Phase I/II Study of TP-3654, a Selective Oral PIM1 Kinase Inhibitor, in Patients with Myelofibrosis Previously Treated with or Ineligible for JAK Inhibitor Therapy

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Myelofibrosis: Background & Evolving Treatment Landscape

- JAK inhibitors, current standard of care treatment, are limited by thrombocytopenia, anemia, and lack of disease modifying effects\(^1\)
  - Most patients have either inadequate response, or eventually lose response to JAK inhibitors
  - Patients with cytopenia or who have progressed from JAK inhibitors have poor prognosis
  - Anemia and thrombocytopenia are common and prevents JAK inhibitor dose optimization
- Novel therapies with unique MOA are needed for MF patients who have progressed from JAK inhibitors and/or have cytopenia
- Evolving treatment landscape includes doublet combination regimen; however, are challenged by overlapping toxicities including cytopenia\(^2\)
- An ideal combination partner should have disease modifying effects and minimal cytopenia, in addition to spleen reduction and symptoms improvement

Background: PIM1 Kinase Signaling

- PIM1 is a proto-oncogene regulated in part through the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway.

- PIM1 kinase also has an essential role in cytokine-induced signal transduction by controlling transcription factors.

- Upregulation of PIM1 kinase leads to increased cytokines relevant to immune activation and fibrosis including RANTES and TGF-β.

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PIM1 Kinase: A Novel Target in MF

- PIM1 expression was shown to be significantly increased in MF patients’ bone marrow and PBMC samples

- PIM1 knockout was shown to prevent myelofibrosis progression, but PIM2 knockout has no effect in MF mouse models

- PIM1 knockout was shown not to cause platelet count decrease, while pan-PIM knockout resulted in thrombocytopenia in mice

- Novel therapies which selectively inhibit PIM1 kinase may provide disease-modifying benefits for MF patients while avoiding cytopenia adverse effects

4. Dutta et al. Leukemia 2021
5. An et al. JH&O, 2013
TP-3654: An Oral Selective PIM1 Inhibitor in Murine MPL\textsuperscript{W515L} MF Model

- ✓ Spleen Size Reduction
- ✓ Bone Marrow Fibrosis Reduction
- ✓ Overall Survival Increase

- Similar TP-3654 activity was observed in murine JAK2\textsuperscript{V617F} MF model\textsuperscript{4}

\*\*p<0.005
TP-3654 Phase I/II Study Design in MF

Key Eligibility
- DIPSS Intermediate-1, 2, or high-risk
- Platelet count $\geq 25 \times 10^9$/L
- ECOG $\leq 2$
- Splenomegaly (volume of $\geq 450$ cm$^3$)
- At least 2 symptoms by MF-SAF v4.0

Endpoints
- **Primary:**
  - Safety and tolerability
- **Secondary**
  - Spleen volume reduction
  - Total symptoms score reduction (MF-SAF v4.0)
  - Overall survival
  - Bone marrow fibrosis change
  - Pharmacokinetics
## TP-3654 Phase 1: Baseline Characteristics

### Patient Characteristics, n=9

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong>, median (range)</td>
<td>71 years (61 - 77)</td>
</tr>
<tr>
<td><strong>Spleen length</strong>, median (range)</td>
<td>12 cm (0 - 25)</td>
</tr>
<tr>
<td><strong>Spleen volume</strong>, median (range)</td>
<td>2231 cm³ (857 - 4407)</td>
</tr>
<tr>
<td><strong>Total Symptoms Score</strong>&lt;br&gt;(MF- SAF v4.0), median (range)</td>
<td>18 (4 - 62)</td>
</tr>
<tr>
<td><strong>Platelet count</strong>, median (range)</td>
<td>120 x10⁹/L (68 - 237)</td>
</tr>
<tr>
<td>≥ 100 x10⁹/L</td>
<td>6 (66%)</td>
</tr>
<tr>
<td>&lt; 100 x10⁹/L</td>
<td>3 (33%)</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong>, median (range)</td>
<td>10.1 g/dL (5.9 - 13.7)</td>
</tr>
<tr>
<td>≥ 10 g/dL</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>&lt; 10 g/dL</td>
<td>4 (44%)</td>
</tr>
<tr>
<td><strong>Transfusion dependent</strong></td>
<td>2 (22%)</td>
</tr>
</tbody>
</table>

### Disease Characteristics, n=9

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myelofibrosis subtypes</strong></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Post-PV</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Post-ET</td>
<td>1 (11%)</td>
</tr>
<tr>
<td><strong>DIPSS Risk Group</strong></td>
<td></td>
</tr>
<tr>
<td>Int-1</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Int-2</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>High</td>
<td>2 (22%)</td>
</tr>
<tr>
<td><strong>Driver Mutations</strong></td>
<td></td>
</tr>
<tr>
<td>JAK2V617F</td>
<td>7 (78%)</td>
</tr>
<tr>
<td>CALR</td>
<td>2 (22%)</td>
</tr>
<tr>
<td><strong>Prior Treatment</strong> n(%)&lt;br&gt;median duration (range)</td>
<td>9 (100%), 33 weeks (10 - 268)</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>2 (22%), 36 weeks (36 - 49)</td>
</tr>
<tr>
<td>Fedratinib</td>
<td></td>
</tr>
<tr>
<td><strong>Response to JAK Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Primary refractory</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Loss of response</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Intolerant</td>
<td>2 (22%)</td>
</tr>
</tbody>
</table>

Preliminary data as of 11-OCT-2022
No DLT or related serious AE.

The most common AEs are Grade 1 diarrhea, nausea, and vomiting, and transient resolving within 1-2 weeks.

Transient Grade 3 anemia and thrombocytopenia were observed in 1 patient.

No dose reduction or discontinuation due to AE.

*G3 Bilirubin and G3 Anemia from a patient with baseline G2 bilirubin and transfusion-dependent.
TP-3654: Stable Lab Values in the Dose Escalation with No Worsening of Blood Counts

*Platelet Count During Treatment*  
*Hemoglobin During Treatment*  
*Neutrophil During Treatment*

*N=9; Mean ± SD  

Preliminary data as of 11-OCT-2022
TP-3654: Best Spleen Volume Response in Dose Escalation

- 8 evaluable patients on treatment ≥ 12 weeks
- Baseline spleen volume median 2535 cm$^3$ (1189 to 4407)
- 6 of 8 have SVR
  - Median -11%
  - 5 of 8 patients have ≥ 10% SVR
  - 2 of 8 patients have ≥ 35% SVR

**Individual Patients**

- **Dose**
  - 480mg QD
  - 720mg QD
  - 360mg BID
  - 480mg BID
  - 720mg BID

**Response to JAK Inhibitor:**
- $\times$ = Primary Refractory
- $\star$ = Loss of Response
- $-$ = Intolerant

Preliminary data as of 11-OCT-2022
TP-3654: Best Symptoms Response in Dose Escalation

- MF-SAF v4.0 (Max TSS 70): Baseline symptom burden median 21 (4 to 62)
- 8 evaluable patients on treatment ≥ 12 weeks
- 7 of 8 have TSS reduction
  - Median -66%
  - 5 of 8 patients have ≥ 50% TSS reduction

Individual Patients

<table>
<thead>
<tr>
<th>Dose</th>
<th>480mg QD</th>
<th>720mg QD</th>
<th>360mg BID</th>
<th>480mg BID</th>
<th>720mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to JAK Inhibitor:</td>
<td>≠ Primary Refractory</td>
<td>≠ Loss of Response</td>
<td>≠ Intolerant</td>
<td></td>
<td></td>
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</tbody>
</table>

Preliminary data as of 11-OCT-2022
TP-3654: Duration of Treatment

- No discontinuation due to AE

Reasons for Discontinuation
- Physician Withdrawal (2)
- Progression (2)
- Patient Withdrawal (1)

Preliminary data as of 11-OCT-2022
TP-3654: PIM1 Inhibition Leads to Early Reduction in Cytokines

- Cytokine reduction observed as early as Week 4 from initial dose cohorts
- Cytokine reduction generally correlate with TSS reduction
- 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 change relative to baseline

<table>
<thead>
<tr>
<th>Cytokine change relative to baseline</th>
<th>&gt;0 - 25%</th>
<th>&gt;25 - 50%</th>
<th>&gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>&gt;0 - 25%</td>
<td>&gt;25 - 50%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>No change</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Preliminary data as of 11-OCT-2022
Conclusions: TP-3654 an Oral Selective PIM1 Inhibitor for MF

- PIM1, a novel target in MF, is a proto-oncogene regulated in part through the JAK / STAT, ERG and NF-kB pathways and modulates multiple downstream signaling pathways including induction of cytokines RANTES and TGF-B.

- PIM1 kinase inhibition leads to reduced bone marrow fibrosis, splenomegaly, and improved overall survival in MF mouse models with minimal effect on platelet count.

- **TP-3654 is an oral selective PIM1 kinase inhibitor**
  - Dose escalation is ongoing and TP-3654 appears to be well tolerated, no DLT to date, and the most common AE are Grade 1 GI toxicities that resolved in 1-2 weeks.
  - Preliminary signs of clinical activity include spleen volume reduction, symptom improvement, and broad cytokine reduction.

- Enrollment is ongoing as monotherapy and current data support the development of TP-3654 as potential partner combination with JAK inhibitors given preliminary activity signals observed and the lack of cytopenia.