# NKTR-181: A novel opioid analgesic with slowed CNS entry shows reduced abuse liability and CNS side effects

C. S. Fishburn, S. Wong, L. Tonkin, J. Pfeiffer, H. Gursahani, E. Muthukrishnan, C. Ali, I. Choi, D. McWeeney, J. Riggs-Sauthier, T.A. Riley, T. Sweeney, S.D. Harrison, S.K. Doberstein
Nektar Therapeutics, San Carlos, CA

NEKTAR

## Introduction

- Abuse liability and CNS side effects such as sedation, respiratory depression and 'opioid fog' limit the use of opioids in treating pain.
- Separation of the analgesic properties of opioids from their abuse potential and CNS side effects is hampered by their rapid entry to the brain and the resulting high peak concentrations in brain tissue.
- To slow the rate of transfer across the blood-brain barrier (BBB) and avoid these CNS side effects, we have applied our polymer conjugation technology to generate a novel opioid analgesic, NKTR-181.
- This molecule has been engineered to incorporate a stable polymer side chain and is designed to reduce brain penetration while enabling oral absorption and retaining activity at opioid receptors.

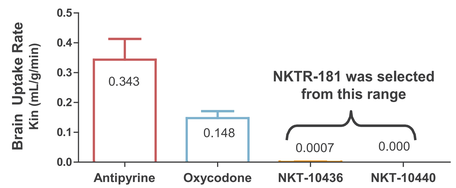
## Methods

- **Brain uptake rate (*in situ* perfusion in rats)**
  The rate of brain uptake of test compounds was measured using an *in situ* brain perfusion method in Sprague Dawley rats. The left common carotid artery was cannulated and test compounds diluted in Kreb's Ringer buffer were perfused for 30 seconds. The left brain hemisphere was excised, homogenized and the concentrations of test articles were measured using LC-MS/MS. The unidirectional brain permeability, Kin, was calculated as Kin = [Cbr/Cpf ]/t, where Cbr and Cpf represent the concentration of compound in brain and perfusate respectively and t is the perfusion time.
- **Brain to plasma ratios**
  Oxycodone (1 mg/kg) and NKTR-181 (10 mg/kg) were administered orally to rats: these different concentrations were used to avoid toxicity (oxycodone) and enable detection (NKTR-181). Subsequent studies demonstrated linear PK for NKTR-181. At specified time points following dosing, animals were euthanized, exsanguinated and concentrations of test articles in brain and plasma samples were measured using LC-MS/MS.
- **Oral bioavailability in mice**
  Oxycodone and NKTR-181 were administered to mice orally at 5 mg/kg, or intravenously at 1 mg/kg. Plasma samples were taken at specified time points following dosing and test articles were measured using LC-MS/MS.
- **Self-administration studies**
  Self-administration studies were performed on cocaine-trained rats, involving intravenous bolus infusions of test article or vehicle (saline) at the specified unit doses. In the progressive ratio test, the number of lever presses required to deliver a unit dose of the indicated value was progressively increased until the breakpoint was reached at which the animal discontinued pressing and no longer would work for reward.
- **Acetic acid writhing studies and Straub Tail Response**
  For acetic acid writhing studies, CD-1 mice were treated orally with test article, and 30 minutes later were injected intraperitoneally with 0.5% acetic acid (0.1 mL/10 g body weight). After 5 minutes, writhes were counted over a 20 minute period. For the Straub tail response, mice were treated with test articles orally and the Straub tail response was monitored for up to 24 hours. Data shown represent the response 30 minutes post-dose, but is representative for NKTR-181 at all time points measured.

## Results

### NKTR-181 Shows Dramatically Slower Brain Uptake Than Oxycodone

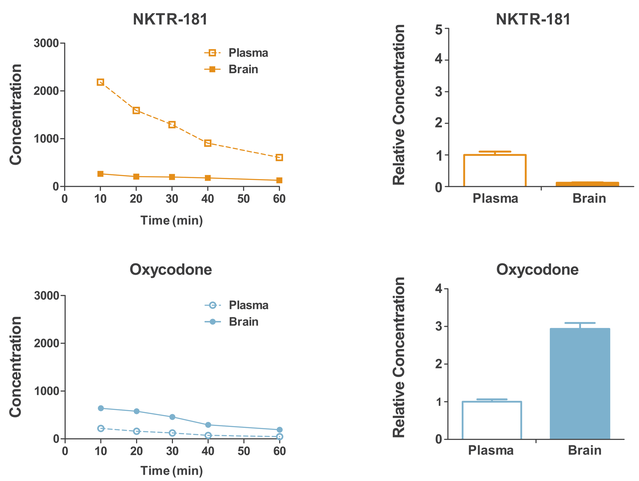
**NKTR-181 was selected from a range of opioid-polymer conjugates with dramatically slower brain uptake than oxycodone as measured by *in situ* brain perfusion studies in rats**




Brain uptake rates were determined in rats using the *in situ* brain perfusion method as described in the Methods section. Polymer-opioid conjugates displayed brain uptake rates that were significantly slower than that of oxycodone or the highly CNS permeant compound, antipyrine. Bars represent mean + SEM (n=3).

### NKTR-181 Displays Markedly Different Distribution Between Brain and Plasma Compared with Oxycodone

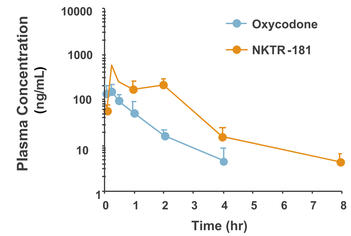
**NKTR-181 shows a low brain:plasma ratio at all time points tested following oral dosing in rats**




NKTR-181 (10 mg/kg) and oxycodone (1 mg/kg) were administered orally to rats, and concentrations in brain and plasma were measured at the time points shown. Whereas oxycodone distributed rapidly into brain, producing a brain:plasma ratio of 3:1 ten minutes after dosing, NKTR-181 showed lower concentrations in the brain compared with plasma at all time points, and displayed a brain:plasma ratio of approximately 1:5 ten minutes after dosing. Bar graphs show values from 10 minutes post-dose time point. Data represent mean values + SD (n=3).

### NKTR-181 Exhibits Significantly Greater Oral Bioavailability than Oxycodone

**NKTR-181 displays greater plasma exposure than oxycodone following oral administration in mice**

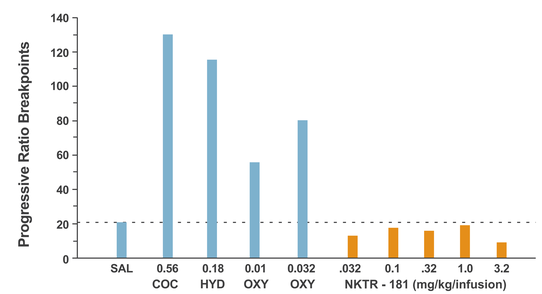



| | Oxycodone | NKTR-181 |
|---|---|---|
| AUC | 160 (ng.h/mL) | 699 (ng.h/mL) |
| Oral Bioavailability | 16% | 25% |

Oral administration of oxycodone or NKTR-181 at 5 mg/kg in mice produced a profile similar to that seen in rats, with a significantly greater plasma exposure for the polymer conjugated opioid. Oral bioavailability was determined from AUC values following oral and IV (not shown) exposure in mice. Data in the graph represent mean values + SD (n=3).

### NKTR-181 Shows Very Low Abuse Liability in Preclinical Studies

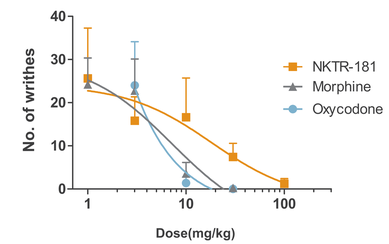
**NKTR-181 displays very low abuse potential in self-administration studies in rats using progressive ratio tests**




Self-administration studies were performed in rats as described in Methods, on cocaine (COC)-treated animals using NKTR-181, Hydrocodone (HYD), Oxcodone (OXY) or Saline (SAL), at the indicated unit doses. NKTR-181 produced a response similar to that in saline-treated animals, with lever pressing rates typical of sampling behavior. Bars represent group means (n=6).

### NKTR-181 Displays Lower CNS Activity at Equianalgesic Doses to Morphine and Oxycodone

**NKTR-181 produces full suppression of writhing in the acetic acid writhing model in mice following oral administration**




**NKTR-181 produces no Straub tail effect at the maximal analgesic dose, in contrast to morphine and oxycodone**

| | $ED_{100}$ | Straub Tail |
|---|---|---|
| Morphine | 20 mg/kg | 100 % |
| Oxycodone | 14 mg/kg | 100 % |
| NKTR-181 | 100 mg/kg | 0 % |

Mice were treated orally with NKTR-181, morphine or oxycodone and submitted to the acetic acid writhing test as described in methods (top panel). Data represent the mean + SEM (n=5). Doses for maximal analgesia ($ED_{100}$, lower panel) were used in different mice to examine the Straub tail response. Data represent the proportion of mice showing the Straub tail response 30 minutes after dosing. (n≥ 4).

## Conclusions

- NKTR-181 represents a novel opioid analgesic with low abuse potential and reduced CNS side effects compared with commonly used opioids.
- NKTR-181 displays slowed entry to the brain and increased plasma exposure following oral administration, when compared with oxycodone in rats and mice.
- NKTR-181 exhibits full efficacy in the acetic acid writhing model in mice, and shows a marked reduction in CNS-based activity compared with oxycodone and morphine at equianagesic doses.

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