Neuropharmacodynamic Profile of NKTR-181: Correlation to Low Abuse Potential

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LV, TM, IC, ME, XG, HG, FH, AO, JZ, and SD are current or former employees of Nektar Therapeutics
Characteristics of Drugs of Abuse

- Shorter intervals between drug intake and perceived effect (euphoric “high”) correlate with greater abuse potential

- Fast rate of drug uptake into brain

- Rapid activation of dopamine reward circuits in the brain
  - Rapid dopamine release in the striatum is associated with euphoria
  - Speed of dopamine release and the magnitude of effect is directly linked to the likelihood that a drug will be abused

- An opioid that avoids these characteristics is expected to have less abuse potential than conventional opioids
NKTR-181: A Novel Opioid for Treatment of Chronic Pain

- New molecular entity, full mu-opioid receptor agonist designed to have slow rate of entry into the brain relative to conventional opioids
  - Slow CNS entry rate dependent on unique physicochemical properties that are inherent to the NKTR-181 molecule
  - No known chemical or physical methods to alter NKTR-181 to increase its CNS entry rate

- Significant, clinically meaningful analgesia in phase 3 clinical trial in patients with moderate-to-severe chronic low back pain

- Significantly lower mean peak Drug Liking scores at therapeutic doses relative to oxycodone in human abuse potential studies
  - Poster 36: Henningfield et al. Thursday 12-2 pm

- Low abuse potential in preclinical models

Time Course of Pupil Constriction Delayed Relative to Oxycodone in Human Subjects

Double-blind, randomized, placebo-controlled, single-dose crossover study in recreational opioid users
Similar Time Course of Peak Pupil Constriction and Peak Oxycodone Plasma Concentration

- Reflects rapid distribution of oxycodone into CNS
Peak Pupil Constriction is Delayed Relative to NKTR-181 Plasma $T_{\text{max}}$

- NKTR-181 time of maximum pupil constriction observed 2-3 hours after time to peak plasma concentration, consistent with slow entry of NKTR-181 into the CNS
Objective: Characterize Components of NKTR-181 Abuse Potential MOA

- Rate of brain entry
- Mu-opioid receptor binding kinetics
- Time profile of dopamine release in nucleus accumbens
NKTR-181 Demonstrates 70-fold Slower Brain Uptake than Oxycodone in Rat

**In situ** brain perfusion in rat

- Single 30 second perfusion into carotid artery of anesthetized rats
- Brain uptake rate ($K_{in}$) calculated from drug concentrations measured in brain at end of perfusion

<table>
<thead>
<tr>
<th>Compound</th>
<th>$K_{in, perfusion}$ (mL/g/min)</th>
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<tbody>
<tr>
<td>Oxycodone</td>
<td>0.497 ± 0.121</td>
</tr>
<tr>
<td></td>
<td>0.560 ± 0.056</td>
</tr>
<tr>
<td>NKTR-181</td>
<td>0.007 ± 0.005</td>
</tr>
<tr>
<td></td>
<td>0.008 ± 0.005</td>
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N = 4 male Sprague-Dawley rats/group

Data are presented as mean ± SEM
NKTR-181 Binds Mu-Opioid Receptor with Slower Association Rate and Moderate Affinity

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$k_{on}$ (M$^{-1}$min$^{-1}$)</th>
<th>$k_{off}$ (min$^{-1}$)</th>
<th>$K_d$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKTR-181</td>
<td>$5.45 \times 10^5$</td>
<td>0.443</td>
<td>813</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>$8.68 \times 10^6$</td>
<td>0.554</td>
<td>63.8</td>
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</tbody>
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Competition binding of [$^3$H]naloxone to hMOR in CHO-hMOR cell membrane preparations
Method of Motulsky and Mahan 1984 Mol Pharmacol 25; 1-9
NKTR-181 Induces Slower Onset of Dopamine Release in Rat Nucleus Accumbens

- Single intravenous dose in awake rats
- Dopamine levels measured in nucleus accumbens shell using microdialysis

N = 2-3 male Sprague-Dawley rats/group
90 second sampling interval
Differential Kinetics of Dopamine Response to NKTR-181 and Oxycodone

- Reduced magnitude of dopamine release relative to 10-fold lower dose of oxycodone
- Slower offset of dopamine effect

N = 6-7 male Sprague-Dawley rats/group
5 minute sampling interval
Conclusions

- NKTR-181 has a pharmacodynamic profile distinct from oxycodone
  - Slower rate of uptake into brain
  - Slower association with target receptor
  - Slower onset of dopamine release consistent with its slower target site distribution and receptor binding kinetics

- This unique profile supports a mechanism for the low abuse potential observed with NKTR-181