Introduction

- JAK inhibitors are the standard of care treatment for myelofibrosis (MF), however, they are limited by cytopenias due to disease and treatment.
- JAK inhibitors lack disease modifying effects.
- Therapies with unique mechanisms of action are needed for patients whose disease has progressed, or are unable to tolerate JAK inhibitors.

Inhibition of PIM1 in Myelofibrosis

- Provisional integration site of moloney murine leukemia virus viruses 1 (PIM1) is a proto-oncogene regulated in part through JAK/STAT, NF-kappa B, and ERG pathways.
- PIM1 kinase expression was significantly increased in bone marrow and PBMC samples from patients with MF.

In preclinical MF mouse models:
- PIM1 knockout prevented MF progression, but PIM2 knockout showed no effect, and (c) PIM1 knockout does not cause platelet count decrease.

TP-3654 Showed Reduction in Spleen Size and Bone Marrow Fibrosis in Myelofibrosis Mouse Models

- In preclinical studies in MPLW515L and JAK2V617F MF mouse models, TP-3654 alone or in combination with ruxolitinib treatment lead to reduction of splenic size and resolution of bone marrow fibrosis vs ruxolitinib alone.

Study Design

**Ongoing global phase 1/2 study**

**Study Population**

- Primary, Post-PV, Post-ET MF
- Relapsed, refractory, intolerant, or ineligible for JAK inhibitors
- DSFS intermediate or high risk
- Platelet count ≥ 25 x 10⁹/L
- ECOG 0-2
- Spleen volume ≥ 400 cm³
- ≤ 2 symptoms by MF-SAF v4.0
- ≥ 25 x 10⁹/L Platelet count

**Treatment**

- Phase 1 Dose Escalation
  - Guided by the BLRM
  - 400 mg QD - 1440 mg QD
- Phase 2 Dose Escalation
  - Recommended Dose: 400 mg QD

**Endpoints**

- Primary: Safety and tolerability
- Secondary: Primary efficacy
- Non-hematological

**Phase 1**

- Phase 1 Dose Escalation
  - Guided by the BLRM
- 400 mg QD - 1440 mg QD

- Phase 2 Dose Escalation
  - Recommended Dose: 400 mg QD

**Phase 2**

- Primary: Safety and tolerability
- Secondary: Efficacy
- Non-hematological

**Preclinical Studies**

- PIM1 kinase expression was significantly increased in bone marrow and PBMC samples from patients with MF.

**TP-3654**

- An oral investigational selective PIM1 kinase inhibitor
- In preclinical MF mouse models:
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**Results**

**Patient Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69 (51-77)</td>
</tr>
<tr>
<td>Splenome, cm³</td>
<td>12.2 (6-25)</td>
</tr>
<tr>
<td>Spleen volume, cm³</td>
<td>1055.5 cm³ (287-4408)</td>
</tr>
<tr>
<td>Total Symptom Score (MF-SAF v4.0)</td>
<td>19 (9-42)</td>
</tr>
<tr>
<td>Platelet count, ×10⁹/L</td>
<td>126 ×10⁹/L (84-520)</td>
</tr>
<tr>
<td>Hemoglobin, mg/dL</td>
<td>9.7 g/dL (5.9-13.7)</td>
</tr>
</tbody>
</table>

**Response to JAK Inhibitors**

- Primary refractory
- Loss of response
- Intolerance
- Grade 3

**Hematological**

- Response to JAK Inhibitors
- Primary refractory
- Loss of response
- Intolerance

**Conclusions**

- TP-3654 is an oral investigational selective PIM1 kinase inhibitor
- TP-3654 appears to be well tolerated, no DLT to date, and the most common AE are Grade 1 and 2 GI toxicities.

**Cytokine Reduction and TSS Improvement**

- Broad cytokine reduction observed as early as Week 4 from initial dose cohorts
- Cytokines associated with MF (IL-6, IL-10, IL-12, IL-18, TGF-b, EGFR, Ferritin, GRO-a, IL-1RA, MMP-9, PAI-1, RANTES, TIMP-1, TNFR-2, VCAM-1) show reduction after treatment
- Cytokine reduction generally correlates with TSS reduction (week 12 presented on the right)

**TP-3654 Treatment Leads to Early Reduction in Cytokines**

- 10 evaluable patient on treatment ≥ 12 weeks
- Median spleen volume reduction -14%
- 2 of 10 patients have ≥ 35% SVR
- 6 of 10 patients have ≥ 50% TSS reduction

**Changes in Inflammatory Cytokines**

- No dose limiting toxicities (DLT) were observed.
- Maximum tolerated dose (MTD) not yet reached, enrollment is ongoing.

**Safety and Tolerability**

- 10 evaluable patient on treatment ≥ 12 weeks
- Median total symptom score (TSS) reduction -75%
- 8 of 15 patients are ongoing on treatment
- Reasons for treatment discontinuation include disease progression (7%), patient withdrawal (7%), physician decision (13%), and other (20%)

**Patient Disposition and Safety Summary**

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