TD-1211 Phase 2b Study Demonstrates Increased Bowel Movement Frequency and Constipation-Related Symptom Improvement in Patients with Opioid-Induced Constipation

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Disclosures

- Dr. Canafax is an employee of Theravance, Inc.

- Theravance, Inc., is investigating TD-1211 as a potential new treatment option for Opioid-Induced Constipation (OIC)
TD-1211 for Opioid-Induced Constipation

- Theravance-discovered, multivalent, $\mu$-opioid receptor neutral antagonist
- Designed to be peripherally selective
  - Non-opioid core
  - Polar
  - Hydrophilic
  - P-gp substrate
- Goal to normalize bowel movement frequency and quality
- Once daily oral dosing
Randomized, double-blind, placebo-controlled study

Non-cancer pain patients with chronic OIC
- Onset of constipation after starting opioid
- \( \leq 5 \) SBMs in 2-week baseline period, and
- \( \geq 1 \) symptom of constipation for \( \geq 25\% \) of bowel movements

Chronic opioid use
- Daily dose \( \geq 30 \) mg morphine equivalent units
- Taking opioid \( \geq 3 \) months

TD-1211 oral doses: 5, 10, 15 mg, or placebo, once daily
- Initiation 5 mg TD-1211 or placebo daily for 4 days

Study treatment duration 5-weeks

Rescue laxatives permitted
## Patient Characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized (# treated)</td>
<td>217 (215)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>49 (21–65)</td>
</tr>
<tr>
<td>% Female</td>
<td>59%</td>
</tr>
<tr>
<td>Mean duration of OIC, years ± SD</td>
<td>6.0 ± 5.6</td>
</tr>
<tr>
<td>Mean baseline SBMs/week</td>
<td>1.1–1.2</td>
</tr>
<tr>
<td>Mean baseline CSBMs/week</td>
<td>0.1–0.3</td>
</tr>
<tr>
<td>Mean opioid dose, MEU (range)</td>
<td>145 (30–1740)</td>
</tr>
<tr>
<td>Most common reason for chronic opioid use</td>
<td>Back pain, 43%</td>
</tr>
</tbody>
</table>

Baseline characteristics similar for all treatment groups

CSBM = complete spontaneous bowel movement. MEU = morphine equivalent unit.
Change From Baseline in Average Weekly CSBMs Over Weeks 2 to 5 of Treatment (Primary Endpoint)

Complete Spontaneous Bowel Movements (CSBMs)

**LS means difference = least squares mean difference from placebo.**

**Efficacy Analysis (EA) population = compliant with medication and diary entries per protocol.**
Change From Baseline in Weekly CSBMs During Week 5 (End of Treatment)

**Complete Spontaneous Bowel Movements (CSBMs)**

<table>
<thead>
<tr>
<th></th>
<th>Bsl</th>
<th>Wk5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>(n=52)</td>
<td></td>
<td>(n=53)</td>
</tr>
<tr>
<td>TD-1211 5 mg</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>(n=50)</td>
<td></td>
<td>(n=49)</td>
</tr>
<tr>
<td>TD-1211 10 mg</td>
<td>2.5</td>
<td>2.9</td>
</tr>
<tr>
<td>(n=47)</td>
<td></td>
<td>(n=46)</td>
</tr>
<tr>
<td>TD-1211 15 mg</td>
<td>2.5</td>
<td>2.9</td>
</tr>
<tr>
<td>(n=47)</td>
<td></td>
<td>(n=46)</td>
</tr>
</tbody>
</table>

**LS mean difference**:
- Placebo vs. TD-1211 5 mg: 2.04 (p=0.0001)
- Placebo vs. TD-1211 10 mg: 1.36 (p=0.0095)
- Placebo vs. TD-1211 15 mg: 0.95 (p=0.0637)

LS means difference = least squares mean difference from placebo; EA population
Change From Baseline in Average Weekly SBMs Over Weeks 2 to 5 of Treatment

**Spontaneous Bowel Movements (SBMs)**

- **Placebo**
  - Baseline: 1.2 (n=52)
  - Week 2-5: 3.1 (n=50)
- **TD-1211 5 mg**
  - Baseline: 1.2 (n=53)
  - Week 2-5: 3.9 (n=46)
- **TD-1211 10 mg**
  - Baseline: 1.1 (n=49)
  - Week 2-5: 4.5 (n=47)
- **TD-1211 15 mg**
  - Baseline: 1.2 (n=47)
  - Week 2-5: 4.9 (n=45)

- **LS mean difference**
  - Placebo vs. TD-1211 5 mg: 0.88, p=0.0739
  - Placebo vs. TD-1211 10 mg: 1.46, p=0.0038
  - Placebo vs. TD-1211 15 mg: 1.83, p=0.0003

**LS means difference** = least squares mean difference from placebo; EA population
SBM Responder Analysis (Pre-Specified)

Responders: ≥3 SBMs/week and increase of at least 1 SBM/week from baseline for ≥3 weeks over Weeks 2 to 5

- Placebo: 39% (n=52)
- TD-1211 5 mg: 59% (p=0.0401, n=53)
- TD-1211 10 mg: 61% (p=0.0222, n=49)
- TD-1211 15 mg: 70% (p=0.0016, n=47)

EA population
Patients reported amount of straining for each SBM on a 5-point scale with “not at all” and “extreme” as anchors.
Rectal Pain Improvement with SBMs

 Patients reported amount of rectal pain with each SBM on a 5-point scale with “none” and “very severe” as anchors
Patients rated their constipation symptoms over the past 7 days on a 5-point scale with “none” and “very severe” as anchors.

**Constipation Symptoms Global Assessment**

- **“None” or “Mild” Constipation Symptoms**
  - Placebo: 0% (n=51)
  - TD-1211 5 mg: 22% (n=50)
  - TD-1211 10 mg: 44% (n=46)
  - TD-1211 15 mg: 48% † (n=42)
  - 57% * (n=44)

* † p=0.0175 vs placebo
* * p=0.0020 vs placebo

EA population
Bristol Stool Scale Scores for SBMs at Week 5 (End of Treatment)

- At baseline, 54-67% of patients across treatment groups had “hard, dry” average BSS scores and 29-43% had “normal” scores

BSS = Bristol Stool Scale; SBMs = spontaneous bowel movements; EA Population
## Adverse Events

### Safety Population

<table>
<thead>
<tr>
<th>Any TEAE</th>
<th>Placebo n=54</th>
<th>5 mg n=56</th>
<th>10 mg n=53</th>
<th>15 mg n=52</th>
<th>All TD-1211 n=161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>24 (44)</td>
<td>22 (39)</td>
<td>29 (55)</td>
<td>22 (42)</td>
<td>73 (45)</td>
</tr>
<tr>
<td>GI disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(occurring in ≥2 patients in any group)</td>
<td>11 (20)</td>
<td>13 (23)</td>
<td>15 (28)</td>
<td>14 (27)</td>
<td>42 (26)</td>
</tr>
<tr>
<td>Abdominal pain (cramps)</td>
<td>6 (11)</td>
<td>7 (13)</td>
<td>6 (11)</td>
<td>8 (15)</td>
<td>21 (13)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>4 (7)</td>
<td>6 (11)</td>
<td>4 (8)</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4)</td>
<td>4 (7)</td>
<td>8 (15)</td>
<td>3 (6)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2)</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>0</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

- **Majority of GI adverse events:**
  - Associated with treatment initiation
  - Resolved in a few days
  - Were mild/moderate

**TEAEs = treatment-emergent adverse event; GI = gastrointestinal**
Average Daily Pain Scores (0-10 Scale) Per Week

EA population. Weeks 6 +7 = follow-up period
Summary of TD-1211 OIC Study 0084

- TD-1211 increased BM frequency during 5 weeks of therapy
  - Placebo adjusted increase in CSBM (1.79/wk) and SBM (1.83/wk) at 15 mg QD
  - SBM responder rate of 70% at 15 mg QD versus 39% with placebo
- Patients reported improvement in measures of constipation-related symptoms, including straining, rectal pain, and global assessment
- TD-1211 was generally well tolerated
- No clinically significant laboratory, ECG, or vital sign abnormalities
- No treatment-related SAEs
- No evidence of CNS penetration, interference with analgesia, or central opioid withdrawal
- Results support further development of TD-1211 as a peripherally-selective μ-opioid antagonist for treatment of OIC