Myelofibrosis (MF)
A clonal hematopoietic stem cell disorder defined by progressive bone marrow fibrosis, the result of the response to inflammatory cytokines produced by aberrant clonal myeloid progenitor cells.

Drivers of Disease in MF: Aberrant JAK1, JAK2 and ACVR1 Signaling
- Inflammation and aberrant cytokine signaling producing debilitating constitutional symptoms.
- Clonal proliferation leading to extramedullary hematopoiesis and burdensome splenomegaly.
- Aberrant activation of hepcidin transcription via hyperactivated ACVR1 signaling resulting in profound functional iron deficiency and an iron restricted anemia.

Momelotinib: An Inhibitor of JAK1, JAK2 and ACVR1

Momelotinib: Unique MOA Potentially Addresses the Key Needs in MF
- Momelotinib’s unique mechanism of action due to JAK1, JAK2 and ACVR1 inhibition, has been associated with improvements in the anemia of myelofibrosis, as well as constitutional symptoms and splenomegaly.
- Momelotinib has been shown to decrease aberrant inflammatory cytokine signaling, mutant hematopoietic stem cell proliferation and red blood cell (RBC) sequestration, consistent with inhibition of JAK1, JAK2 and the downstream JAK-STAT pathway.
- In addition, through differentiated inhibition of ACVR1, a notable decrease in circulating hepcidin occurs. Hepcidin is often markedly elevated in MF and contributes to iron restricted anemia. By lowering hepcidin, an increase in serum iron occurs, resulting in clinically relevant increases in both hemoglobin and RBCs as more serum iron is available for erythropoiesis.
- Data from more than 820 clinical trial patients with MF suggest that momelotinib can markedly improve constitutional symptoms and splenomegaly while also substantially addressing the chronic anemia associated with this condition.
Role of Hepcidin in Anemia of MF

Anemia of inflammation, a major contributor to the anemia of MF, is a dynamic complex process that produces an iron restricted anemia and is characterized by increased hepcidin levels, increased inflammatory cytokines, decreased serum iron and decreased hemoglobin.

- Hepcidin maintains systemic iron homeostasis. Elevated hepcidin levels result in iron sequestration causing a severe functional iron deficiency anemia.
- Chronically activated ACVR1 signaling leads to markedly elevated hepcidin levels in MF.
- High hepcidin correlates with severe anemia and poor survival in MF.
- Inhibition of ACVR1 by momelotinib has been seen to acutely and chronically lower hepcidin levels which can potentially improve anemia and transfusion dependency.

Momelotinib's Impact on Anemia of MF:
Reducing Hepcidin Restores Red Blood Cell Production

Data from a momelotinib Phase 2 clinical translational biology study in transfusion dependent patients (GS-US-352-1672 study, N=41) demonstrated:

- Acute and chronic decrease in plasma hepcidin.
- Significant rate of conversion to transfusion independence (41%).
- Decreased transfusion burden in patients who maintained a transfusion requirement.
- Improved iron homeostasis.
- Increased erythropoiesis.
- At every study visit, median blood hepcidin decreased 6 hours after dosing with momelotinib.
- Overall trend to reduced hepcidin over time.
- Reinforces ACVR1i mechanism of action.

Hepcidin Levels

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<tr>
<th>Visit/Timepoint</th>
<th>Median Actual Value (Q1, Q3)</th>
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<td>Baseline</td>
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<td>Enrollment</td>
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References: