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Efficacy, Safety, and Tolerability of NKTR-181 in Patients With Moderate to Severe Chronic Low-Back Pain: A Phase 3 Study

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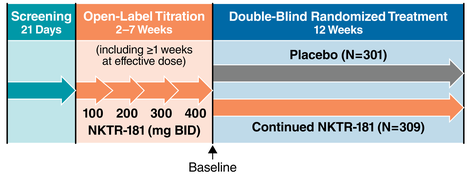
Purpose

- Opioid analgesics are commonly used in the treatment of chronic pain; however, their use is limited by poor tolerability and a high prevalence of abuse and drug-related mortality.[1-3] Although abuse-deterrent formulations have been developed, FDA-approved options include only conventional opioid agonists combined with opioid antagonists or with tamper-resistant reformulations. In patients with poorly-controlled chronic pain on non-opioid analgesics, there remains a great unmet need for safer opioid medication.[4]
- NKTR-181 is a new chemical entity, full mu-opioid receptor (MOR) agonist designed to provide relief from chronic pain with less abuse potential than conventional opioid therapy.[5] NKTR-181 was designed to have a reduced rate of entry into the central nervous system (CNS) compared with standard opioids, thereby reducing a key pharmacokinetic risk factor related to potential for euphoria and abuse.[5] The slowed rate of CNS entry observed with NKTR-181 is inherent to its molecular structure and defies alteration by physical, chemical, or thermal means into a rapid-acting MOR agonist. In a recent study of recreational opioid users, patient-reported drug-high and drug-liking scores for NKTR-181 administered as single doses of 100 to 400 mg were lower than those for oxycodone and closely resembled placebo.[6] Additionally, pupillometry data confirmed a delayed onset of CNS effect associated with NKTR-181.[6]
- Here we present the results of SUMMIT-07, a phase 3, enriched-enrollment, randomized-withdrawal study which evaluated the analgesic efficacy, safety, and tolerability of NKTR-181 administered at 100 to 400 mg twice daily to patients with chronic low-back pain, the most common indication for opioid analgesics in the United States.

Methods

- SUMMIT-07 compared NKTR-181 and placebo in opioid-naïve adult patients with moderate to severe chronic, non-neuropathic, low-back pain of at least 6-month duration, for which non-opioid analgesia had been inadequate. This enriched-enrollment, randomized-withdrawal study included a screening period, an open-label titration period, and a double-blind, placebo-controlled treatment period lasting 12 weeks (**Figure 1**).

Figure 1. Study Design



- Throughout the study, patients scored their daily pain on an 11-point numerical rating scale ranging from 0 ("No pain") to 10 ("Pain as bad as you can imagine"). For inclusion, a patient's 7-day average score at the end of screening was required to be 5 to 9 points. Among eligible patients, open-label NKTR-181 initiated at 100 mg twice daily could be increased to a maximum of 400 mg twice daily. Patients achieving a 7-day average pain score of ≤4 points, representing a decrease of ≥2 points, were randomized to double-blind treatment with NKTR-181 per patient dose or placebo.
- The study's primary efficacy endpoint was change in weekly pain score at the end of the double-blind, randomized treatment period (week 12) relative to the baseline pain score. Key secondary endpoints included the percentages of study completers with week-12 pain scores ≥30% and ≥50% lower than their screening score, and the percentages of patients reporting improvement on the Patient Global Impression of Change (PGIC) scale. Sleep quality was evaluated using the Medical Outcomes Study (MOS) Sleep Scale–Revised. Assessments of study-drug safety and tolerability included the frequency of reported adverse events (AEs).

Results

- Of 1,189 patients exposed to open-label NKTR-181 during the titration period, 610 were randomized, 309 to NKTR-181 and 301 to placebo (the study's intention-to-treat population). Their baseline characteristics are summarized in **Table 1**.

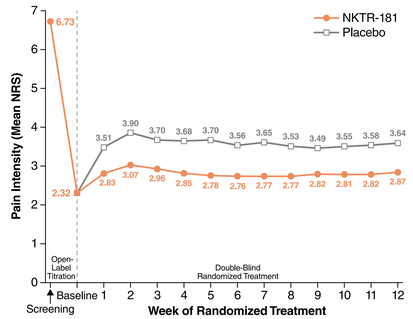
Table 1. Patients' Characteristics By Randomized Treatment Group (ITT Population)

Characteristic	NKTR-181 Group (N=309)	Placebo Group (N=301)
Age (years)		
Mean (SD)	52.0 (12.7)	50.7 (12.5)
Range	20–74	20–75
Sex, n (%)		
Female	187 (60.5%)	170 (56.5%)
Male	122 (39.5%)	131 (43.5%)
Race, n (%)		
White	205 (66.3%)	196 (65.1%)
Black	95 (30.7%)	93 (30.9%)
Other	9 (2.9%)	12 (4.0%)
BMI (kg/m^2), mean (SD)	30.5 (5.4)	30.5 (5.1)[a]
Time since LBP onset (years), mean (SD)	13.3 (10.0)	13.0 (9.8)
Pain score,[b] mean (SD)		
At screening	6.70 (0.98)	6.76 (0.91)
At baseline[c]	2.29 (1.08)	2.35 (1.09)
MOS Sleep Scale–Revised scores at screening, mean (SD)		
Sleep disturbance	47.8 (23.7)[d]	47.8 (23.1)[a]
Sleep problems	42.2 (18.4)[d]	42.7 (18.0)[a]
Respiratory impairments	25.4 (21.4)[d]	26.4 (21.6)[a]
Sleep adequacy	48.1 (23.1)[d]	46.7 (23.1)[a]
Day-time sleepiness (somnolence)	32.5 (20.1)[d]	33.7 (20.8)[a]
Sleep quantity (hrs/night)	6.0 (1.2)[d]	5.8 (1.2)[a]

[a]N=300; [b]Seven-day average of daily scores on an 11-point numerical rating scale ranging from 0 ("No pain") to 10 ("Pain as bad as you can imagine"); [c]The end of open-label NKTR-181 titration, immediately preceding randomization; [d]N=307.
BMI, body mass index; ITT, intention-to-treat; LBP, low-back pain; MOS, Medical Outcomes Study; SD, standard deviation.

- Among randomized patients, the least-squares mean change in weekly pain score after 12 weeks of double-blind treatment was +0.92 points for NKTR-181 vs +1.46 points for placebo, indicating a statistically significant analgesic effect in patients randomized to NKTR-181 (P=0.0019).
- Mean weekly pain scores at screening, at baseline, and during randomized treatment are displayed in **Figure 2**. The difference between treatment groups was statistically significant at week 1 and at all subsequent weeks (P<0.0001 at all weeks).

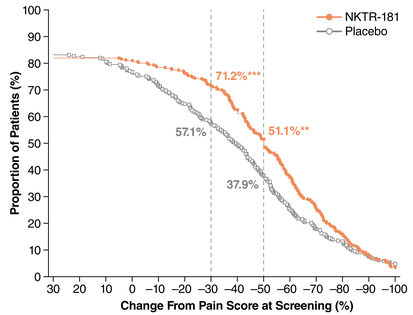
Figure 2. Mean Weekly Pain Scores[a] at Screening, at Baseline,[b] and During Randomized Treatment (ITT Population)



[a]Seven-day average of daily scores on an 11-point numerical rating scale ranging from 0 ("No pain") to 10 ("Pain as bad as you can imagine"); [b]The end of open-label NKTR-181 titration, immediately preceding randomization.
ITT, intention-to-treat; NRS, numeric rating scale.

- Use of rescue medication in NKTR-181 patients was less than placebo throughout the randomized treatment period.
- The distribution of percent reduction in pain score at 12 weeks is presented in **Figure 3**. A reduction ≥30% from a patient's pre-treatment score was reported by 71.2% of the NKTR-181 group vs 57.1% of the placebo group (P=0.0003), and a reduction ≥50% by 51.1% vs 37.9% (P=0.001).

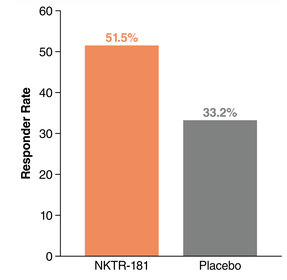
Figure 3. Cumulative Distribution of Percent Reduction in Pain Score at 12 Weeks (ITT Population)[a]



**P<0.01, ***P<0.001 vs placebo. [a]Patients discontinued before 12 weeks were counted as non-responders.
ITT, intention-to-treat.

- Patient responses on the PGIC scale are shown in **Figure 4**. A greater proportion of patients randomized to NKTR-181 characterized themselves as "Improved" or "Very much improved" at week 12 (51.5% vs 33.2%; P<0.0001).
- Changes in MOS Sleep Scale scores among observed cases at week 12 are summarized in **Table 2**. The differences between treatment groups showed statistically significant improvement in the domains of sleep disturbance (P<0.0001), sleep problems (P=0.0004), sleep adequacy (P=0.0015), and sleep quantity (P=0.0477) for NKTR-181 compared with placebo. Scores for day-time sleepiness (somnolence) and respiratory impairments were not statistically different between groups.

Figure 4. Patient Global Impression of Change (ITT Population)



ITT, intention-to-treat.

Table 2. Twelve-Week Change in MOS Sleep Scale–Revised Scores (Observed Cases)

LS Mean Change (SE)	NKTR-181 Group (N=254)	Placebo Group (N=253)
Negative change indicates improvement		
Sleep disturbance	−16.8 (1.3)***	−9.4 (1.3)
Sleep problems	−11.9 (1.0)***	−6.7 (1.0)
Positive change indicates improvement		
Sleep adequacy	+9.8 (1.4)**	+3.4 (1.4)
Sleep quantity (hrs/night)	+0.4 (0.1)*	+0.2 (0.1)
Comparability to placebo is preferred		
Respiratory impairments	−3.9 (1.1)	−1.8 (1.1)
Day-time sleepiness (somnolence)	−6.5 (1.2)	−7.0 (1.2)

*P<0.05; **P<0.01; ***P<0.001 vs placebo.
LS, least-squares; MOS, Medical Outcomes Study; SE, standard error.

- AEs during double-blind treatment were reported by 54.4% of the NKTR-181 group and 49.8% of the placebo group. The preferred terms reported by ≥2.0% of either group are presented in **Table 3**. In the NKTR-181 group, the most frequent AEs were nausea (10.4%, vs 6.0% for placebo), constipation (8.7% vs 3.0%), and vomiting (4.9% vs 1.7%). AEs commonly associated with opioid therapy such as somnolence, dizziness, and sedation were infrequent (2.6% vs 0.3%, 2.3% vs 0.3%, and 0.0% vs 0.3%). During double-blind treatment, AEs led to study discontinuation of 8.7% of patients in the NKTR-181 group vs 3.0% in the placebo group.

Table 3. Adverse Events During Double-Blind Treatment[a]

	Open-Label Titration	Double-Blind Treatment Period	
Incidence, n (%)	NKTR-181 Group (N=1190)	NKTR-181 Group (N=309)	Placebo Group (N=301)
Constipation	425 (35.7%)	27 (8.7%)	9 (3.0%)
Nausea	176 (14.8%)	32 (10.4%)	18 (6.0%)
Day-time sleepiness (somnolence)	107 (9.0%)	8 (2.6%)	1 (0.3%)
Headache	83 (7.0%)	10 (3.2%)	14 (4.7%)
Vomiting	67 (5.6%)	15 (4.9%)	5 (1.7%)
Dry mouth	66 (5.6%)	7 (2.3%)	1 (0.3%)
Fatigue	61 (5.1%)	4 (1.3%)	1 (0.3%)

[a]The listing includes all preferred terms reported by ≥5.0% during open-label titration.

Conclusions

- This study demonstrated a strong efficacy and favorable safety/tolerability profile for NKTR-181, a full mu-opioid receptor agonist with delayed CNS entry, in subjects with moderate to severe chronic low-back pain. In this patient population, NKTR-181 administered at 100 to 400 mg twice daily was associated with statistically significant analgesia throughout 12 weeks of randomized, double-blind treatment. In the NKTR-181 group, as compared with the placebo group, significantly greater proportions of patients experienced at least a 30% or 50% reduction in pain, and a significantly greater proportion reported their condition as improved or very much improved. Patients in the NKTR-181 group reported a low incidence of CNS-related AEs such as somnolence (ie, daytime sleepiness), dizziness, and sedation than might be expected with conventional opioid therapies. Thus, NKTR-181 may present as a potential therapy to address the unmet need for a safer opioid medication for the treatment of patients with chronic pain.

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