IND 10

Abuse Potential of NKTR-181 in Recreational Opioid Users: Results from a Randomized, Double-Blind Crossover Oral Study

Xue Snow Ge,[1] Lin Lu,[1] Janet Jobes,[1] John Silowsky,[1] Margaret Ziola,[1] Sunny Xie,[1] Stephen K. Doberstein,[1] Jack E. Henningfield,[2] Michael A. Eldon[1]

[1]Nektar Therapeutics, San Francisco, CA, USA; [2]The Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Baltimore, and Pinney Associates, Bethesda, MD

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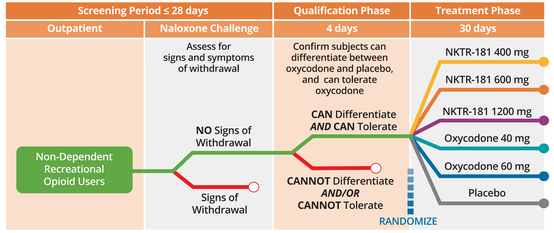
Background

- 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 physicochemical 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[1]
- 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[2]
- 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[3]
- Here we present results of a second double-blind, randomized, single-dose, cross-over 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

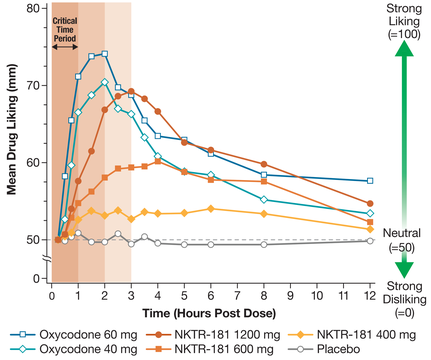


- NKTR-181 (400 mg, 600 mg, and a supratherapeutic dose of 1200 mg) and its matching placebo were administered as oral tablets
- Oxycodone (40 mg and 60 mg) was administered as over-encapsulated oral tablets, and its matching placebo as capsules
- Abuse potential was evaluated with subjective visual analog scale (VAS) ratings for Drug Liking "at this moment," Drug High, Overall Drug Liking, Take Drug Again, Any Drug Effects, Good Drug Effects, Bad Drug Effects, Nausea, Alertness/Drowsiness, and Drug Similarity at scheduled times for 24 hours post dose, consistent with FDA abuse-potential guidance[4]
  - Results from study completers were tested for statistically significant differences between treatments (at the 0.05 level) by a linear mixed-effects model
- Other outcome measures included pupil diameter pharmacokinetics and opioid- and abuse-related adverse events

Results

- A total of 111 subjects entered the qualification phase, and 69 subjects were randomized to the treatment phase and received study drugs (safety analysis population), 54 subjects completed all 6 treatments (completer population)
  - Mean age of subjects was 31.7 years; 95.7% were male, 65.2% were Black, 33.3% were white; mean weight was 79.6 kg

Figure 2. Time Course of Mean Drug Liking "At This Moment," by Study Drug (Study Completers)



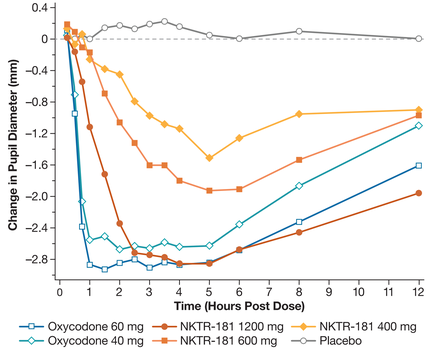
- Time course of mean Drug Liking "at this moment" is displayed in **Figure 2**
- Abuse-potential outcomes are summarized in **Table 1**
  - Peak Drug Liking "at this moment" (primary outcome measure) for NKTR-181 400 and 600 mg was significantly lower than for oxycodone 40 and 60 mg, ($P<0.0001$ for NKTR-181 and oxycodone comparisons)
  - Peak Drug Liking for NKTR-181 supratherapeutic dose 1200 mg was significantly lower than oxycodone 60 mg ($P=0.0071$)
  - 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 ($P<0.0001$; 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 ($P<0.0001$ 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
  - E_{max} 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 21.3 vs 22.6, respectively[3]

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

Outcome Measure	Placebo (n=54)	NKTR-181 400 mg (n=54)	NKTR-181 600 mg (n=54)	NKTR-181 1200 mg (n=54)	Oxycodone 40 mg (n=54)	Oxycodone 60 mg (n=54)
Drug Liking E_{max}, mm, LS mean (SE)	53.2 (1.7)	62.0 (1.6)	67.9 (1.6)	76.7 (1.7)	76.6 (1.7)	81.5 (1.6)
Rate of increase in Drug Liking during hour 1, mm/h, LS mean (SE)	1.0 (1.5)	1.6 (1.5)	4.5 (1.5)	6.1 (1.5)	14.2 (1.5)	20.5 (1.5)
Rate of increase in Drug Liking during hours 0–2, mm/h, LS mean (SE)	0.5 (1.0)	1.8 (1.0)	4.3 (1.0)	7.6 (1.0)	11.9 (1.0)	15.1 (1.0)
Drug Liking AUE_{0-1h}, LS mean (SE)	0.1 (0.7)	0.8 (0.7)	1.7 (0.7)	2.4 (0.7)	5.8 (0.7)	9.5 (0.7)
Drug Liking AUE_{0-2h}, LS mean (SE)	1.0 (2.1)	3.7 (2.1)	8.5 (2.1)	14.2 (2.1)	24.5 (2.1)	32.3 (2.1)
Drug High E_{max}, mm, LS mean (SE)	3.1 (3.2)	21.3 (3.2)	33.7 (3.2)	57.8 (3.2)	53.8 (3.2)	67.2 (3.2)
Take Drug Again E_{max}, mm, LS mean (SE)	50.3 (2.2)	65.5 (2.2)	66.9 (2.2)	77.7 (2.2)	79.8 (2.2)	83.6 (2.2)

AUE, area under the effect curve; E_{max}, maximum effect; LS, least-squares; SE, standard error.

Figure 3. Time Course of Mean Change in Pupil Diameter From Baseline (Study Completers)



- Time course of mean change in pupil diameter from baseline is displayed in **Figure 3**
- Pupillometry outcomes are summarized in **Table 2**
  - Maximum pupil diameter change from baseline E_{min} was significantly lower for NKTR-181 400 and 600 mg than for oxycodone 40 mg and 60 mg ($P<0.0001$)
  - Time to reach E_{min} was significantly longer for all NKTR-181 dose levels than for both oxycodone dose levels (for NKTR-181 1200 mg vs oxycodone 40 mg, $P=0.0011$; all other P-values <0.0001)
  - Slower onset of pupil constriction for all NKTR-181 dose levels vs both oxycodone dose levels was demonstrated by significant differences in AUE for pupil-diameter change in the first 2 hours ($P<0.0001$)
  - Time to achieve maximum pupil constriction for NKTR-181 (3.4 to 5.4 hours) occurred approximately 2-3 hours after time to peak plasma concentration (1.8-2.8 hours), indicating slow entry of NKTR-181 into the CNS

Table 2. Summary of Pupil Diameter Change from Baseline, by Study Drug (Study Completers)

Outcome Measure	Placebo (n=50)	NKTR-181 400 mg (n=53)	NKTR-181 600 mg (n=52)	NKTR-181 1200 mg (n=52)	Oxycodone 40 mg (n=53)	Oxycodone 60 mg (n=54)
E_{min}, mm, LS mean (SE)	−0.76 (0.12)	−1.95 (0.12)	−2.38 (0.12)	−3.15 (0.12)	−3.00 (0.12)	−3.29 (0.11)
Time to E_{max}, h, LS mean (SE)	8.7 (0.6)	5.4 (0.5)	4.5 (0.5)	3.4 (0.5)	2.5 (0.5)	2.2 (0.5)
AUE_{0-2h}, LS mean (SE)	+0.19 (0.20)	−0.44 (0.20)	−0.77 (0.20)	−2.24 (0.20)	−3.70 (0.20)	−4.29 (0.20)

AUE, area under the effect curve; E_{min}, minimum effect; LS, least-squares; SE, standard error.

- Treatment-emergent adverse events (TEAEs) reported during the study are summarized in **Table 3**
  - Pruritus, nausea, somnolence, and vomiting were more frequent with oxycodone (40 mg and 60 mg) than with NKTR-181 (400 mg and 600 mg)

Table 3. Treatment-emergent Adverse Events by Study Drug and Preferred Term (Safety Analysis Population)*

Incidence, n (%)	Placebo (n=61)	NKTR-181 400 mg (n=59)	NKTR-181 600 mg (n=62)	NKTR-181 1200 mg (n=62)	Oxycodone 40 mg (n=60)	Oxycodone 60 mg (n=62)
Summary						
Any TEAE	13 (21.3)	26 (44.1)	35 (56.5)	50 (80.6)	43 (71.7)	49 (79.0)
Any severe TEAE	0	0	0	0	0	0
Any serious TEAE	0	0	0	0	0	0
By Preferred Term						
Pruritus	0	1 (1.7)	8 (12.9)	19 (30.6)	13 (21.7)	24 (38.7)
Nausea	2 (3.3)	5 (8.5)	3 (4.8)	12 (19.4)	8 (13.3)	9 (14.5)
Headache	4 (6.6)	5 (8.5)	3 (4.8)	6 (9.7)	3 (5.0)	7 (11.3)
Somnolence	1 (1.6)	3 (5.1)	3 (4.8)	6 (9.7)	7 (11.7)	10 (16.1)
Vomiting	0	3 (5.1)	0	9 (14.5)	4 (6.7)	6 (9.7)
Feeling abnormal	0	2 (3.4)	4 (6.5)	0	0	0
Dry mouth	0	0	1 (1.6)	4 (6.5)	1 (1.7)	1 (1.6)
Pruritus generalized	0	1 (1.7)	0	3 (4.8)	4 (6.7)	3 (4.8)
Dizziness	0	1 (1.7)	0	1 (1.6)	3 (5.0)	2 (3.2)

TEAE, treatment-emergent adverse event.

*>5% in subjects

Excludes subjective opioid effects such as "feeling high" and "euphoria" represented in Drug Effect Questionaire (DEQ) scores

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 at therapeutic dose levels of 40 and 60 mg
  - The rate and extent of onset of Drug Liking for all NKTR-181 doses in the critical first 1 and 2 hours was significantly lower than all oxycodone doses
  - Drug High and Take Drug Again ratings likewise favored NKTR-181 versus oxycodone
- For all doses of NKTR-181, the time profiles of Drug Liking and pupil constriction 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)

Factor	Key Findings
1. Known abuse potential (includes human and animal abuse potential assessment data)	NKTR-181 is a full mu-opioid receptor agonist and is thus expected to carry some level of abuse potential, however, its comparatively low mu-opioid receptor binding affinity and slow CNS entry relative to classic opioids suggests lower abuse potential. Rat and monkey self-administration data suggest relatively weak reinforcing effects and low abuse potential. In two HAP studies, compared to oxycodone, NKTR-181 was slow onsetting and offsetting on all measures and with placebo-like subjective effects at clinical doses and lower value assessed by "take drug again" at supratherapeutic doses.
2. Pharmacology (overall pharmacologic profile)	Following systemic absorption, NKTR-181 diffuses across the blood brain barrier at the slow rate intended by the design of the conjugated molecule. Pharmacologic profile in comparison to oxycodone, morphine, and/or other CII opioids: • Dopamine release following 5-second injections to rats is slow and low compared to oxycodone and cocaine • Weak respiratory depressant effects and apparent low toxicity at very high doses in nonclinical toxicology studies • Nonclinical studies indicate mu-opioid like analgesia with slow onset predicted by slow rate of CNS entry • Pivotal phase 3 clinical study confirms effective analgesic effects • Human pupil constriction and subjective effects delayed by 1–2 hours compared to oxycodone
3. Current state of science (including *in vitro* manipulation)	Extensive evaluation of physicochemical properties and stability of molecule have revealed no known chemical, enzymatic, or physical method to hydrolyze, deconjugate, or otherwise alter NKTR-181 to produce a known abusable opioid or enable rapid entry into the CNS.
4. History of abuse of substance and related substances	NKTR-181 is a new molecular entity and as such does not have a history of or a current pattern of abuse. As a full mu-opioid analgesic there will likely be exploratory abuse and evaluation by people who use opioids for nonmedical reasons, posting results on websites such as Erowid and Bluelight. It is predicted to be rated more like tramadol or buprenorphine than oxycodone, heroin, or fentanyl and will not substitute for them as a euphoriant or emerge as a major target for diversion or nonmedical use.
5. Scope and nature of problems	There is wide variation across opioids with respect to nonmedical use, abuse, and associated overdose deaths, with highest rates of nonmedical use and overdose occurring with those that produce rapid and strong euphoriant effects. Findings to date suggest that NKTR-181 will be less of a target for abuse than prototypic CII drugs because it is designed to have a slow rate of entry into the CNS, a property resulting from its novel molecular structure, to minimize euphoriant effects or use for fast relief of acute pain regardless of route of administration. The same pharmacological profile that will confer relatively low risk of iatrogenic addiction relative to that of prototypic mu-opioid receptor agonists will also confer reduced risk of acute overdose and respiratory depression.
6. Public health implications (positive and negative)	The dosage form is not extended release; therefore, unit doses will not be expected to carry a high risk of overdose if the patient or abuser crushes or chews the tablet before swallowing. Among those who accidentally ingest NKTR-181 or nonmedically sample it, adverse effects and public health risks are predicted to be substantially less than those carried by CII opioids. Displacement of prescribing of CII opioids with NKTR-181 may contribute to the gradual emergence of an analgesic market place that is less dominated by opioids with the highest risks of abuse and overdose.
7. Psychic & physiological dependence	Assessment of abuse, diversion, and withdrawal in phase 2 and 3 studies suggest a low risk of psychic and physiological dependence or iatrogenic addiction. Abrupt discontinuation of NKTR-181 did not precipitate requests for interventions to manage withdrawal symptoms. The results of the phase 3 study included intensive assessment by the COWS and SOWS following both abrupt and tapered drug discontinuation, as well as the expert adjudicated potential abuse, diversion, and withdrawal signaling events of the MADDERS.
8. Chemistry	NKTR-181 is not a prodrug or a reformulation of a marketed opioid, but a small molecule, new molecular entity that was engineered to have slower penetration into the CNS.

CII, Schedule II drugs as defined by the US Controlled Substance Act; CNS, central nervous system; COWS, Clinical Opiate Withdrawal Scale; HAP, human abuse potential; MADDERS, Misuse, Abuse, and Diversion Drug Event Reporting System; SOWS, Subjective Opioid Withdrawal Scale.

Recommendation for Scheduling (Disclaimer: This recommendation was developed by Drs. Henningfield, Fant, Buchhalter et al. of Pinney Associates as part of their ongoing abuse potential study needs assessment and scheduling analysis.)

Proposed Pinney Associates recommendation: NKTR-181 is characterized as a drug substance with a lower abuse potential than prototypic CII opioids. This includes slower onsetting and lower euphoriant and other CNS mediated effects, low psychological and physical dependence/withdrawal risk, and a favorable safety profile with respect to respiratory effects and overdose risk compared to CII opioids. The overall abuse potential profile of NKTR-181 is more similar to CIV pentazocineand tramadol, and CIII buprenorphine than to CII opioids such as morphine and oxycodone.

References: **1.** Miyazaki T, Choi IY, Rubas W, et al. NKTR-181: A novel mu-opioid analgesic with inherently low abuse potential. *J Pharmacol Exp Ther.* 2017;363(1):104–13; **2.** Markman J, Gudin J, Rauck R, et al. Efficacy, safety, and tolerability of NKTR-181 in patients with moderate to severe chronic low-back pain: A Phase 3 study. *Postgraduate Medicine.* 2017;129(sup1): 28–9; **3.** Webster L, Henningfield J, Buchhalter AR, et al. Human abuse potential of the new opioid analgesic molecule NKTR-181 compared with oxycodone. *Pain Med.* 2018;19(2):307–18; **4.** U.S. Food and Drug Administration (FDA). Assessment of Abuse Potential of Drugs: Guidance for Industry. https://www.fda.gov/downloads/drugs/guidances/ucm198650.pdf. Accessed November 9, 2017.

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