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

Ross Vickery1, Yu-Ping Li1, Roger Kohler1, Lynn Webster2, Neil Singla3, and Oranne Daniels1

1 Theravance, Inc., South San Francisco, CA; 2 Lifetree Clinical Research, Inc., Salt Lake City, UT; 3 Lotus Clinical Research, Inc., Pasadena, CA

Poster 340, 2011 ACG, Washington, DC

vickery@theravance.com

Introduction

Opioid analgesics such as morphine continue to play a critical role in chronic cancer and non-cancer pain control1. Despite their effectiveness, opioids have significant drawbacks, notably the development of analgesic tolerance and physical dependence; sedation, respiratory depression and bowel dysfunction2. 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 tolerance2. Consisting of constipation, delayed gastric emptying, abdominal discomfort, and nausea, OIC can be debilitating in patients2,3. The phenomenon of OIC results from the interaction of an opioid agonist with receptors on enteric neurons in the myenteric and submucous layers and smooth muscle to inhibit coordinated myenteric contractions associated with GI transit and secretion4. The ability of prototypic μ-opioid receptor antagonists such as naloxone and naltrexone, 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 occur5,6. 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. Pragmatically, TD-1211 demonstrates a high degree of peripheral selectivity, a safety profile which supports further clinical studies, and favorable pharmacokinetics. 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 analgesia7.

Methods

1. A double-blind, placebo-controlled, randomized, double-dose escalation study.
2. Thirty patients requiring chronic opioid therapy for non-cancer pain were randomized into the study, consisting of a 2-week baseline, 2-week treatment and 1-week follow-up period.
3. Treatment groups included Placebo or TD-1211 (0.25, 0.5, 1, 2, 4, or 10 mg qd) for the 2-week treatment period.
4. OIC was defined as ≥ 5 spontaneous bowel movements (SBMs)/week or ≥ 3 SBMs/day in the 7 days prior to randomization
5. Patients needed to be willing to stop all other laxatives and bowel regimens throughout the entire treatment period.
6. Willingness to stop all laxatives and bowel regimens during the 5 week study period was defined as an inclusion criteria
7. 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.
8. Electronic diaries were used to record use of rescue laxatives

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