**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 opioid-induced constipation (OIC).

**Methods**

- A 5-week, double-blind, randomized, multi-center, placebo-controlled, parallel-group study was conducted in chronic non-cancer pain patients with OIC, defined as ≤5 spontaneous bowel movements (SBMs) over a 2-week baseline period and at least one additional symptom of constipation in at least 25% of the bowel movements.
- For the first 4 days of dosing, patients randomized to TD-1211 received 5mg daily and on Day 5, remained on 5mg or were dose-escalated to 10mg or 15mg daily for the remainder of the treatment period. Patients randomized to placebo received placebo for all 5 weeks.
- 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 movements; use of laxatives and opioids; daily pain scores; and bowel dysfunction.
- Week 1 was excluded from the primary analysis in order to confirm treatment with resolved OIC within a few days, and were mild or moderate.

**Results**

**Patient baseline demographics**

- As shown in Table 1, baseline characteristics were similar for all treatment groups.
- Subjects were on a representative spectrum of opioids.
- Daily opioid doses ranged from 60-1740 oral MEU.
- Back pain was the most commonly reported reason for chronic use.

**Table 1: Patient Baseline Demographics**

<table>
<thead>
<tr>
<th></th>
<th>TD-1211 5mg</th>
<th>TD-1211 10mg</th>
<th>TD-1211 15mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.87</td>
<td>0.90</td>
<td>0.91</td>
<td>0.97</td>
</tr>
<tr>
<td>Female Gender</td>
<td>0.37</td>
<td>0.33</td>
<td>0.36</td>
<td>0.35</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.26</td>
<td>0.26</td>
<td>0.25</td>
<td>0.28</td>
</tr>
<tr>
<td>Duration of OIC (weeks)</td>
<td>0.55</td>
<td>0.63</td>
<td>0.64</td>
<td>0.63</td>
</tr>
</tbody>
</table>

**TD-1211 Conclusions**

- TD-1211 was generally well-tolerated, with overall treatment-emergent adverse events (TEAEs) similar between TD-1211 and placebo and gastrointestinal (GI) TEAEs predominant.
- The majority of treatment-related GI AEs were associated with initiation of treatment, resolved within a few days, and were mild or moderate.

**Methods**

- TD-1211 was an investigational, peripherally selective, mu-opioid receptor antagonist designed to alleviate gastrointestinal side effects of opioid therapy without affecting analgesia.
- Safety and efficacy results, including the primary and key secondary endpoints, from a 5-week, Phase 2b study in chronic non-cancer pain OIC patients have been previously reported (see PAINFWeek 2013 Poster #124).
- As mu-opioid receptor antagonists can quickly reverse the effects of opioid agonists on gastrointestinal opioid receptors, demonstration of a sustained response on bowel movement frequency is necessary for a therapy intended for patients taking opioids chronically.

**Figure 1:** Mean Number of Complete and Spontaneous Bowel Movements (CSBMs) at Each Week.

**Figure 2:** Mean Number of Days per Week with at Least 1 SBM.

**Figure 3:** Mean Number of Days per Week with at Least 1 SBM.

**Figure 4:** Percent of Patients Reporting ≥5 SBMs per Week on Treatment.

**Table 2: GI-Related Adverse Events Occurring After the Dose Initiation Period (≥5 Days)**

<table>
<thead>
<tr>
<th>AE Category</th>
<th>TD-1211 5mg</th>
<th>TD-1211 10mg</th>
<th>TD-1211 15mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0.6%</td>
<td>3.6%</td>
<td>5.4%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.6%</td>
<td>1.8%</td>
<td>3.8%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.9%</td>
<td>1.9%</td>
<td>3.8%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.6%</td>
<td>1.8%</td>
<td>3.8%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.6%</td>
<td>1.8%</td>
<td>3.8%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

**Tolerability and Safety (cont)**

- At target doses (i.e., after the first 4 days of treatment initiation), ≥5% of patients randomized to TD-1211, ≤13% of patients reported any GI-related TEAE (Table 2). Two severe AEs (diarrhea and vomiting) were noted.
- No treatment-related serious adverse events (SAEs) were reported.
- No clinically significant laboratory, ECG, or vital sign abnormalities were observed.

**References**