REGULAR ARTICLE

blood advances

The lysine-specific demethylase 1 (LSD1) inhibitor bomedemstat in myelofibrosis: results from a phase 1/2 study

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The full-text version of this article contains a data supplement.

Key Points

- Bomedemstat had a manageable safety profile, and 26% of 35 evaluable participants had a reduction in spleen volume of ≥20% at week 24.
- Key symptoms, including fatigue, improved; 83% had stable or improved bone marrow fibrosis, and 56% had a reduction in driver mutations.

Novel therapies are needed for myelofibrosis (MF), particularly after Janus kinase (JAK) inhibitor failure. This open-label, phase 1/2 study evaluated bomedemstat, an irreversible inhibitor of lysine-specific demethylase 1, in participants with MF refractory or resistant to, inadequately controlled by, or intolerant of approved therapies. Eighty-nine participants initially received bomedemstat at doses 0.25, 0.5, or 0.6 mg/kg orally once per day, titrated to achieve a target platelet count of ≥50 × 10^9/L to ≤75 × 10^9/L. Primary end points were safety and change in spleen volume. Hematologic response and change in symptom burden, bone marrow fibrosis score, and variant allele frequency (VAF) were exploratory. Eighty-seven (97%) participants experienced ≥1 any-cause adverse event (AE), most commonly thrombocytopenia (48%) and dysgeusia (36%); 62 (69%) participants experienced ≥1 grade 3 to 5 AE. Three participants (3%) experienced AEs that led to death; none were related to treatment. Of 35 participants with spleen volume data at week 24, 23 (66%) had a reduction in spleen volume; 9 (26%) had a reduction of ≥20%. Mean platelet and white blood cell counts normalized over 24 weeks; hemoglobin levels remained stable. Participants reported improvement in most symptoms, including fatigue. Of 35 participants with baseline and week 24 data, 8 (23%) had improved bone marrow fibrosis by ≥1 grade per central review, and 21 (60%) were stable. Of 36 participants with *CALR*, *JAK2*, or *MPL* mutations and data at week 24, 56% had a reduction in VAF. Bomedemstat had manageable safety and clinical activity in participants with MF in need of an alternative therapy. This trial was registered at www.ClinicalTrials.gov as NCT03136185.

Introduction

Myelofibrosis (MF) is a hematologic neoplasm characterized by bone marrow fibrosis, splenomegaly, progressive bone marrow failure, and constitutional symptoms that significantly impair quality of life and survival.[1] Median overall survival is ~6 years; bone marrow failure and subsequent infection, cardiovascular disease, hemorrhagic events, and hematologic malignancies are the main causes of death.[2,3] Somatic mutations in Janus kinase 2 (*JAK2*), calreticulin (*CALR*), and the thrombopoietin receptor (*MPL*) are considered the "driver" mutations in MF, along with a host of secondary mutations that influence its clinical course.[4] These mutations cause constitutive activation of the JAK-STAT signaling pathway, which triggers a cascade of growth factor and cytokine production responsible for inflammation, bone marrow remodeling, and clonal evolution.[5,6]

Hematopoietic stem cell transplantation is currently the only curative treatment available for MF; however, it is not feasible for many patients.[1,7] Other treatments are targeted toward managing the associated splenomegaly and cytokine-mediated symptoms, with JAK inhibitors such as ruxolitinib recommended in patients with significant symptom burden or high-risk disease.[1,7] Although JAK inhibitors are effective in the short to medium term, a large proportion of patients develop resistance or intolerance, and complete molecular remissions are rare.[8,9] Increased risk of infection, nonmelanoma skin cancers, and lymphoid malignancies are also a growing concern with long-term JAK inhibitor treatment.[10-12] Novel treatments that can improve symptoms and alter disease trajectory in MF are thus needed, particularly in the setting of JAK inhibitor failure.

Lysine-specific demethylase 1 (LSD1 [or KDM1A]) is a histone demethylase that is a promising target for the treatment of myeloproliferative neoplasms.[8] LSD1 is essential for the terminal differentiation of megakaryocytes and neutrophils, 2 key cell types that, under constitutive JAK-STAT activation, stimulate the production of growth factors and inflammatory cytokines that drive the bone marrow pathology, clonal evolution, and symptomatology of MF.[5,6,13] LSD1 inhibition disrupts both the maturation of megakaryocytes from progenitors as well as the functioning of mature megakaryocytes, resulting in decreased production of platelets and cytokines.[13] Further, LSD1 plays a central role in regulating the balance between proliferation and differentiation of hematopoietic stem/progenitor cells, suggesting that LSD1 inhibition may have a beneficial impact on mutation-bearing hematopoietic stem/progenitor cells compared with their wild-type counterparts.[13] Thus, targeting LSD1 offers 2 potential benefits in MF: improvement in the signs and symptoms of MF and reduction in the burden of mutant cells.

In murine models, LSD1 knockdown results in neutropenia, anemia, reversible thrombocytopenia, and reduced clonogenicity in leukemia-initiating cells, an observation that may have a bearing on clonal evolution.[14] Bomedemstat (IMG-7289 or MK-3543) is an irreversible inhibitor of LSD1 that has been shown to normalize or improve blood cell counts, reduce spleen volume, normalize splenic architecture, reduce bone marrow fibrosis, lower inflammatory cytokine levels, reduce mutant allele burden, and improve survival in murine models of myeloproliferative neoplasms.[8] In this open-label, phase 1/2 clinical trial, we investigated whether bomedemstat could improve splenomegaly and constitutional symptoms in participants with MF who were intolerant of or resistant to ≥1 standard-of-care therapy.

Methods

Study design and participants

This was a multicenter, open-label, phase 1/2 study evaluating the safety and tolerability and pharmacodynamics of bomedemstat administered orally once daily in participants with MF (NCT03136185). Eligible participants were aged ≥18 years and had a diagnosis of primary MF per World Health Organization diagnostic criteria for myeloproliferative neoplasms[15,16] or post-polycythemia vera MF or post-essential thrombocythemia MF per International Working Group–Myeloproliferative Neoplasms Research and Treatment diagnostic criteria.[17] Participants were required to have MF that was refractory or resistant to, inadequately controlled by, or intolerant of available approved therapy or, in the investigator's judgment, were not candidates for available approved therapy. Participants were required to have discontinued all previous therapy for their myeloproliferative neoplasm, including ruxolitinib or chemotherapy, for ≥2 weeks before study day 0 and interferon for ≥4 weeks before study day 0. All participants had to have an Eastern Cooperative Oncology Group performance status score of 0 to 2, a baseline peripheral blast count of ≤10%, and a baseline platelet count of ≥100 × 10^9/L. Participants with a spleen of any size were eligible.

Through a series of protocol amendments, the starting dose of bomedemstat was increased from 0.25 mg/kg administered orally once daily for 12 weeks followed by a 2- to 4-week washout period (phase 1/2a) to 0.5 to 0.6 mg/kg once daily with continuous dosing for 24 weeks (phase 2b). Participants were dose adjusted, if needed, to an initial target platelet count of 100 × 10^9/L to 200 × 10^9/L; with progressive clarity on dose and response, the target platelet count range was subsequently amended to 50 × 10^9/L to 75 × 10^9/L. Participants received bomedemstat for the 24-week treatment course unless the participant or physician decided to withdraw, the participant experienced intolerable toxicity or treatment failure, or other discontinuation criteria were met. Participants deriving clinical benefit could continue to receive treatment beyond 24 weeks.

Objectives

The primary objectives were to evaluate the safety and tolerability of bomedemstat and its effect on spleen volume. Exploratory objectives included evaluating hematologic response, patient-reported symptom burden using the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), bone marrow fibrosis grade (using a scale of 0-3), and the frequency of mutant alleles.

Assessments

Participants were monitored for treatment-emergent adverse events (AEs) throughout the study and for 28 days after the last dose of study treatment. Data on AEs were collected and summarized in terms used in the Medical Dictionary for Regulatory Activities. AEs were categorized as serious if they resulted in death, were a life-threatening experience, required or prolonged inpatient hospitalization, resulted in persistent or significant disability/incapacity, resulted in a congenital anomaly, or were considered an important medical event. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. An independent safety advisory board performed at least quarterly reviews of safety parameters and pharmacodynamic markers. Spleen volume was determined by magnetic resonance imaging or computed tomography at baseline, week 12, and week 24. Peripheral blood samples for hematologic testing were collected at screening, predose on day 0, weekly until week 8, every 2 weeks until week 20, and then at week 24 or end of treatment. Bone marrow aspirate and biopsy were performed at baseline and at week 24. Genomic blood samples were taken on the same day as bone marrow samples, if possible. The 24-hour recall tool of the MPN-SAF TSS was completed for the 7 days preceding the first dose of study

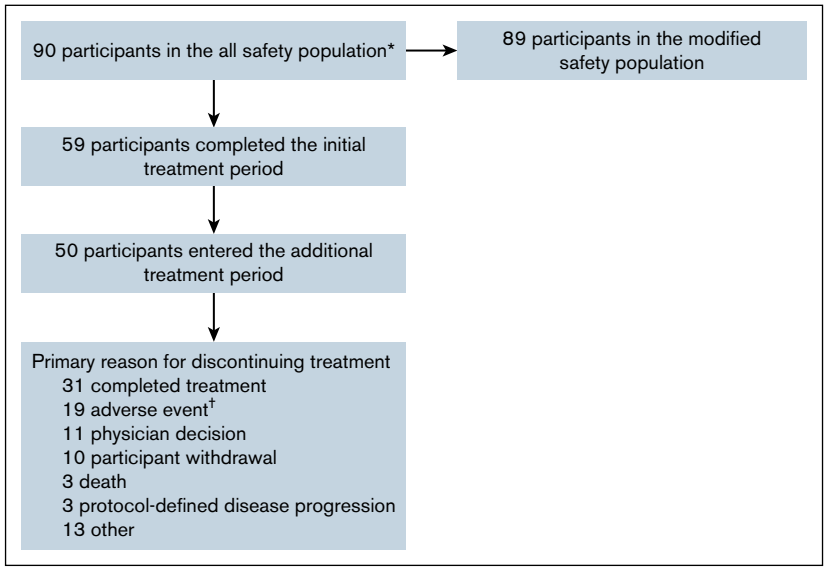


Figure 1. Participant disposition and analysis populations. *Only 89 unique participants were treated; 1 participant was taken off study after a prolonged period without treatment and subsequently re-enrolled. †For 19 participants, the primary reason for discontinuing treatment was an AE; 4 additional participants discontinued with AE involvement as a secondary reason (eg, an AE may have led to withdrawal of consent or physician decision to discontinue). The initial treatment period was 12 or 24 weeks. Participants considered to be deriving clinical benefit could continue to receive treatment beyond 24 weeks (additional treatment period).

treatment, and the 7-day recall tool of the MPN-SAF TSS was completed weekly from day 7 through to the end of the study.

Using participants' germ line and somatic DNA, exon capture was performed for 261 genes recurrently mutated in hematologic malignancies, which were sequenced to an average exonic depth of >1686 reads. The proportion of peripheral cells homozygous and heterozygous for a mutation in *JAK2*, *CALR*, or *MPL* vs wild type was determined by calculating the differences between the minor allele frequencies of single-nucleotide polymorphisms in the 2 samples (supplemental Methods).

Statistical analysis

Two safety populations were included for analysis purposes: the all-safety population (N = 90) and the modified safety population (n = 89). This distinction was made because 1 participant was initially enrolled in the 0.5 mg/kg per day starting dose group, subsequently discontinued, and then re-enrolled in the 0.6 mg/kg per day starting dose group. For the all-safety population, the participants' data from both periods of enrollment are included in the corresponding dose groups; for the modified safety population, the participants' data are summarized once. The pharmacodynamic metrics were exploratory in nature; hence, the study was not powered to make statements about the statistical significance of any changes observed. Continuous variables were summarized by means, standard deviations, medians, and ranges. Categorical variables were summarized by counts and by percentage of participants in corresponding categories. Results were summarized descriptively. All analyses were performed using Statistical Analysis Software, version 9.4 or higher (SAS Institute Inc, Cary, NC). The data cutoff date for this analysis was 26 August 2022.

The study was conducted in accordance with principles of good clinical practice and was approved by the appropriate institutional review boards and regulatory agencies. All participants provided written informed consent.

Results

Participants

Between 18 July 2017 and 24 May 2021, 89 participants were enrolled at 24 centers in Australia, Germany, Hong Kong, Italy, the United Kingdom, and the United States (Figure 1). The median age was 68 years (range, 35-88), 46 (52%) participants were male, and 86 (97%) participants had an Eastern Cooperative Oncology Group performance status score of 0 or 1 (Table 1). Forty-one participants (46%) were diagnosed with primary MF, 29 (33%) participants with post-essential thrombocythemia MF, and 19 (21%) participants with post-polycythemia vera MF. The median time from diagnosis to screening for this study was 30.3 months (range, 0-203). Sixty-eight (76%) participants had received prior treatment with ruxolitinib or fedratinib. The median spleen volume at baseline was 1354 mL (range, 99-6819). Thirty-three participants (37%) had received ≥1 red blood cell transfusion before dosing. Per International Prognostic Scoring System criteria, 47 (53%) participants were classified as high risk, 36 (40%) as intermediate-2, and 6 (7%) as intermediate-1. At screening, deep sequencing (average exonic read, 1686) identified *JAK2* V617F mutations in 56 of 88 participants (64%) with genetic data available, *CALR* mutations in 21 (24%), and *MPL* mutations in 6 (7%);

Table 1. Demographics and baseline characteristics

	Bomedemstat n = 89*
Age, median (range), y	68 (35-88)
Sex, n (%)	
Male	46 (52)
Female	43 (48)
ECOG performance status, n (%)	
0	40 (45)
1	46 (52)
2	3 (3)
Disease subtype, n (%)	
PMF	41 (46)
PET-MF	29 (33)
PPV-MF	19 (21)
IPSS risk classification, n (%)	
Intermediate-1	6 (7)
Intermediate-2	36 (40)
High	47 (53)
Blood values, mean (SE)	
Platelet count, $\times 10^9$/L	394.1 (38.6)
WBC count, $\times 10^9$/L	20.8 (2.3)
Hemoglobin level, g/dL	99.7 (2.6)
Spleen volume, median (range), mL	1354 (99-6819)
Mutations,† n (%)	
JAK2	56 (64)
CALR	21 (24)
MPL	6 (7)
Triple negative	5 (6)
High molecular risk‡	38 (43)
Prior treatment with an interferon, n (%)	0
Prior treatment with hydroxyurea, n (%)	42 (47)
Prior treatment with ruxolitinib or fedratinib, n (%)	68 (76)
Outcome of most recent treatment	
Resistant/refractory to or inadequately controlled	46 (52)
Disease progression	17 (19)
Loss of initial benefit	14 (16)
Discontinued due to nonhematologic side effects	13 (15)
Intolerant due to treatment-related hematologic complications	13 (15)
Prior radiation therapy, n (%)	8 (9)
Prior cancer-related procedure, n (%)	20 (22)
Prior cancer chemotherapy, n (%)	84 (94)
Prior hematopoetic stem cell transplant, n (%)	4 (4)
Prior red blood cell transfusion, n (%)	33 (37)

ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; PET-MF, post-essential thrombocythemia MF; PMF, primary MF; PPV-MF, post-polycythemia vera MF; SE, standard error.

*Only 89 unique participants were treated; 1 participant was taken off study after a prolonged period without treatment and subsequently re-enrolled.

†Genetic data were available for 88 participants.

‡*ASXL1*, *EZH2*, *CBL*, *U2AF1*, *SRSF2*, *IDH1*, *IDH2*, *TP53*, *NRAS*, *KRAS*.

Table 2. Treatment-emergent AEs occurring in more than 10% of participants and corresponding grade 3 to 5 AEs

	Bomedemstat N = 90	
n (%)	Any grade	Grade 3-5
Any	87 (97)	62 (69)
Thrombocytopenia	43 (48)	37 (41)
Dysgeusia	32 (36)	0
Anemia	30 (33)	20 (22)
Diarrhea	29 (32)	0
Nausea	27 (30)	2 (2)
Fatigue	23 (26)	4 (4)
Constipation	21 (23)	1 (1)
Peripheral edema	21 (23)	1 (1)
Arthralgia	21 (23)	1 (1)
Abdominal pain	16 (18)	2 (2)
Contusion	16 (18)	0
Decreased appetite	15 (17)	2 (2)
Pruritus	14 (16)	2 (2)
Pain in extremity	13 (14)	0
Pyrexia	13 (14)	1 (1)
Weight decreased	13 (14)	1 (1)
Back pain	12 (13)	1 (1)
Dyspnea	12 (13)	1 (1)
Epistaxis	12 (13)	0
Bone pain	10 (11)	0
Myalgia	10 (11)	2 (2)
Vomiting	10 (11)	1 (1)
Dizziness	9 (10)	0
Headache	9 (10)	1 (1)
Hyperuricemia	9 (10)	2 (2)

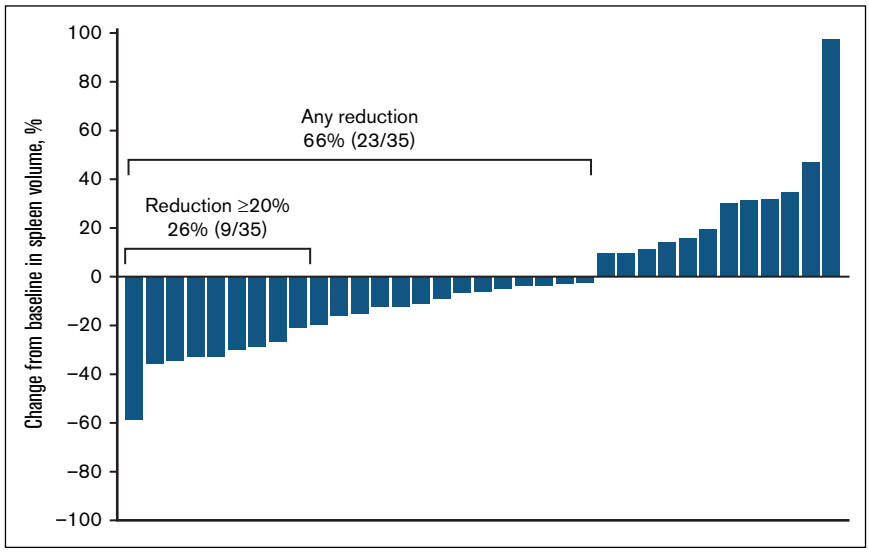
5 (6%) were triple negative, and 38 (43%) had additional high-molecular-risk mutations (eg, *ASXL1*, *EZH2*, *CBL*, *U2AF1*, *SRSF2*, *IDH1*, *IDH2*, *TP53*, *NRAS*, *KRAS*). The most common secondary mutations were those in *ASXL1* (28 participants, 32%).

Among participants included in the all-safety population (N = 90), 18 initiated bomedemstat at 0.25 mg/kg per day, 24 at 0.5 mg/kg per day, and 48 at 0.6 mg/kg per day. Fifty-nine participants completed the initial treatment period (12 or 24 weeks), and 50 entered the additional treatment period (Figure 1). At the end of the study, 29 participants were enrolled in the extension. No participant received subsequent allogeneic stem cell transplantation during the study follow-up.

Safety

The all-safety population included 90 participants. The median duration of treatment was 199.5 days (range, 25-882). Eighty-nine (99%) participants underwent dose adjustment per dose titration guidelines; 80 (89%) had at least 1 dose increase, 68 (76%) had at least 1 dose decrease, 26 (29%) had at least 1 dose interruption, and 13 (14%) had bomedemstat withdrawn before completing 24 weeks of treatment (supplemental Table 1). As of the data cutoff, 87 (97%) participants had reported ≥1 any-cause AE of any grade, and 62 (69%) had reported ≥1 grade 3 to 5 AE (Table 2). The most frequently occurring AEs of any grade (≥30% of participants) were thrombocytopenia (n = 43 [48%]), dysgeusia (n = 32 [36%]), anemia (n = 30 [33%]), diarrhea (n = 29 [32%]), and nausea (n = 27 [30%]) (Table 2). Bleeding events occurred in 14 (16%) participants, and 8 (9%) experienced both thrombocytopenia and a bleeding event. Forty-four (49%) participants experienced serious AEs. Twenty-three (26%) participants discontinued treatment due to AEs (either as the primary reason to discontinue or as a secondary reason) (supplemental Table 2). Three (3%) participants experienced an AE that led to death, none of which were deemed related to treatment (septic shock, cerebrovascular accident, acute respiratory failure). Treatment-related AEs were reported in 71 (79%) participants, grade 3 to 5

Figure 2. Change from baseline in spleen volume at week 24 in evaluable participants (n = 35).



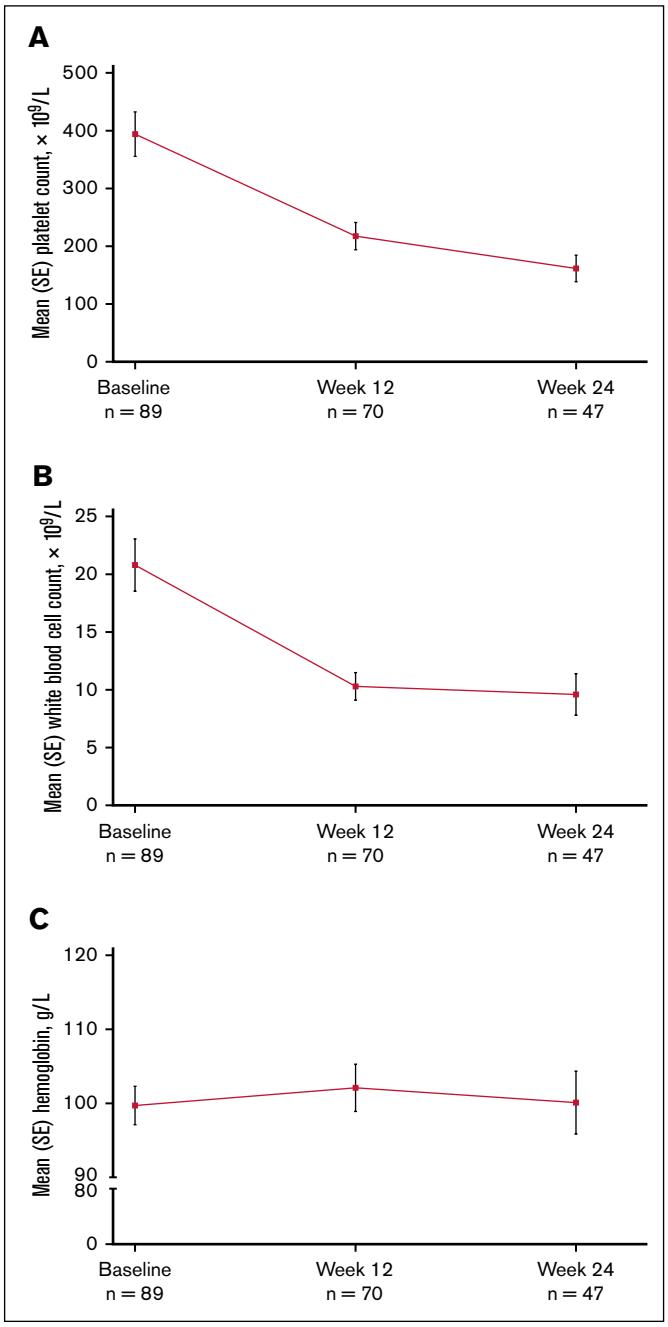


Figure 3. Changes in laboratory measures. Mean (SE) change in platelet count (A), WBC count (B), and hemoglobin levels (C) from baseline. SE, standard error.

treatment-related AEs in 50 (56%) participants, and serious treatment-related AEs in 13 (14%) participants.

Efficacy

Spleen data were available at week 24 for 35 participants. Among those participants, 23 (66%) had any reduction from baseline in spleen volume, and 9 (26%) had a spleen volume reduction of ≥20% (Figure 2; supplemental Table 3; supplemental Figure 1). When considered among participants in the modified safety population, 23 of 89 (26%) had any reduction from baseline in spleen volume, and 9 (10%) had a spleen volume reduction of ≥20%. Mean platelet count and white blood cell (WBC) count normalized over 24 weeks, and hemoglobin levels remained stable (Figure 3). Mean change in symptom burden, measured using the MPN-SAF TSS, demonstrated a numerical improvement in most symptom scores at week 12 and week 24, including fatigue (Figure 4). Among 35 participants with baseline and 24-week bone marrow fibrosis scores available per central review, 8 (23%) had an improvement of ≥1 grade, 21 (60%) were stable, and 6 (17%) had scores that worsened by ≥1 grade (supplemental Figure 2). No participant's disease progressed to acute myeloid leukemia during the course of treatment.

Mutational burden

Genetic data were available for 88 individual participants. Baseline sequencing was not performed for 1 participant in the modified safety population. A somatic mutation in *JAK2*, *CALR*, or *MPL* was identified in 83 (94%) participants; 5 (6%) were triple negative. Among participants with known somatic mutations in *JAK2*, *CALR*, or *MPL*, 29 of 56 were homozygous (allele frequency >50% and/or loss of heterozygosity at driver gene) for *JAK2* mutations, 2 of 21 participants were homozygous for a *CALR* mutations, and 3 of 6 were homozygous for *MPL* mutations (supplemental Table 4). In any follow-up sample, no new somatic mutation was detected that was not already detected in the baseline sample. Thirty-six participants with *JAK2*, *CALR*, or *MPL* mutations had follow-up genetic analysis at week 24, of whom 56% had a reduction in variant allele frequency (Figure 5). Among nondriver mutations, *ASXL1* mutations were the most affected by treatment; 56% of participants had stable *ASXL1* VAF, and 33% had a decrease in *ASXL1* VAF.

Discussion

In this open-label, phase 1/2 study of participants with advanced MF and limited treatment options, the LSD1 inhibitor bomedemstat provided clinical benefit while having a manageable safety profile. At week 24, 66% of participants with data available had a reduction from baseline in spleen volume, and 26% had a reduction of ≥20%. Platelet count and WBC count normalized over 24 weeks, and hemoglobin levels remained stable. A numerical improvement in most key symptoms was observed, especially fatigue. Most evaluable participants (83%) exhibited improvement or stability in bone marrow fibrosis score, which may be associated with the anti-inflammatory effect of LSD1 inhibition.[8]

In this study, participants were enrolled regardless of spleen size, a departure from most clinical trials in MF, which require participants to have baseline splenomegaly of ≥5 cm below the left costal margin.[18-20] Consequently, the median spleen volume in this study was considerably lower at 1354 mL compared with other trials, such as 2566 to 2598 mL in the COMFORT-1 trial or 2318 to 2408 mL in COMFORT-2.[18,19] Thus, in this study population, of whom most had the benefit of treatment with prior ruxolitinib or fedratinib, we would not expect to observe the same volume reductions as seen in the first-line setting. Notwithstanding, 26% of evaluable participants treated with bomedemstat had a spleen volume reduction of ≥20%, an improvement generally regarded as clinically meaningful, particularly with any single agent therapy after JAK inhibitor failure.

Figure 4. Change in symptom scores of the myeloproliferative neoplasm symptom assessment form. Mean (SD) change from baseline at week 12 (A) and week 24 (B). SD, standard deviation.

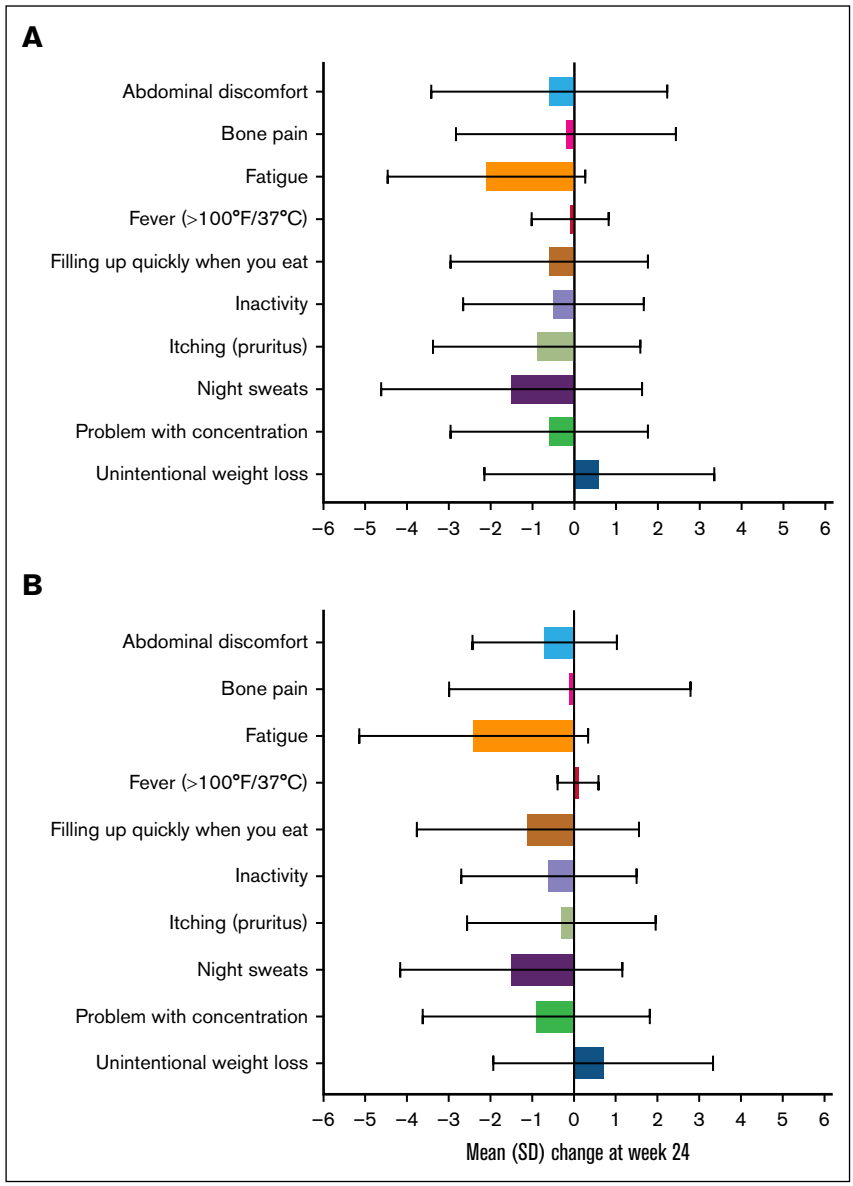
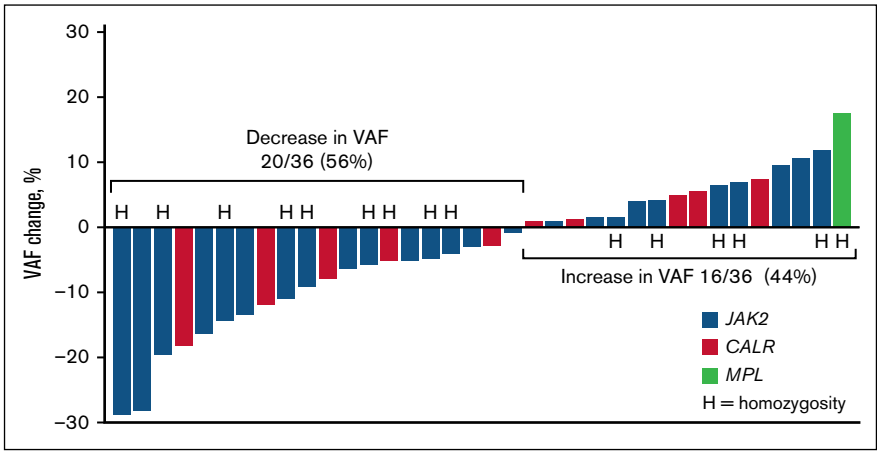


Figure 5. Variant allele frequency (VAF) change of driver mutations at week 24 in evaluable participants (n = 36).



In the current analysis, dose titration rules were predicated on the requirement that LSD1 should be inhibited only for a portion of the 24-hour dosing interval to ensure sufficient thrombopoiesis and granulopoiesis, the 2 lineages most dependent on LSD1.[13] As such, dose titration used platelet count as a biomarker of bomedemstat activity on megakaryocyte function; the final target platelet count of 50 × 10^9/L to 75 × 10^9/L offered an acceptable safety margin yet anticipated instances of thrombocytopenia. Indeed, thrombocytopenia was the most frequent AE. Neutrophil maturation from progenitors also relies on LSD1 function. Consequently, bomedemstat effected a decrease in the mean WBC count over 24 weeks of treatment, with few episodes of neutropenia. This study identified 0.6 mg/kg per day as an appropriate starting dose and demonstrated the feasibility and desirability of titrating bomedemstat in each participant to maximize the therapeutic effects while minimizing the risk of clinically significant cytopenias.

As measured by the variant allele frequency in isolated granulocytes, bomedemstat reduced the frequency of *JAK2*, *CALR*, and *MPL* mutations in 56% of evaluable participants. The absence of any new mutations or progression to acute myeloid leukemia in a participant population in whom 43% had "high-molecular-risk" mutations, and many with homozygous driver mutations, is noteworthy. The combined effects of VAF reduction without new mutations, improvements in fibrosis, and the absence of progression even in participants with "high-risk" secondary mutations may suggest a potential disease-modifying effect of bomedemstat in MF[21]; however, further evaluation in larger clinical trials is needed.

To the authors' knowledge, this is the only clinical study to have investigated an LSD1 inhibitor in participants with MF. The primary limitation was the single-arm design preventing direct comparison with other treatment options. In addition, data collection at week 24 was limited by the number of participants who were able to attend the clinic within a week on either side of this specific time point, which was exacerbated by the COVID-19 pandemic. Having spleen data available for only 35 participants at week 24 limited the strength of the efficacy findings; however, the results remain indicative of a splenic response. A phase 3 study investigating bomedemstat vs hydroxyurea in participants with cytoreductive therapy–naive essential thrombocythemia (NCT06456346) and a phase 3 study investigating bomedemstat compared with the best available therapy in participants with essential thrombocythemia with an inadequate response to or intolerance of hydroxyurea (NCT06079879) are currently underway. A phase 2 extension study is evaluating the long-term safety and efficacy of bomedemstat in participants with a myeloproliferative neoplasm who participated in the current study or in the phase 2 study in essential thrombocythemia (NCT05223920). Bomedemstat is also being evaluated in combination with ruxolitinib for the treatment of MF in an ongoing phase 2 study (NCT05569538).

In summary, bomedemstat as monotherapy demonstrated promising clinical activity in a population of participants with advanced MF, 76% of whom had received a prior JAK inhibitor, warranting continued development for the treatment of MF.

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Authorship

Contribution: R.M., A.M.V., J.C.W., J.P., and H.Y.R. Jr conceived, designed, or planned the study; H.G., A.Y., A.T.G., J.S., J.M.R., A.J.M., J.R.G., S.K., J.E., A.B.H., F. Palandri, F. Passamonti, R.M., M.M., C.H., A.M.V., J.M.W., D.M.R., J.P., and H.Y.R. Jr acquired the data; H.G., A.Y., R.M., J.M.W., J.C.W., J.P., G.N., and H.Y.R. Jr analyzed the data; H.G., A.Y., A.T.G., J.S., J.M.R., A.J.M., J.R.G., S.K., A.B.H., F. Palandri, F. Passamonti, R.M., M.M., C.H., J.M.W., J.C.W., D.M.R., J.P., G.N., and H.Y.R. Jr interpreted the results; H.G., R.M., G.N., and H.Y.R. Jr drafted the manuscript; and H.G., A.Y., A.T.G., J.S., J.M.R., A.J.M., J.R.G., S.K., J.E., A.B.H., F. Palandri, F. Passamonti, R.M., M.M., C.H., A.M.V., J.M.W., J.C.W., D.M.R., and J.P. critically reviewed or revised the manuscript for important intellectual content.

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