

TD-1211 demonstrates peripheral selectivity and constipation-relieving effects in patients with opioid-induced constipation

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

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

Purpose

To investigate the safety, tolerability, and constipation-relieving effects of TD-1211, a potent, peripherally-selective, neutral, μ -opioid receptor antagonist (P μ MA) that is being developed for the treatment of opioid-induced constipation (OIC) without interfering with centrally-mediated opioid analgesia.

Method

We conducted an IRB-approved, placebo-controlled, double-blind, multiple ascending dose study in both healthy volunteers and in patients requiring chronic opioid therapy with OIC (defined as ≤ 5 spontaneous bowel movements [SBMs] and at least one additional symptom of constipation during a two-week baseline). Frequency, timing, and symptoms of bowel movements (BMs) were collected via daily electronic patient reported outcome diaries during baseline, the 2-week treatment period, and one-week follow-up. Additionally, use of analgesics and daily pain scores were recorded with the daily diaries. Seventy OIC patients were randomized to receive either TD-1211, administered to sequential cohorts at dose levels ranging from 0.25 mg to 10 mg, or placebo QD for 14 days.

Results

A dose-dependent change from baseline in the average number of SBMs/week was observed over the treatment period, with a mean increase of 1.6 for the placebo group vs 3.2 and 4.9 at the two highest doses examined (5 mg and 10 mg, respectively). This effect was sustained over the 2-week treatment period. Median time to first SBM was 28.7 hours for placebo compared to 8.6 hours and 3.6 hours for 5 mg and 10 mg, respectively. Importantly, no CNS withdrawal or analgesic impairment was noted, as patients' daily pain assessments and opioid use remained unchanged for the duration of the study. In healthy volunteers administered repeat doses of 20 mg TD-1211 for one week, no interference with morphine's effect on pupil diameter was observed, providing further evidence that TD-1211 is peripherally-selective. The most common TD-1211 adverse events (AEs) in OIC patients were abdominal cramping, nausea, vomiting, diarrhea, and headache. The GI AEs were temporally associated with initial BMs and generally resolved within 48 hours. No serious AEs were reported, and no clinically significant findings in clinical lab tests, ECGs, or vital signs were observed.

Conclusions

These study results demonstrate that oral, peripherally-selective, once-daily TD-1211 increased the frequency of SBMs in OIC patients without impacting analgesia.