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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Introduction

- Opioid analgesics such as morphine continue to play a critical role in chronic cancer and non-cancer pain control.[1] Despite their effectiveness, opioids have significant drawbacks, notably the development of analgesic tolerance and physical dependence, sedation, respiratory depression and bowel dysfunction.[2]
- Opioid-induced constipation (OIC) is common, affecting up to 80% of patients receiving opioids for chronic non-cancer pain.[3]
- TD-1211 is 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.[4]
- Additional assessments on daily pain score, opioid dose, and central opioid withdrawal are reported here to demonstrate that TD-1211 is peripherally selective and does not impact centrally-mediated analgesia.

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 at 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 satisfaction / quality of life metrics.
- The Clinician Opiate Withdrawal Scale (COWS) was used to assess symptoms of opioid withdraw at baseline and on Day 1 and Day 35.
- The primary efficacy endpoint was the change from 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 studies.

Results

Patient baseline characteristics

- 217 patients were randomized.

Opioid Use

- Majority of patients were on opioids for >3 years.
- Mean and median baseline daily oral opioid dose were 145 and 89 MEU, respectively, with a range of 30-1740 MEU.
- Subjects were on a representative spectrum of opioids.
- Back pain was the most commonly reported reason for chronic opioid use.

OIC

- Mean duration of OIC was 6 years.
- Mean baseline SBMs/week was 1.1-1.2.
- Mean satisfaction with ability to manage OIC was 3.0 (on 1-6 scale); 45% of patients were notably dissatisfied (score ≤2).
- 20% of patients reported sometimes taking less pain medication (typically a few days each month) because of OIC.

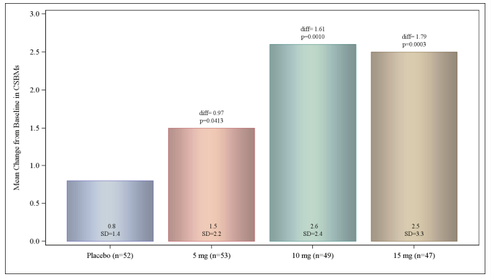
Primary efficacy endpoint

- All doses of TD-1211 achieved statistical significance for the change from baseline in weekly average CSBMs over weeks 2-5 of treatment. (**Figure 1**).

Measures demonstrating no evidence of analgesic interference

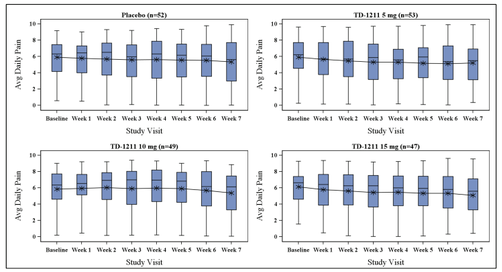
- The mean average daily pain score (0 - 10 VAS with 10 as worst imaginable pain) was 5.9 – 6.1 across treatment groups at baseline, and the change from baseline at Week 5 ranged from -0.7 to 0.1 across the 4 treatment groups (**Figure 2**).
- The mean change from baseline in daily opioid dose at Week 5 was -6, -8.9, and -4.3 MEU for the 5, 10, and 15mg TD-1211 treatment groups, respectively, compared with +4.8 MEU for placebo (**Figure 3**).
- On the COWS, with a maximum possible score of 48, the maximum post-treatment score reported was 6 for patients receiving TD-1211 (2 patients) and placebo (3 patients), indicating no evidence of CNS withdrawal. (One patient in the 15mg TD-1211 group had a score of 7 at baseline.) (**Figure 4**)

Figure 1: Primary Efficacy Endpoint: Change from Baseline in Weekly Average CSBMs over Weeks 2-5



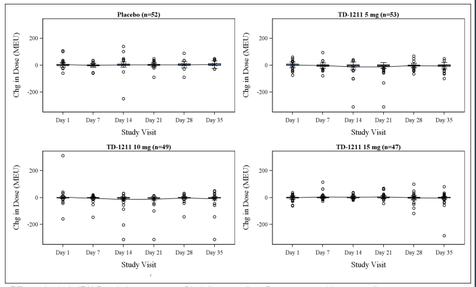
Efficacy Analysis (EA) Population, diff = Least Squares (LS) Mean Differences from placebo

Figure 2: Average Daily Pain Scores Per Week



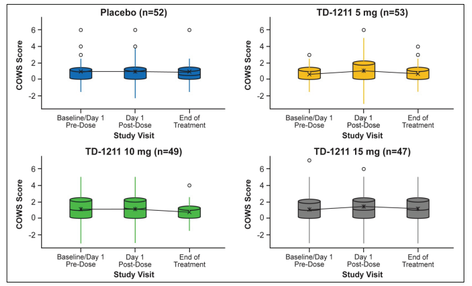
Efficacy Analysis (EA) Population. Weeks 6+7 = follow-up period. Asterisk =mean. Black line = median. Blue box = upper and lower quartiles. Whiskers = minimum and maximum score range.

Figure 3: Mean Change from Baseline in Daily Opioid Use on Study Visit Days



Efficacy Analysis (EA) Population. x = mean. Black line = median. Box = upper and lower quartiles. Whiskers = Q1 - 1.5*IQR, Q3 + 1.5*IQR, where IQR = Q3-Q1. Circles = outliers beyond the whisker range.

Figure 4: Clinician Opiate Withdrawal Scale



Efficacy Analysis (EA) Population. x = mean. Black line = median. Cylinder = upper and lower quartiles. Whiskers = Q1 - 1.5*IQR, Q3 + 1.5*IQR, where IQR = Q3-Q1. Circles = outliers beyond the whisker range.

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

Safety Population	TD-1211				
	Placebo (N=54)	5 mg (N=56)	10 mg (N=53)	15 mg (N=52)	All TD-1211 (N=161)
No. of Patients and Percentage with GI AEs	11 (20.4%)	13 (23.2%)	15 (28.3%)	14 (26.9%)	42 (26.1%)
Abdominal Pain	6 (11.1%)	7 (12.5%)	6 (11.3%)	8 (15.4%)	21 (13.0%)
Abdominal Pain Upper	1 (1.9%)	2 (3.6%)	3 (5.7%)	2 (3.8%)	7 (4.3%)
Diarrhea	0	4 (7.1%)	6 (11.3%)	4 (7.7%)	14 (8.7%)
Flatulence	3 (5.6%)	1 (1.8%)	2 (3.8%)	1 (1.9%)	4 (2.5%)
Nausea	2 (3.7%)	4 (7.1%)	8 (15.1%)	3 (5.8%)	15 (9.3%)
Vomiting	1 (1.9%)	4 (7.1%)	1 (1.9%)	0	5 (3.1%)

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

TD-1211 Conclusions

- 10mg and 15mg demonstrated sustained, clinically meaningful response over the 5-week treatment period.
- Met primary endpoint of change from baseline in CSBMs / week in moderate to severely constipated OIC population.
- No evidence of interference with analgesia, as noted by stable average daily pain scores and daily opioid doses over the treatment period.
- No evidence of centrally-mediated opioid withdrawal.
- Generally well-tolerated with no treatment-related SAEs.

References

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3. Holzer, P. (2012). Current Pharmaceutical Design, 18, 6010-6020.
4. Vickery, R., et al. PainWeek 2012, Las Vegas, NV, September 5-8. Poster #121.