No Evidence of Analgesic Interference or CNS Opioid Withdrawal for TD-1211 in a Phase 2b Study in Opioid-Induced Constipation

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Table 1: GI-Related Adverse Events Occurring in at Least 2 Patients in Any Group

<table>
<thead>
<tr>
<th>GI-Related AEs (N)</th>
<th>(%)</th>
<th>Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>1211</td>
<td>Approved</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1211</td>
<td>Approved</td>
</tr>
<tr>
<td>Nausea</td>
<td>1211</td>
<td>Approved</td>
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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 15mg daily and on Day 5, if not at 15mg 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 ≥30 mg morphine equivalent units (MEU). Patients were required to stop laxatives and bowel regimens, except for 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 satisfaction with quality of life metrics. The Clinician Opiate Withdrawal Scale (COWS) was used to assess symptoms of opioid withdrawal at baseline and on Day 1 and Day 25. The primary efficacy endpoint was the change in baseline in weekly average complete spontaneous bowel movements (CSBMs) over weeks 2-5 of treatment. Week 1 was excluded from the primary analysis in order to confirm durability of response and predictability of longer term efficacy outcomes.

Results

No evidence of analgesic interference, as noted by stable average daily pain scores and no evidence of CNS withdrawal. (One patient in the placebo (N=53) group had a score of 7 at baseline.) (Figure 1)

No evidence of interference with analgesia, as noted by stable average daily pain scores and daily opioid doses over the treatment period. (Figure 2)

Tolerability and Safety

TD-1211 was generally well tolerated, with overall treatment-emergent adverse events (TEAEs) similar between TD-1211 and placebo and gastrointestinal (GI) TEAEs predominant. (Table 1)

1 The majority of treatment-related GI AEs were associated with initiation of treatment, resolved within a few days, and were mild or moderate.
2 No treatment-related serious adverse events (SAEs) were reported.
3 No clinically significant laboratory, ECG, or vital sign abnormalities were observed.

References

Vickery, R. et al., PainWeek 2013, Las Vegas, NV.
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