A Phase I, First-in-Human, Open-Label, Dose Escalation, Safety, Pharmacokinetic, and Pharmacodynamic Study of Oral TP-3654 Administered Daily for 28 Days to Patients with Advanced Solid Tumors

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I. Background

TP-3654 is a second-generation oral inhibitor of Pim kinases (see Table 1): Pim-1 plays an important role in cancer, through its modulation of downstream JAK/STAT signaling as shown in Figure 1.

Figure 1: The Pim kinases are major effectors of JAK/STAT proliferative signaling downstream of multiple growth factors and cytokines, driving tumor cell survival and progression

Table 1: TP-3654 has selectivity toward Pim-1 kinase, and represents an improvement over its first-generation analogue with respect to selectivity and predicted safety

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (µM)</th>
<th>NEHER IC50 (µM)</th>
</tr>
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<tbody>
<tr>
<td>PIM1</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>PIM2</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>PIM3</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>TP-3654</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>PIMK1</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>Patch Clamp</td>
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<td>1000</td>
</tr>
</tbody>
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II. Study Design

One patient missed ≥ 3 doses in Cycle 1 and was replaced

Dosing size and volume determined to be limiting (12 capsules QD, Size 00; two patients discontinued for this reason without further AES), schedule changed to twice-daily

Current dose level, no patients enrolled as of cutoff

If clinically indicated, dose levels higher than 2400 mg may be investigated

The primary objective of this study is to determine the safety and tolerability of TP-3654 in patients with advanced solid tumors. Secondary objectives include the determination of a pharmacokinetic profile, clinical activity, and pharmacodynamic modulation of on-target markers to establish proof-of-mechanism. This multi-center and open-label Phase I study of TP-3654 in patients with metastatic solid tumor includes dose escalation as seen here following a 3+3 design and dose expansion

III. Results (Cutoff Date: April 17, 2020)

Figure 2: A) Pharmacokinetic profile of TP-3654 in subjects in Cohort 3 Day 1. B) Summary table of pharmacokinetic parameters in Cohorts 1-3. Values are averages of subjects in each cohort. Partial anti-tumor effects in preclinical solid tumor models were observed at approximately 1300 ng/ml. C) Modulation of BAD phosphorylation in PBMC from subjects in dose Cohorts 1-3. The height of the bar indicates the baseline level of phosphorylation. The green bars indicate a greater than 20% reduction in phosphorylation was observed during the first 24hr while red bars indicate less than 20% reduction. Modulation was more pronounced if phosphorylation was higher at baseline.

Figure 3: TP-3654-101 Patient Characteristics, N=13

Table 3: TP-3654-101 Clinical Activity in Patients

IV. Conclusions

- TP-3654 has been tolerated up to doses of 1440mg QD
- No dose-limiting toxicities have been observed
- Grade 3 adverse events were not treatment-related and not confined to a particular organ system. There have been no Grade 4 or Grade 5 adverse events thus far
- Treatment-related AEs are dominated by GI symptoms (nausea, vomiting and diarrhea) as well as limb spasms, paresthesia and rash. 6/13 (46%) of patients experienced Grade 2 GI toxicities
- Other treatment-related AEs include fatigue, hypocalcemia, CNS issues, and rash / alopecia
- Patient-driven issues with dosing volume (number of capsules) and size (00) informed the decision to move to twice-daily (BID) dosing (amendment in progress)
- Preliminary data from the TP-3654-101 study indicate clinical activity, with stable disease > 16 weeks seen in 3 patients (peritoneal cancer, sarccoma, and penile cancer) despite heavily-pre-treated, advanced disease (Table 3)
- 6 out of 13 patients have experienced a best response of stable disease in the dose escalation, and 4 patients have experienced a best response of stable disease (Table 4)
- TP-3654 demonstrates modulation of a downstream biological pathway (phosphorylation of BAD) within 24 hours of first dosing. Additional biomarker data are pending to evaluate the impact on the Pim kinase pathway

NEXT STEPS

- Continue dose escalation with BID schedule to determine a Maximum Tolerated Dose and Recommended Phase 2 Dose
- A Phase 1 trial (BBI-TP-3654-102, NCT01248618) in myelofibrosis is currently enrolling, based on the roles of Pim-1 and Pim-2 in this indication and supportive preclinical data. Data from TP-3654-101 will inform the progression of this trial

Data Extract 17APR20: t_14_01_05_bl.sas, t_14_01_04_dm.sas
Data Extract 17APR20: t_14_03_01_03b_ae.sas
Data Extract 17APR20:Patient Profiles