Phase 1 First-in-Human Study of Programmed Cell Death Receptor-1 (PD-1) Inhibitor Monoclonal Antibody (mAb) JTX-4014 in Adult Subjects with Advanced Refractory Solid Tumor Malignancies

**Background**

JTX-4014 is a fully human mAb containing a bi-identical immunoglobulin gamma 4 (IgG4) heavy and two identical lambda (kappa) light chains, that specifically binds to PD-1 and is designed to augment antitumor T cell activity by blocking the interaction of PD-1 with its ligands, PD-L1 and PD-L2. The desired mechanism of action of JTX-4014 is to block the interaction of PD-1 with its ligands, PD-L1 and PD-L2, and augment T cell functionality through enhanced antitumor T cell activity. Therefore, JTX-4014 is a fully human IgG4 and has a singlingleptide structure. JTX-4014 has been developed as an agent to be used either as a monotherapy or in combination with other treatments for the treatment of cancer in which inhibition of PD-1 is beneficial. The clinical development of JTX-4014 in patients with advanced solid tumors demonstrates lack of target markdown in pre-clinical studies, as well as cross-resistance to both immunomodulators and PD-1 inhibitors.

JTX-4014 is being developed as an agent to be used either as a monotherapy or in combination with other treatments for the treatment of cancer in which inhibition of PD-1 is beneficial. The clinical development of JTX-4014 in patients with advanced solid tumors demonstrates lack of target markdown in pre-clinical studies, as well as cross-resistance to both immunomodulators and PD-1 inhibitors.

**Objectives**

- **Primary Objectives**
  - Evaluate the efficacy and tolerability of JTX-4014.
  - Determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D).

- **Secondary Objectives**
  - Evaluate for pharmacokinetics (PK) of JTX-4014.
  - Evaluate optimal duration of therapy after JTX-4014.

- **Exploratory Objectives**
  - Evaluate the PK of JTX-4014 according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (investigator assessed).

**Key Inclusion/Exclusion**

- **Inclusion Criteria**
  - Age 18-65 yrs.
  - Histologically or cytologically confirmed advanced solid tumor that is refractory or intolerable to at least one prior line of therapy with a better standard treatment option.
  - No concurrent or concomitant treatment with other systemic treatments within 14 days of starting JTX-4014.
  - Women not pregnant or lactating.
  - No requirement for selection based on PD-L1 expression.
  - No history of immune-mediated conditions.
  - No symptomatic or untreated brain metastases.
  - Adequate renal, hepatic, and bone marrow function.

- **Exclusion Criteria**
  - Patients with prior malignancy.
  - Patients with autoimmune diseases.
  - Patients who have received prior immune checkpoint inhibitors.

**Trial Design**

- **Standard 3+3 design** with dose escalation after review of at least 3 subjects in each cohort.
- **Clinical endpoints**:
  - DLT period: up to 14 days.
  - 21 day cycle.
  - Safety data:
  - DLT period: first 21 day cycle.

**Results**

**Table 1: Subject Demographics**

<table>
<thead>
<tr>
<th>Race, n (%)</th>
<th>White</th>
<th>Black</th>
<th>Asian</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=18 (%</td>
<td>61.54%</td>
<td>12.99%</td>
<td>12.99%</td>
<td>12.91%</td>
</tr>
</tbody>
</table>

**Table 2: Subject Tumor Types**

**Figure 1: Tumor Types**

**Figure 2: Safety Evaluation**

- **Grade 3/4 Adverse Events**
  - **Diarrhea**: 2 (11.1%)
  - **Fatigue**: 1 (5.6%)
  - **Arthralgia**: 1 (5.6%)
  - **Nausea**: 1 (5.6%)

- **Related Treatment Emergent Adverse Events**
  - **Diarrhea**: 1 (5.6%)
  - **Fatigue**: 1 (5.6%)
  - **Arthralgia**: 1 (5.6%)

**Table 3: Pharmacokinetics of JTX-4014**

**Figure 3: Pharmacokinetics**

**Figure 4: Toxicity and Response**

**Conclusion**

- JTX-4014 is an active PD-1 inhibitor; safety data was safe and well tolerated in this Phase 1 study. There were no deaths or DLTs occurring in the study. The only grade 3 adverse event was pneumonitis, which occurred after the second dose at 600 mg QW.
- Antitumor activity was observed in the difficult to treat lesions in patients with: 1) Complete Response (CR) or PR at 9 weeks and 18 weeks.
- 2) Partial Response (confirmed).
- 3) Stable Disease (SD) less than or equal to 10%.
- 4) Disease Control Rate - B16 (MHK).
- JTX-4014 has a typical IgG4 profile with linear PK.
- Recommended Phase 2 dose is either 600 mg QW or 800 mg Q3W.

**Figure 5: Overview of JTX-4014 Phase 1 Study**