Hepcidin Suppression by Momelotinib Is Associated With Increased Iron Availability and Erythropoiesis in Transfusion-Dependent Myelofibrosis Patients

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INTRODUCTION

Patients develop anemia as a result of organ fibrosis, development, progression, and/or its treatment, including with cytokines and other experimental Janus kinase (JAK) inhibitors.

Key Inclusion Criteria

- Age ≥18 years with diagnosis of primary MF (PMF), post-polycythemia vera MF (post-PV MF), or post-essential thrombocythemia MF (post-ET MF) and requiring RBC therapy (at the opinion of the investigator)
- Patellar spindle or intermediate-malignancy within 3 months prior to the first dose of MMB
- Prior treatment with JAK inhibitor within 21 days of the planned first dose of MMB
- Free of active infection (as per institutional standards) and previous ≤2 antecedent anemia in a rodent model

In this translational biology study, we determined the impact of MMB on plasma hepcidin, markers of iron metabolism, and clinical outcomes in patients with myelofibrosis.

OBJECTIVES

- Primary objective: determine the hepcidin suppression response rate for transfusion independence (TD) subjects with MF treated with MMB
- Secondary objectives:
  - Evaluate baseline levels and changes in markers of iron metabolism
  - Evaluate baseline levels and changes in markers of hepcidin

METHODS

- Patients with primary or secondary myelofibrosis were randomized in a 1:1 ratio to MMB or no treatment.
- Key exclusion criteria:
  - Prior treatment with MMB or JAK inhibitor within 21 days of the planned first dose of MMB
  - History of active infection (as per institutional standards) and previous ≤2 antecedent anemia in a rodent model
- Transfusion Independence Response (TI-R), transfusion independence responders; TI-NR, transfusion independence non-responders
- By Week 24, 14 (34.1%, 90% CI: 22.0–48.1%) patients had a TI-R and 39.0% had no RBC transfusion for ≥8 weeks at any time on study
- Serum iron peaked at Week 2 (Figure 2A) and thereafter declined, consistent with the restoration of transfusion independence and iron homeostasis
- CRP also decreased a median 54.8% from Baseline, indicating overall reduced inflammation and improved erythropoiesis

CONCLUSIONS

- MMB treatment elicited a significant rate of transfusion independence in this advanced, TD population (34.1% for ≥8 weeks at any time on study).
- These data are consistent with the optimized and differentiated activity of MMB against JAK1, JAK2, and ACVR1 and leading to decreased plasma hepcidin, improved iron homeostasis and clinical outcomes.
- Rates of TI-R were similar to those for TD MF patients in other MMB trials
- Safety was consistent with previous studies of MMB in MF
- Overall, the study suggests that modulation of hepcidin by MMB is sufficient to boost erythropoiesis, particularly in MF patients with lower baseline inflammation and greater erythropoietic potential.