

Original Research Article

Human Abuse Potential of the New Opioid Analgesic Molecule NKTR-181 Compared with Oxycodone

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Partial results from this study previously presented at the 2013 College on Problems of Drug Dependence Annual Meeting (without abstract publication): Webster L, Smith S, Silowsky J, et al. Abuse potential assessment of novel opioid analgesic NKTR-181: Implications for labeling and scheduling. *Drug Alcohol Depend* 2014;140:e239.

Abstract

Objective. Evaluate the human abuse potential, pharmacokinetics, pharmacodynamics, and safety

of NKTR-181, a novel mu-opioid agonist molecule, relative to oxycodone.

Design. This randomized, single-center, double-blind, active- and placebo-controlled five-period crossover study enrolled healthy, adult, non-physically dependent recreational opioid users.

Setting. Inpatient clinical research site.

Subjects. Forty-two randomized subjects (73.8% male, 81% white, mean age = 25 years).

Methods. The primary objective was to evaluate single orally administered 100, 200, and 400 mg NKTR-181 doses in solution compared with 40 mg oxycodone and placebo solutions using the Drug Liking visual analog scale. Secondary measures included the Drug Effects Questionnaire, Addiction Research Center Inventory/Morphine Benzedrine Group Subscale, Price Value Assessment Questionnaire, Global Assessment of Overall Drug Liking, and Take Drug Again Assessment. Central nervous system mu-opioid effects were assessed using pupillometry. The study included qualifying and treatment phases. Subjects received each of the five treatments using a crossover design.

Results. NKTR-181 at all dose levels had significantly lower Drug Liking E_{max} than oxycodone ($P < 0.0001$). Drug Liking scores for oxycodone increased rapidly within 15 minutes and peaked at approximately one hour postdose, whereas Drug Liking (and most secondary abuse potential measures) for all doses of NKTR-181 were comparable with placebo for at least the first hour. Only the 400 mg Drug Liking scores were minimally differentiated vs placebo from one and a half to four hours, but remained significantly lower than oxycodone ($P < 0.003$). NKTR-181 treatment-related adverse effects were mild and occurred at a lower rate compared with oxycodone.

Conclusions. NKTR-181 demonstrated delayed onset of CNS effects and significantly lower abuse

potential scores compared with oxycodone in recreational opioid users.

Key Words. NKTR-181; Oxycodone; Abuse Potential; Chronic Pain; Opioid; Drug Liking

Introduction

Opioid analgesics have a long history of use as a treatment for moderate to severe chronic pain [1]. Unfortunately, abuse of these medicines has become a growing epidemic. In the United States, it is estimated that between the years 2002 and 2011, 25 million people used pain relievers for nonmedical, recreational use, and in 2014, nearly 2 million people were addicted to or abused these drugs [2,3]. Deaths from overdoses involving prescription opioids have almost quadrupled in the last 15 years, with nearly 19,000 such deaths reported in the United States in 2014 alone [4].

Although rate of brain entry is not the sole determinant of abuse potential, it is understood that rapid entry into the central nervous system (CNS) is an important factor in the overall attractiveness of a drug as a target for abuse [5–8]. Volkow et al., using positron emission tomography (PET) studies in humans, demonstrated a link between rapid brain uptake (leading to rapid striatal dopamine changes) of drugs subject to abuse and increased reinforcing effects [9]. Self-reported feelings of “high” increased in proportion to rapid increases of striatal dopamine in subjects receiving intravenous methylphenidate but were essentially absent after slow increases of striatal dopamine following methylphenidate oral administration [10]. These PET studies provide a mechanistic basis for understanding widespread observations that drug abusers seek drugs such as heroin, fentanyl, or oxycodone that have rapid CNS uptake related to their intrinsic physicochemical properties and routes of administration. Rapid onset of CNS effects can also contribute to respiratory depression, sedation, intoxication, or other potentially dangerous and undesirable effects, increasing the risk of overdose and death [11,12]. Therefore, it is our hypothesis that drugs with inherently slow CNS uptake could have less abuse potential and improved safety.

There is a need for safer medications that provide desired analgesic benefits while reducing the potential for abuse and tampering [8,13,14]. NKTR-181 is being developed to meet these needs. Specifically, NKTR-181’s molecular structure was engineered with the goal of providing analgesia comparable with morphine and other prototypic mu-opioid analgesics, but with lower abuse potential and decreased incidence and severity of adverse effects. The unique physicochemical properties of NKTR-181 result in a relatively slow rate of entry into the CNS, independent of dose level or route of administration. Despite the reduced rate of CNS entry, NKTR-181 displays full analgesic activity comparable with morphine and oxycodone in mouse and rat pain

models, while demonstrating reduced locomotor impairment in the rotarod test [15]. Moreover, NKTR-181 has a reduced abuse potential compared with oxycodone in rats and monkeys, measured by self-administration and progressive ratio breakpoint methods, where response to NKTR-181 is similar to that of saline. In other preclinical models, NKTR-181 has reduced CNS-mediated adverse effects such as sedation and respiratory depression when compared with oxycodone and morphine [15–21].

In phase I studies in opioid-naïve healthy subjects, NKTR-181 was safe and well tolerated as single doses of 1,000 mg or less and as multiple doses up to 400 mg twice daily for 14 days [22,23]. NKTR-181 exhibits a delayed and prolonged plasma pharmacokinetic profile compared with prototypic mu-opioids such as oxycodone and morphine, with C_{max} occurring approximately three hours postdose and an elimination half-life of approximately 12 hours independent of dose, even when administered as a solution (Figure 1) [15,22–25]. The prolonged exposure profile of NKTR-181 supports twice-daily dosing for the treatment of chronic pain, without the need for a controlled release formulation, and most likely contributes to the slow rate of CNS entry when compared with the rapid absorption of prototypic opioids.

Figure 1 displays the onset and duration of pupil constriction relative to plasma concentration time profiles after administration of oxycodone [25] or NKTR-181 to healthy subjects [24]. The time course of miosis, a direct measure of CNS mu-opioid effects, significantly lags the time course of NKTR-181 in plasma, whereas these time courses are essentially superimposable for oxycodone. The approximately three-hour lag in achieving maximal miosis reflects slow entry of NKTR-181 into the CNS from the plasma. The half-life of the blood-to-CNS equilibration process, estimated using plasma drug concentration vs time and pupil diameter vs time data, for NKTR-181 (2.9 hours) is 16 times longer than the reported equilibration half-life for oxycodone (0.18 hour) [15,24,25]. Slow CNS entry is a property inherent in the molecular design of the NKTR-181 that is independent of formulation, dose level, and route of administration. These promising preclinical and clinical findings supported the granting of fast-track development status for NKTR-181 by the US Food and Drug Administration [26].

This study evaluated the pharmacodynamics and abuse potential, pharmacokinetics, and safety of NKTR-181 doses used in ongoing phase III trials, relative to oxycodone and placebo.

Methods

Ethical Conduct

This study was conducted on an inpatient basis at CRI Lifetree (now known as PRA Health Sciences) in Salt Lake City, Utah, in accordance with the Declaration of

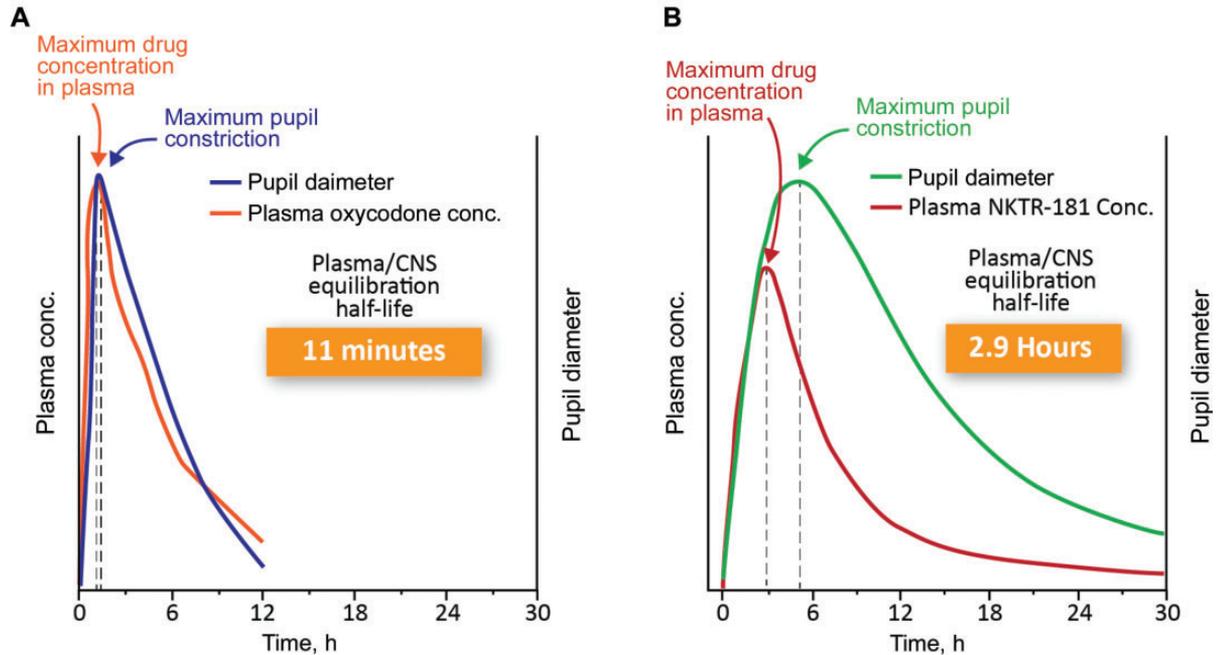


Figure 1 Pharmacokinetic and pharmacodynamic results from phase I studies [22,25,26]. Onset and duration of pupil constriction relative to opioid concentration-time profile for **(A)** 15 mg oxycodone and **(B)** 200 mg NKTR-181.

Helsinki and its amendments as outlined by the International Conference on Harmonisation. The study was approved by the New England Institutional Review Board, and the trial was conducted in compliance with good clinical practice and applicable regulatory requirements.

Subjects

The study enrolled eligible healthy male and female adults (age 18–55 years, inclusive) who reported recreational (i.e., nonmedical) opioid use at least 10 times in the preceding year and at least once within the 12 weeks before screening. Subjects were not physically dependent on opioids, as determined by interview and naloxone challenge. Subjects were also in good health, as indicated by medical history and physical exam, and able to speak, read, and understand English. Voluntary consent was obtained from all subjects before participating in the study. Key exclusion criteria included: 1) pregnancy or lactation; 2) history or current diagnosis of substance dependence (except nicotine and caffeine) or alcohol abuse (based on DSM-IV-TR criteria; corresponding to current nomenclature from DSM-V, “use disorder”); 3) oxygen saturation value of less than 90% or other clinically significant health problems at screening; and 4) consumption of any substance that interfered with the trial as defined by the protocol.

Overall Study Design

This was a single-center, randomized, double-blind, active- and placebo-controlled, five-period crossover study that assessed the abuse potential, pharmacodynamics, pharmacokinetics, and safety of NKTR-181 compared with oxycodone and placebo, consistent with principles provided in the 2010 US Food and Drug Administration (FDA) draft guidance for Assessment of Abuse Potential of Drugs [27]. Single doses of 100, 200, or 400 mg NKTR-181 in solution were compared with single doses of 40 mg oxycodone and placebo in solution. The study consisted of a screening phase, a qualification phase, a treatment phase, and a follow-up phase.

After initial screening, subjects entered into the qualification phase, which consisted of a naloxone challenge and oxycodone discrimination testing. The naloxone challenge determined if subjects were physically opioid dependent. After an initial dose of 0.2 mg naloxone was administered by intravenous bolus, subjects were observed for signs or symptoms of withdrawal as defined by a Clinical Opiate Withdrawal Scale (COWS) score of 5 or higher. If no evidence of withdrawal occurred within 30 seconds, an additional dose of 0.6 mg naloxone was administered and subjects received an additional assessment using COWS. Subjects with COWS scores of less than 5 after the naloxone challenge were defined as not physically opioid dependent and remained as inpatients in the clinical unit to complete the Drug Discrimination Test. In a two-way crossover, 1:1

ratio, double-blind, randomized design, subjects received 15 mg oxycodone and matching placebo 24 hours apart and after a minimum eight-hour fast. Subjects were eligible to enter the treatment phase if they tolerated oxycodone and demonstrated the following within the first two hours after dosing: 1) a placebo response between 40 and 60 mm, maximum effect (E_{max}) of 65 mm or greater in response to oxycodone treatment, and 15 mm or greater difference between oxycodone and placebo treatments on a 0–100 point, 100 mm bipolar Drug Liking Visual Analog Scale (VAS) where 50 mm represented a “neutral” response; 2) 30 mm or greater difference between oxycodone and placebo treatments, placebo response between 0 and 10 mm on a 0–100 point unipolar Drug High VAS. The volunteers must also have been generally able to comply with study procedures and must have responded adequately to study-specific instructions made by clinical staff. Those eligible to continue with the study were subjected to a 24-hour washout period before beginning the five-session abuse potential treatment phase.

During the approximately two-week, inpatient, blinded treatment phase, subjects were randomized to one of the treatment sequences as depicted in Figure 2. Each sequence consisted of five dosing periods, where subjects would receive a single treatment of one of the study medications or placebo as defined by the sequence, followed by a 72-hour washout period. Study procedures were the same for each treatment. The five treatments were 100, 200, and 400 mg of NKTR-181 in solution, 40 mg oxycodone in solution, and the matching placebo solution that contained the bittering agent denatonium benzoate. Drug or placebo administration generally occurred around 8 AM after an eight-hour fast and was immediately followed by consumption of 240 mL of sugar-free cranberry grape juice.

Pharmacodynamic Assessments

Abuse potential and other behavioral and subjective end points were assessed using the various computer-administered VASs detailed in Table 1. Additional abuse potential-related end points included the Addiction Research Center Inventory/Morphine Benzodrine Group (ARCI/MBG) scale and the Price Value Assessment Questionnaire (PVAQ). Pupil Diameter was measured immediately prior to each pharmacokinetic blood sample to determine the time course of the mu-opioid CNS effect.

The ARCI/MBG subscale, measured at one-half, one, one and a half, two, three, four, five, six, seven, and eight hours postdose, consisted of 16 statements used to assess euphoria and positive mood, with each item scored on a two-point scale (0 to 1), where 0 = false and 1 = true. The total score was calculated by adding the individual scores, with a possible total score of 16.

The PVAQ assessment asked subjects to estimate how much they would pay (street value) for each of the medications they received if the medications were illicitly made available. Street value was assessed 24 hours after each dosing session and was selected from a \$0–10 scale divided into 50 cent increments.

Pharmacokinetic Assessments

Plasma drug concentrations were quantified from blood samples obtained predose ($t=0$) and at five, 10, 15, 30, 45 minutes; one, one and a half, two, three, four, five, six, seven, eight, 12, and 24 hours postdose.

Safety Assessments

Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, 12-lead electrocardiogram (ECG), continuous three-lead telemetry, continuous oxygen saturation monitoring for at least eight hours postdose, and clinical laboratory tests. Vital signs were measured predose and one, two, four, eight, and 12 hours postdose. Laboratory tests were completed at screening and at study discharge; 12-lead ECG readings were completed at screening, qualification, and discharge, and three-lead telemetry was performed continuously from predose through at least eight hours postdose.

Statistical Analysis

The study was powered to detect a mean difference between 40 mg oxycodone and 200 mg NKTR-181 of 0.35 relative effect size (in terms of standard deviation units of Drug Liking score 0–100 VAS) with 80% power, resulting in a planned sample size of approximately 35 completing participants. Approximately 40 randomized subjects were planned to participate in the study to achieve the goal of 35 participants completing the five-period crossover study.

The primary study objective was to compare the relative abuse potential of NKTR-181 doses with 40 mg oxycodone. The primary abuse potential-related end points, Drug Liking effect (E_{max}), area under the drug effect curve from time zero to half an hour (AUE0–0.5h), zero to one hour (AUE0–1h), zero to two hours (AUE0–2h), and zero to three hours (AUE0–3h) for the bipolar Drug Liking VAS were analyzed using a linear mixed model to compare the treatment groups. The analysis population was the modified intention-to-treat (MITT) population, which included all randomized subjects who received at least one dose of study medication and who had at least one postdose assessment. The analysis model included sequence, period, and treatment as fixed effects and a random effect for subject nested within sequence. The time course of treatment of Drug Liking was investigated using Mixed-Model Repeated Measures (MMRM) to compare the drug liking between treatment groups across time. The MMRM model included sequence, period, treatment, time, and time by

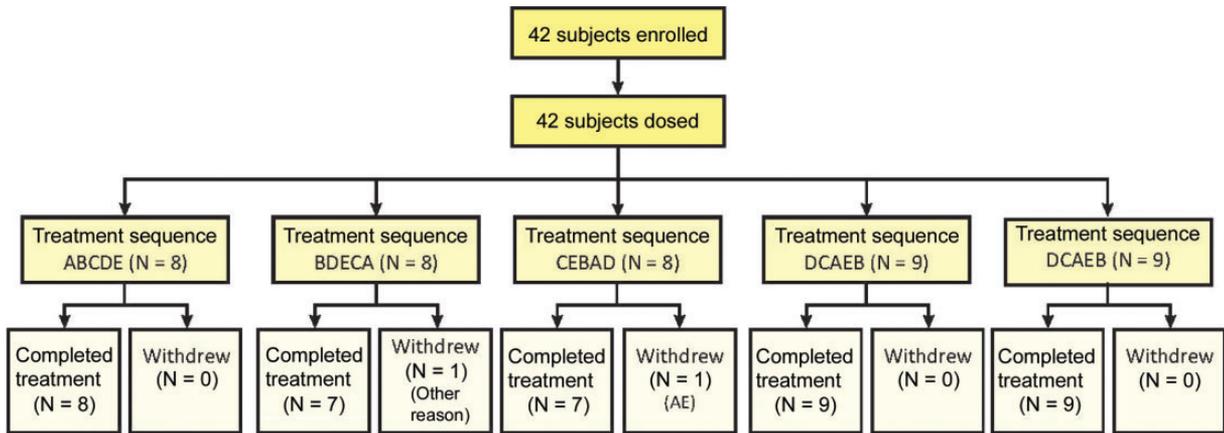


Figure 2 Subject disposition. Forty-two subjects completed the qualification phase and entered into the blinded treatment phase where subjects were randomized to one of the five treatment sequences. Treatment A: 100mg NKTR-181 in solution. Treatment B: 200mg NKTR-181 in solution. Treatment C: 400mg NKTR-181 in solution. Treatment D: 40mg oxycodone in solution. Treatment E: matching placebo solution.

Table 1 Bipolar and unipolar visual analog scales

0–100 VAS

VAS	Type	0	50	100
Drug Liking ^{†,‡}	Bipolar	“Do you like the drug effect you are feeling now?”		
		Strong disliking	Neutral	Strong liking
Overall Drug Liking [§]		“Overall, my liking for this drug is”		
		Strong disliking	Neutral	Strong liking
Take Drug Again [§]		“Would you want to take the drug you just received again, if given the opportunity?”		
		Definitely not	Do not care	Definitely would
Drug Effects Questionnaire: [‡]	Unipolar			
Drug High				
Any Effects [†]				
Good Effects		None		Extremely
Bad Effects				
Feel Sick				
Nausea*				
Sleepy*				
Dizzy*				

VAS = visual analog scale.

*Also measured at approximately 30 minutes prior to dosing.

[†]Also measured at five, 10, and 15 minutes.

[‡]Administered at 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, 480, 720, and 1,440 minutes postdose.

[§]Administered at 24 hours postdose.

treatment interaction as fixed effects and a random effect for subject nested within treatment sequence. Least squares means, least squares mean differences between the treatment groups, and 95% confidence intervals were reported. No adjustments for multiplicity were made for these analyses. Secondary end points included maximal effect (E_{max}) for Drug High and ARCI/MBG, Overall Drug Liking, and Take Drug Again (bipolar

scales) at 24 hours postdose, the PVAQ assessment, and the Drug Effects Questionnaire. Secondary pharmacodynamic end points, including pupillometry results, were analyzed similar to the primary pharmacodynamic end point, without adjustment of *P* values.

Pharmacokinetic analyses were conducted on all randomized subjects who received at least one dose of

study medication and had adequate plasma concentration time data to allow meaningful pharmacokinetic analyses. Pharmacokinetics parameters analyzed included time to maximum observed plasma concentration for each subject (T_{max}), maximum observed plasma concentration for each subject (C_{max}), and area under the plasma concentration vs time curve from time 0 to time of the last observed concentration (AUC_{0-last}).

Safety analyses were conducted on all randomized subjects who received at least one dose of study drug during the treatment phase.

Results

Disposition and Demographic Data

Forty-two subjects completed the qualification phase and were randomized to the treatment phase (Figure 2). Of these, two subjects prematurely discontinued the study during the treatment phase (one for an AE of pain in an extremity after one dosing session and one due to childcare issues after three dosing sessions). Demographically, subjects were predominantly male (73.8%) and white (81%). The mean (standard deviation) age was 25.1 (5.3) years, and the mean (SD) body mass index was 24.1 (3.5) kg/m². All subjects had a history of recreational opioid use, with the most prevalent major medication classifications cited as opioids (100%, per study protocol), cannabinoids (85.7%), stimulants (50.0%), hallucinogens (31.0%), sedative hypnotics (26.2%), and dissociative anesthetics (ketamine, 2.4%).

Pharmacodynamics

Mean Drug Liking scores for oxycodone increased rapidly, were near maximal within the first hour, and were significantly elevated above values for placebo and all dose levels of NKTR-181 (Figure 3A). For the primary end point (Drug Liking E_{max}) and AUE over one-half, one, two, and three hours postdose, scores for oxycodone were significantly greater compared with all doses of NKTR-181 and placebo ($P < 0.0001$ all comparisons) (Table 2). Drug Liking E_{max} for the 100 and 200 mg NKTR-181 treatments were similar to those for placebo ($P = 0.16$ and $P = 0.24$, respectively). Only the 400 mg dose of NKTR-181 showed a Drug Liking E_{max} greater than placebo (62.3 vs 55.0 mm, respectively), but the onset of Drug Liking effects was delayed as seen in the treatment time course of Drug Liking (Figure 3A). Comparison of AUE values between NKTR-181 and oxycodone yielded patterns similar to those for Drug Liking E_{max} (Table 2). Time course data shows that Drug Liking scores for oxycodone increased rapidly (within 0.25 hour) and reached near maximum within the first hour (Figure 3A). These effects remained significantly higher (strong liking) than placebo until five hours postdose. In contrast, NKTR-181 doses had slower onset (beginning approximately one and a half hours postdose), shorter duration (two and a half hours), and

Drug Liking scores similar to placebo, with only a few occurrences of statistically significant separation from one and a half to four hours after the 400 mg NKTR-181 dose (Figure 3A).

Similar to Drug Liking, Mean Drug High scores for oxycodone also increased rapidly, were near maximal within the first hour, and were significantly elevated above values for placebo and all dose levels of NKTR-181 (Figure 3B). The mean Drug High E_{max} for oxycodone was significantly greater compared with all doses of NKTR-181 and placebo ($P < 0.0001$) (Table 2). In contrast to oxycodone, all NKTR-181 doses had a slower onset (beginning approximately one and a half hours postdose), shorter duration (three and a half hours), and Drug High scores similar to placebo, with only a few occurrences of statistically significant separation from one and a half to five hours after the 400 mg NKTR-181 dose (Figure 3B). Consistent with Drug Liking and Drug High, values for DEQ Good, Bad, Dizzy, Sleepy, Sick, and Nausea after oxycodone administration were statistically greater than those for NKTR-181 and placebo (Table 2 and Figure 4). Oxycodone produced robust effects on the ARC/MBG scale, yielding a mean E_{max} significantly greater than that for any NKTR-181 dose and placebo ($P < 0.0001$). In contrast, only the mean E_{max} for 400 mg NKTR-181 differed significantly from placebo (Table 2). Based on the PVAQ, the mean dollar value attributed to oxycodone was significantly higher compared with all NKTR-181 doses ($P < 0.0001$) (Table 2). Global Assessment of Overall Drug Liking and Take Drug Again scale were measured 24 hours post-drug administration and were the least sensitive to detect differences; results of these measures were inconsistent (Table 2).

Pupillometry

Pupillometry showed an early and extensive pharmacodynamic response for oxycodone and delayed and reduced pharmacodynamic response for NKTR-181 (Figure 3C). Compared with oxycodone, all NKTR-181 doses had substantially slower onset of miosis, beginning approximately 0.75 hours or later postdose (Figure 3C). Consistent with slower onset of miosis, mean E_{min} was reached later postdose for all NKTR-181 doses compared with oxycodone. Mean times to pupil diameter E_{min} for oxycodone and 400 mg NKTR-181 were 1.4 and 4.3 hours (Table 2), consistent with previously reported values of 1.1 [25] for oxycodone and 4.0 hours for NKTR-181 (data on file).

Pharmacokinetics

The mean time to reach C_{max} for oxycodone was approximately one hour, whereas mean times to reach C_{max} for NKTR-181 were longer and similar for all dose groups (mean = 2.0–2.5 hours after dosing). Dose-normalized NKTR-181 C_{max} (mean range = 6.33–6.55 ng/mL/mg) and AUC values (mean range = 32.47–34.53 h*ng/mL/mg) from this study were comparable among dose levels and consistent with values observed

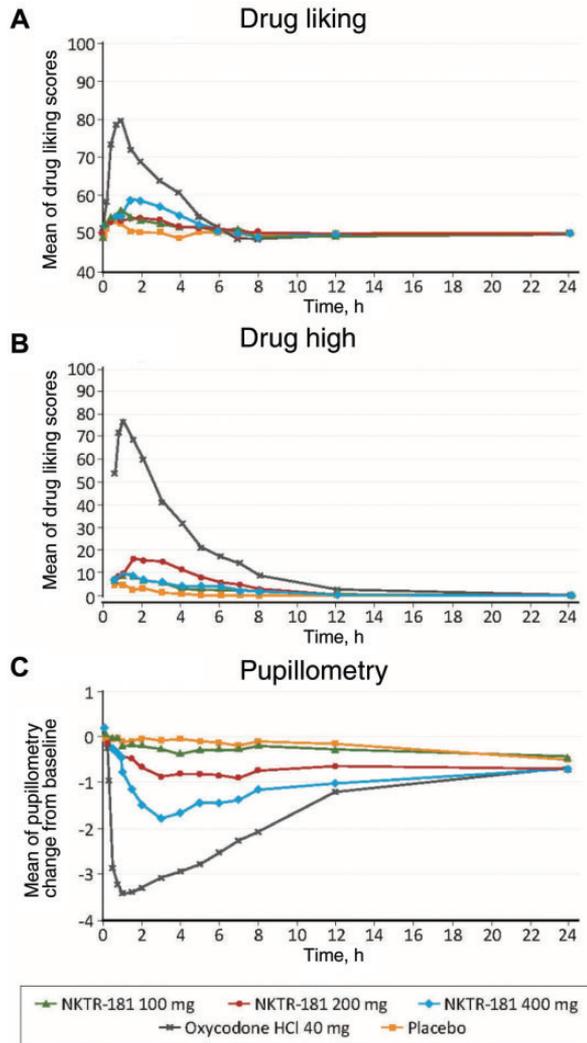


Figure 3 Drug Liking VAS, Drug High VAS, and pupillometry results in the (MITT Population). Mean Drug Liking and Drug High scores (**A and B**) for oxycodone increased rapidly, were near maximal within the first hour, and were significantly elevated above values for placebo and all dose levels of NKTR-181. Pupillometry profiles (**C**) show a rapid, early, and extensive pharmacodynamic response for oxycodone and a delayed and reduced pharmacodynamic response for NKTR-181.

in phase I studies, indicating that exposure was proportional to dose. Overall, oxycodone and NKTR-181 systemic exposures were comparable with those previously reported [23–25, 34].

Safety

There were no serious adverse events. As shown in Table 3, all TEAEs were those typically associated with

the use of opioids, and the majority occurred following oxycodone administration. The most frequently occurring TEAE was generalized pruritus following administration of oxycodone (41.5%) and 200 or 400mg NKTR-181 (7.3% and 4.9%, respectively). This was followed by nausea with oxycodone (29.3%) in contrast to 100 mg (2.5%), 200 mg (2.4%), and 400 mg (7.3%) of NKTR-181. Vomiting occurred in 2.4% of subjects receiving 200 and 400mg NKTR-181 compared with 24.4% of subjects following administration of oxycodone.

Discussion

Results of this study demonstrate that the novel mu-opioid analgesic NKTR-181 showed a lower occurrence of CNS effects associated with abuse potential. Designed and performed according to the FDA’s 2010 Guidance for Industry Assessment of Abuse Potential of Drugs in Humans, the study enrolled and randomized non-physically dependent recreational drug users with a history of opioid use who were able to discern between oxycodone and placebo. As noted, NKTR-181 has been shown to exhibit a relatively slow rate of entry into the CNS that is inherent to the molecule and independent of dose level, route of administration, or employment of a controlled-release or abuse-deterrent formulation. In addition, NKTR has innate properties of an IR opioid. Therefore, in this study, immediate-release oxycodone was selected as the comparator and both substances were administered in liquid form in order to remove any potential confounding effects of formulation from the analysis.

Consistent with many other studies of oxycodone abuse potential, 40 mg oxycodone produced rapid and strong drug liking effects indicative of high abuse potential [18–30] and differed significantly compared with placebo on key abuse potential outcome measures (eg, E_{max} of Drug Liking VAS and Drug High VAS, $P < 0.0001$), confirming the validity of this study. In contrast, the onset of effects related to Drug Liking for all doses of NKTR-181 were slower and demonstrated significantly lower abuse potential, including delayed and less robust CNS effects as measured by pupil diameter changes in comparison with oxycodone.

The pattern of separation between the times that plasma C_{max} and maximum pupil constriction were achieved, shown in Figure 1, is maintained for single doses of NKTR-181 up to 1,200 mg, the highest dose level studied to date [24, data on file], as well as after pharmacokinetic steady-state is achieved using the phase III dosing schedule of q12h [22]. These PK/PD findings, combined with the results of the present human abuse potential study, support the hypotheses that reducing the rate of drug transfer from blood into the CNS by controlling the molecular structure of an opioid can reduce abuse potential yet preserve CNS mu-opioid agonist activity.

Table 2 Pharmacodynamic results

Pharmacodynamic parameters	Placebo (N = 41)	NKTR-181 100 mg (N = 40)	NKTR-181 200 mg (N = 41)	NKTR-181 400 mg (N = 41)	Oxycodone 40 mg (N = 41)
Drug Liking VAS					
E_{max} , mean (SD)	55.0 (6.28)**†	58.1 (10.73)**†	57.7 (9.00)**†	62.3 (12.58)**†,‡	85.0 (10.97)**‡
AUE _{0-0.5h} , mean (SD)	0.38 (1.60)**†	0.86 (2.01)**†	0.73 (1.60)**†	0.98 (1.65)**†	3.99 (3.04)**‡
AUE _{0-1h} , mean (SD)	1.73 (4.11)**†	3.33 (6.25)**†	2.43 (4.06)**†	3.27 (4.53)**†	17.74 (8.21)**‡
AUE _{0-2h} , mean (SD)	2.64 (8.63)**†	7.80 (15.00)**†	6.17 (10.82)**†	11.00 (13.60)**†,‡	40.64 (22.12)**‡
AUE _{0-3h} , mean (SD)	2.86 (11.54)**†	10.70 (22.43)**†	9.90 (18.14)**†	18.71 (25.62)**†,‡	56.97 (36.51)**‡
DEQ Drug High VAS					
E_{max} , mean (SD)	7.93 (10.67)**†	13.78 (20.49)**†	13.88 (15.97)**†	22.59 (24.18)**†,‡	80.29 (17.20)**‡
DEQ Any Effect VAS					
E_{max} , mean (SD)	8.21 (2.86)**†	15.20 (2.90)**†	14.52 (2.86)**†	25.95 (2.86)**†,‡	79.55 (2.86)**‡
DEQ Nausea VAS					
E_{max} , mean (SD)	2.02 (2.78)**†	2.43 (2.81)**†	4.21 (2.78)**†	9.26 (2.78)**†	27.44 (2.78)**‡
DEQ Good Effect VAS					
E_{max} , mean (SD)	8.07 (3.21)**†	15.54 (3.25)**†	13.86 (3.21)**†	24.95 (3.21)**†,‡	76.92 (3.21)**‡
DEQ Bad Effect VAS					
E_{max} , mean (SD)	2.96 (2.45)**†	3.30 (2.48)**†	4.48 (2.45)**†	9.74 (2.45)**†	32.92 (2.45)**‡
DEQ Dizzy VAS					
E_{max} , mean (SD)	1.85 (2.09)**†	3.15 (2.12)**†	2.43 (2.09)**†	5.23 (2.09)**†	26.65 (2.09)**‡
DEQ Sick VAS					
E_{max} , mean (SD)	2.27 (2.40)**†	2.05 (2.43)**†	1.98 (2.40)**†	6.64 (2.40)**†	24.23 (2.40)**‡
DEQ Sleep VAS					
E_{max} , mean (SD)	4.33 (3.16)**†	9.97 (3.20)**†	8.51 (3.16)**†	17.66 (3.16)**†,‡	43.89 (3.16)**‡
ARCI/MBG					
E_{max} , mean (SD)	3.98 (4.10)**†	4.93 (4.86)**†	5.49 (5.31)**†	6.22 (5.45)**†,‡	11.73 (4.08)**‡
PVAQ					
LS, mean (SE)	10.0 (55.70)**†	52.5 (152.31)**†	67.5 (152.14)**†	145.0 (227.53)**†,‡	432.5 (387.55)**‡
Overall Drug Liking VAS					
LS, mean (SE)	51.42 (2.56)	54.01 (2.59)	51.01 (2.56)**†	53.96 (2.56)	58.46 (2.56)
Take Drug Again VAS					
LS, mean (SE)	45.23 (3.01)**†	50.39 (3.05)	48.35 (3.01)**†	52.47 (3.01)	58.57 (3.01)**‡
Pupillometry					
E_{min} , mean (SD)	5.4 (0.86)**†	5.3 (0.67)**†	4.9 (0.75)**†,‡	4.2 (0.77)**†,‡	2.8 (0.51)**‡
T_{Emin} , mean (SD)	10.8 (9.75)**†	9.1 (8.88)**†	9.1 (7.31)**†	4.3 (3.43)**‡	1.4 (1.18)**‡

ARCI/MBG = Addiction Research Center Inventory/Morphine Benzedrine Group; AUE = area under the effect curve; E_{max} = maximum effect (mm); E_{min} = minimum effect (mm); LS = least squares; PVAQ = Price Value Assessment Questionnaire; VAS = visual analog scale. SD = standard deviation; SE = standard error

* P value < 0.05.

** P value < 0.0001.

†Significantly different from oxycodone.

‡Significantly different from placebo.

The primary abuse potential end point, E_{max} of Drug Liking VAS score, is considered among the most direct, robust, and sensitive self-reported measures indicative of opioid abuse potential [8,31–33]. All NKTR-181 doses produced significantly lower Drug Liking E_{max} scores compared with the active comparator, 40 mg oxycodone ($P < 0.0001$). The 100 and 200 mg doses of NKTR-181 exhibited Drug Liking scores that were indistinguishable from placebo. The 400 mg NKTR-181 dose was slightly differentiated from placebo, but the AUE analysis showed this did not occur until more than one

hour postdose. Similar results were seen for the secondary end points, as well as for the incidence of opioid TEAEs. Scores for the DEQ components Drug High, Nausea, and Sleepy for all dose levels of NKTR-181 were typically not statistically different from placebo but were statistically lower than those for oxycodone. Collectively, the study showed that in recreational opioid users NKTR-181 resulted in a slower onset and lower magnitude of CNS effects and substantially lower scores for measures of abuse potential and side effects typical of prototypic opioid analgesics.

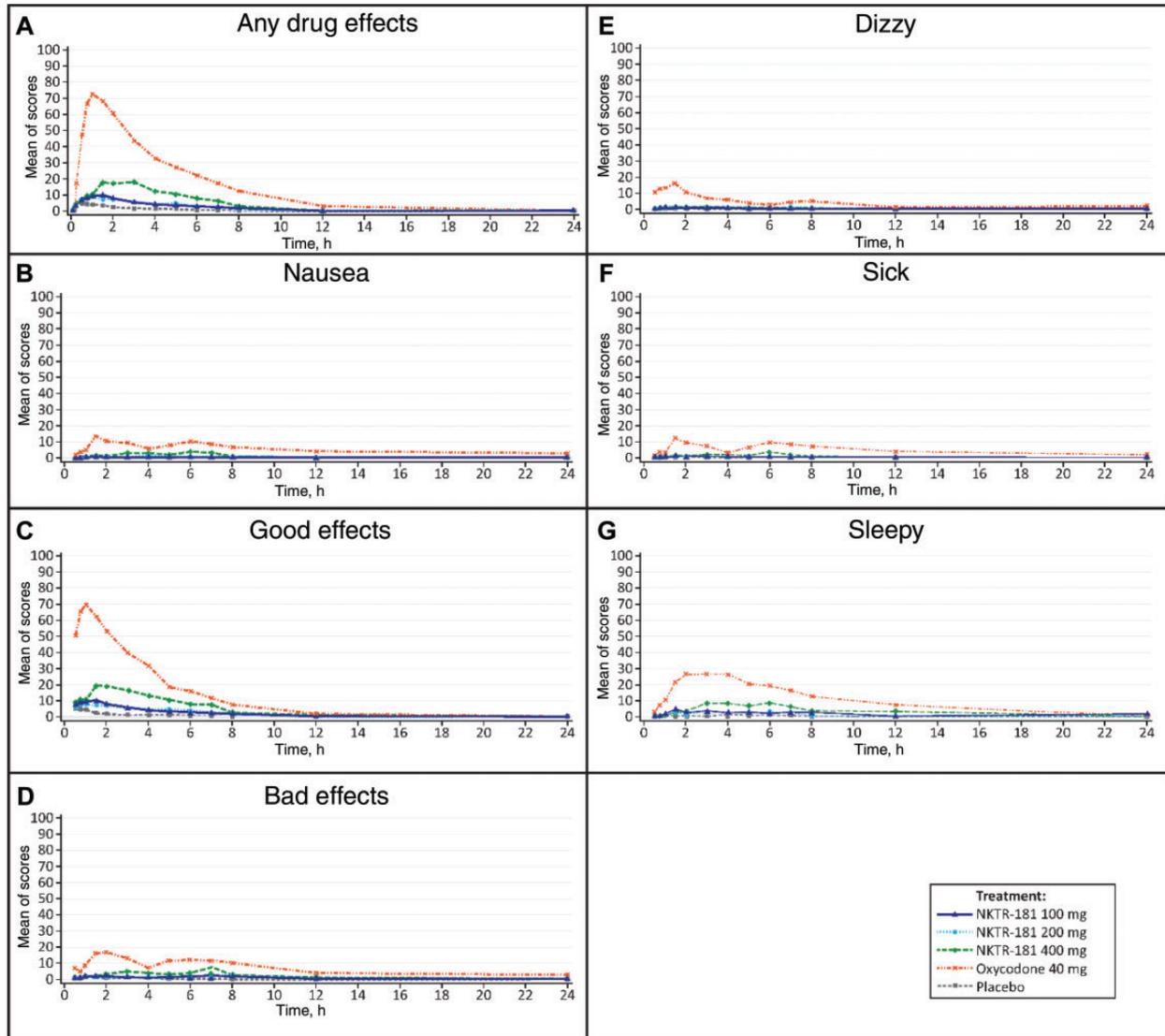


Figure 4 Mean responses to the DEQ questions at each observation time by treatment. Consistent with Drug Liking and Drug High responses over time, mean values for all DEQ responses after oxycodone administration were statistically greater than those for NKTR-181 and placebo.

Concentration time profiles and pharmacokinetic parameters for NKTR-181 in this study were comparable with those previously observed at the same dose levels in healthy subjects participating in phase I studies [15,22,23]. When adjusted for differences in administered dose, the pharmacokinetic profile of oxycodone solution observed in the study was consistent with previously published data [25,34].

The FDA is encouraging pharmaceutical companies to develop new analgesics that deter tampering and abuse through 1) formulations with physical/chemical barriers that deter crushing, grinding, and dissolving; 2) prodrugs that prevent the *in vitro* conversion to the parent opioid; and 3) new molecular entities,

including those that result in slower penetration into the central nervous system [8]. NKTR-181 is a new molecular entity (NME), and modulation of NKTR-181 entry into the CNS is achieved via physicochemical properties at the molecular level, rather than through formulation. To date, no conventional chemical or physical methods that alter the NKTR-181 molecule to accelerate the entry of a mu-opioid agonist into the CNS have been identified. Efforts to chemically manipulate the molecule have degraded the pharmacophore to render it inactive as a mu-opioid agonist (data on file).

NKTR-181 was placed in Schedule II during development, as are all thebaine-derived opioid molecules.

Table 3 Treatment-emergent adverse events by preferred term (safety population)

Preferred term	No. (%) of subjects				
	NKTR-181 100 mg (N = 40)	NKTR-181 200 mg (N = 41)	NKTR-181 400 mg (N = 41)	Oxycodone 40 mg (N = 41)	Placebo (N = 41)
Total No. of TEAEs	3	10	15	64	3
Subjects reporting at least one TEAE	3 (7.5)	5 (12.2)	8 (19.5)	29 (70.7)	3 (7.3)
Pruritus generalized	0	3 (7.3)	2 (4.9)	17 (41.5)	0
Nausea	1 (2.5)	1 (2.4)	3 (7.3)	12 (29.3)	0
Vomiting	0	1 (2.4)	1 (2.4)	10 (24.4)	0
Headache	0	1 (2.4)	2 (4.9)	6 (14.6)	1 (2.4)
Pruritus	0	0	2 (4.9)	6 (14.6)	0
Irritability	0	1 (2.4)	2 (4.9)	2 (4.9)	1 (2.4)
Dizziness	0	1 (2.4)	1 (2.4)	2 (4.9)	0
Flushing	0	0	0	2 (4.9)	0
Hiccups	0	0	1 (2.4)	1 (2.4)	0
Abdominal pain upper	0	1 (2.4)	0	0	0
Back pain	0	0	0	1 (2.4)	0
Chills	0	0	0	1 (2.4)	0
Dry eye	1 (2.5)	0	0	0	0
Dry mouth	0	0	0	1 (2.4)	0
Laceration	0	0	0	1 (2.4)	0
Lymphadenopathy	1 (2.5)	0	0	0	0
Pain in extremity	0	0	1 (2.4)	0	0
Presyncope	0	1 (2.4)	0	0	0
Rhinorrhea	0	0	0	0	1 (2.4)

TEAE = treatment-emergent adverse event.

Results of this human abuse potential study raise the possibility that NKTR-181 may merit less restrictive Controlled Substances Act (CSA) scheduling than prototypic Schedule II opioids and/or may warrant abuse-deterrent labeling claims consistent with the FDA's 2010 and 2015 Guidance pertaining to abuse potential, CSA scheduling, and abuse deterrence.

In summary, results of this human abuse potential study provide clinical evidence that NKTR-181 has lower abuse potential than oxycodone at NKTR-181 doses currently being tested in an ongoing phase III safety and efficacy trial (clinicaltrials.gov NCT02362672). Although NKTR-181 at the highest dose (400 mg) demonstrated more drug liking than placebo, the magnitude of these effects was small and the onset was delayed (>1 hour) compared with oxycodone. Future studies are planned to evaluate the effect of suprathreshold doses of NKTR-181 as well as the impact of intranasal and inhaled administration. We conclude that NKTR-181 may fulfill an unmet need in providing safe and effective treatment for moderate to severe chronic pain

conditions with reduced abuse potential and a lower incidence of CNS-mediated opioid adverse events.

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