

A randomized, double-blind study of zinpentraxin alfa in patients with myelofibrosis who were previously treated with or ineligible for ruxolitinib: stage 2 of a phase II trial

Higher-grade bone marrow (BM) fibrosis is associated with worse survival in patients with myeloproliferative neoplasms.^{1,2} Moreover, fibrotic changes in myelofibrosis (MF) progressively remodel the BM niche, resulting in impaired hematopoiesis and progressive worsening of anemia and thrombocytopenia, which are associated with reduced quality of life and poor prognosis.³⁻⁵ Zinpentraxin alfa (previously PRM-151) is a recombinant form of human pentraxin-2, an endogenous regulator of the tissue damage inflammatory response, and a natural inhibitor of fibrosis.⁶⁻⁸ A two-stage phase II trial (NCT01981850) evaluated the efficacy and safety of zinpentraxin alfa in patients with MF. In the open-label stage 1, zinpentraxin alfa showed evidence of clinical activity and tolerable safety as monotherapy and in combination with ruxolitinib in patients with primary or secondary MF.⁹ Here we report the findings of stage 2 of this trial, which suggested signs of clinical activity of zinpentraxin alfa in patients with difficult-to-treat MF.

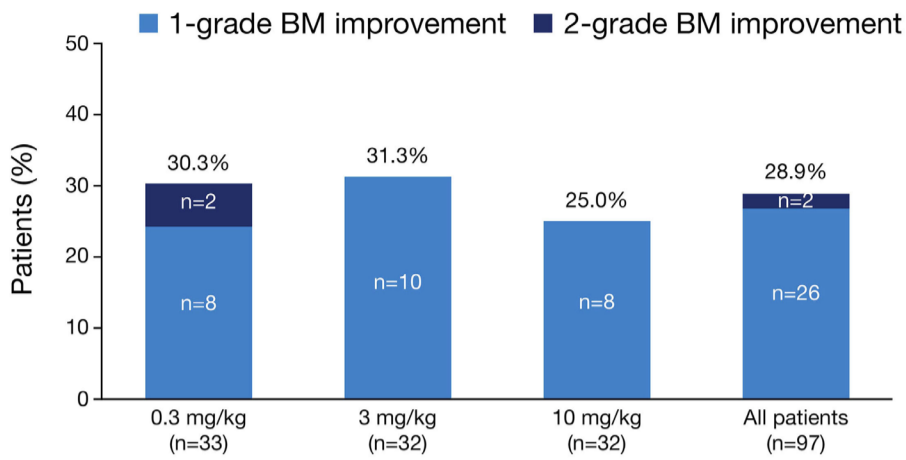
This randomized, double-blind, phase II trial (NCT01981850) evaluated the efficacy and safety of three different doses of zinpentraxin alfa as monotherapy in patients aged ≥ 18 years with intermediate-1/2 and high-risk primary or secondary MF who were anemic or thrombocytopenic and ineligible for, intolerant of, or had an inadequate prior response to ruxolitinib. Eligible patients had MF grade ≥ 2 BM fibrosis and had had a BM biopsy within 4 weeks prior to treatment initiation to establish the baseline fibrosis score. The trial comprised three periods: a 4-week screening period, the main phase (9 \times 4-week treatment cycles; total of 36 weeks), and a 4-week follow-up (*Online Supplementary Figure S1*). Patients without disease progression or discontinuation due to toxicity and with potential clinical benefit could continue zinpentraxin alfa 10 mg/kg treatment in an open-label extension phase. In the main phase, patients stratified by baseline hematologic status (anemia and/or thrombocytopenia) were randomized 1:1:1 using an interactive response system to receive zinpentraxin alfa 0.3 mg/kg (group 1), 3 mg/kg (group 2), or 10 mg/kg (group 3) on days 1, 3, and 5 of cycle 1, and day 1 of each subsequent 28-day cycle. The patients, investigators, assessors, and sponsor were blinded to study treatment. Patients provided written informed consent before enrollment. The primary endpoint was BM response rate, defined as the percentage of patients with reduction from baseline in BM fibrosis by ≥ 1 grade per European Consensus criteria¹⁰ at any time, as determined by a central adjudication panel. Secondary and exploratory endpoints included hemoglobin concentration,

platelet count, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), spleen size improvements, and best overall response per International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria. Adverse events, serious adverse events, and infusion-related reactions were recorded.

In stage 2 of this study, 98 patients were randomized to group 1 (n=33), group 2 (n=32), or group 3 (n=33) between November 23, 2015, and November 11, 2016. *Online Supplementary Figure S2* provides full details of the patients' disposition in the study. The patients' baseline characteristics are summarized in *Online Supplementary Table S1*. The population of patients had a poor prognosis: 85.6% had intermediate-2 or high-risk disease, and 64.2% had centrally determined BM fibrosis grade 3 at baseline. Most patients (83.5%) had a baseline hemoglobin < 100 g/L and 39.2% were dependent on red blood cell transfusions at baseline. Overall, 60.8% of patients had severe thrombocytopenia (platelets $\leq 50 \times 10^9/L$), and 15.5% were dependent on platelet transfusions at baseline.

In total, 28/97 patients (28.9%; 95% confidence interval: 19.85-37.88) had a BM response (group 1: n=10, 30.3%; group 2: n=10, 31.3%; group 3: n=8, 25.0%) (*Figure 1A*). Logistic regression analysis of pairwise comparisons between the three groups showed no statistically significant differences ($P=0.58-0.93$). Of the 28 patients with a BM response in the main phase, 26 (26.8% of all patients) had a best shift of 1-grade improvement, and two (2.1% of all patients) had a 2-grade improvement per European Consensus/World Health Organization criteria (*Figure 1B*). In the main phase, hemoglobin improvements were observed in 12/97 (12.4%) patients (group 1: n=5, 15.2%; group 2: n=5, 15.6%; group 3: n=2, 6.3%), and platelet count improvements were observed in 32/97 (33.0%) patients (group 1: n=9, 27.3%; group 2: n=11, 34.4%; group 3: n=12, 37.5%). Packed red blood cell and platelet transfusion requirements and changes in platelet count are shown in *Figure 1C* and *D*, respectively. During the combined main phase and open-label extension period, of the 15 patients with hemoglobin improvement, eight (53%) had a BM response, and of the 37 patients with a platelet count improvement, 12 (32%) had a BM response (*Figure 2*). The duration of hemoglobin and platelet improvements among BM responders and non-responders is shown in *Figure 2*. Hemoglobin and platelet count trajectories among BM responders and non-responders indicated relatively stable hemoglobin and platelet levels over time in most patients.

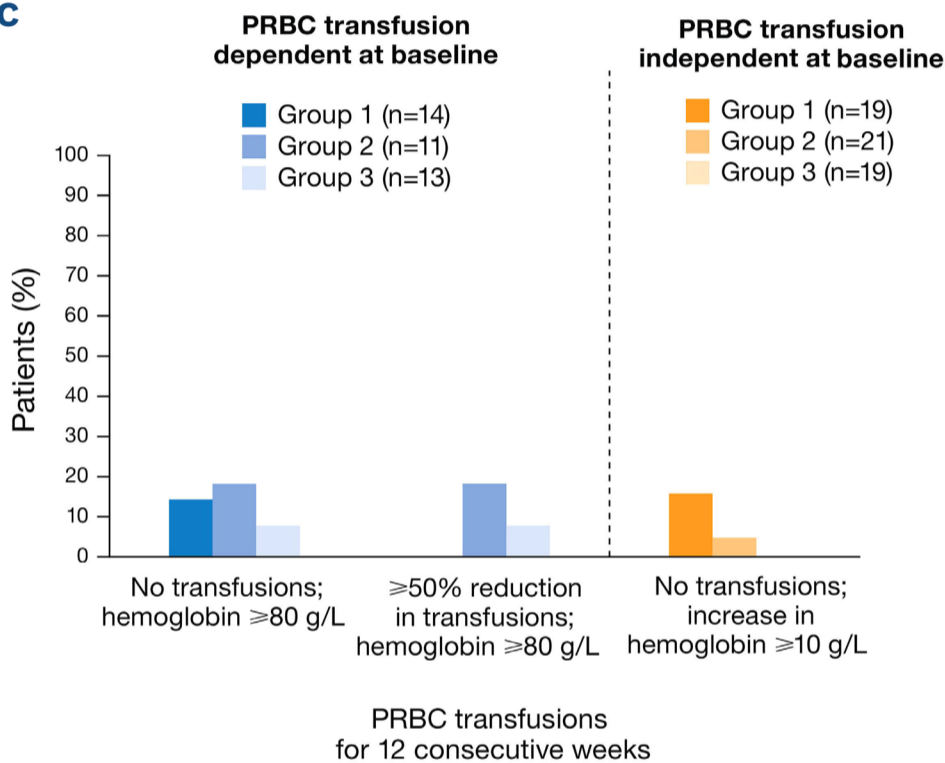
A



B



C



D

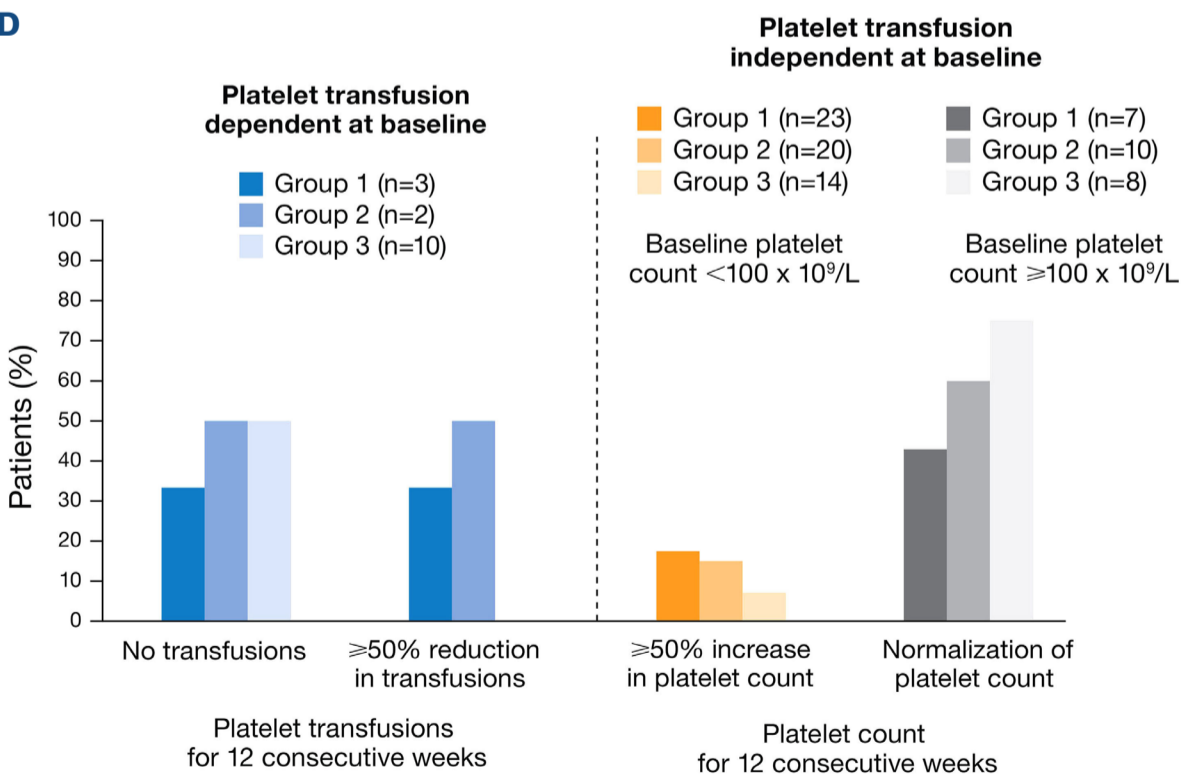
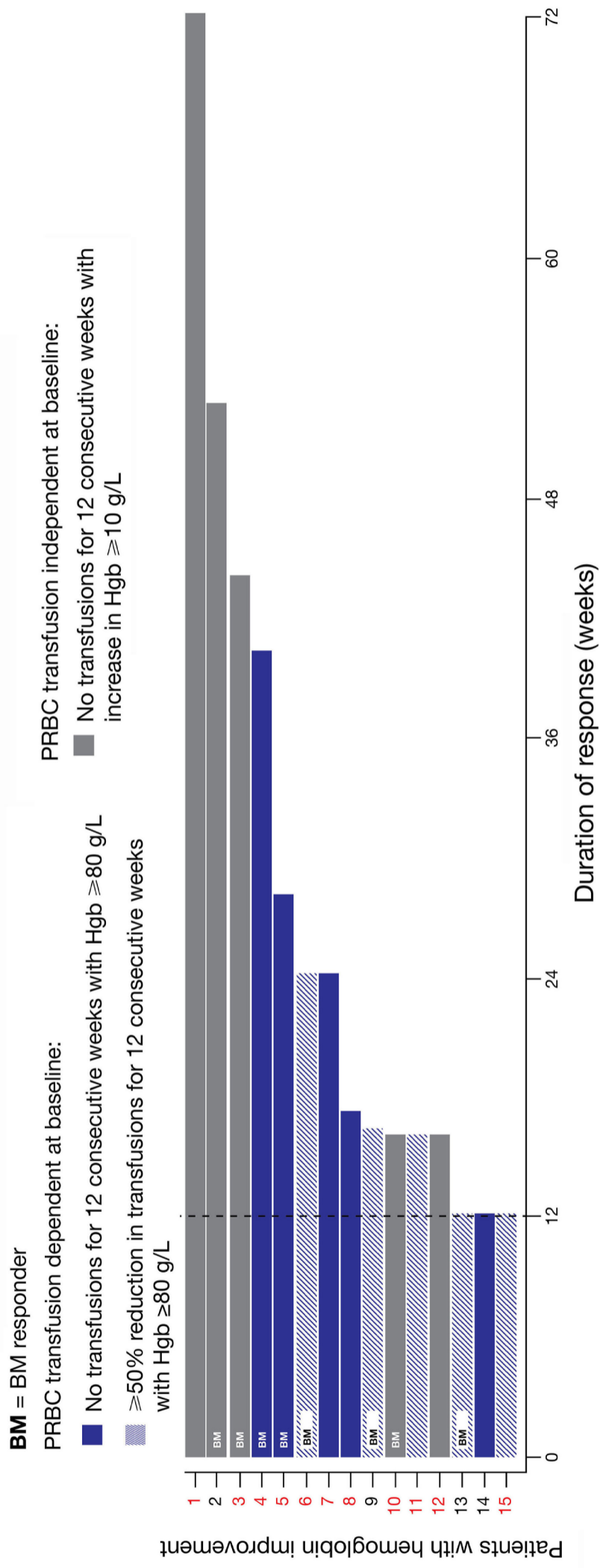


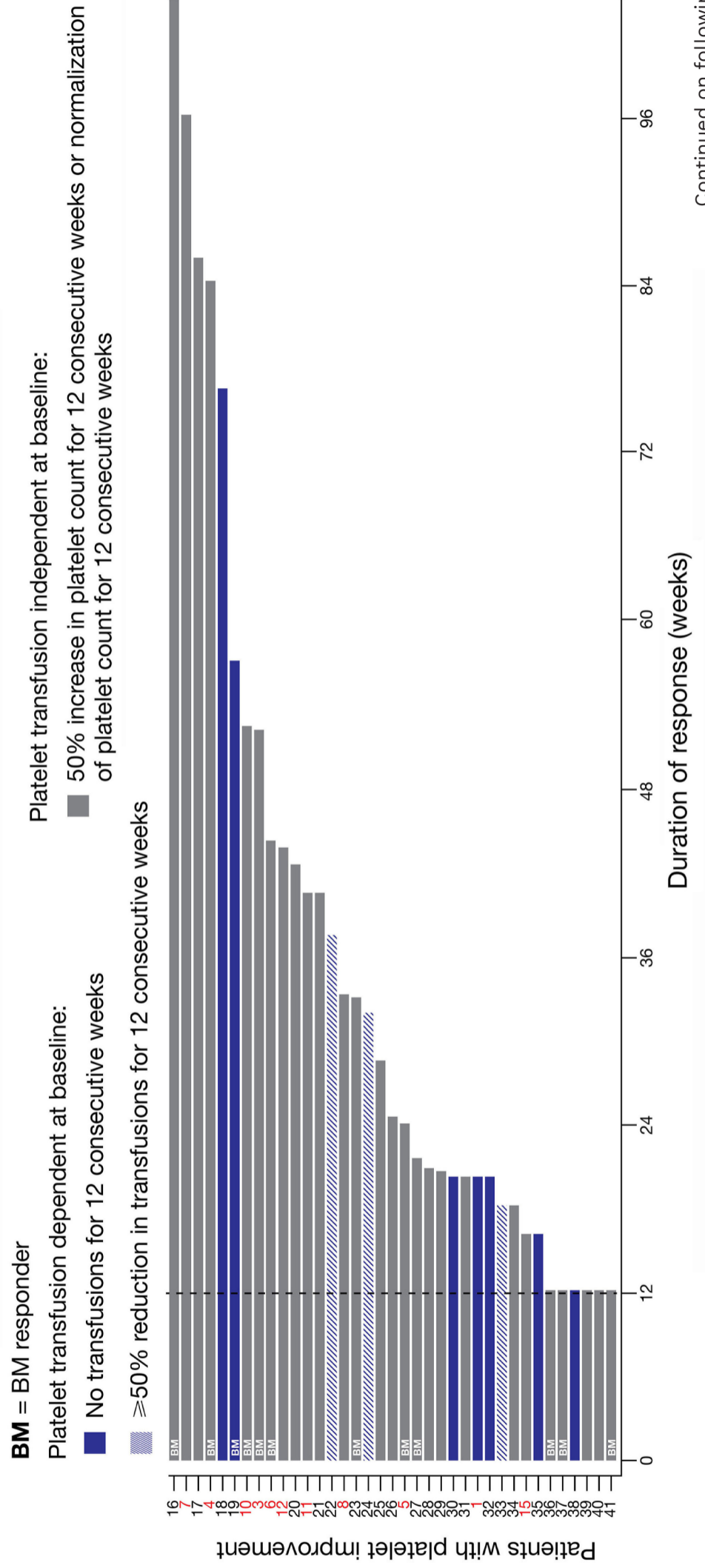
Figure 1. Efficacy outcomes in the main study phase.

(A) Bone marrow (BM) response rate by central review at any time. (B) Best shifts in BM fibrosis score during the main phase of the study. (C) Improvement in hemoglobin level during the main phase of the study. (D) Improvement in platelet count during the main phase of the study. *Baseline BM fibrosis data were missing for two patients. BM response rate was defined as the percentage of patients with a reduction from baseline in BM fibrosis by ≥ 1 grade per European Consensus criteria.¹⁰ The primary endpoint of BM response rate was analyzed using logistic regression, with BM response at any time as the response variable and treatment group as the explanatory variable. The analysis was adjusted on a randomized stratum. Two pairwise comparisons (group 2 vs. group 1 and group 3 vs. group 1) were computed with the aim of demonstrating superiority and, consequently, an adjusted two-sided level of significance of 0.025 was used. A third comparison (group 3 vs. group 2) was not expected to have enough power to demonstrate any difference with the planned sample size. This comparison was considered exploratory and was conducted using an unadjusted two-sided level of significance of 0.05. Baseline red blood cell transfusion dependency was defined as ≥ 2 units packed red blood cells every 4 weeks for 12 weeks prior to day 1 of cycle 1, regardless of baseline hemoglobin level. Baseline platelet transfusion dependency was defined as ≥ 2 platelet transfusions in any 12 weeks prior to day 1 of cycle 1, regardless of baseline platelet level. BM: bone marrow; PRBC: packed red blood cell.

A



B



Continued on following page.

Figure 2. Duration of hemoglobin and platelet count improvements. (A, B) Duration of improvement in hemoglobin concentration (A) and platelet count (B) during the main study phase and the open-label extension period combined. The x axis shows the duration of response and does not necessarily start from week 0 of the study period. Each bar represents an individual patient; the patients' identities are shown as consecutive numbers, with patients who had both hemoglobin and platelet improvements in red text. "BM" indicates patients who had a bone marrow response. Hemoglobin improvement for red blood cell transfusion-dependent patients was defined as either an absence of any red blood cell transfusion during any consecutive 12-week interval with a hemoglobin level of ≥ 80 g/L, or a $\geq 50\%$ reduction from baseline in red blood cell transfusions for 12 consecutive weeks with a hemoglobin level of ≥ 80 g/L. For red blood cell transfusion-independent patients, improvement was defined as a ≥ 10 g/L increase in hemoglobin level for 12 consecutive weeks without transfusions. Platelet improvement for platelet transfusion-dependent patients was defined as either becoming transfusion independent for 12 consecutive weeks, or a reduction in transfusion need from baseline of $\geq 50\%$ for 12 consecutive weeks. For platelet transfusion-independent patients with a baseline platelet count $< 100 \times 10^9/L$, improvement was defined as a $\geq 50\%$ increase in the number of platelets for 12 consecutive weeks or normalization of platelet count (above lower limit of normal). BM response was defined as a reduction from baseline in bone marrow fibrosis by ≥ 1 grade per European Consensus criteria. BM: bone marrow; PRBC: packed red blood cell; RBC: red blood cell; Hgb: hemoglobin.

MPN-SAF TSS, spleen size, and best overall response per IWG-MRT criteria were evaluated across the combined main phase and open-label extension. Of evaluable patients, 32/94 (34%) had a $\geq 50\%$ reduction in MPN-SAF TSS compared to the baseline score at any time, 32/76 (42.1%) had any reduction in spleen volume at any time, and no patients had $\geq 35\%$ reduction in spleen volume at week 36.

Clinical improvement was seen in 16/97 (16.5%) patients, and 67 (69.1%) had stable disease.

Safety results are summarized in Table 1. Generally, zinpentraxin alfa was well tolerated across all doses; 97 patients experienced ≥ 1 treatment-emergent adverse event. In total, 77 serious treatment-emergent adverse events were reported in 39 patients, most frequently pneumonia (n=5;

Table 1. Summary of treatment-emergent adverse effects in the safety population during the main phase, by cohort and overall.

Patients, N (%)	Group 1 ^a N=33	Group 2 ^b N=32	Group 3 ^c N=32	Overall N=97
Any TEAE	33 (100)	32 (100)	32 (100)	97 (100)
Most common TEAE ($\geq 10\%$ of patients overall)				
Fatigue	8 (24.2)	8 (25.0)	11 (34.4)	27 (27.8)
Cough	10 (30.3)	7 (21.9)	5 (15.6)	22 (22.7)
Weight decrease	6 (18.2)	8 (25.0)	8 (25.0)	22 (22.7)
Dyspnea	4 (12.1)	8 (25.0)	7 (21.9)	19 (19.6)
Peripheral edema	6 (18.2)	3 (9.4)	9 (28.1)	18 (18.6)
Diarrhea	8 (24.2)	5 (15.6)	3 (9.4)	16 (16.5)
Abdominal pain	5 (15.2)	6 (18.8)	4 (12.5)	15 (15.5)
Anemia	5 (15.2)	6 (18.8)	3 (9.4)	14 (14.4)
Epistaxis	6 (18.2)	4 (12.5)	4 (12.5)	14 (14.4)
Headache	4 (12.1)	7 (21.9)	3 (9.4)	14 (14.4)
Pyrexia	4 (12.1)	7 (21.9)	3 (9.4)	14 (14.4)
Constipation	4 (12.1)	4 (12.5)	4 (12.5)	12 (12.4)
Decreased appetite	4 (12.1)	4 (12.5)	4 (12.5)	12 (12.4)
Arthralgia	3 (9.1)	5 (15.6)	2 (6.3)	10 (10.3)
Dizziness	6 (18.2)	3 (9.4)	1 (3.1)	10 (10.3)
Pneumonia	3 (9.1)	2 (6.3)	5 (15.6)	10 (10.3)
Thrombocytopenia	5 (15.2)	4 (12.5)	1 (3.1)	10 (10.3)
Treatment-related TEAE	14 (42.4)	18 (56.3)	16 (50.0)	48 (49.5)
Grade 3-4 TEAE	12 (36.4)	18 (56.3)	12 (37.5)	42 (43.3)
Grade 5 TEAE ^d	5 (15.2)	4 (12.5)	6 (18.8)	15 (15.5)
AE leading to discontinuation of zinpentraxin alfa	7 (21.2)	11 (34.4)	12 (37.5)	30 (30.9)
Serious AE	11 (33.3)	14 (43.8)	14 (43.8)	39 (40.2)

^aGroup 1 was treated with zinpentraxin alfa 0.3 mg/kg Q4W. ^bGroup 2 was treated with zinpentraxin alfa 3 mg/kg Q4W. ^cGroup 3 was treated with zinpentraxin alfa 10 mg/kg Q4W. ^dFatal treatment emergent adverse events were reported as the following preferred terms: acute myeloid leukemia, malignant neoplasm progression, myelofibrosis, primary myelofibrosis, transformation to acute myeloid leukemia, death, pancytopenia, cardiopulmonary failure, obstructive femoral hernia, cachexia, cerebral hemorrhage (all N=1), pneumonia (N=2), disease progression (N=2). Q4W: every 4 weeks; TEAE: treatment-emergent adverse event; AE: adverse event.

5.2%) and epistaxis (n=3; 3.1%). Because of the small sample size and the low number of serious treatment-emergent adverse events, conclusions cannot be drawn regarding potential differences in the safety of different doses. Of the 15 fatal treatment-emergent adverse events (15.5%), one death was reported as related to the study treatment; however, the investigator reported that the death was likely related to underlying thrombocytopenia due to MF, leading to a bleed. Infusion-related reactions were reported in four (4.1%) patients; all these reactions were grade 1/2, except for grade 3 urticaria in one patient in group 2. No new safety signals were reported during the open-label extension phase of the study.

Genetic analysis revealed similar mutational profiles across all treatment groups. No notable changes were identified in variant allele frequency in any treatment group during the study and most patients had changes of $\pm 5\%$, which could be due to variation or background noise.

Overall, zinpentraxin alfa treatment showed some improvements in BM fibrosis and hematologic parameters across all doses, with reduction in BM fibrosis at any time observed in approximately 30% of patients. Despite the lack of a clear dose–response relationship observed within the tested dose range, the lack of a control arm, and the fact that only around half of patients had biopsy results available at all three post-baseline timepoints, responses in patients with advanced BM failure are suggestive of clinical activity of zinpentraxin alfa in MF. Furthermore, some of these patients with very poor prognosis were treated with zinpentraxin alfa for a prolonged period, up to 46.7 months, which was also somewhat unexpected.

Despite advanced and high-risk disease, improvements in hemoglobin levels and platelet counts were reported across all treatment groups. Reductions in red blood cell transfusion dependence in various populations of patients have been observed previously with other treatments; however, to our knowledge, only pacritinib has achieved notable results in patients with severe thrombocytopenia (platelet counts $\leq 50 \times 10^9/L$) and red blood cell transfusion dependence, albeit in the setting of limited or no prior JAK inhibitor exposure.¹¹ Ruxolitinib discontinuation leads to a poor prognosis and progressive worsening of anemia and thrombocytopenia.^{12,13} However, most patients in the current study, of whom 76.3% had previously received ruxolitinib, had stable or improved hemoglobin levels and platelet counts. The hematologic improvements observed with zinpentraxin alfa are important because analysis of recent momelotinib trials suggests that hematologic improvement may serve as a surrogate endpoint predictive of improved overall survival.¹⁴ The current study did not assess overall survival and numbers of patients were small; however, some patients with high-risk features and poor prognosis following ruxolitinib discontinuation had long-lasting treatment (median 7.5 months; range, 0.2–46.7). Furthermore, since transfusion dependence is

burdensome to patients, the reported reductions in red blood cell and platelet transfusions in transfusion-dependent patients are also important from a quality-of-life perspective.³

Limitations of this study include the lack of a placebo arm, a heterogeneous population of patients, and a small sample size, which make it difficult to interpret trends. Advanced disease stage and negative prognostic factors may also have reduced the likelihood of observing effects on fibrosis. Finally, it is unclear whether a 35% threshold for reduction in spleen size is appropriate in the setting of relapsed/refractory patients with advanced disease, and in several studies few or no patients have achieved $\geq 35\%$ spleen volume reduction in this setting.¹⁵

In summary, zinpentraxin alfa treatment showed signs of clinical activity, including improvements in fibrosis, disease-related hematologic parameters, and symptoms, in difficult-to-treat patients with MF who were ineligible for, intolerant of, or had inadequate response to ruxolitinib. Results should be interpreted with caution because of the small sample sizes and lack of a placebo arm. The potential for additional clinical benefit in newly diagnosed patients and those with less fibrosis remains a hypothesis to be examined in future clinical trials. The results from stage 1 and stage 2 of this trial will inform future investigations of zinpentraxin alfa in patients with MF.

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Contributions

SV and CNH conceived and designed the work. SV, AI, PtB, MRS, KT, MT, MW, JO'S, TCE-G, and CNH acquired data. SV, PtB, MRS, BH, KT, OP, SK, KG, JO'S, and TCE-G analyzed the data. SV, AI, PtB, MRS, BH, BT, KT, OP, SK, MW, KG, and JO'S interpreted the results. All authors were involved in reviewing/revising the manuscript, approved the final version, and vouch for the accuracy of the content included in the manuscript.

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Data-sharing statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (<https://vivli.org>). Further details on Roche's criteria for eligible studies are available at <https://vivli.org/members/ourmembers>. For further details on Roche's global policy on the sharing of clinical information and how to request access to related clinical study documents, visit https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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