

Clinical Investigation of NKTR-118 as a Selective Oral Peripheral Opioid Antagonist

¹Theresa A. Neumann, PhD; ²Huib van Paaschen, MD; ¹Annette Marcantonio, MBA; ¹Di Song, PhD; ²Paul J. Morrison; ¹Michael A. Eldon, PhD; ¹Alan R. Kugler, PhD
¹Nektar Therapeutics, San Carlos, CA, USA; ²Kendle Clinical Pharmacology Unit, Utrecht, The Netherlands

Abstract

NKTR-118 (PEG-naloxol) is under development for treatment of opioid bowel dysfunction (OBD).

Preclinical studies showed that conjugation of naloxol with selected PEGs reduced central nervous system (CNS) uptake of NKTR-118, and that oral NKTR-118 is rapidly and extensively absorbed. In rats, oral NKTR-118 reversed morphine-induced slowing of GI transit (peripheral opioid antagonism) without compromising morphine analgesia (central opioid antagonism), indicating it is a selective peripheral opioid antagonist (POA).

A Phase I safety, tolerability, and PK/PD study was conducted to investigate whether NKTR-118 is a POA in humans. Healthy male subjects received a single 5 mg/70 kg IV dose of morphine with placebo or a single oral dose of 8-1000 mg NKTR-118 in a randomized, double-blind crossover fashion (n=6 in each of 8 dose groups). NKTR-118 antagonized morphine-induced delay in oral-cecal transit time (OCTT) in a dose-dependent manner (measured using the hydrogen lactulose breath test). A maximal 27.5% reduction in median OCTT was observed at doses ≥ 125 mg, with an ED₅₀ of 55.5 mg. This maximal OCTT effect is comparable to or greater than that reported for IV methylnaltrexone and PO alvimopan. Real-time pupillometry showed no significant difference in central opioid antagonism between morphine alone or with NKTR-118 at any dose level. No differences in the incidence or severity of morphine-induced nausea/vomiting were noted at any dose. The incidence of CNS-related events was similar between NKTR-118 (52 events) and placebo (53 events), further indicating that NKTR-118 is not a central opioid antagonist. Vital signs and EKGs indicated no cardiovascular changes at any dose level. NKTR-118 was rapidly and extensively absorbed with an apparent half-life of 4-8 hours.

These results indicate that NKTR-118 is a well-tolerated, selective POA with substantial oral bioavailability that warrants further clinical development for the treatment of 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 (OBD).

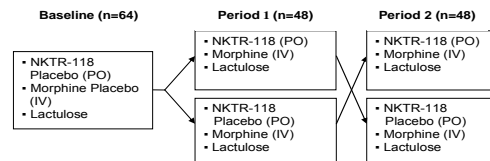
Introduction of the PEG moiety reduces the ability of NKTR-118 to enter the central nervous system (CNS) so that the central analgesic effect of opioid therapy is maintained. In rats, the rate of NKTR-118 blood brain barrier (BBB) entry was greatly reduced compared to that of naloxone (Nektar, data on 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.

Methods

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



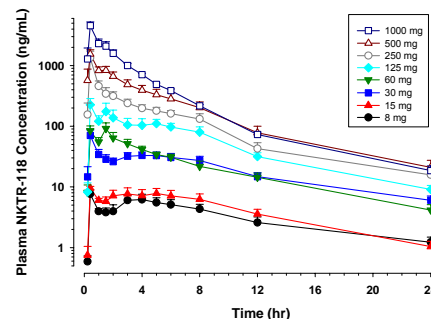
After an overnight fast, subjects received a single oral dose (PO) of NKTR-118 or placebo solution, followed by a 1-minute intravenous (IV) infusion of 5 mg/70 kg morphine 14 minutes later. Twenty-five minutes after dosing NKTR-118 or placebo, subjects received lactulose solution (10 g in 100 mL of water) 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 coadministered with morphine was comparable to NKTR-118 placebo coadministered with morphine. Moreover, no dose-dependent relationship was observed for AE intensity.

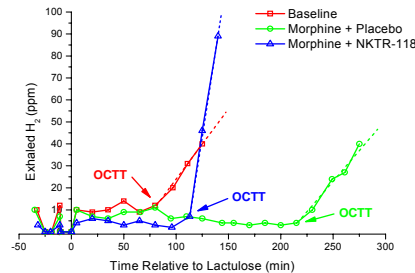
Oral NKTR-118 showed rapid absorption with a rapid attainment of maximal plasma NKTR-118 concentrations and an apparent elimination half-life of 4-8 hours (Figure 2). NKTR-118 C_{max} and AUC_{0-8h} values increased in a dose-proportional manner over the 8-1000 mg dose range.

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



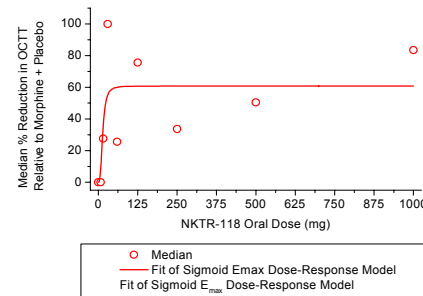
Intravenous morphine alone resulted in a 50% or greater prolongation in the oral-cecal transit time (OCTT) via hydrogen breath testing, compared to the baseline OCTT (Figure 3).

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.

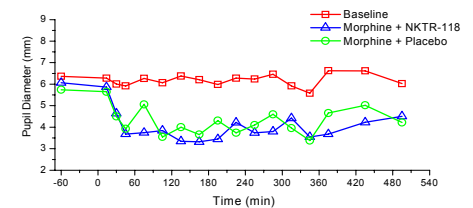
Figure 4. Effect of Morphine + NKTR-118 on Median OCTT Percent Change from Morphine + Placebo



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 coadministered (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.

Acknowledgements: The authors wish to thank the study subjects, Kendle International B.V., Alta Analytical Laboratory, and the Nektar Research and Development Team for their contributions.