TD-1211 Demonstrates Tolerability and Clinical Activity Following Multiple Treatment Administration Strategies in Patients with 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.
- TD-1211 was assessed in a Phase 2, single-blind exploratory study in 95 adult patients with OIC.
- The safety and tolerability of various doses, dosing strategies and dose escalations of TD-1211, as well as efficacy results, from this study are reported here.

Methods

- A single-blind, multi-center, six-cohort 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.
- The first four cohorts received an oral dose of TD-1211 5mg once daily for either 4 days (Cohorts 1 and 2) or 2 days (Cohorts 3 and 4), followed by an increase in daily dose to either 10mg or 15mg for two weeks. Cohort 5 received 2mg once daily and cohort 6 received 2.5mg q6h for two weeks without dose escalation (**Figure 1**).
- 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; and daily pain scores.
- The primary study objective was to evaluate the safety and tolerability of TD-1211 5mg once daily as an initiation dose, for 4 or 2 days, escalated to 10mg or 15mg once daily as maintenance therapy for 2 weeks.
- Additional study objectives were to examine the tolerability and effects of a TD-1211 2mg qd dose and a TD-1211 2.5mg q6h dose administered for two weeks; and to assess the efficacy of TD-1211 10mg and 15mg doses.

Results

Patient baseline characteristics

- 95 patients were enrolled, 16 patients per cohort, except Cohort 6 which enrolled 15 patients.
- 12 (12.6%) patients terminated study early; 6 due to adverse events (AEs); 2 each for physician decision and withdrawal by subject; and 1 each for other and protocol deviation.

Demographics

- Mean age was 48.0 years (range = 22.0 to 65.0) and was similar across cohorts.
- 55.8% of patients were female and 78.9% were white.

OIC

- Mean baseline daily oral opioid dose ranged across cohorts from 93 to 170 MEU, with the lowest and highest doses being 30 and 745 MEU, respectively.
- During the baseline period, 55% of patients used bisacodyl, and bisacodyl was not used more than 3 days by any patient.
- Mean baseline SBMs/week was 0.9 to 1.7; mean baseline complete spontaneous bowel movements (CSBMs)/week was 0.1 to 0.6.

Figure 1: Study Schematic

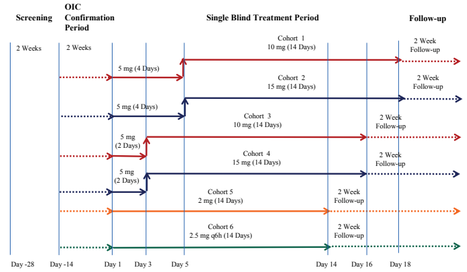


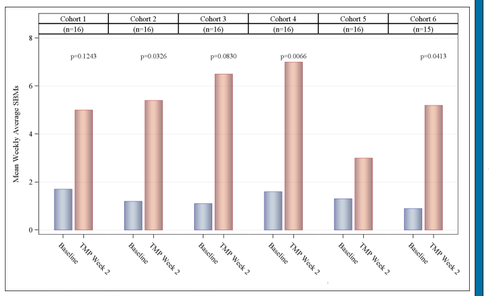
Table 1: Adverse Events Reported in ≥ 5% of Patients

Safety Population	TD-1211						
	Cohort 1 (n=16)	Cohort 2 (n=16)	Cohort 3 (n=16)	Cohort 4 (n=16)	Cohort 5 (n=16)	Cohort 6 (n=15)	All TD-1211 (N=95)
Any AEs, n (%)	7 (43.8)	11 (68.8)	9 (56.3)	8 (50.0)	3 (18.8)	6 (40.0)	44 (46.3)
Gastrointestinal Disorders	5 (31.3)	7 (43.8)	6 (37.5)	4 (25.0)	3 (18.8)	6 (40.0)	31 (32.6)
Abdominal Distension	2 (12.5)	1 (6.3)	0	1 (6.3)	0	1 (6.7)	5 (5.3)
Abdominal Pain	1 (6.3)	1 (6.3)	3 (18.8)	3 (18.8)	2 (12.5)	4 (26.7)	14 (14.7)
Diarrhea	0	2 (12.5)	3 (18.8)	0	1 (6.3)	0	6 (6.3)
Flatulence	0	2 (12.5)	2 (12.5)	1 (6.3)	0	3 (20.0)	8 (8.4)
Nausea	1 (6.3)	3 (18.8)	3 (18.8)	1 (6.3)	0	1 (6.7)	9 (9.5)
Nervous System Disorders	2 (12.5)	2 (12.5)	4 (25.0)	0	0	1 (6.7)	9 (9.5)
Headache	2 (12.5)	2 (12.5)	2 (12.5)	0	0	0	6 (6.3)

Table 2: GI-Related Adverse Events; 4-Day and 2-Day Initiation Periods

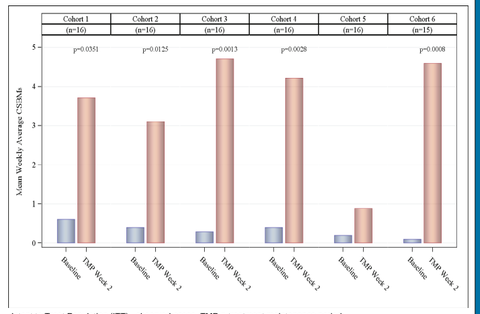
Safety Population	TD-1211					
	Cohort 1 (n=16)	Cohort 2 (n=16)	Combined 1 & 2 (n=32)	Cohort 3 (n=16)	Cohort 4 (n=16)	Combined 3 & 4 (n=32)
	4-Day Initiation Period			2-Day Initiation Period		
Any GI-related AEs of interest, n (%)	1 (6.3)	2 (12.5)	3 (9.4)	3 (18.8)	3 (18.8)	6 (18.8)
Abdominal Pain	0	1 (6.3)	1 (3.1)	3 (18.8)	3 (18.8)	6 (18.8)
Diarrhea	0	0	0	2 (12.5)	0	2 (3.1)
Nausea	1 (6.3)	1 (6.3)	2 (6.3)	2 (12.5)	1 (6.3)	3 (9.4)
Vomiting	0	0	0	1 (6.3)	0	1 (3.1)

Figure 2: Spontaneous Bowel Movements



Intent to Treat Population (ITT) - observed cases TMP = treatment maintenance period.

Figure 3: Complete Spontaneous Bowel Movements



Intent to Treat Population (ITT) - observed cases. TMP = treatment maintenance period.

Primary study objective

- TD-1211 was generally well tolerated at all dose levels tested (**Table 1**) .
- Initiating treatment with TD-1211 5mg for 4 days resulted in fewer GI-related AEs (**Table 2**).
- Escalating TD-1211 to 10mg versus 15mg did not produce unexpected AEs or events of greater severity (**Table 1**).

Secondary tolerability and safety objectives

- The majority of treatment-related GI AEs were associated with initiation of treatment, resolved within a few days, and were mild or moderate in severity.
- No treatment-emergent serious adverse events (SAEs) were reported.
- There were no reports of central opioid withdrawal.
- No clinically significant laboratory, ECG, or vital sign abnormalities were observed.

Efficacy

- Study 0076 was not powered to show statistical differences between the various doses of TD-1211.
- TD-1211 10mg and 15mg mean change from baseline at Week 2 in SBM frequency ranged from 3.3 to 5.4.
- TD-1211 10mg and 15mg mean change from baseline at Week 2 in CSBM frequency ranged from 2.8 to 4.4.
- TD-1211 2mg demonstrated minimal activity with a mean increase from baseline at Week 2 of 1.8 SBMs and 0.7 CSBMs
- TD-1211 2.5mg q6h was clinically active with a mean increase from baseline at Week 2 of 4.3 SBMs and 4.5 CSBMs.

TD-1211 Conclusions

- TD-1211 was generally well-tolerated at dose levels up to 15mg. Majority of GI AEs resolved within a few days, and all GI AEs resolved without sequelae.
- There were no treatment-emergent SAEs.
- Initiation of dosing at 5mg before escalating to 10mg or 15mg resulted in fewer GI-related AEs.
- No evidence of centrally-mediated opioid withdrawal.
- TD-1211 10mg and 15mg administered orally once a day demonstrated a clinically meaningful response at Week 2.
- These results support further development of a 5mg treatment initiation dose followed by maintenance therapy at up to 15mg qd.

References

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2. Walsh, T.D. (1990). J. Pain Symptom Manage., 5, 362-367.
3. Holzer, P. (2012). Current Pharmaceutical Design, 18, 6010-6020.