Phase 2b Evaluation of TD-1211 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 more than 50% of patients receiving chronic morphine treatment for cancer pain and, unlike the majority of opioid-induced effects, is not prone to tolerance.[3] Consisting of constipation, delayed gastric emptying, abdominal discomfort, and nausea, OIC can be debilitating in patients.[3,4,5] The phenomenon of OIC results from the interaction of an opioid agonist with receptors on enteric neurons in the myenteric and submucous plexuses and smooth muscle to inhibit coordinated rhythmic contractions associated with GI transit and secretion.[4] The ability of prototypical μ-opioid receptor antagonists, such as naltrexone and naloxone, to attenuate OIC has been demonstrated clinically. However, because these agents readily cross the blood brain barrier, attenuation of opioid induced analgesia and provocation of an opioid behavioral withdrawal syndrome can occur.[3,6] TD-1211 is an investigational, orally-administered, peripherally selective, multivalent inhibitor of the mu-opioid receptor designed with the goal of alleviating gastrointestinal side effects of opioid therapy without affecting analgesia. This Phase 2b study evaluated the safety, tolerability, and efficacy of three doses of TD-1211 compared to placebo.

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) and at least one additional symptom of constipation for at least 25% of the bowel movements per week over a 2-week baseline.
- 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 (MEUs).
- Patients were required to stop laxatives and bowel movement (BM) regimens, except protocol-permitted rescue bisacodyl use, throughout the study.
- Electronic diaries collected frequency, timing, and symptoms of BMs; use of laxatives and opioids; daily pain scores; and satisfaction / quality of life metrics.
- Primary efficacy endpoint was the change from baseline in weekly average complete spontaneous bowel movements (CSBMs) over weeks 2-5 of treatment.
- Key secondary endpoint was the change from baseline in weekly average spontaneous bowel movements (SBMs) over the same period.
- Week 1 was excluded from the primary analysis in order to confirm durability of response and predictability of longer term efficacy studies.

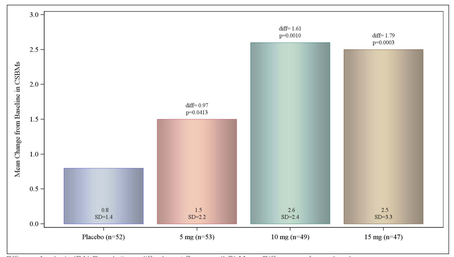
Results

Table 1: Patient Baseline Demographics

Modified Intent to Treat Population	Placebo (N=54)	TD-1211 5 mg (N=55)	TD-1211 10 mg (N=53)	TD-1211 15 mg (N=53)
Mean Age (years)	47.6	48.3	49.2	48.9
Female Gender	28	37	32	30
BMI Mean (kg/m^2)	28.3	27.8	27.8	28.1
Duration of OIC Mean (years)	5.5	6.4	6.7	5.3

- Baseline characteristics similar across all treatment groups
- Subjects were on a representative spectrum of opioids
- Daily opioid doses ranged from 30 - 1740 oral MEUs (mean=145)
- Back pain was the most commonly reported reason for chronic opioid use

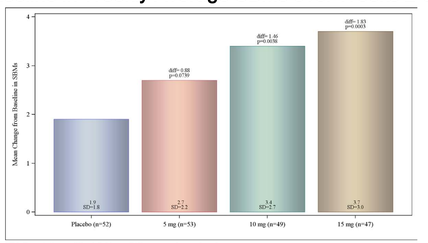
Figure 1: Primary Efficacy Endpoint: Change from Baseline in Weekly Average CSBMs over Weeks 2-5



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

- All doses of TD-1211 achieved statistical significance for the primary efficacy endpoint

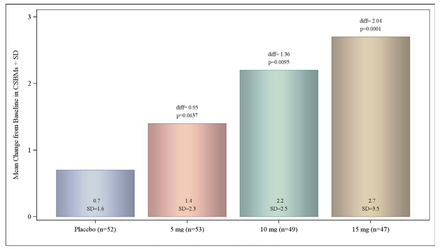
Figure 2: Secondary Efficacy Endpoint: Change from Baseline in Weekly Average SBMs over Weeks 2-5



EA Population, diff = LS Mean Differences from placebo

- 10mg and 15mg TD-1211 achieved statistical significance for this secondary efficacy endpoint

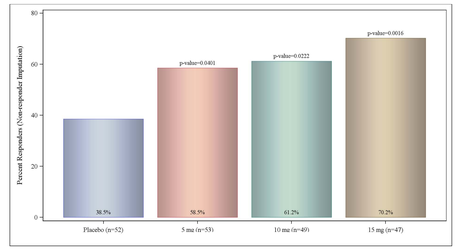
Figure 3: Secondary Efficacy Endpoint: Change from Baseline in Weekly CSBMs at Week 5



EA Population, diff = LS Mean Differences from placebo

- Durability of response demonstrated for all TD-1211 doses

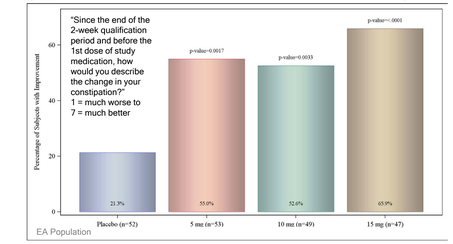
Figure 4: Pre-Specified SBM Responder Analysis



EA Population with non-responder imputation

- Responder definition: ≥3 SBMs per week and an increase of ≥ 1 SBM per week from baseline for ≥3 weeks over Weeks 2-5

Figure 5: Patient Global Impression of Change



EA Population

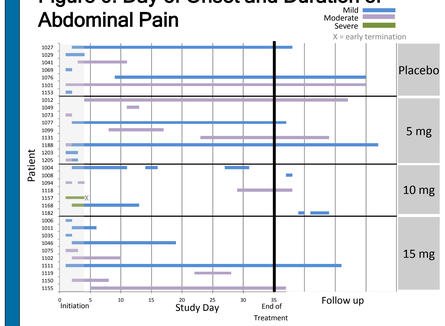
- Significantly more TD-1211 patients indicated improvement in constipation (score ≥6 on 7 point scale) vs. placebo

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

Safety Population	Placebo (N=54)	TD-1211 5 mg (N=56)	TD-1211 10 mg (N=53)	TD-1211 15 mg (N=52)	TD-1211 All (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%)

- Majority of GI-related AEs were associated with treatment initiation, mild-to-moderate, and resolving within a few days

Figure 6: Day of Onset and Duration of Abdominal Pain



- Abdominal pain was reported at a similar frequency across treatment groups, including placebo

TD-1211 Conclusions

- 10mg and 15mg demonstrated sustained clinically meaningful response over the treatment period
- Met primary and secondary endpoints in a moderate to severely constipated OIC population
- Generally well-tolerated with no treatment-related SAEs
- No evidence of central penetration or interference with analgesia
- No abnormal clinically significant labs, ECGs, or vital sign findings

References

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