**NKTR-181: An Orally Available Mu-Opioid Agonist with Slow Rate of Uptake into the CNS, Exhibits Comparable Analgesic Efficacy with Reduced Abuse Liability and CNS Mediated Side Effects Compared to Oxycodone**

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**Introduction**

- **Opioids are highly effective for the treatment of pain.**
- **Opioids are associated with serious CNS-related side effects, including respiratory depression, sedation and abuse liability.**
- **The abuse properties of opioid analogs are believed to relate to their rapid entry into the CNS.**
- **NKTR-181 is a mu-opioid molecular designed to provide clinically relevant analgesia while reducing CNS-mediated side effects.**
- **NKTR-181 binds to the mu-opioid receptor and acts as a full agonist at adenosine cyclase inhibition assays.**
- **NKTR-181 exhibits a slower rate of CNS uptake in rats compared to commonly used opioids.**
- **NKTR-181 displays markedly lower abuse liability than commonly used opioids when evaluated in self-administration studies in non-human primates and rats.**

**Background**

NKTR-181 exhibits pharmacological behavior characteristic of opioids and has been shown to have minimal analgesic activity in preclinical models of pain following oral administration in mice.

NKTR-181 Shows Analgesic Activity in a Preclinical Model of Pain

**NKTR-181 shows comparable efficacy to oxycodone in the acetic acid writhing model in mice.**

**Acetic Acid-Writhing**

- **NKTR-181 produces full suppression of acetic acid writhing.**
- **Minimal efficacy is achieved at 100 mg/kg p.o.**
- **Potency is reduced 1 to 4 hours after oral dosing.**
- **Acetate sustained for > 6 hours after oral dosing.**

For acetic acid writhing studies, CD-1 mice were treated orally with test articles, and 30 minutes later were injected intraperitoneally with 0.5% acetic acid (0.1 mL/10 g body weight). Writhes were counted over a 20 minute period. Data shown represent mean ± SEM values (n=5). The response 30 minutes post-dose, and is representative of NKTR-181 at all time points measured.

**Results**

NKTR-181 Displays Slow Distribution into the Brain Compared to Oxycodone

NKTR-181 displays a dramatically different distribution between brain and plasma following oral delivery in mice. Oxycodone (10 mg/kg, p.o.) produces > 80% oxycodone appropriate responding, whereas NKTR-181 produces > 80% NKTR-181 appropriate responding.

**NKTR-181 exhibits less impact on CNS coordination compared to oxycodone**

**Reference**


**Conclusions**

- **NKTR-181 is a new chemical entity, is a mu-opioid agonist that exhibits a slow rate of brain uptake following oral administration compared to oxycodone.**
- **NKTR-181 exhibits full efficacy in the acute writhing model in mice.**
- **NKTR-181 has reduced CNS mediated sedation.**
- **NKTR-181 shows low abuse liability in multiple animal models.**
- **NKTR-181 displays a wider therapeutic window through more favorable separation of analgesia from side effects compared with oxycodone.**
- **Subsequent Phase 1 clinical data validate preclinical observations and NKTR-181 is currently being prepared for Phase 2 development for chronic pain patients in 2012.**

**References**


2. Pharmacoecon Bolha Behav. 2007; 85:43-54.


NKTR-181 Demonstrates Less Sedative Potential Than Oxycodone at Emissograph Doses

**NKTR-181 exhibits a wide therapeutic window compared to oxycodone.**

**Conclusions**

- **NKTR-181 shows a more favorable separation of analgesia from side effects compared with oxycodone.**

**References**


2. Pharmacoecon Bolha Behav. 2007; 85:43-54.


