TD-1211 Demonstrates Constipation-relieving Effects, Including Decrease in Rescue Laxative Use, in Patients with Opioid-Induced Constipation

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Introduction

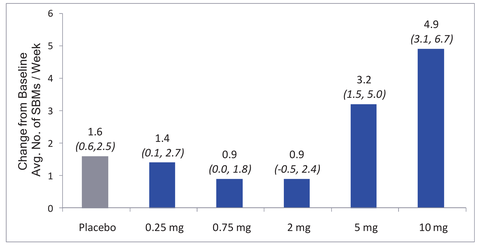
Opioid analgesics such as morphine continue to play a critical role in chronic cancer and non-cancer pain control[1]. Despite their effectiveness, opioids have significant drawbacks, notably the development of analgesic tolerance and physical dependence, sedation, respiratory depression and bowel dysfunction[2]. Opioid-induced constipation (OIC) is common, affecting 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 a peripherally selective μ-opioid receptor antagonist which has the potential to be effective in the treatment of OIC without interfering with centrally mediated opioid effects. Preclinically, TD-1211 demonstrates a high degree of peripheral selectivity, a safety profile which supports further clinical studies, and favorable pharmacokinetics[7]. This study represents the first multiple dose administration of TD-1211 to humans in an OIC patient population, and the results of this study collectively demonstrate that oral, once-daily TD-1211 increased the frequency of SBMs and CSBMs while decreasing rescue laxative use in OIC patients without impacting analgesia[8].

Methods

- Double-blind, placebo-controlled, sequential cohort dose-escalation study
- 70 patients requiring chronic opioid therapy for non-cancer pain were randomized into the study, consisting of a 2-wk baseline, 2-wk treatment and 1-wk follow-up
- Treatment groups included Placebo or TD-1211 (0.25, 0.75, 2, 5 or 10 mg qd)
- OIC was defined as ≤ 5 Spontaneous Bowel Movements (SBMs) with at least one additional symptom of constipation during the 2 week baseline period
- Patients needed to be willing to stop all other laxatives and BM regimens throughout baseline, treatment, and follow-up periods. Protocol defined use of a rescue laxative (bisacodyl) was permitted if an SBM had not occurred within the previous 72 hours of the last recorded SBM.
- Subjects remained in the clinic for the first three days of the treatment period and were fasted overnight prior to the initial dose of TD-1211
- Daily electronic Patient Reported Outcome (ePRO) diary to collect bowel movement symptoms, use of analgesics, rescue laxatives and daily pain scores
- Primary endpoint: Change from baseline in average number of SBMs per week over a 2-week treatment period

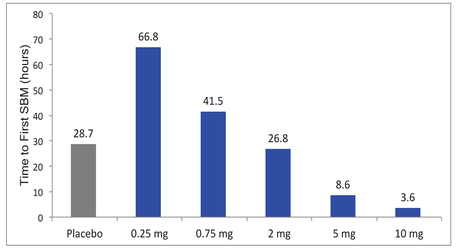
Results

Figure 1: Primary Efficacy Endpoint: Change from Baseline in Average Number of SBMs per Week



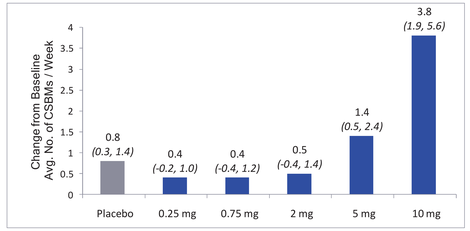
Efficacy Analysis (EA) Last Observation Carried Forward (LOCF) Population;
The numbers in parentheses represent the 95% CI

Figure 2: Secondary Efficacy Endpoint: Median Time to First Spontaneous Bowel Movement (SBM)



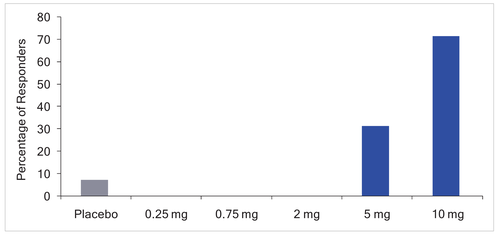
Efficacy Analysis (EA) Last Observation Carried Forward (LOCF) Population

Figure 3: Additional Efficacy Endpoint: Change from Baseline in Average No. of Complete Spontaneous Bowel Movements (CSBMs) per Week



Efficacy Analysis (EA) Last Observation Carried Forward (LOCF) Population;
The numbers in parentheses represent the 95% CI

Figure 4: Additional Efficacy Endpoint: Responder Analysis for ≥ 3 CSBMs per week



Efficacy Analysis (EA) Last Observation Carried Forward (LOCF) Population

Table 1: Rescue Laxative Use

		TD-1211				
	Placebo (N=14)	0.25 mg (N=8)	0.75 mg (N=8)	2 mg (N=7)	5 mg (N=16)	10 mg (N=14)
Baseline period (2 weeks prior to treatment)						
Days of laxative use per week (mean)	0.5	0.9	1.2	0.9	1.3	0.9
Percent of patients using laxatives	29%	75%	75%	57%	81%	71%
During treatment period (Days 1-14)						
Days of laxative use per week (mean)	0.1	0.4	0.7	0.8	0.3	0.04
Percent of patients using laxatives	14%	38%	50%	57%	38%	7%
Mean Change from Baseline						
Days of laxative use per week (mean)	- 0.4	- 0.5	- 0.5	- 0.1	- 1.0	- 0.9
Percent of patients using laxatives	- 15%	- 37%	- 25%	0%	- 43%	- 64%

Efficacy Analysis (EA) Last Observation Carried Forward (LOCF) Population

- Willingness to stop all laxatives and other bowel regimens during the entire 5-wk study period was defined as an inclusion criteria
- Subjects were permitted to use only bisacodyl (up to a maximum daily dose of 15 mg) as rescue laxative medication if an SBM had not occurred within 72 hours of the last recorded SBM.
- Electronic diaries were used to record use of rescue laxatives

Table 2: GI-Related Adverse Events

		TD-1211				
	Placebo (N=14)	0.25 mg (N=8)	0.75 mg (N=8)	2 mg (N=8)	5 mg (N=16)	10 mg (N=16)
No. of Patients with GI AEs	2	1	3	3	9	13
Abdominal Pain						
Mild	1	0	3	1	5	7
Moderate	0	0	0	1	3	2
Severe	0	0	0	0	0	3
Diarrhea						
Mild	1	0	0	0	1	2
Moderate	0	0	0	1	0	2
Severe	0	0	0	0	0	1
Nausea						
Mild	0	1	2	0	2	5
Moderate	0	0	0	2	1	1
Severe	0	0	0	0	0	2
Vomiting						
Mild	0	0	0	2	3	0
Moderate	0	0	0	1	1	2
Severe	0	0	0	0	0	1

- AEs were generally mild and the majority of GI-related AEs resolved after Days 1 or 2
- Moderate/severe abdominal pain temporally coincided with bowel movements
- The verbatim term for all abdominal pain AEs was abdominal cramping
- No clinically significant changes in vital signs, ECGs, laboratory tests, and physical exam were observed
- No serious adverse events (SAEs) reported

Conclusions

- TD-1211 increases bowel movement frequency in OIC patients
- TD-1211 dose-dependently accelerates time to first SBM
- TD-1211 is generally well tolerated in OIC patients
- Patients receiving 5 and 10 mg TD-1211 had a greater decrease in rescue laxative use compared to patients receiving placebo
- Results support further clinical development of TD-1211 for treatment of OIC

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. Pappagallo, M. (2001). Am. J. Surgery, 182, 11S-18S.
4. De Luca, A. and Coupar, I.M. (1996). Pharmacol. Ther., 69, 103-115.
5. Kurz, A. and Sessler, D.I. (2003). Drugs, 63, 649-671.
6. Culpepper-Morgan, J.A., et. al. (1992). Clin.Phar. & Therap., 52, 90-95.
7. Beattie, D.T. et. al. (2010). IASP. Poster # PW 262.
8. Vickery, R.G., et. al. (2011). PainWeek. Poster#0215.