NKTR-181 Demonstrates Low Abuse Potential in Recreational Opioid Users in Two Double-Blind, Randomized Crossover Human Abuse Potential Studies

Jack E. Henningfield[1], Lynn Webster[2], Debra Kelsh[3], Bradley Vince[3], Lin Lu[4], Janet Jobes[4], August R. Buchhalter[1], Suresh Siddhanti[4], Margaret Ziola[4], John Silowsky[4], Aleksandrs Odinecs[4], Sunny Xie[4], Carlo J. Di Fonzo[4], Michael A. Eldon[4], Xue Snow Ge[4]

[1]Pinney Associates; [2]Lifetree Clinical Research; [3]Vince and Associates/Altasciences; [4]Nektar Therapeutics

INTRODUCTION

- NKTR-181 is a new molecular entity, full mu-opioid receptor agonist in clinical development for the treatment of moderate-to-severe pain
- Its unique physicochemical properties result in a relatively slow rate of entry into the central nervous system (CNS) compared to conventional opioids, and there is no known chemical or physical method to alter NKTR-181 to increase its CNS entry speed[1]
- Because rapid entry into the CNS is an important factor that makes an opioid attractive for abuse, NKTR-181 may have less potential for abuse, without sacrificing clinically meaningful analgesia, relative to conventional opioids[2,3]
- In a phase 3 clinical trial (SUMMIT-07), NKTR-181 administered at 100 mg to 400 mg twice daily for 12 weeks produced clinically meaningful, highly statistically significant analgesia in patients with moderate-to-severe chronic low-back pain[4]
- Here we present the results of two double-blind, randomized, placebo-controlled, crossover human abuse potential (HAP) studies conducted in recreational opioid users to assess abuse potential across a wide range of NKTR-181 doses relative to therapeutic doses of a commonly prescribed opioid
  - Study I compared NKTR-181 doses of 100 mg, 200 mg, and 400 mg to oxycodone 40 mg and placebo
  - Study II compared NKTR-181 doses of 400 mg, 600 mg, and a supratherapeutic 1200 mg dose to oxycodone 40 mg and 60 mg and placebo

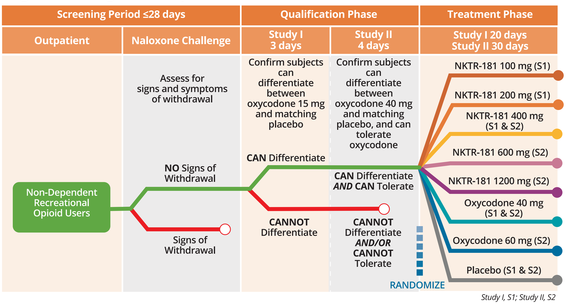
METHODS

- Subjects were healthy, non-opioid dependent adults (18 to 55 years of age) who reported recreational opioid use on at least 10 occasions within the last year and at least once within 8 (Study II) or 12 (Study I) weeks of study screening
- Each study included Screening, Qualification, and Treatment Phases (**Figure 1**)
- Each subject received single doses of NKTR-181, oxycodone, and placebo in a randomized, double-blind, crossover fashion:

  Study I: NKTR-181 was administered at 100 mg, 200 mg, and 400 mg as an oral solution compared with 40 mg oxycodone solution and matching placebo solution; 72-hour washout period between doses

  Study II: NKTR-181 was administered at 400 mg, 600 mg, and 1200 mg as oral tablets compared with 40 mg and 60 mg oxycodone over-encapsulated oral tablets and matching placebo; each treatment was administered in a double-dummy manner consisting of NKTR-181 tablets (6 tablets, NKTR-181 and/or its matching placebo tablet) and a capsule (oxycodone or its matching placebo capsule); ≥ 5-day washout period between doses
- Abuse potential was evaluated using subjective visual analog scale (VAS) ratings from 0 -100 mm for Drug Liking "at this moment," and for Drug High using the Drug Effects Questionnaire (DEQ) in both studies
- In Study I, the mean E_{max} for Drug Liking was analyzed using a linear mixed effects model in the modified intention-to-treat population
- In Study II, the mean E_{max} for Drug Liking was analyzed using a linear mixed effects model in the population who received all planned treatments
- Other outcome measures included pupil diameter, PK and safety

Figure 1. Design of Study I-II



Study I, S1; Study II, S2

RESULTS

- 94 subjects received all study treatments

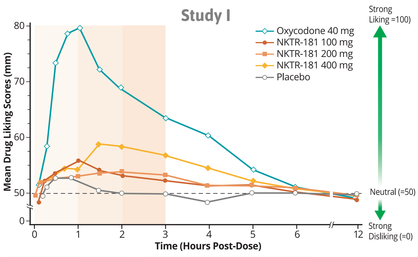
  Study I: 42 subjects completed the qualification phase and were enrolled and randomized in the treatment phase; 40 completed the treatment phase

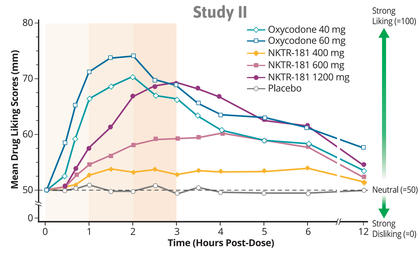
  Study II: 71 subjects completed the qualification phase and were enrolled and randomized in the treatment phase; 69 subjects received at least one treatment, and 54 completed the treatment phase
- Baseline characteristics

  Study I: The mean age of subjects was 25.1 years, the majority (73.8% and 81.0%) were male and Caucasian, respectively, and the mean BMI was 24.1

  Study II: The mean age of subjects was 31.7 years, the majority (95.7% and 65.2%) were male and African American, respectively, and the mean BMI was 25.5

Figure 2. Time Course of Mean Drug Liking "At This Moment," Mean E_{max}, and Drug Liking AUE Summary Data





Drug Liking	Oxycodone	NKTR-181			Placebo
	40 mg (n=41)	100 mg (n=40)	200 mg (n=41)	400 mg (n=41)	(n=41)
E_{max}, mean (SD)	85.0 (11.0)$^{\#\#\#,\$}$	58.1 (10.7)***	57.7 (9.0)***	62.3 (12.6)$^{***,\#,\$}$	55.0 (6.3)***
$AUE_{0\text{-}1h}$, mean (SD)	3.99 (3.0)$^{\#\#\#,\$}$	0.86 (2.0)***	0.73 (1.6)***	0.98 (1.7)$^{***,\#,\$}$	0.38 (1.6)***
$AUE_{0\text{-}1h}$, mean (SD)	17.7 (8.2)$^{\#\#\#,\$}$	3.3 (6.3)***	2.4 (4.1)***	3.3 (4.5)$^{***,\#,\$}$	1.7 (4.1)***
$AUE_{0\text{-}3h}$, mean (SD)	40.6 (22.1)$^{\#\#\#,\$}$	7.8 (15.0)***	6.2 (10.8)***	11.0 (13.6)$^{***,\#,\$}$	2.6 (8.6)***
$AUE_{0\text{-}3h}$, mean (SD)	57.0 (36.5)$^{\#\#\#,\$}$	10.7 (22.4)***	9.9 (18.1)***	18.7 (25.6)$^{***,\#,\$}$	2.9 (11.5)***

AUE, area under the effective curve; E_{max}, maximum effect; SD standard deviation
*P value < 0.05; **P value < 0.001; ***P value < 0.0001; P-values based on 2-sided test
#Significantly different from oxycodone; $Significantly different from placebo

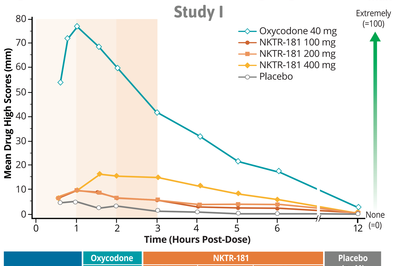
Drug Liking	Oxycodone		NKTR-181			Placebo
	40 mg (n=54)	60 mg (n=54)	400 mg (n=54)	600 mg (n=54)	1200 mg (n=54)	(n=54)
E_{max}, mean (SD)	76.8 (11.3)$^{\#\#\#,\$}$	81.9 (13.1)$^{\#\#\#,\$}$	61.6 (13.2)$^{\#\#\#,\$}$	67.4 (14.0)$^{\#\#\#,\$}$	77.0 (13.1)$^{\#,\$}$	52.3 (5.6)$^{\#\#\#,\$}$
$AUE_{0\text{-}1h}$, LS mean	5.8	9.5	0.8$^{\#\#\#,\$}$	1.7$^{\#\#\#,\$}$	2.4$^{\#\#,\$}$	0.1
$AUE_{0\text{-}2h}$, LS mean	24.5	32.3	3.7$^{\#\#\#,\$}$	8.5$^{\#\#\#,\$}$	14.2$^{\#\#,\$}$	1.0
$AUE_{0\text{-}3h}$, LS mean	41.8	52.6	7.0$^{\#\#\#,\$}$	17.6$^{\#\#\#,\$}$	32.4$^{\#,\$}$	2.1

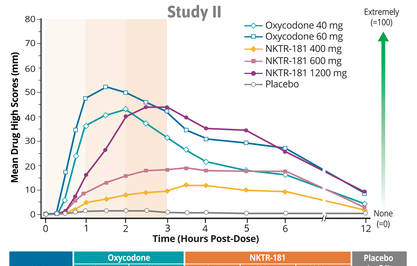
AUE, area under the effective curve; E_{max}, maximum effect; LS, least square; SD standard deviation
Comparisons between oxycodone and placebo were not performed for the AUE data
*P value < 0.05; **P value < 0.001; ***P value < 0.0001; P-values based on 1-sided test
#Significantly different from both oxycodone doses; $Significantly different from placebo; ^Significantly different from oxycodone 60 mg, *P* value = 0.0071

Outcomes for Drug Liking (**Figure 2**)

- Strong Drug Liking effects for the 40 mg or 60 mg oxycodone doses were evident within the first hour of administration in both studies
- Oxycodone Drug Liking remained elevated compared with all doses of NKTR-181, including a 1200 mg supratherapeutic dose, for at least 2 hours post drug administration
- All NKTR-181 doses showed substantially slower rates of rise compared to both doses of oxycodone in the first 2 hours post-dose
- The mean E_{max} scores for all therapeutic doses of NKTR-181 (ie, ≤ 600 mg) were significantly lower than for 40 mg and 60 mg of oxycodone (all $P < 0.001$)
- The supratherapeutic dose of NKTR-181 (1200 mg) had a significantly lower mean Drug Liking E_{max} compared to oxycodone 60 mg ($P = 0.007$) but not to oxycodone 40 mg ($P = 0.52$)
- All NKTR-181 doses were significantly lower than oxycodone on mean area under the effect-time curve (AUE) over 1, 2, and 3 hours post-dose (all $P < 0.05$)

Figure 3. Time Course of Mean Drug High, Mean E_{max}, and Drug High AUE Summary Data





Drug High	Oxycodone	NKTR-181			Placebo
	40 mg (n=41)	100 mg (n=40)	200 mg (n=41)	400 mg (n=41)	(n=41)
E_{max}, mean (SD)	80.3 (17.2)$^{\#\#\#,\$}$	13.8 (20.5)***	13.9 (16.0)***	22.6 (24.12)$^{***,\#,\$}$	7.9 (10.7)***
$AUE_{0\text{-}1h}$, mean (SD)	33.9 (9.3)	4.1 (8.0)***	3.7 (5.6)***	4.3 (6.5)$^{***,\#,\$}$	2.3 (3.9)
$AUE_{0\text{-}2h}$, mean (SD)	101.8 (28.0)	12.9 (26.0)***	11.6 (16.9)***	19.0 (22.8)$^{***,\#,\$}$	5.5 (11.0)
$AUE_{0\text{-}3h}$, mean (SD)	152.0 (49.1)	19.1 (41.5)***	18.3 (28.1)***	34.3 (41.4)$^{***,\#,\$}$	7.6 (16.3)

AUE, area under the effective curve; E_{max}, maximum effect; SD standard deviation
Comparisons were not made for AUE between oxycodone and placebo
*P value < 0.05; **P value < 0.001; ***P value < 0.0001; P-values based on 2-sided test
#Significantly different from oxycodone; $Significantly different from placebo

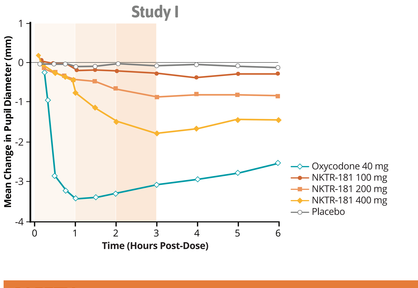
Drug High	Oxycodone		NKTR-181			Placebo
	40 mg (n=54)	60 mg (n=54)	400 mg (n=54)	600 mg (n=54)	1200 mg (n=54)	(n=54)
E_{max}, mean (SE)	53.8 (3.2)	67.2 (3.2)	21.3 (3.2)$^{\#\#\#,\$}$	33.7 (3.2)$^{\#\#\#,\$}$	57.8 (3.2)$^{\#,\$}$	3.1 (3.2)
$AUE_{0\text{-}1h}$, LS mean	13.5	20.7	1.6$^{\#\#\#,\$}$	3.2$^{\#\#\#,\$}$	4.9$^{\#\#\#,\$}$	0.4
$AUE_{0\text{-}2h}$, LS mean	53.7	70.1	7.4$^{\#\#\#,\$}$	17.4$^{\#\#\#,\$}$	32.9$^{\#\#,\$}$	3.2
$AUE_{0\text{-}3h}$, LS mean	90.6	115.8	15.7$^{\#\#\#,\$}$	35.7$^{\#\#\#,\$}$	76.1$^{\#,\$}$	5.5

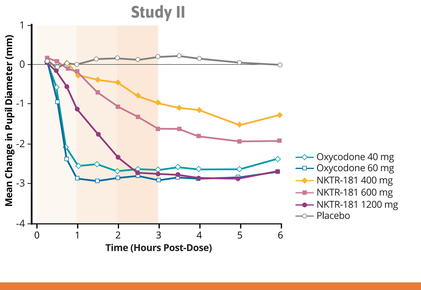
AUE, area under the effective curve; E_{max}, maximum effect; LS, least square; SE standard error
Comparisons were not made between oxycodone and placebo or NKTR-181 and placebo
*P value < 0.05; **P value < 0.001; ***P value < 0.0001; P-values based on 1-sided test
#Significantly different from both oxycodone doses; $Significantly different from oxycodone 60 mg, *P* value = 0.0071

Outcomes for Drug High (**Figure 3**)

- Mean E_{max} scores for all therapeutic doses of NKTR-181 (≤ 600 mg) were significantly lower than for oxycodone 40 mg and 60 mg (all $P < 0.0001$)
- The supratherapeutic dose of NKTR-181 (1200 mg) had a significantly lower mean E_{max} score compared to oxycodone 60 mg ($P = 0.007$) but not relative to oxycodone 40 mg ($P = 0.86$)
- All NKTR-181 doses were significantly lower than both doses of oxycodone on mean or LS mean AUE over 1, 2, and 3 hours post-dose (all $P < 0.0001$)
- There was no difference in AUE between 100 mg or 200 mg NKTR-181 and placebo at any timepoint

Figure 4. Time Course of Mean Change in Pupil Diameter from Baseline





Outcomes for Effect on Pupil Constriction **(Figure 4)**

- Pupil diameter after oxycodone administration declined rapidly and achieved maximum pupil constriction between 1 and 2.5 hours post-dose
- Time course of pupil constriction for NKTR-181 was delayed and prolonged compared to oxycodone, with the time of maximum pupil constriction typically occurring between 3 and 6 hours post-dose
- For Study II, time to achieve maximum pupil constriction for NKTR-181 (3.4 to 5.5 hours post-dose) occurred approximately 2-3 hours after time to peak plasma concentration (1.8 to 2.8 hours post-dose), indicating slow entry of NKTR-181 into the CNS. Similar or longer delay was observed for NKTR-181 doses in Study I

SAFETY

- 32 of 42 subjects (76%) in the safety population reported at least one TEAE in Study I
  - The majority of TEAEs (67%) were associated with oxycodone
- 65 of 69 subjects (94%) in the safety population reported at least one TEAE in Study II
  - The number of events was higher with oxycodone and the 1200 mg NKTR-181 dose than with the 400 mg and 600 mg NKTR-181 doses
- **Table 1** summarizes TEAEs that were reported by > 5% of subjects in any treatment arm

Table 1. TEAEs in > 5% of Subjects*

TEAE, %	Study I					Study II				
	NKTR-181			Oxy	Placebo	NKTR-181			Oxycodone		Placebo
	100 mg (n=40)	200 mg (n=41)	400 mg (n=41)	40 mg (n=41)	(n=41)	400 mg (n=59)	600 mg (n=62)	1200 mg (n=62)	40 mg (n=60)	60 mg (n=62)	(n=61)
Pruritus	0	0	5%	15%	0	2%	13%	31%	22%	39%	0
Nausea	3%	2%	7%	29%	0	9%	5%	19%	13%	15%	3%
Somnolence	0	0	0	0	0	5%	5%	10%	12%	16%	2%
Vomiting	0	2%	2%	24%	0	5%	0	15%	7%	10%	0
Headache	0	2%	5%	15%	2%	9%	5%	10%	5%	11%	7%
Feeling abnormal	0	0	0	0	0	3%	7%	0	0	0	0
Dry mouth	0	0	0	2%	0	0	2%	7%	2%	2%	0
Pruritus generalized	0	7%	5%	42%	0	2%	0	5%	7%	5%	0

*Excludes subjective opioid effects such as "feeling high" and "euphoria" represented in DEQ scores

DISCUSSION

- At therapeutic doses (≤ 600 mg), NKTR-181 was generally well-tolerated, particularly in comparison to oxycodone
- Drug Liking and Drug High E_{max} (peak effects), and the rate of rise and extent of Drug Liking and Drug High onset at the critical first and second post-dose hours, were significantly lower for the NKTR-181 therapeutic dose range than for oxycodone, which indicates a reduced potential for abuse
- For the 400 mg NKTR-181 dose, the only dose level evaluated in both studies, results for E_{max} of Drug Liking and Drug High were consistent across trials
- The supratherapeutic dose of NKTR-181 (1200 mg) produced a Drug Liking and Drug High peak effect significantly lower than oxycodone 60 mg, and similar to oxycodone 40 mg but retained the longer times to onset and slower rates of rise seen with the therapeutic doses of NKTR-181

CONCLUSIONS

- In recreational opioid users in two HAP studies, therapeutic doses of NKTR-181 consistently exhibit significantly less abuse potential than therapeutic doses of oxycodone, a conventional and commonly prescribed opioid

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Presented June 14, 2018, at CPDD 80th Annual Scientific Meeting, San Diego, CA