NKTR-118 Significantly Reverses Opioid-Induced Constipation

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Abstract

NKTR-118, a novel PEGylated naloxol conjugate, is an oral, once daily pharmacological agent in development for treatment of opioid-induced constipation (OIC). NKTR-118 blocks peripheral opioid receptors in the gastrointestinal tract to reverse OIC, but was designed to avoid entry into the brain to maintain centrally mediated analgesia. The objective of this phase 2 study was to determine the safety and efficacy of NKTR-118 in patients with opioid-induced constipation. Eligible patients had OIC (fewer than three spontaneous bowel movements (SBMs) per week) and were on a stable opioid regimen of 30 to 1000 morphine equivalent units per day for a minimum of two weeks. A total of 388 patients were randomized 1:1 into 3 sequential cohorts receiving a once daily oral dose of placebo for one week (single-blind) followed by a once daily oral dose of placebo or NKTR-118 at doses of 5, 25 or 50 mg for four consecutive weeks. The primary endpoint was change from baseline in SBMs per week during the first week of double-blind study treatment. Patients receiving 25 mg NKTR-118 had a mean of 5.0 SBMs during the first week of treatment as compared to 1.4 SBMs at baseline. Patients receiving 50 mg NKTR-118 had a statistically significant for both the 25 mg and 50 mg once daily doses.

Results of this study showed that oral NKTR-118 restores gastrointestinal function by increasing the frequency of SBMs to essentially normal in patients with OIC. There was no reversal or reduction of opioid-mediated analgesia at the 5 mg, 25 mg, or 50 mg dose groups (no shift in pain scores or increase in opioid use). NKTR-118 was well tolerated with the most commonly reported side effects being dose dependent GI-related effects.

Background

Constipation is commonly associated with use of opiates for chronic pain and can significantly reduce quality of life. Dietary changes, exercise and stimulant laxatives do not provide effective relief. NKTR-118, a PEGylated conjugate of naloxol is under development for the treatment of opioid-induced constipation. Naloxol is the gold standard opioid antagonist used to reverse the effects of opioids. However, when used as treatment for opioid induced constipation, it can also enter the brain and may lead to reversal of analgesia or opioid withdrawal. NKTR-118 has been specifically engineered to act peripherally to normalize bowel function while maintaining opioid induced central analgesia.

Methods

Eligible patients had OIC (<3 SBMs per week) and were on a stable opioid regimen of 30 to 1000 MEU per day for a minimum of 2 weeks. A total of 288 patients were randomized 1:1 into 3 sequential cohorts receiving a once daily oral dose of placebo for one week (single-blind) followed by a once daily oral dose of placebo or NKTR-118 at doses of 5, 25 or 50 mg for four consecutive weeks. This study was supported by Nektar Therapeutics, San Carlos, CA. © 2009 Nektar Therapeutics.

Conclusion

• Oral NKTR-118 restores gastrointestinal function by increasing the frequency of SBMs to essentially normal in patients with OIC.

• There was no reversal or reduction of opioid-mediated analgesia at the 5 mg, 25 mg, or 50 mg dose groups (no shift in pain scores or increase in opioid use).

• NKTR-118 was well tolerated with the most commonly reported side effects being dose dependent GI-related effects.

References:


Mallinckrodt Medical Inc. Neulasta®, Cimzia®, PEG-INTRON™, and PEGASYS®). Nektar Therapeutics is developing proprietary polyethylene glycol technology for the administration of biotherapeutics and small molecules. For additional information, visit www.nektar.com.