

NKTR-118 (Oral PEG-Naloxol), a PEGylated Derivative of Naloxone: Demonstration of Selective Peripheral Opioid Antagonism After Oral Administration in Preclinical Models

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Abstract

Conjugation of biologicals and small molecule drugs with polyethylene glycol (PEGylation) can enhance the effectiveness of the parent molecule by altering its pharmacokinetic properties.

NKTR-118 (PEG-naloxol) is under development for treatment of opioid bowel dysfunction (OBD). It was specifically designed to reduce or eliminate central nervous system (CNS) drug uptake while retaining the opioid antagonist characteristics of naloxone to yield a selective peripheral opioid antagonist (POA). CNS permeation of NKTR-118 in rats was reduced ~15-fold relative to naloxone and comparable to that of atenolol, a reference drug with negligible CNS permeation. *In vitro*, NKTR-118 ($K_i=33.8$ nM) has approximately 20-fold lower affinity for the μ -opioid receptor than naloxone ($K_i=1.68$ nM).

However, oral NKTR-118 is rapidly absorbed in rats, dogs, and humans, resulting in plasma NKTR-118 concentrations that are orders of magnitude greater than those of oral naloxone. This greater systemic exposure compensates for reduced binding affinity. In rats, 30 mg/kg oral NKTR-118 antagonized morphine-induced slowing of GI transit while maintaining substantial morphine analgesia. In contrast, oral naloxone at 30 mg/kg completely reversed both effects, demonstrating no resolution between desired peripheral and undesired central antagonism.

Oral NKTR-118 was rapidly absorbed in rats and dogs with T_{max} values typically between 0.25-0.5 hour, and $t_{1/2}$ values of ~2 and ~4-7 hours, respectively. In rats, 5 mg/kg oral naloxone was not detectable in plasma, whereas 5 mg/kg oral NKTR-118 was detectable for 8 hours after dosing. In dogs, absolute oral bioavailability after 0.4-20 mg/kg NKTR-118 was between ~7%-22%. In a 14-day dog toxicology study of oral NKTR-118, no adverse effects were observed at any dose level (NOAEL ≥ 200 mg/kg), and there was no evidence of drug accumulation. Based on these preclinical results, NKTR-118 is an active, oral, selective peripheral opioid antagonist with favorable safety and pharmacokinetic profiles.

Background and Objectives

NKTR-118 (PEG-naloxol) is a new oral peripheral opioid antagonist (POA) being developed for the treatment of opioid-induced constipation (OIC) 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) relative to naloxone, with the goal of alleviating constipation while preserving the central analgesic effect of opioid therapy. NKTR-118 was developed using Nektar's proprietary PEGylation technology for small molecules.

The objective of this body of preclinical work was to investigate whether NKTR-118 could antagonize the peripheral constipative effect of morphine without reversing analgesia.

Results of a Phase 1 study in healthy subjects are detailed in another poster at this meeting (Poster 27). NKTR-118 at single doses up to 1000 mg was safe and well-tolerated; it also antagonized a morphine-induced delay in gastrointestinal (GI) transit time without reversing central opiate effect at doses that did not reverse central opioid effect, as measured by pupillometry.

Methods

Receptor binding potency and selectivity at μ -opioid receptors was performed using competitive inhibition assays on cloned human isoforms of the receptor, heterologously expressed in Chinese hamster ovary cells.

Permeation of NKTR-118 into the brain was measured using a 30-second rat carotid artery perfusion model. Antipyrine and atenolol were used as positive and negative controls, respectively. For comparison, permeation for naloxone was also measured.

Evaluation of the *in vivo* pharmacological activity of NKTR-118 was performed in rat models for the peripheral and CNS-mediated effects of opioid antagonists. In both models, antagonism of a morphine-induced effect was employed to evaluate the activity of NKTR-118 and was compared with that produced by naloxone.

To determine the potency of NKTR-118 for providing relief from OIC, a rat model for constipative action involving transit distance of a charcoal meal was employed. To determine whether peripheral antagonism could be achieved at a dose that did not reverse the CNS-mediated analgesia of opioids, a hotplate model of nociception was used. Data were analyzed using dose-response modelling to obtain ED_{50} values for GI transit time and reversal of analgesia. Analysis was performed to demonstrate the separation between the ED_{50} values for NKTR-118 and naloxone.

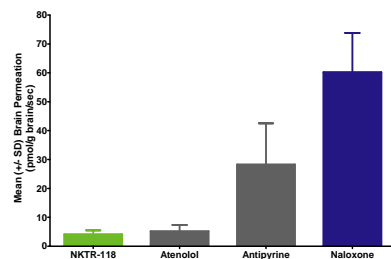
Oral NKTR-118 toxicology (14-day dog) and pharmacokinetic (single-dose rat and dog) studies with LC-MS/MS bioanalytical quantitation were completed and summarized.

Results

In vitro receptor binding studies using μ -, Δ -, and K -opioid receptors showed that NKTR-118 had greater affinity for μ -opioid receptors, characterized by a K_i of 33.8 nM. This represented 20-fold less affinity compared with that of naloxone ($K_i=1.68$ nM).

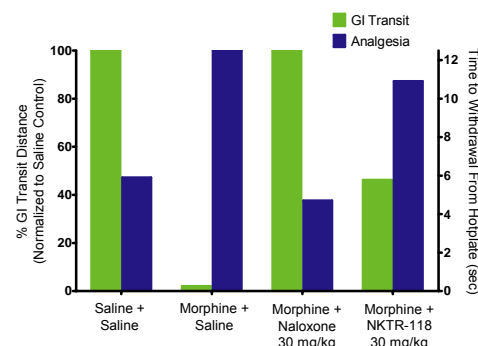
NKTR-118 showed brain permeation similar to atenolol (low permeation standard with no appreciable BBB penetration), whereas naloxone showed brain permeation similar to antipyrine (high permeation standard) (Figure 1). Relative to naloxone, permeation of NKTR-118 was reduced ~15-fold.

Figure 1. Permeation of NKTR-118, Naloxone, and Reference Standards in Rats



NKTR-118 demonstrated the ability to reverse morphine-induced GI transit delay while maintaining substantial analgesic effect (Figure 2). Morphine extensively reduced GI transit distance and prolonged time on the hotplate as compared to saline. Naloxone 30 mg/kg coadministered with morphine completely reversed both effects, whereas NKTR-118 30 mg/kg coadministered with morphine improved GI transit while extending time to withdrawal from the hotplate.

Figure 2. Effect of Oral NKTR-118 and Naloxone on Morphine-Induced GI Transit Delay and Analgesia in Rats (30-min Post-Dose)



The ED_{50} values for these effects indicate that NKTR-118 can improve GI transit at doses that have less effect on opioid analgesia, whereas there was less separation for naloxone effects (Table 1). Furthermore, NKTR-118 had a greater separation between ED_{50} for analgesia reversal and ED_{50} for GI transit, in comparison to naloxone.

Table 1. Summary of ED_{50} for NKTR-118 and Naloxone in Rat Models after Oral Administration

Treatment	ED_{50} for Analgesia Reversal (mg/kg)	ED_{50} for GI Transit (mg/kg)
NKTR-118	55.4	23.1
Naloxone	1.14	0.71

Pharmacokinetics in rats after a single 5 mg/kg oral dose showed NKTR-118 was rapidly absorbed, with a mean T_{max} of 0.7 hour and an apparent terminal half-life of ~2 hours.

NKTR-118 was rapidly absorbed following single oral administrations of 2, 10, and 20 mg/kg in Beagle dogs. Both C_{max} and AUC increased as dose increased. The apparent terminal half-life values ranged between 4.0-6.7 hours at different oral doses, approaching the IV (0.4 mg/kg) terminal mean half-life of 5.7 hours. Oral bioavailability increased from 7% at the lowest dose to 22% at the 20 mg/kg dose, indicating that systemic exposure is dose-dependent in dogs over this dose range.

An oral NKTR-118 toxicology study in Beagle dogs with once-daily dosing up to 200 mg/kg over 14 consecutive days was not associated with any dose-limiting toxicology. The NOAEL was ≥ 200 mg/kg/day.

Conclusions

- Oral NKTR-118 antagonized the peripheral constipative effect of morphine in a rat model, as demonstrated by an improvement in GI transit.
- PEGylation of naloxol greatly reduced (by 15-fold) permeation into the brain compared to naloxone. This finding provides evidence that Nektar's proprietary PEGylation technology can significantly reduce CNS permeation of small molecule drugs.
- At 30 mg/kg, oral NKTR-118 demonstrated improvement in GI transit while maintaining substantial analgesic effect. Additionally, NKTR-118 had a greater separation between ED_{50} for analgesia reversal and ED_{50} for GI transit, in comparison to naloxone.
- Orally-administered NKTR-118 has a favorable safety and pharmacokinetic profile in preclinical models.
- Further investigation is warranted for oral NKTR-118 as a potential treatment for opioid-induced constipation and other manifestations of opioid bowel dysfunction.

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* Expressed as mass of NKTR-118.

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