TD-1211 Demonstrates Peripheral Selectivity and Constipation-Relieving Effects in Patients with Opioid-Induced Constipation

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Introduction

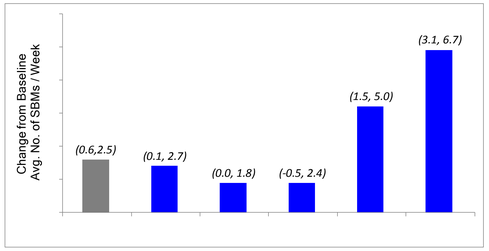
Opioid analgesics such as morphine continue to play a critical role in chronic cancer and non-cancer pain control[1]. Despite their effectiveness, opioids have significant drawbacks, notably the development of analgesic tolerance and physical dependence, sedation, respiratory depression and bowel dysfunction[2]. 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 TD-1211 preferentially antagonizes the peripheral GI effects of opioid agonists without interfering with the centrally mediated pharmacological effects.

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 period and 1-wk follow-up
- OIC was defined as ≤ 5 Spontaneous Bowel Movements (SBMs) with at least one additional symptom of constipation during the baseline period
- Subjects remained in the study unit 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, and daily pain scores
- Primary endpoint: Change from baseline in average number of SBMs per week over a 2-week treatment period
- To evaluate peripheral selectivity using pupillometry[8], 8 healthy volunteers were administered repeat doses of TD-1211 in the presence of 30 mg IR morphine

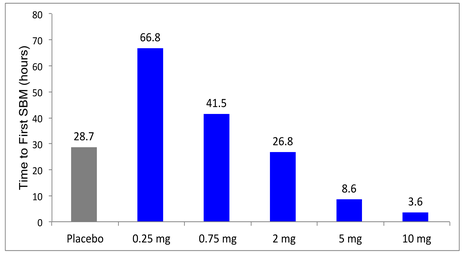
Results

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



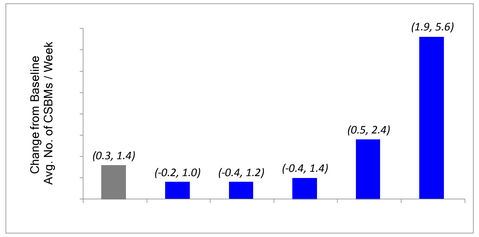
Efficacy Analysis (EA) Last Observation Carried Forward (LOCF) Population

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



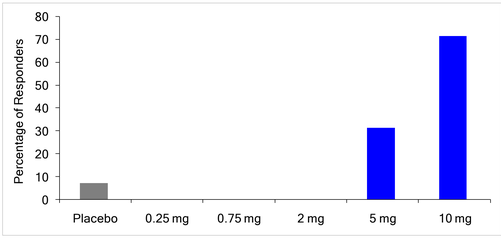
Efficacy Analysis (EA) Last Observation Carried Forward (LOCF) Population

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

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



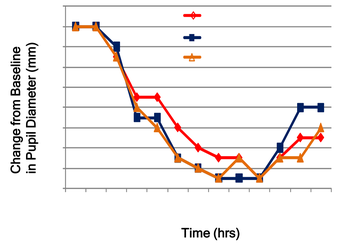
Efficacy Analysis (EA) Last Observation Carried Forward (LOCF) Population

Table 1: GI-Related Adverse Events

	Placebo (N=14)	TD-1211 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

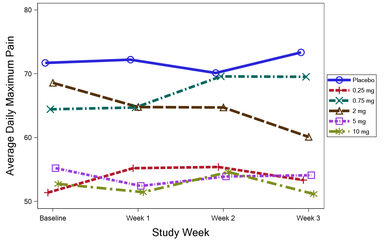
- AEs were generally mild and the majority of GI-related AEs resolved after Days 1 or 2
- Moderate/severe abdominal pain temporally coincided with bowel movements
- All abdominal pain AEs mapped to the verbatim terminology of abdominal cramping
- No clinically significant changes in vital signs, ECGs,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

Figure 5. TD-1211 Does Not Antagonize Morphine-Mediated Pupillary Constriction



Observed Data

Figure 6. Average Daily Pain Scores Do Not Change Over the Duration of Treatment



Conclusions

- TD-1211 increases bowel movement frequency in OIC patients
- TD-1211 dose-dependently accelerates time to first SBM
- TD-1211 is generally safe and well tolerated in OIC patients
- Repeat doses of TD-1211 did not interfere with the centrally mediated effect of morphine on pupil diameter
- Daily pain assessments and opioid use remained unchanged for the duration of the study

References

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