TD-1211 Demonstrates a Durable Increase in Bowel Movement Frequency and Return Toward Normal Bowel Function in a 5-Week Phase 2b Opioid-Induced Constipation Study

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Poster 411

APS 2013, New Orleans, LA

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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 (see also **APS 2013 Poster #421**).[4]
- As mu-opioid receptor antagonists can quickly reverse the effects of opioid agonists on gastrointestinal opioid receptors, demonstration of a sustained response on bowel movement frequency is necessary for a therapy intended for patients taking opioids chronically.
- Therefore, additional pre-specified week-by-week efficacy analyses are reported here.

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.
- Week 1 was excluded from the primary analysis in order to confirm the durability of response and predictability of longer term efficacy studies.

Results

Patient baseline demographics

- As shown in **Table 1**, baseline characteristics were similar for all treatment groups.
- Subjects were on a representative spectrum of opioids.
- Daily opioid doses ranged from 30-1740 oral MEU.
- Back pain was the most commonly reported reason for chronic opioid use.

Table 1: Patient Baseline Demographics

Modified Intent to Treat Population		TD-1211		
	Placebo (N=54)	5 mg (N=55)	10 mg (N=53)	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

Durability of Response

- An increase in complete spontaneous bowel movements (CSBMs) was observed in Week 1 vs. baseline for each treatment group (**Figure 1**). The increased CSBMs per week was sustained for each week during Weeks 2-5, ranging from between 2.5 to 3.3 for 10mg TD-1211 patients, 2.5 to 2.9 for 15mg TD-1211 patients, and 0.9 to 1.2 for placebo patients.
- Similarly, an increase in SBMs was observed in Week 1 vs. baseline for each treatment group (**Figure 2**). The increased SBMs per week was sustained for each week during Weeks 2-5, ranging from between 4.1 to 4.9 for 10mg TD-1211 patients, 4.6 to 5.2 for 15mg TD-1211 patients, and 2.6 to 3.3 for placebo patients.
- In an exploratory analysis, the mean number of days per week with at least 1 SBM ranged weekly between 3.3 to 3.8 for 10mg TD-1211 patients, 3.6 to 3.9 for 15mg TD-1211 patients, and 2.4 to 2.8 for placebo patients. (**Figure 3**)
- During Weeks 2-5 of treatment, 51-53% of 15mg TD-1211 patients reported ≥5 SBMs per week compared to 14-29% of placebo patients, indicating a return toward normal bowel function for treated patients. (**Figure 4**)

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.
- The majority of treatment-related GI AEs were associated with initiation of treatment, resolved within a few days, and were mild or moderate.

Figure 1: Mean Number of Complete and Spontaneous Bowel Movements (CSBMs) at Each Week

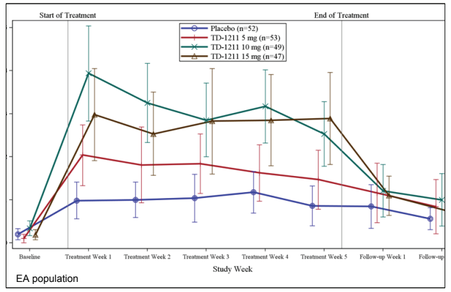

Figure 2: Mean Number of Spontaneous Bowel Movements (SBMs) at Each Week

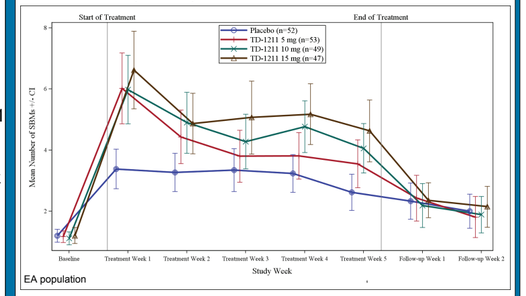

Figure 3: Mean Number of Days per Week with at Least 1 SBM

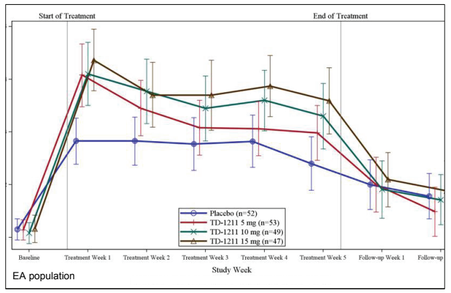

Figure 4: Percent of Patients Reporting ≥5 SBMs per Week on Treatment

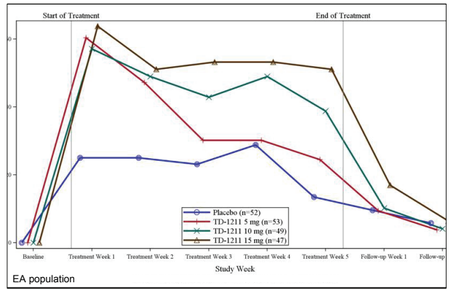

Table 2: GI-Related Adverse Events Occurring After the Dose Initiation Period (≥ Day 5)

	Placebo (n=54)	TD-1211 Randomization Group			
		5 mg (n=56)	10 mg (n=53)	15 mg (n=52)	All (n=161)
Any GI-related TEAE of interest	3 (5.6%)	7 (12.5%)	10 (18.9%)	3 (5.8%)	20 (12.4%)
Abdominal pain	1 (1.9%)	3 (5.4%)	4 (7.5%)	1 (1.9%)	8 (5.0%)
Mild	1 (1.9%)	0	3 (5.7%)	0	3 (1.9%)
Moderate	0	3 (5.4%)	1 (1.9%)	1 (1.9%)	5 (3.1%)
Severe	0	0	0	0	0
Abdominal cramping	1 (1.9%)	1 (1.8%)	3 (5.7%)	0	4 (2.5%)
Mild	1 (1.9%)	0	2 (3.8%)	0	2 (1.2%)
Moderate	0	1 (1.8%)	1 (1.9%)	0	2 (1.2%)
Severe	0	0	0	0	0
Diarrhea	0	4 (7.1%)	5 (9.4%)	2 (3.8%)	11 (6.8%)
Mild	0	0	3 (5.7%)	2 (3.8%)	5 (3.1%)
Moderate	0	3 (5.4%)	2 (3.8%)	0	5 (3.1%)
Severe	0	1 (1.8%)	0	0	1 (0.6%)
Nausea	1 (1.9%)	2 (3.6%)	6 (11.3%)	1 (1.9%)	9 (5.6%)
Mild	1 (1.9%)	0	5 (9.4%)	1 (1.9%)	6 (3.7%)
Moderate	0	2 (3.6%)	1 (1.9%)	0	3 (1.9%)
Severe	0	0	0	0	0
Vomiting	1 (1.9%)	2 (3.6%)	0	0	2 (1.2%)
Mild	0	0	0	0	0
Moderate	1 (1.9%)	1 (1.8%)	0	0	1 (0.6%)
Severe	0	1 (1.8%)	0	0	1 (0.6%)

Tolerability and Safety (con't)

- At target doses (i.e., after the first 4 days of treatment initiation at 5mg for patients randomized to TD-1211), <13% of all patients reported any GI-related TEAE (**Table 2**). Two severe AEs (diarrhea and vomiting) were noted.
- 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 a clinically meaningful, sustained response in CSBM and SBM frequency over the duration of the treatment period in OIC patients.
- CSBM and SBM frequency measures indicated a return toward normal bowel function for the 2 highest doses.
- Generally well-tolerated with no treatment-related SAEs.
- Majority of treatment-related GI AEs were associated with initiation of treatment, resolved within a few days, and were mild or moderate.

References

1. Walsh, T.D. (2000). Seminars in Oncology, 27, 45-63.
2. Walsh, T.D. (1990). J. Pain Symptom Manage., 5, 362-367.
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.