



## CNS/PAIN

# NKTR-181: New Mu-Opioid Analgesic with Novel Molecular Structure in Clinical Development as a Safer, Abuse-Deterrent Pain Therapeutic

### **About NKTR-181**

NKTR-181 is a novel mu-opioid analgesic investigational drug candidate engineered using Nektar's small molecule polymer conjugate technology. NKTR-181 has been designed to enter the central nervous system (CNS) at a substantially lower rate compared to existing opioid therapies. By slowing the entry of the drug into the CNS, NKTR-181 has the potential to eliminate not only the euphoria that underlies opioid abuse liability and dependence, but also the serious CNS-related side effects of respiratory depression and sedation. The unique molecular design of the polymer conjugate also prevents conversion of NKTR-181 into a free opioid or an abusable form of an opioid. As a result, NKTR-181 has the potential to be a highly effective analgesic with a favorable safety profile and reduced potential for abuse, misuse and diversion.

In preclinical trials, NKTR-181 has demonstrated:

- Significantly slower rate of entry into the CNS
- Equal analgesia to oxycodone
- Lower abuse liability
- Reduced CNS side effects, including respiratory distress and sedation

### **Clinical Development**

Phase 1 studies are currently underway to assess the pharmacokinetics, pharmacology, safety and efficacy of NKTR-181.

**About Opioids and Pain Management**

Pain is the most common symptom for which patients seek medical attention.<sup>1</sup> According to the American Pain Society, the prevalence of chronic pain in the United States is estimated to be 35.5% or 105 million people. Chronic pain costs more than \$100 billion per year in direct health-care expenditures and lost work time. Opioids are considered to be the most effective therapeutic option for pain and have over \$10 billion a year in sales in the U.S. alone.<sup>2,3</sup> However, opioids cause significant problems for physicians and patients because of their serious side effects such as respiratory depression and sedation, as well as the risks they pose for addiction, abuse, misuse and diversion. The U.S. Food and Drug Administration has cited prescription opioid analgesics as being at the center of a major public health crisis of addiction, misuse, abuse, overdose and death.<sup>4</sup> A 2010 recent report from the Centers for Disease Control and Prevention (CDC) notes that emergency room visits tied to the abuse of prescription painkillers is at an all-time high, having increased 111 percent over a five-year period.<sup>5</sup>

<sup>1</sup> Harstall, C. How prevalent is chronic pain? Pain Clinical Updates X, 1-4 (2003).

<sup>2</sup> IMS, NSP, NPA and Defined Health 2010 Estimates.

<sup>3</sup> Melnikova, I, Pain Market, Nature Reviews Drug Discovery, Volume 9, 589-90 (August 2010).

<sup>4</sup> Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, "Risk Evaluation and Mitigation Strategies (REMS) for Extended-Release and Long-Acting Opioid Analgesics" July 23-4, 2010.

<sup>5</sup> Morbidity and Mortality Weekly Report (MMWR), Emergency Department Visits Involving Nonmedical Use of Selected Prescription Drugs --- United States, 2004-2008, 59(23):705-709 (June 2010).

*Targeting the \$10B U.S. Opioid Market with a Next Generation Mu-Opioid Analgesic*

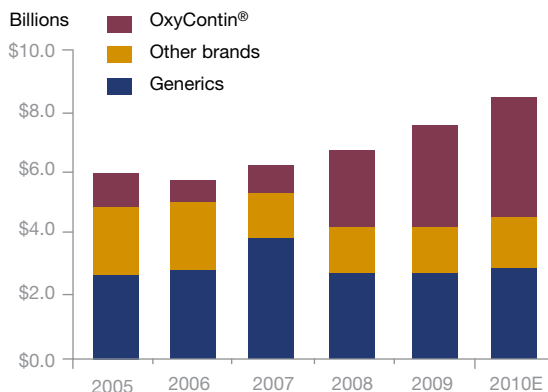


Figure 1. NKTR-181 is a next-generation opioid designed to address abuse liability, side effects and diversion.

*NKTR-181 Behaves as a Mu-Opioid Agonist*

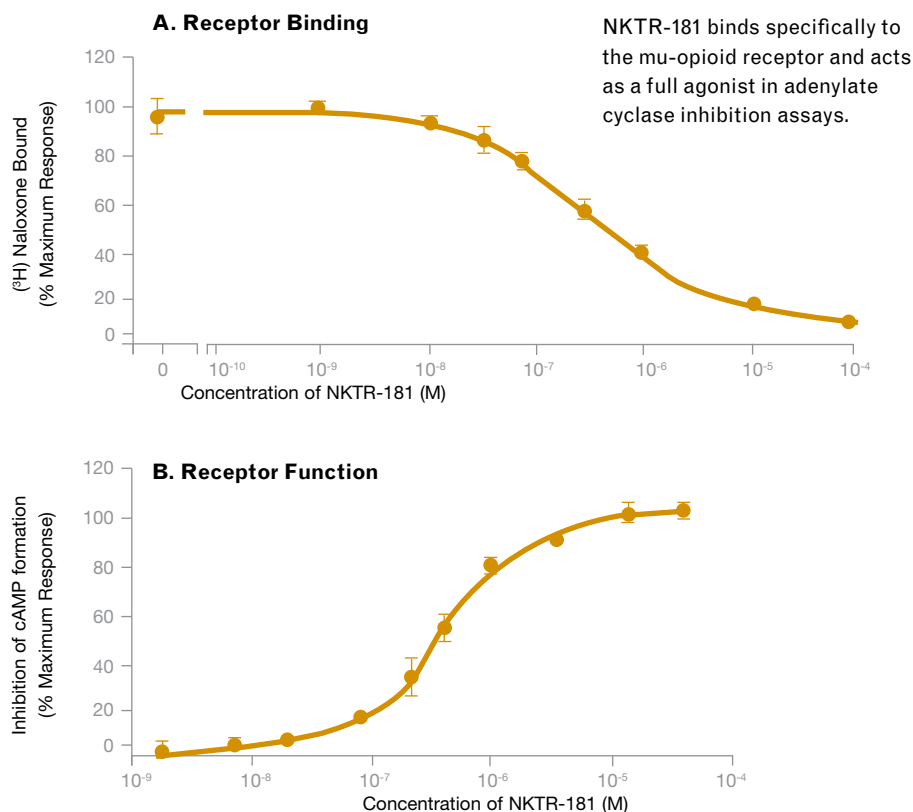


Figure 2. Receptor binding and function studies using CHO cells heterologously expressing the recombinant human mu-opioid receptor:

(A) Competitive displacement studies using the high-affinity mu ligand [<sup>3</sup>H]Naloxone (2nM, K<sub>d</sub>: 2 nM). Data indicate the mean ± SEM (n=3) from a representative experiment.

(B) Adenylate cyclase inhibition studies performed by incubating NKTR-181 in the presence of forskolin-treated cells for 30 min at room temperature. cAMP levels were quantitated using a competitive immunoassay (Cisbio, Bedford, MA). Data represent the mean ± SEM for three independent experiments.

*NKTR-181 Has Significantly Reduced Brain Entry Rate with Equal Analgesia to Oxycodone in Preclinical Studies*

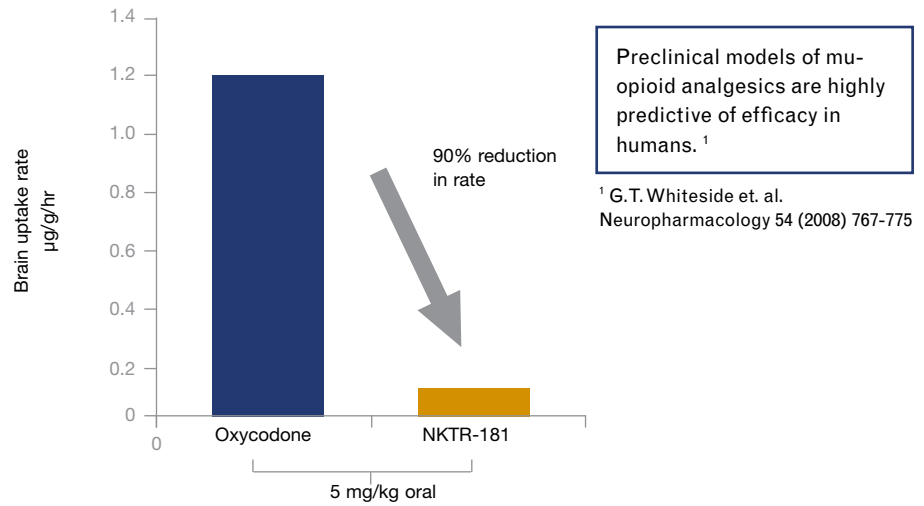


Figure 3: Reduced brain entry rate lowers potential for euphoria, sedation and respiratory depression.

*NKTR-181 Demonstrates Antinociceptive Activity in a Preclinical Model of Pain Analgesia to Oxycodone*

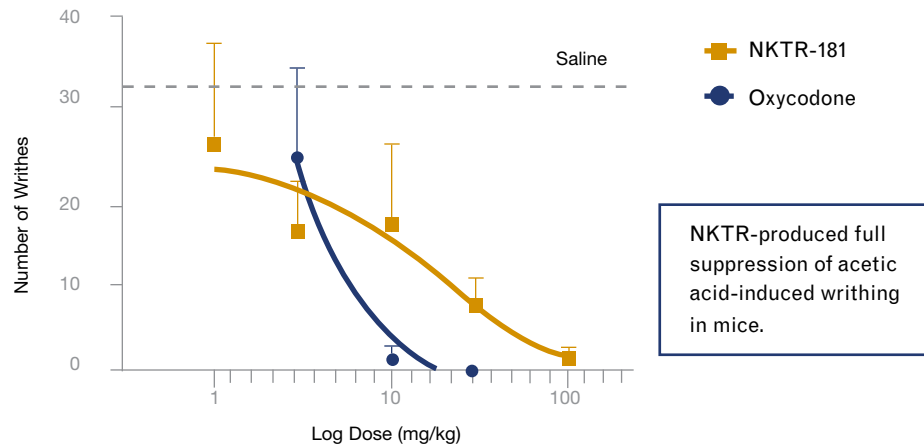


Figure 4: CD-1 mice were treated orally with NKTR-181, oxycodone or saline. 30 minutes later animals were given an intraperitoneal injection of 0.5% acetic acid (0.1 mL/10 g body weight). After 5 minutes, writhes were counted over a 20-minute period. Data represent the mean + SEM (n=5). The average number of writhes produced by saline is shown by the dotted line.

*NKTR-181 Displays Dramatically Reduced Abuse Liability in Validated Primate Model*

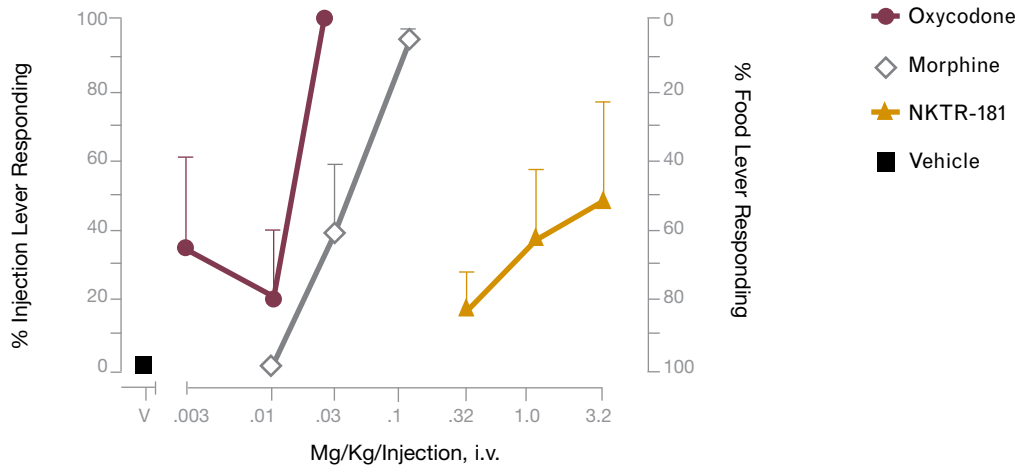


Figure 5: Even at a 100 fold higher dose, NKTR-181 shows less abuse potential than oxycodone.

**NKTR-181 Exhibits Less CNS-Related Side Effects Compared to Other Opioid Therapies**

The significance of NKTR-181 goes beyond its considerable potential to address addiction and abuse to include potential reduction of CNS-related side effects such as respiratory depression and sedation.

By slowing the rate of uptake, we have designed NKTR-181 to have the potential for less respiratory depression and sedation. In preclinical models, no sedation or CNS side effects were observed with NKTR-181 at equi-analgesic doses to oxycodone and morphine. Even at five times the lethal dose of oxycodone, NKTR-181 does not cause death from respiratory depression in animal models (Figure 6).










*NKTR-181 Displays No Significant CNS Side Effects at Analgesic Doses in Rats*

NKTR-181 Dose (mg/kg)	Abnormal Observations in Modified Irwin Assay			
	Home Cage	Hand Held	Open field	Elicited Behaviors
0 (Vehicle)	0/2	0/9	0/8	0/15
50	0/2	0/9	0/8	1/15*
150	0/2	0/9	0/8	2/15**

Figure 6: Evaluation of neurological effects was based on observations collected pre-dose and approximately 0.5, 2, 4, 8, and 24 hours post-dose in a modified Irwin battery in male rats given NKTR-181 orally (n=6/group). Observers were uninformed of each animal's dose level. Data is presented as # of abnormal observations /total # of parameters measured for each type of observation.

\* 2% increase in mean body temperature noted relative to controls 4 hrs post-dose (0.7°C↑)  
 \*\* Abnormal approach response noted in 4/6 animals at 2 hrs post-dose and 5/6 animals 4 hrs post-dose. 2% increase in mean body temperature relative to controls noted 4 hrs post-dose (0.8°C↑).

## The Nektar Product Candidate Pipeline

Products by Therapeutic Area	Nektar Discovered	Indication	Phase	Partner
<b>Oncology</b>				
<a href="#">NKTR - 102</a>	✓	Metastatic Breast Cancer	Phase 3	
<a href="#">NKTR - 102</a>	✓	Platinum-Resistant Ovarian Cancer	Phase 2	
<a href="#">NKTR - 102</a>	✓	Second-Line Colorectal Cancer	Phase 2	
<a href="#">NKTR - 102</a>	✓	GI and solid tumors In combination with 5-FU	Phase 1	
<b>CNS/Pain</b>				
<a href="#">Oral NKTR - 118</a>	✓	Opioid-induced constipation (OIC)	Phase 3	
<a href="#">Oral NKTR - 119</a>	✓	Analgesic for pain	Preclinical	
<a href="#">NKTR - 181</a>	✓	Moderate to severe chronic pain	Phase 1	
<a href="#">NKTR - 171</a>	✓	Neuropathic pain	Preclinical	
<a href="#">NKTR - 192</a>	✓	Moderate to severe acute pain	Preclinical	
<b>Immunology /Inflammation</b>				
<a href="#">Cimzia®</a>		Crohn's Disease (US) Rheumatoid Arthritis	Approved US/Approved EU	
<a href="#">Cimzia®</a>		Psoriatic Arthritis Ankylosing Spondylitis	Phase 3	
<a href="#">NKTR - 125</a>	✓	Allergic Rhinitis	Preclinical	
<b>Anti-Infectives</b>				
<a href="#">Cipro Inhale</a> (BAY Q3939)	✓	Cystic Fibrosis Infection	Phase 2	
<a href="#">NKTR 061: Amikacin Inhale</a> (BAY41-6551)	✓	Gram-negative pneumonia	Phase 2	
<a href="#">NKTR - 140</a>	✓	HIV	Preclinical	
<b>Hemophilia</b>				
<a href="#">BAX 855 (pegylated rFVIII molecule)</a>	✓	Hemophilia A	Phase 1	
<a href="#">Longer-acting therapeutic clotting proteins</a>	✓	Hemophilia and bleeding disorders	Preclinical	
<b>Other Licensing Partnerships</b>				
<a href="#">LEVADEX™</a>		Migraine	Phase 3 complete - NDA filed	
<a href="#">Peginesatide</a> a product under development by Takeda and Affymax		Renal Anemia	Phase 3 complete - NDA filed	Affymax

\* LEVADEX™ is a trademark and TEMPO® is a registered trademark of MAP Pharmaceuticals; Cimzia® is a registered trademark of UCB.

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Nektar Therapeutics is a biopharmaceutical company developing novel therapeutics based on its Advanced Polymer Conjugate Chemistry Technology platform. Nektar's technology and drug development expertise have enabled seven approved products for partners, which include leading biopharmaceutical companies. Nektar is also developing a robust pipeline of its own high-value therapeutics that addresses unmet medical needs by leveraging and expanding its technology platforms to improve and enable molecules. For more information on Nektar Therapeutics, please visit [www.nektar.com](http://www.nektar.com).