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

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DISCLOSURES

SV has received research support from BMS, Constellation, CTI BioPharma, Galecto, Geron, Incyte, Kartos, Novartis, NS Pharma, Protagonist, PharmaEssentia, Roche, and Sierra, and consulting fees from BMS, Celgene, Constellation, Incyte, and Novartis.

MT has served as a member on a board or advisory committee for BMS, Novartis, and Sumitomo; has received support for attending meetings from Sumitomo; has received research support from Promedior and Roche; and has a leadership role with the Society of Hematologic Oncology.

MW has no conflicts of interest to disclose.

AI has no conflicts of interest to disclose.

PtB has no conflicts of interest to disclose.

MRS has received royalties or licenses from Boehringer Ingelheim; received consulting fees from Geron, Karyopharm and Ryvu; received support for attending meetings from Ryvu and Taiho; received patents from Boehringer Ingelheim; served as a member on a board or advisory committee for AbbVie, Bristol Myers Squibb, CTI, Geron, GSK, Karyopharm, Novartis, Rigel, Ryvu, Taiho, and Treadwell; has stock or stock options in Karyopharm and Ryvu; and has received research funding from ALX Oncology, Astex, Incyte, Takeda, and TG Therapeutics.

PB has received research support from Blueprint, BMS, Cogent, CTI, Disc, Geron, Incyte, Ionis, Janssen, Kartos, Karyopharm, MorphoSys, Sumitomo, and Telios, and honoraria/consulting fees from AbbVie, Blueprint, BMS, Cogent, CTI, GSK, Incyte, Ionis, Jubilant, Karyopharm, Morphic, MorphoSys, Novartis, PharmaEssentia, and Sumitomo.

OP has no conflicts of interest to disclose.

RM has received consulting fees and honoraria from AbbVie, Blueprint, BMS, CTI BioPharma, Genentech, Geron, GSK, Incyte, MorphoSys, Novartis, Sierra, Sierra Oncology, and Telios.

TCE-G was employed by Roche at the time this work was performed.

JO’S has no conflicts of interest to disclose.
KG is an employee of Roche.

BH is an employee of Roche/Genentech and owns stocks.

SK has no conflicts of interest to disclose.

BT was contracted by Roche at the time this work was performed.

KT is an employee of Roche and owns stocks.

CNH has received consulting fees from AbbVie, AOP, BMS, Constellation Pharmaceuticals, CTI BioPharma, Galecto, GSK, Karyopharm, Keros, MorphoSys, Novartis, Promedior, and Roche; honoraria from AbbVie, BMS, GSK, and Novartis; has advisory roles for Galecto and Keros; has received support from Novartis for attending meetings; and has a leadership or fiduciary role with the European Hematology Association and MPN Voice.

**AUTHOR CONTRIBUTIONS**

Conception/design of the work: SV, CNH.

Data acquisition: SV, AI, PtB, MRS, KT, MT, MW, JO’S, TCE-G, CNH.

Data analysis: SV, PtB, MRS, BH, KT, OP, SK, KG, JO’S, TCE-G.

Interpretation of results: SV, AI, PtB, MRS, BH, BT, KT, OP, SK, MW, KG, JO’S.

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.

**Short/running title:** Zinpentraxin alfa in myelofibrosis: Phase II, Stage 2

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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 here (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, see here
(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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Higher-grade bone marrow (BM) fibrosis is associated with worse survival in patients with myeloproliferative neoplasms.\textsuperscript{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 (QoL) and poor prognosis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 \( \geq 18 \) 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 \( \geq 2 \) BM fibrosis and a BM biopsy within 4 weeks prior to treatment initiation to establish the baseline fibrosis score. The trial comprised three periods: 4-week screening, main phase (9×4-week treatment cycles; total of 36 weeks), and 4-week follow-up (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 (OLE) 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 (BMRR), defined as the percentage of patients with reduction from baseline in BM fibrosis by \( \geq 1 \) grade per European Consensus criteria\textsuperscript{10} at any time, as determined by a central
adjudication panel. Secondary and exploratory endpoints included hemoglobin, platelet, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), and spleen size improvements, and best overall response per International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria. Adverse events (AEs), serious AEs, and infusion-related reactions (IRRs) were recorded.

In Stage 2, 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. For full details of patient disposition, see Supplementary Figure S2. Baseline characteristics are summarized in Supplementary Table S1. The patient population had 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 baseline hemoglobin <100 g/L and 39.2% were red blood cell (RBC) transfusion dependent at baseline. Overall, 60.8% of patients had severe thrombocytopenia (platelets ≤50×10⁹/L), and 15.5% were platelet transfusion dependent at baseline.

In total, 28/97 patients (28.9%; 95% CI: 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 the European Consensus/WHO 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 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 RBC (PRBC) and platelet transfusion requirements and changes in platelet count are shown in Figure 1C and D. During the combined main phase and OLE, of the 15 patients with hemoglobin improvement, 8 (53%) had a BM response, and of the 37 patients with platelet improvement, 12 (32%) had a BM response (Figure 2). The duration of hemoglobin and platelet improvement among BM responders and non-responders is shown in Figure 2. Hemoglobin and platelet trajectories among BM responders and non-responders indicated relatively stable
hemoglobin and platelet levels over time in most patients. MPN- SAF TSS, spleen size, and best overall response per IWG-MRT criteria were evaluated across the combined main phase and OLE. Of evaluable patients, 32/94 (34%) had a ≥50% reduction in MPN- SAF TSS versus baseline at any time, 32/76 (42.1%) had any reduction in spleen volume at any time, and no patients had ≥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 AE (TEAE). In total, 77 serious TEAEs were reported in 39 patients, most frequently pneumonia (n=5; 5.2%) and epistaxis (n=3; 3.1%). Because of the small sample size and the low number of serious TEAEs, conclusions cannot be drawn regarding potential differences in the safety of different doses. Of the 15 fatal TEAEs (15.5%), one death was reported as related to study treatment; however, the investigator reported that the death was likely related to underlying thrombocytopenia due to MF, leading to a bleed. IRRs were reported in four (4.1%) patients; all IRR events were grade 1/2, except for grade 3 urticaria in one patient in Group 2. No new safety signals were reported during the OLE phase.

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 ±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 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 RBC transfusion dependence in various patient populations have been observed previously with other treatments; however, to our knowledge, only pacritinib has achieved notable results in patients with severe thrombocytopenia (platelet counts ≤50×10^9/L) and RBC transfusion dependence, albeit in the setting of limited or no prior JAK inhibitor exposure.\(^1\) Ruxolitinib discontinuation leads to poor prognosis and progressive worsening of anemia and thrombocytopenia.\(^1\),\(^2\) 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 zinzentraxin alfa are important because analysis of recent momelotinib trials suggests that hematologic improvement may serve as a surrogate endpoint predictive of improved overall survival.\(^1\) The current study did not assess overall survival and patient numbers were small; however, some patients with high-risk features and poor prognosis following ruxolitinib discontinuation had long treatment duration (median 7.5 [0.2-46.7] months). Also, transfusion dependence is burdensome to patients; therefore, reductions reported in PRBC and platelet transfusions in transfusion-dependent patients are also important from a QoL perspective.\(^3\)

Limitations of this study include the lack of a placebo arm, a heterogeneous patient population, and a small sample size, which make it difficult to interpret trends. The advanced disease stage and negative prognostic factors may have also reduced the likelihood of observing effects on fibrosis. Finally, it is unclear if a 35% threshold for reduction in spleen size is appropriate in the relapsed/refractory setting of patients with advanced disease, and several studies have achieved little or no ≥35% spleen volume reduction in this setting.\(^1\)

In summary, zinzentraxin alfa treatment showed signs of clinical activity, including improvement in fibrosis, disease-related hematologic parameters, and symptoms, in difficult-to-treat patients with MF who were ineligible for, intolerant to, 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 for 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.
REFERENCES


### TABLES

**Table 1. Summary of TEAEs in the safety population during the main phase, by cohort and overall.**

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

<sup>a</sup>Group 1 was treated with zinpentraxin alfa 0.3 mg/kg Q4W.

<sup>b</sup>Group 2 was treated with zinpentraxin alfa 3 mg/kg Q4W.

<sup>c</sup>Group 3 was treated with zinpentraxin alfa 10 mg/kg Q4W.

<sup>d</sup>Fatal TEAEs 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).

AE: adverse event; Q4W: every 4 weeks; TEAE: treatment-emergent adverse event.
FIGURE LEGENDS

Figure 1. Efficacy outcomes in the main study phase. (A) BMRR by central review at any time, (B) best shifts in BM fibrosis during the main study phase, and (C) hemoglobin and (D) platelet improvements during the main study phase.

*Two patients were missing baseline BM fibrosis data.

BMRR was defined as the percentage of patients with a reduction from baseline in BM fibrosis by $\geq 1$ grade per European Consensus criteria.10

The primary endpoint of BMRR was analyzed using logistic regression, with BM response at any time as the response variable and treatment group as 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, used an adjusted two-sided 0.025 level of significance. 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 0.05 level of significance.

Baseline PRBC transfusion dependency was defined as $\geq 2$ units PRBC every 4 weeks for 12 weeks prior to Cycle 1 Day 1, regardless of baseline hemoglobin level.

Baseline platelet transfusion dependency was defined as $\geq 2$ platelet transfusions in any 12 weeks prior to Cycle 1 Day 1, regardless of baseline platelet level.

BM: bone marrow; BMRR: bone marrow response rate; PRBC: packed red blood cell.

Figure 2. Duration of hemoglobin and platelet improvements. Duration of (A) hemoglobin improvement and (B) platelet improvement during the main study phase and OLE 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; patient IDs are shown as consecutive numbers, with patients who had both hemoglobin and platelet improvements in red text. “BM” indicates patients who had a BM response.

Hemoglobin improvement for RBC transfusion-dependent patients was defined as either an absence of any PRBC transfusion during any consecutive 12-week interval with hemoglobin level of $\geq 80$ g/L, or a $\geq 50\%$ reduction from baseline in PRBC transfusions for 12 consecutive weeks with hemoglobin level of $\geq 80$ g/L. For RBC transfusion-independent patients, improvement was defined as a $\geq 10$ 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 BM fibrosis by $\geq 1$ grade per European Consensus criteria.

BM: bone marrow; Hgb: hemoglobin; OLE: open-label extension; PRBC: packed red blood cell; RBC: red blood cell.
SUPPLEMENTARY MATERIAL

for

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

Srdan Verstovsek, Moshe Talpaz, Martha Wadleigh, Alessandro Isidori, Peter te Boekhorst, Michael R Savona, Prithviraj Bose, Olga Pozdnyakova, Ruben Mesa, Tarec C El-Galaly, Jen O'Sullivan, Katia Gamel, Brian Higgins, Sudhakar Katakam, Boyan Todorov, Kerstin Trunzer, Claire N Harrison
Stage 2 was a randomized, double-blind phase II study to determine the efficacy and safety of three different doses of zinpentraxin alfa in patients with PMF and post ET/PV MF who had discontinued or were not eligible for ruxolitinib treatment. Each patient participated in the main study phase for approximately 44 weeks, comprising a 4-week screening period, a treatment period of 9×4-week cycles, and an end of study visit 4 weeks after the end of the last cycle. After completion of 9 cycles, patients could continue with zinpentraxin alfa at 10 mg/kg in the OLE in the absence of disease progression or toxicity warranting discontinuation of therapy.

*Patients in the main phase of Stage 2 received additional loading doses of the assigned strength of zinpentraxin alfa at Days 3 and 5 during the first cycle.

†Patients in the OLE of Stage 2 received additional loading doses of 10 mg/kg zinpentraxin alfa at Days 3 and 5 of their first cycle after entering the OLE.

ET: essential thrombocythemia; MF: myelofibrosis; OLE: open-label extension; PMF: primary MF; PV: polycythemia vera; Q4W: every 4 weeks; R: randomized.
Supplementary Figure S2. Patient disposition.

96 patients enrolled
1 patient not treated (10 mg/kg cohort)
97 patients received study treatment

0.3 mg/kg (n=33)
- 20 patients completed main study phase
  - AE: 8 (46.2%)
  - Informed consent withdrawn: 4 (30.8%)
  - Lack of efficacy: 1 (7.7%)
  - Other: 2 (15.4%)

3 mg/kg (n=32)
- 16 patients completed main study phase
  - Progressive disease: 6 (37.5%)
  - AE: 5 (31.3%)
  - Informed consent withdrawn: 3 (18.8%)
  - Lack of efficacy: 2 (12.5%)

10 mg/kg (n=32)
- 18 patients discontinued
  - AE: 7 (38.9%)
  - Progressive disease: 6 (33.3%)
  - Informed consent withdrawn: 3 (16.7%)
  - Exclusion criterion: 1 (5.6%)
  - Other: 1 (5.6%)

Overall (n=97)
- 47 patients discontinued
  - AE: 18 (38.3%)
  - Progressive disease: 12 (25.5%)
  - Informed consent withdrawn: 10 (21.3%)
  - Lack of efficacy: 3 (6.4%)
  - Exclusion criterion: 1 (2.1%)
  - Other: 3 (6.4%)

19 patients entered the OLE
- Reasons for end of OLE:
  - Lack of efficacy: 8 (42.1%)
  - Progressive disease: 4 (21.1%)
  - AE: 2 (10.5%)
  - Informed consent withdrawn: 2 (10.5%)
  - Other: 3 (15.8%)

15 patients entered the OLE
- Reasons for end of OLE:
  - Lack of efficacy: 7 (46.7%)
  - Informed consent withdrawn: 4 (26.7%)
  - Progressive disease: 2 (13.3%)
  - AE: 1 (6.7%)
  - Lost to follow-up: 1 (6.7%)

14 patients entered the OLE
- Reasons for end of OLE:
  - AE: 5 (35.7%)
  - Lack of efficacy: 4 (28.6%)
  - Progressive disease: 3 (21.4%)
  - Informed consent withdrawn: 2 (14.3%)

48 patients entered the OLE
- Reasons for end of OLE:
  - Lack of efficacy: 19 (39.6%)
  - Progressive disease: 9 (18.8%)
  - AE: 8 (16.7%)
  - Informed consent withdrawn: 8 (16.7%)
  - Lost to follow-up: 1 (2.1%)
  - Other: 3 (6.3%)

AE: adverse event; OLE: open-label extension.
Supplementary Table S1. Key baseline demographics and disease characteristics in the all-treated population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1&lt;sup&gt;a&lt;/sup&gt; (n=33)</th>
<th>Group 2&lt;sup&gt;b&lt;/sup&gt; (n=32)</th>
<th>Group 3&lt;sup&gt;c&lt;/sup&gt; (n=32)</th>
<th>Overall (N=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age, years</td>
<td>70.0 (52-82)</td>
<td>71.0 (54-79)</td>
<td>69.0 (49-87)</td>
<td>70.0 (49-87)</td>
</tr>
<tr>
<td>Type of MF, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary MF</td>
<td>20 (60.6)</td>
<td>20 (62.5)</td>
<td>26 (81.3)</td>
<td>66 (68.0)</td>
</tr>
<tr>
<td>Post-PV MF</td>
<td>8 (24.2)</td>
<td>6 (18.8)</td>
<td>2 (6.3)</td>
<td>16 (16.5)</td>
</tr>
<tr>
<td>Post-ET MF</td>
<td>5 (15.2)</td>
<td>6 (18.8)</td>
<td>4 (12.5)</td>
<td>15 (15.5)</td>
</tr>
<tr>
<td>Mean (SD) time since diagnosis, years</td>
<td>3.48 (5.90)</td>
<td>3.28 (2.49)</td>
<td>4.69 (5.06)</td>
<td>3.81 (4.72)</td>
</tr>
<tr>
<td>Risk group (IWG-MRT DIPSS), n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>5 (15.2)</td>
<td>6 (18.8)</td>
<td>3 (9.4)</td>
<td>14 (14.4)</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>24 (72.7)</td>
<td>22 (68.8)</td>
<td>20 (62.5)</td>
<td>66 (68.0)</td>
</tr>
<tr>
<td>High</td>
<td>4 (12.1)</td>
<td>4 (12.5)</td>
<td>9 (28.1)</td>
<td>17 (17.5)</td>
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<tr>
<td>Baseline central BM fibrosis grade,&lt;sup&gt;d&lt;/sup&gt; n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF – 0</td>
<td>0</td>
<td>1 (3.1)</td>
<td>0</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>MF – 1</td>
<td>2 (6.1)</td>
<td>2 (6.3)</td>
<td>1 (3.1)</td>
<td>5 (5.2)</td>
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<tr>
<td>MF – 2</td>
<td>12 (36.4)</td>
<td>6 (18.8)</td>
<td>10 (31.3)</td>
<td>28 (28.9)</td>
</tr>
<tr>
<td>MF – 3</td>
<td>19 (57.6)</td>
<td>21 (65.6)</td>
<td>21 (65.6)</td>
<td>61 (62.9)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
<td>2 (6.3)</td>
<td>0</td>
<td>2 (2.1)</td>
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<tr>
<td>Previously treated with ruxolitinib, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (75.8)</td>
<td>27 (84.4)</td>
<td>22 (68.8)</td>
<td>74 (76.3)</td>
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<tr>
<td>No</td>
<td>8 (24.2)</td>
<td>5 (15.6)</td>
<td>10 (31.3)</td>
<td>23 (23.7)</td>
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<tr>
<td>Intolerant to ruxolitinib, n (%)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>n</td>
<td>25</td>
<td>27</td>
<td>22</td>
<td>74</td>
</tr>
<tr>
<td>Yes</td>
<td>18 (72.0)</td>
<td>20 (74.1)</td>
<td>10 (45.5)</td>
<td>48 (64.9)</td>
</tr>
<tr>
<td>No</td>
<td>7 (28.0)</td>
<td>7 (25.9)</td>
<td>12 (54.5)</td>
<td>26 (35.1)</td>
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<tr>
<td>RBC transfusion dependency,&lt;sup&gt;e&lt;/sup&gt; n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>14 (42.4)</td>
<td>11 (34.4)</td>
<td>13 (40.6)</td>
<td>38 (39.2)</td>
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<tr>
<td>Independent</td>
<td>19 (57.6)</td>
<td>21 (65.6)</td>
<td>19 (59.4)</td>
<td>59 (60.8)</td>
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<tr>
<td>Hemoglobin at baseline, n (%)</td>
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<td></td>
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<tr>
<td>&lt;100 g/L</td>
<td>26 (78.8)</td>
<td>27 (84.4)</td>
<td>28 (87.5)</td>
<td>81 (83.5)</td>
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<tr>
<td>≥100 g/L</td>
<td>7 (21.2)</td>
<td>5 (15.6)</td>
<td>4 (12.5)</td>
<td>16 (16.5)</td>
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</tbody>
</table>
**Zinpentraxin alfa in MF: Phase II Stage 2**

<table>
<thead>
<tr>
<th>Platelet transfusion dependency, n (%)</th>
<th>Dependent</th>
<th>Independent</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3 (9.1)</td>
<td>10 (31.3)</td>
</tr>
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<td></td>
<td>2 (6.3)</td>
<td>82 (84.5)</td>
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</table>

<table>
<thead>
<tr>
<th>Platelet count at baseline, n (%)</th>
<th>≤25×10⁹/L</th>
<th>&gt;25×10⁹/L to ≤50×10⁹/L</th>
<th>&gt;50×10⁹/L to ≤100×10⁹/L</th>
<th>&gt;100×10⁹/L</th>
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<tbody>
<tr>
<td></td>
<td>30 (90.9)</td>
<td>10 (31.3)</td>
<td>10 (31.3)</td>
<td>5 (15.2)</td>
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<tr>
<td></td>
<td>30 (93.8)</td>
<td>10 (31.3)</td>
<td>10 (31.3)</td>
<td>7 (21.2)</td>
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<tr>
<td></td>
<td>22 (68.8)</td>
<td>8 (25.0)</td>
<td>4 (12.5)</td>
<td>10 (31.3)</td>
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<tr>
<td></td>
<td>82 (84.5)</td>
<td>29 (29.9)</td>
<td>13 (13.4)</td>
<td>25 (25.8)</td>
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</table>

<table>
<thead>
<tr>
<th>Driver mutation, n (%)</th>
<th>n</th>
<th>Yes</th>
<th>No</th>
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<td></td>
<td>26</td>
<td>24 (92.3)</td>
<td>2 (7.7)</td>
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<td>25</td>
<td>22 (88.0)</td>
<td>3 (12.0)</td>
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<td></td>
<td>79</td>
<td>71 (89.9)</td>
<td>8 (10.1)</td>
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</table>

<table>
<thead>
<tr>
<th>HMR mutation status, n (%)</th>
<th>n</th>
<th>≥1 high-risk mutation</th>
<th>No high-risk mutation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>26</td>
<td>13 (50.0)</td>
<td>13 (50.0)</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>12 (48.0)</td>
<td>13 (52.0)</td>
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<td>28</td>
<td>14 (50.0)</td>
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<tr>
<td></td>
<td>79</td>
<td>39 (49.4)</td>
<td>40 (50.6)</td>
</tr>
</tbody>
</table>

*Group 1 was treated with zinpentraxin alfa 0.3 mg/kg Q4W.*

*Group 2 was treated with zinpentraxin alfa 3 mg/kg Q4W.*

*Group 3 was treated with zinpentraxin alfa 10 mg/kg Q4W.*

*BM fibrosis grades according to World Health Organization criteria (as determined by central adjudication). Results were available for 95 patients. Local BM fibrosis grade was used to determine study eligibility.*

*Baseline PRBC transfusion dependency was defined as ≥2 units PRBC every 4 weeks for 12 weeks prior to Cycle 1 Day 1, regardless of baseline hemoglobin level.*

*Baseline platelet transfusion dependency was defined as ≥2 platelet transfusions in any 12 weeks prior to Cycle 1 Day 1, regardless of baseline platelet level.*

*Results from at least one timepoint were available for 79 patients. Driver mutation status was derived irrespective of the timepoint the sample was taken.*

*High-risk mutation was defined as having mutations in the following genes: ASXL1, IDH1, IDH2, SRSF2, EZH2 or U2AF1 Q157 mutation.*
Zinpentraxin alfa in MF: Phase II Stage 2