

Evaluation of PEG-Naloxol (NKTR-118) as an Oral Peripheral Opioid Antagonist in Healthy Male Subjects: A Double-Blind, Placebo-Controlled, Dose Escalation Crossover Study

NEKTAR[™]
Nektar Therapeutics
201 Industrial Road
San Carlos, CA, USA, 94070
MEldon@Nektar.com

¹Theresa A. Neumann, PhD; ²Huib van Paaschen, MD; ¹Annette Marcantonio, MBA; ¹Di Song, PhD; ¹Alan R. Kugler, PhD; ¹Michael A. Eldon, PhD, FCP

¹Nektar Therapeutics, San Carlos, CA, USA; ²Kendle Clinical Pharmacology Unit, Utrecht, The Netherlands

Abstract

Opioid bowel dysfunction (OBD), including constipation, affects patients using opioids for pain control. Naloxone, an opioid antagonist, reverses constipation but also reverses analgesia.¹ NKTR-118 (PEG-naloxol) is a PEGylated derivative of naloxone which behaves as a peripheral opioid antagonist (POA) in animal models (Nektar, data on file). We evaluated whether oral NKTR-118 antagonizes morphine-induced delay in human oral-cecal transit time (OCTT), a peripheral effect, using the lactulose H₂ breath GI motility test. Pupillometry was used to monitor central antagonism of morphine-induced pupil constriction, a CNS effect. All subjects received morphine + NKTR-118 or morphine alone in random order during two occasions. Subjects received NKTR-118 or placebo PO, morphine 5 mg/70 kg IV and lactulose PO. Vitals, EKG, breath samples for H₂, pupillometry, and PK (NKTR-118 and NKTR-118-glucuronide) were measured. A total of 48 healthy male volunteers (6/dose) received single NKTR-118 PO doses ranging from 8-1000 mg. No differences in centrally-mediated adverse events such as nausea and vomiting between morphine alone and any morphine + NKTR-118 group were noted. Oral NKTR-118 antagonized the median percent change in morphine-induced OCTT delay in a dose-dependent manner. The ED₅₀ was ~15 mg with a maximal effect at doses ≥125 mg. No CNS antagonism of pupil constriction occurred at 8-60 mg NKTR-118 in 6/6 subjects. At NKTR-118 doses ≥125 mg, 5/6 subjects had no pupil constriction reversal with equivocal attenuation observed in 1/6 per cohort. Oral NKTR-118 results in a rapid systemic exposure with dose-dependent increases in plasma NKTR-118 and low NKTR-118-glucuronide levels observed at all doses with a half-life of 4-6 hours. These data show that oral NKTR-118 up to 1000 mg is well-tolerated, orally bioavailable, and behaves as a POA, warranting further clinical investigation in OBD.

Background and Objectives

PEG-naloxol (NKTR-118) is a new, oral peripheral opioid antagonist (POA) for the treatment of opioid-induced constipation and other manifestations of opioid bowel dysfunction.

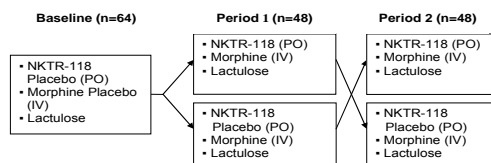
Introduction of the PEG moiety reduces the ability of NKTR-118 to enter the central nervous system (CNS) so that the central analgesic effect of opioid therapy is maintained. In rats, the rate of NKTR-118 blood brain barrier (BBB) entry was greatly reduced compared to that of naloxone (Nektar, data on file). Peripheral to the CNS, NKTR-118 acts as an antagonist of μ -opioid receptors that mediate opioid bowel dysfunction, a symptom complex that encompasses constipation, bloating, abdominal cramping, and gastroesophageal reflux. Constipation is the hallmark of this syndrome, and is generally its most prominent component.

The objective of this Phase I, double-blind, placebo-controlled study was to investigate the safety, tolerability, pharmacokinetic, and pharmacodynamic profile of single rising doses of NKTR-118 in healthy male subjects.

Methodology

Sixty-four subjects completed the baseline period, and 48 (6 per dose level) were enrolled in the treatment periods and analyzed. Eight planned dose levels (8, 16, 30, 60, 125, 250, 500, and 1000 mg) were evaluated (Figure 1).

Figure 1. Clinical Study Design



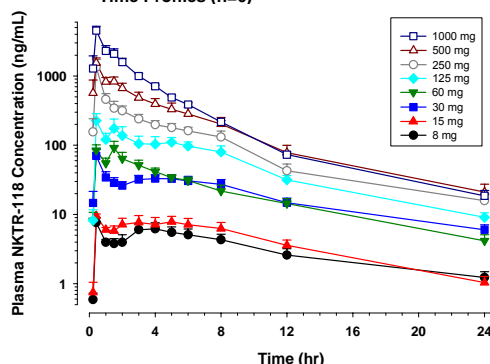
After an overnight fast, subjects received a single dose of NKTR-118 or placebo solution, followed by a 1-minute IV infusion of 5 mg/70 kg morphine 14 minutes later. Twenty-five minutes after dosing NKTR-118 or placebo, subjects received lactulose solution (10 g in 100 mL of water) for hydrogen breath testing.

Results

All treatment-emergent adverse events (AEs) were transient and most were mild. One subject experienced nausea of severe intensity after NKTR-118 placebo. The AE profile of NKTR-118 co-administered with morphine was comparable to NKTR-118 placebo co-administered with morphine. Moreover, no dose-dependent relationship was observed for AE intensity.

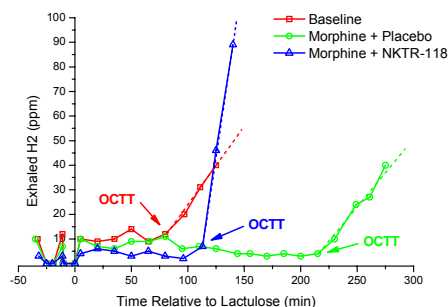
Oral NKTR-118 showed rapid absorption with a rapid attainment of maximal plasma NKTR-118 concentrations and an apparent elimination half-life of 4-8 hours (Figure 2). NKTR-118 C_{max} and AUC_{0-∞} values increased in a dose-proportional manner over the 8-1000 mg dose range.

Figure 2. Mean ± SEM Plasma NKTR-118 Concentration-Time Profiles (n=6)



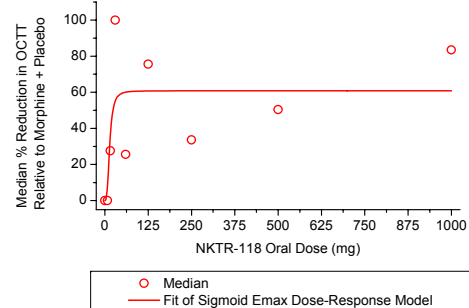
Intravenous morphine alone resulted in a 50% or greater prolongation in the oral-cecal transit time (OCTT) via hydrogen breath testing, compared to the baseline OCTT (Figure 3).

Figure 3. Exhaled H₂ Concentration-Time Profiles for a Subject Receiving 125 mg PO NKTR-118



NKTR-118 antagonized morphine-induced delay in OCTT in a dose-dependent manner (Figure 4). The prolongation of median OCTT (OCTT E_{max}) relative to baseline was 61% less following NKTR-118 with morphine, compared to placebo with morphine (p<0.05), and was achieved at oral doses ≥125 mg. The ED₅₀ for antagonism of morphine-induced delay in OCTT was ~15 mg.

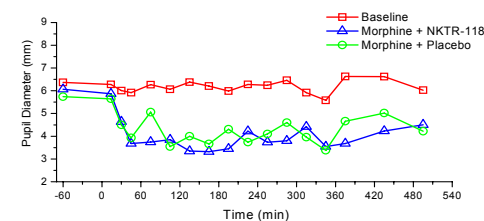
Figure 4. Effect of Morphine + NKTR-118 on Median OCTT Percent Change from Morphine + Placebo



Potential antagonism of morphine's desired CNS effects was monitored using pupillometry to determine whether the time course of morphine-induced miosis was altered when NKTR-118 was co-administered (Figure 5).

Pupil diameter-time profiles after both treatments were essentially superimposable in all subjects (see example at the highest dose level in Figure 5), with the exception of one of six subjects at the 250 mg and one of six subjects at the 1000 mg dose level, who had a possible attenuation after receiving morphine with NKTR-118.

Figure 5. Pupil Diameter-Time Profiles by Treatment for a Subject Receiving 1000 mg PO NKTR-118



Thus, NKTR-118 did not diminish morphine-induced miosis in a dose-dependent manner, and no diminution was observed at doses of 125 mg or less. This finding is consistent with preclinical results showing negligible BBB entry.

Conclusions

- Oral NKTR-118 at single doses up to 1000 mg is safe and well-tolerated when administered to healthy male subjects in combination with morphine and lactulose.
- Oral NKTR-118 is rapidly absorbed, with linear (dose-proportional) pharmacokinetics and modest intersubject pharmacokinetic variability.
- Oral NKTR-118 antagonizes morphine-induced delay in gastrointestinal transit time at doses that do not reverse central opiate effect as measured by pupillometry. This is consistent with preclinical pharmacologic and pharmacokinetic findings.
- Oral NKTR-118 is a promising drug, which is being investigated in further clinical trials as a treatment for opioid-induced constipation and other manifestations of opioid bowel dysfunction.

Reference

- Meissner W, Schmidt U, Hartmann M, Kath R, Reinhart K. Oral naloxone reverses opioid-associated constipation. *Pain* 2000;84: 105-109.

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