**TD-1211 Demonstrates Tolerability and Clinical Activity Following Multiple Treatment Administration Strategies in Patients with Opioid-Induced Constipation**

**Neil Singla**, 1 Daniel Canafax2, Angela Kang2, Yu-Ping Li2, Ullrich Schwertschlag2, Lynn Webster3, and Ross Vickery2

1 Lotus Clinical Research, Inc., Pasadena, CA; 2 Theravance, Inc., South San Francisco, CA; 3 Lifetree Clinical Research, Inc., Salt Lake City, UT

**Poster 376**

**APS2013, New Orleans, LA**

**nvickery@theravance.com**

---

**Introduction**

- Opioid analgesics such as morphine continue to play a critical role in chronic cancer and non-cancer pain control. Despite their effectiveness, opioids have significant drawbacks, notably the development of analgesic tolerance and physical dependence, sedation, respiratory depression, and bowel dysfunction.

- Opioid-induced constipation (OIC) is common, affecting up to 80% of patients receiving opioids for chronic non-cancer pain.

- TD-1211 is an investigational, peripherally selective, mu-opioid receptor antagonist designed to alleviate gastrointestinal side effects of opioid therapy without affecting analgesia.

- TD-1211 was assessed in a Phase 2, single-blind exploratory study in 95 adult patients with OIC.

- The safety and tolerability of various doses, dosing strategies and dose escalations of TD-1211, as well as efficacy results, from this study are reported here.

**Methods**

- A single-blind, multi-center, six-cohort study was conducted in chronic non-cancer pain patients with OIC, defined as ≥3 spontaneous bowel movements (SBMs) per week for 2-week baseline period and at least one additional symptom of constipation in at least 25% of the bowel movements.

- The first four cohorts received an oral dose of TD-1211 5mg once daily for either 4 days (cohorts 1 and 2) or 2 days (cohorts 3 and 4), followed by an increase in daily dose to either 10mg or 15mg for two weeks. Cohort 5 received 2mg once daily and cohort 6 received 2.5mg qID for two weeks without dose escalation (Figure 1).

- For at least 14 days prior to Day 1, patients were on a stable chronic opioid regimen, with a total daily dose of ≥30mg morphine equivalent units (MEU).

- Patients were required to stop laxatives and bowel regimens, except protocol-permitted rescue bisacodyl use, throughout the study.

- Electronic diaries collected frequency, timing, and symptoms of bowel movement, use of laxatives and opioids, and daily pain scores.

- The primary study objective was to evaluate the safety and tolerability of TD-1211 5mg once daily as an initiation dose, for 4 or 2 days, escalated to 10mg or 15mg once daily as maintenance therapy for 2 weeks.

- Additional study objectives were to examine the tolerability and effects of TD-1211 2mg qID and a TD-1211 2.5mg qID dose administered for two weeks, and to assess the efficacy of TD-1211 10mg and 15mg doses.

- The primary study objective was to evaluate the safety and tolerability of TD-1211 5mg once daily as an initiation dose, for 4 or 2 days, escalated to 10mg or 15mg once daily as maintenance therapy for 2 weeks.

- Additional study objectives were to examine the tolerability and effects of TD-1211 2mg qID and a TD-1211 2.5mg qID dose administered for two weeks, and to assess the efficacy of TD-1211 10mg and 15mg doses.

**Results**

- Opioid analgesics such as morphine continue to play a critical role in chronic cancer and non-cancer pain control. Despite their effectiveness, opioids have significant drawbacks, notably the development of analgesic tolerance and physical dependence, sedation, respiratory depression, and bowel dysfunction.

- Opioid-induced constipation (OIC) is common, affecting up to 80% of patients receiving opioids for chronic non-cancer pain.

- TD-1211 is an investigational, peripherally selective, mu-opioid receptor antagonist designed to alleviate gastrointestinal side effects of opioid therapy without affecting analgesia.

- TD-1211 was assessed in a Phase 2, single-blind exploratory study in 95 adult patients with OIC.

- The safety and tolerability of various doses, dosing strategies and dose escalations of TD-1211, as well as efficacy results, from this study are reported here.

**Patient baseline characteristics**

- 95 patients were enrolled, 16 patients per cohort, except Cohort 6 which enrolled 15 patients.

- TD-1211 was generally well-tolerated at dose levels tested (Table 1).

**Efficacy**

- The primary study objective was to evaluate the safety and tolerability of TD-1211 5mg once daily as an initiation dose, for 4 or 2 days, escalated to 10mg or 15mg once daily as maintenance therapy for 2 weeks.

- Additional study objectives were to examine the tolerability and effects of TD-1211 2mg qID and a TD-1211 2.5mg qID dose administered for two weeks, and to assess the efficacy of TD-1211 10mg and 15mg doses.

**Table 1: Adverse Events Reported in ≥5% of Patients**

<table>
<thead>
<tr>
<th>Event</th>
<th>Patient Population</th>
<th>TD-1211 5 mg (4 Days)</th>
<th>TD-1211 5 mg (2 Days)</th>
<th>TD-1211 2 mg</th>
<th>TD-1211 2.5 mg</th>
<th>Combined 1 &amp; 2</th>
<th>Combined 3 &amp; 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1 (6.3%)</td>
<td>1 (6.3%)</td>
<td>1 (6.3%)</td>
<td>1 (6.3%)</td>
<td>0</td>
<td>1 (6.3%)</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (6.3%)</td>
<td>1 (6.3%)</td>
<td>1 (6.3%)</td>
<td>1 (6.3%)</td>
<td>0</td>
<td>1 (6.3%)</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2: GI-Related Adverse Events; 4-Day and 2-Day Initiation Periods**

**Figure 1: Study Schematic**

**Figure 2: Spontaneous Bowel Movements**

**Figure 3: Complete Spontaneous Bowel Movements**

**TD-1211 Conclusions**

- TD-1211 was generally well-tolerated at dose levels up to 15mg. Majority of GI AEs resolved within a few days, and all GI AEs resolved without sequelae.

- There were no treatment-emergent SAEs during the study.

- TD-1211 10mg and 15mg administered orally once a day demonstrated a clinically meaningful response at Week 2.

- These results support further development of a 5mg treatment initiation dose followed by maintenance therapy at up to 15mg qID.

**References**