board or advisory board for Bristol Myers Squibb, Novartis, and Sierra Oncology. DM reports research grants from Bristol Myers Squibb/Celgene, and Constellation Biopharma; honoraria from AbbVie, Celgene, Jazz, and Novartis; meeting attendance or travel support from Jazz; participation on a data safety monitoring board or advisory board for the ALL-RIC study; and leadership role with the European Society of Hematology and the EBMT Chronic Malignancies Working Party. AP reports honoraria, meeting attendance and travel support, and participation on an advisory board from Novartis Oncology. S-SY reports research grants from Kyowa Kirin and Roche/Genentech; consulting fees from Astellas, Amgen, Antengene, and Celgene; and honoraria from Novartis. VG reports consulting fees from AbbVie, Bristol Myers Squibb/Celgene, Constellation Biopharma, Novartis, Pfizer, and Sierra Oncology; honoraria from Bristol Myers Squibb, Constellation Biopharma, and Novartis; and participation on data safety monitoring board or advisory board for AbbVie, Bristol Myers Squibb/Celgene, Pfizer, and Roche. J-JK reports honoraria from Novartis; participation on a data safety monitoring board or advisory board for AbbVie, Bristol Myers Squibb, Incyte, and Novartis. NG reports consulting fees from Alexion, Bristol Myers Squibb/Celgene, Incyte, and Novartis; honoraria from Bristol Myers Squibb/Celgene, Janssen, and Novartis; leadership or fiduciary role for Alexion, Incyte, and Novartis; and meeting attendance or travel support from AbbVie, Genzyme, and Sanofi. FP reports research grant from Bristol Myers Squibb/Celgene; consulting fees from AbbVie, APO, Bristol Myers Squibb/Celgene, Karyopharm, Kyowa Kirin, MEI, Novartis, and Roche; and honoraria from Bristol Myers Squibb/Celgene, Janssen, and Novartis. CNH reports grant support from Bristol Myers Squibb/Celgene, Constellation Biopharma, and Novartis; consulting fees from AOP, Galecto, Keros, and Roche; honoraria from AbbVie, Celgene, Constellation Biopharma, CTI Biopharma, Janssen, and Novartis; participation in data safety monitoring board or advisory board for AbbVie, AOP, CTI Biopharma, Geron, Promedior, Roche, and Sierra Oncology; and leadership or fiduciary role in the European Hematology Association and MPN Voice. BJK, SR, and RD report employment and stock or stock options at Sierra Oncology. JK reports employment and stock or stock options at Sierra Oncology and former employment and stock and stock options from Gilead. RM reports research grants from AbbVie, Celgene, CTI Biopharma, Constellation Biopharma, Genotech, Incyte, Promedior, Samus, and the Mays Cancer Center P30 Cancer Center Support Grant from the National Cancer Institute (CA054174); and consulting fees from Constellation Biopharma, LaJolla, Novartis, and Sierra Oncology. All other authors declare no competing interests.

Data sharing

Sierra Oncology commits to sharing clinical study data with qualified researchers to enable enhancement of public health. As such, Sierra will share anonymised patient-level data on request or if required by law or regulation. Qualified scientific and medical researchers can request patient-level data for studies of Sierra pharmaceutical substances listed on ClinicalTrials.gov and approved by health authorities in the USA and the EU. Patient-level data for studies of newly approved pharmaceutical substances or indications can be requested 9 months after US Food and Drug Administration and European Medicines Agency approvals. Such requests are assessed at Sierra's discretion, and the decisions depend on the scientific merit of the proposed request, data availability, and the purpose of the proposal. If Sierra agrees to share clinical data for research purposes, the applicant is required to sign an agreement for data sharing before data release, to ensure that the patient data are deidentified. In case of any risk of reidentification of anonymised data despite measures to protect patient confidentiality, the data will not be shared. The patients' informed consent will always be respected. If the anonymisation process will provide futile data, Sierra will have the right to refuse the request. Sierra will provide access to patient-level clinical trial analysis datasets in a secured environment upon execution of the data sharing agreement. Sierra will also provide the protocol, statistical analysis plan, and the clinical study report synopsis if needed. For additional information or requests for access to Sierra clinical trial data for research purposes, please contact us at GSKClinicalSupportHD@gsk.com.

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