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Background
- NKTR-181, a new molecular entity, is a full mu-opioid receptor agonist currently in development for the treatment of moderate-to-severe chronic pain. The unique physiochemical properties of NKTR-181 result in a relatively slow rate of entry into the central nervous system (CNS) compared to conventional opioids and is independent of dose level or route of administration.
- The primary hypothesis underlying the development of NKTR-181 is that clinically meaningful opioid analgesia can be achieved in combination with decreases in acute CNS-mediated side effects, such as euphoria, sedation, and respiratory depression, by slowing the rate of drug entry into the brain.
- There is no known chemical or physical method to alter NKTR-181 to increase its speed of entry into the brain, and thus increase its abuse potential and other CNS-mediated effects.
- In a Phase 3 clinical trial of 610 patients, NKTR-181 administered at 100 to 400 mg twice daily produced highly significant analgesia throughout 12 weeks of double-blind treatment in patients with moderate to severe chronic low-back pain.
- For the same dosage range, an initial human abuse potential (HAP) study in recreational opioid users reported Drug Liking and Drug High scores for NKTR-181 significantly lower than scores for oxycodone, and closely resembled scores for placebo.
- Here we present results of a second double-blind, randomized, single-dose, cornell oral HAP study comparing two therapeutic dose levels and a supratherapeutic dose level of NKTR-181 with two therapeutic dose levels of oxycodone.

Methods
- Subjects were healthy adults (18 to 55 years of age), qualified as non-dependent recreational opioid users.
- Study design is shown in Figure 1.

Figure 1. Study Design

Results
- A total of 111 subjects entered the qualification phase, and 69 subjects were randomized to the treatment phase and received study drug (safety analysis population), 54 subjects completed all 6 treatments (complete population).
- Mean age of subjects was 31.7 years; 95.7% were male; 42.7% were Black; 53.3% were white, mean/weight 60 kg.
- Figure 2. Time course of Drug Liking “At this moment,” by Study Drug (Study Completers)

![Figure 2](image)

- Time course of Drug Liking “at this moment” is displayed in Figure 2.
- Abuse-potential outcomes are summarized in Table 1.
- Peak Drug Liking “at this moment” (primary outcome measure) for NKTR-181 400 and 600 mg was significantly lower than for oxycodone 40 and 60 mg, (P = 0.001 for NKTR-181 and oxycodone comparisons).
- Peak Drug Liking for NKTR-181 supratherapeutic dose 1200 mg was significantly lower than oxycodone 60 mg (P = 0.007).
- Rate of onset of Drug Liking as assessed by rate of increase in the first 2 hours was significantly slower for all NKTR-181 dose levels than for both oxycodone dose levels (P < 0.001 for all comparisons, except P = 0.003 for 1200 mg NKTR-181 vs oxycodone 40 mg).
- The extent of onset of Drug Liking (as assessed by area under the effect curve [AUE]) in the first 2 hours was significantly lower for all NKTR-181 dose levels than for both oxycodone dose levels (P < 0.001 for all comparisons, except P = 0.001 for 1200 mg NKTR-181 vs oxycodone 40 mg).
- The rate of onset for NKTR-181 supratherapeutic dose 1200 mg was slower and did not peak until approximately 3 hours after administration.
- Peak ratings on Drug High and Take Drug Again VASs were significantly lower for all NKTR-181 dose levels than for oxycodone 60 mg.
- A trend similar to Drug Liking was also observed for the rate and extent of onset of Drug High.
- Emax values for Drug Liking and Drug High after NKTR-181 400 mg matched the values for NKTR-181 400 mg in the prior HAP study, at 62.0 vs 62.3 and 21 vs 22.6, respectively.

Table 1. Abuse-Potential Outcomes, by Study Drug (Study Completers)

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Placebo (n=54)</th>
<th>NKTR-181 40 mg (n=53)</th>
<th>NKTR-181 60 mg (n=54)</th>
<th>NKTR-181 1200 mg (n=54)</th>
<th>Oxycodone 40 mg (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Liking Emax, mm</td>
<td>53.2 (7.7)</td>
<td>62.0 (8.6)</td>
<td>67.6 (7.7)</td>
<td>76.8 (7.7)</td>
<td>81.5 (12.7)</td>
</tr>
<tr>
<td>Rate of increase Drug Liking during first 2 hours, mm/h</td>
<td>10.0 (1.5)</td>
<td>11.5 (1.5)</td>
<td>11.5 (1.5)</td>
<td>11.2 (1.0)</td>
<td>11.0 (1.2)</td>
</tr>
<tr>
<td>Rate of increase in Drug High during hours 0-2, mm/h</td>
<td>0.5 (0.1)</td>
<td>1.1 (0.9)</td>
<td>1.2 (1.0)</td>
<td>1.2 (1.1)</td>
<td>1.1 (1.0)</td>
</tr>
<tr>
<td>Drug Liking AUE0-2, mm</td>
<td>6.1 (0.7)</td>
<td>8.0 (0.7)</td>
<td>7.7 (0.7)</td>
<td>7.5 (0.7)</td>
<td>7.1 (0.7)</td>
</tr>
<tr>
<td>Drug High AUE0-2, mm</td>
<td>1.0 (0.5)</td>
<td>2.7 (2.1)</td>
<td>3.5 (2.0)</td>
<td>4.1 (2.4)</td>
<td>4.9 (2.1)</td>
</tr>
<tr>
<td>AUE0-2 Drug Liking, mm</td>
<td>3.1 (0.2)</td>
<td>23.2 (0.2)</td>
<td>37.3 (0.2)</td>
<td>57.8 (0.2)</td>
<td>53.8 (0.2)</td>
</tr>
<tr>
<td>AUE0-2 Drug High, mm</td>
<td>3.6 (0.2)</td>
<td>35.3 (0.2)</td>
<td>63.1 (0.2)</td>
<td>77.7 (0.2)</td>
<td>83.8 (0.2)</td>
</tr>
</tbody>
</table>

Conclusions
- In recreational opioid users, NKTR-181 exhibited significantly less abuse potential than oxycodone, a conventional Schedule II opioid.
- The magnitude of Drug Liking at therapeutic dose levels of NKTR-181 400 and 600 mg was significantly lower than oxycodone 40 and 60 mg.
- The rate and extent of onset of Drug Liking for all NKTR-181 doses in the critical first 2 and 2 hours was significantly lower than all oxycodone doses.
- Drug High and Take Drug Again ratings likewise favored NKTR-181.
- For all doses of NKTR-181, the time profiles of Drug Liking and pup construction were consistent with slow brain-entry kinetics.
- Overall, the findings support a less restrictive NKTR-181 scheduling (Table 4).

Table 4. Summary of Properties of NKTR-181 as a Potential Candidate for Scheduling Less Restrictive than CII (Eight-Factor Analysis)

<table>
<thead>
<tr>
<th>Factor</th>
<th>NKTR-181</th>
<th>Oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Abuse Potential (includes human abuse potential and opioid potential assessment data)</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pharmacological (overall pharmacological profile)</td>
<td>Non-dependent scheduling</td>
<td>Schedule II</td>
</tr>
<tr>
<td>Nonclinical</td>
<td>Non-dependent scheduling</td>
<td>Schedule II</td>
</tr>
<tr>
<td>Clinical</td>
<td>Non-dependent scheduling</td>
<td>Schedule II</td>
</tr>
<tr>
<td>Abuse Potency</td>
<td>Non-dependent scheduling</td>
<td>Schedule II</td>
</tr>
<tr>
<td>Potential Candidate for Scheduling Less Restrictive than CII</td>
<td>Non-dependent scheduling</td>
<td>Schedule II</td>
</tr>
</tbody>
</table>

Abbreviations:
- AUE: area under the effect curve
- Emax: maximum effect
- HAP: human abuse potential
- LS: least-squares
- SE: standard error

References: