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SUMMIT-07: a randomized trial of NKTR-181, a new molecular entity, full mu-opioid receptor agonist for chronic low-back pain

John Markman[a,*], Jeffrey Gudin[b], Richard Rauck[c], Charles Argoff[d], Michael Rowbotham[e], Eva Agaiby[f], Joseph Gimbel[g], Nathaniel Katz[h], Stephen K. Doberstein[i], Mary Tagliaferri[i], Lin Lu[i], Suresh Siddhanti[i], Martin Hale[j]

Abstract

NKTR-181, a new molecular entity, mu-opioid receptor agonist with an inherently slow rate of central nervous system (CNS) entry, was designed to provide analgesia while reducing abuse potential. This phase 3, enriched-enrollment, randomized-withdrawal trial evaluated the analgesic efficacy, safety, and tolerability of NKTR-181 in patients with chronic low-back pain (CLBP). Adults with moderate-to-severe CLBP refractory to nonopioid analgesics achieving an analgesic NKTR-181 dosage (100-400 mg twice daily) during the open-label titration period were randomized to continued NKTR-181 treatment, double-blind, or switched to placebo. The study was conducted at 55 sites in the United States. Of 1189 patients exposed to NKTR-181 during the titration period, 610 were randomized to NKTR-181 100 to 400 mg every 12 hours or placebo for 12 weeks. The primary outcome measure was change in weekly pain score (scale, 0-10) at 12 weeks from randomization baseline. Secondary outcome measures included responder rates defined by ≥30% and ≥50% improvement in pain score from screening to 12 weeks. Among 610 randomized patients, the mean pain score decreased from 6.73 to 2.32 during open-label titration. After randomization, the least-squares mean change in pain score was +0.92 for NKTR-181 vs +1.46 for placebo ($P = 0.002$). The ≥30%-improvement responder rate of NKTR-181 vs placebo was 71.2% vs 57.1% ($P < 0.001$), and the ≥50%-improvement responder rate was 51.1% vs 37.9% ($P = 0.001$). NKTR-181 was well tolerated with a low incidence (<3%) of CNS-related adverse events during the randomized treatment phase. In patients with moderate-to-severe CLBP, NKTR-181 demonstrated significant analgesic efficacy and a favorable safety/tolerability profile, with a low incidence of CNS adverse events.

Keywords: NKTR-181, SUMMIT-07, Chronic pain, Opioid, Chronic low-back pain

1. Introduction

Opioid analgesics can be an effective treatment for select patients with severe chronic low-back pain (CLBP).[5,10] However, complications related to opioid tolerability, overdose, diversion, abuse liability, and a lack of long-term randomized controlled efficacy data limit the utility of this drug class.[3,6,8,28] In the United States, deaths linked to opioid overdose have increased dramatically since 2000.[28] In the 12-month period ending in June 2017, 67,000 deaths were related to opioid use,[21] and in 2016, it was the leading cause of death for people under the age of 50.[29] In 2011, total health care costs associated with opioid abuse and misuse were estimated to exceed $50 billion annually.[15] The US Food and Drug Administration (FDA) considers the development of abuse-deterrent formulations to be a high public-health priority.[2] Currently, marketed products combine a conventional opioid with an opioid antagonist, or they are reformulated with tamper-resistant properties.[7] These strategies have been unsuccessful, and opioid misuse and abuse continues to be a public-health crisis.[32]

Research shows that opioid pharmacokinetics significantly affects tolerability, complications related to overdose, and opioid misuse and abuse. Conventional opioids quickly enter the central nervous system (CNS), which allows for rapid mu-opioid receptor occupancy.[1,18,33] Spikes in striatal dopamine produced by rapid

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[a] *Department of Neurosurgery, Translational Pain Research Program, University of Rochester School of Medicine and Dentistry, Rochester, NY, United States,* [b] *Pain Management and Palliative Care Center, Englewood Hospital and Medical Center, Englewood, NJ, United States,* [c] *Carolinas Pain Institute, The Center for Clinical Research, Winston-Salem, NC, United States,* [d] *Department of Neurology, Albany Medical Center, Albany, NY, United States,* [e] *Sutter Health, CPMC Research Institute, San Francisco, CA, United States,* [f] *Clinical Investigation Specialists Inc, Kenosha, WI, United States,* [g] *Arizona Research Center, Phoenix, AZ, United States,* [h] *Tufts University School of Medicine, Department of Anesthesia, Boston, MA, United States,* [i] *Nektar Therapeutics, San Francisco, CA, United States,* [j] *Gold Coast Research, LLC, Plantation, FL, United States*

**Corresponding author. Address: Department of Neurosurgery, Translational Pain Research Program, University of Rochester School of Medicine and Dentistry, 2180 S. Clinton Ave, Rochester, NY 14618, United States. Tel.: (585) 276-3616; fax: (585) 473-1691. E-mail address: john_markman@urmc.rochester.edu (J. Markman).*

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influx of opioids into the CNS are associated with euphoria, positive reinforcement, and drug-seeking behavior.[16,34,35] NKTR-181, a new molecular entity, is a full mu-opioid receptor agonist designed to have a relatively slow rate of CNS entry when compared with conventional opioids. This property is inherent to the molecular structure of NKTR-181.[12,19] After oral administration, maximum plasma NKTR-181 concentration occurs approximately 3 hours after dose, and the elimination half-life is about 14 hours.[36,37] Delayed CNS receptor binding is expected to attenuate the rapid euphoria associated with conventional opioids, while long duration of exposure permits sustained receptor occupancy for prolonged pain relief. In animal models, NKTR-181 produced analgesia comparable with that of oxycodone but differed significantly from oxycodone in its reduced abuse potential.[19] Reduced abuse potential was also observed in a recent Human Abuse Potential study of recreational opioid users, in which peak subject-reported drug-high and drug-liking scores for NKTR-181 administered as single doses of 100 to 400 mg were significantly lower than those for oxycodone (40 mg).[38] SUMMIT-07, a phase 3, enriched-enrollment, randomized-withdrawal (EERW), multicenter clinical trial, was conducted to evaluate the analgesic efficacy, safety, and tolerability of NKTR-181 in patients with CLBP.

2. Methods

2.1. Study design and oversight

The study included a ≤3-week screening period (prescreening analgesics were discontinued ≥7 days before the open-label titration period), a 3- to 7-week open-label titration period, and a 12-week, double-blind, randomized treatment period, followed by a 1-week study-drug taper and a follow-up safety visit approximately 2 weeks after each patient's final study-drug dose (**Fig. 1**).

Patients that met the inclusion criteria entered into the open-label titration period, and NKTR-181 was initiated in all patients at 100 mg twice daily, to be taken orally for 1 week. For patients tolerating treatment, titration to a dose providing adequate analgesia and acceptable side-effect profile proceeded in increments of 100 mg/dose. Dose increases occurred at weekly intervals to a maximum of 400 mg twice daily.

Adequate efficacy was defined as a weekly 7-day average pain score ≤4, with daily scores ≤4 on at least 5 of the 7 days, and rescue medication on no more than 2 days. Additional efficacy criteria included a ≥2-point decrease in the patient's weekly pain score compared with the end of the screening phase. Patients achieving these criteria were randomized in a 1:1 ratio to either continue their NKTR-181 treatment at the patient's effective and tolerated dose or switch to placebo. To preserve double blinding during randomized treatment, study drug was dosed as indistinguishable tablets (2 tablets per dose) in identical blister packaging.

Until randomized treatment, rescue pain medication was permitted as acetaminophen 500-mg tablets at ≤6 tablets/day. For the first 2 weeks of randomized treatment, rescue medication was permitted as hydrocodone/acetaminophen 5-/300-mg tablets at ≤2 tablets/day to alleviate any withdrawal systems caused by stopping the active drug. After 2 weeks, rescue medication was permitted as acetaminophen at ≤1000 mg/day.

The study was conducted in accordance with the Declaration of Helsinki, FDA regulations, and Good Clinical Practice principles of the International Conference on Harmonisation. All study participants provided written informed consent. Before patient enrollment, the study protocol was approved by central and local ethics committees. The study is registered at ClinicalTrials.gov Identifier: NCT02362672.

2.2. Role of the funding source

The study was initiated and funded by Nektar Therapeutics (San Francisco, CA). Nektar Therapeutics was involved in the design, conduct, and reporting of the study. All authors made substantial contributions to the manuscript content and provided final approval of the decision to submit the manuscript for publication.

2.3. Study participants

All enrolled patients were adults, aged 18 to 75 years, with a clinical diagnosis of moderate-to-severe chronic, non-neuropathic low-back pain of ≥6-month duration, consistent with Quebec Task Force Classification for Spinal Disorders grade 1 or 2,[9] for whom nonopioid analgesic treatment had been inadequate. Patients taking short-acting opioids at ≤10 mg/day of morphine-sulfate equivalents during the 14 days before the screening period were classified as "opioid naive" per the study protocol and were eligible to participate, but use of these medications was prohibited during the study. During the last week of screening, each patient's pain-intensity scores, recorded once daily on an eleven-point (0-10) numerical rating scale,[11]

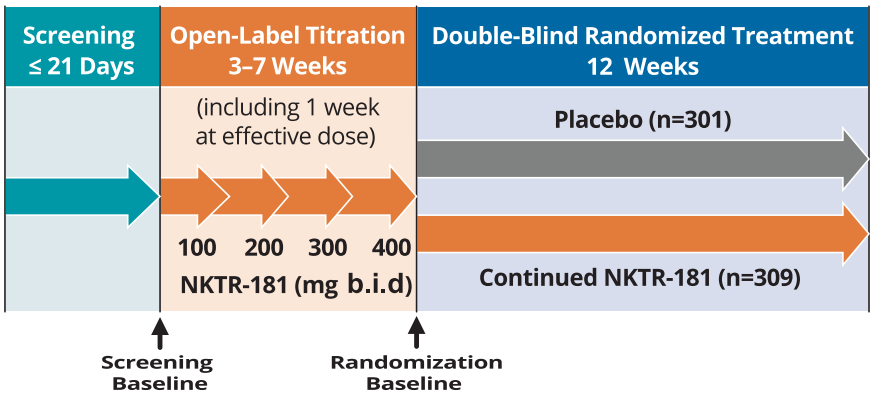

Figure 1. SUMMIT-07 study design. This enriched-enrollment, randomized-withdrawal study included a screening period, an open-label titration period, and a double-blind, placebo-controlled, treatment period lasting 12 weeks.

were required to average 5 to 9 and to include values within this range on at least 5 days. Patients were excluded for any history of low-back surgery or substance or alcohol abuse within the previous year, or physical therapy within the month before enrollment. Patients were also excluded if they had symptoms of opioid withdrawal during screening, as identified by a score >12 on the Clinical Opiate Withdrawal Scale (COWS).[39]

2.4. Efficacy assessments

The study's primary efficacy outcome measure was change in weekly (ie, 7-day average) pain score at the end of double-blind, randomized treatment, compared with the weekly score at the end of titration (double-blind baseline). For this purpose, patients provided once-daily pain scores on the numerical rating scale. Individual pain scores were captured around the same time each day, with reference to the previous 24 hours ("average daily pain"), unless the patient required rescue medication, in which case the score pertained to the patient's current pain ("pain now").

Secondary outcome measures included responder rates, expressed as percentages of patients with week-12 pain scores ≥30% and ≥50% lower than their scores at the end of screening and the percentages with week-12 self-ratings of "better" or "a great deal better" on the Patient Global Impression of Change (PGIC) scale[22] at week 12. Secondary measures also included changes in scores on the Medical Outcomes Study Sleep Scale—Revised,[40] and the Roland–Morris Disability Questionnaire (RMDQ),[26] which patients completed at screening, double-blind baseline, and weeks 6 and 12.

2.5. Safety assessments

Assessments of study-drug safety and tolerability included the type, frequency, seriousness, and severity of adverse events (AEs), as coded by preferred term using the Medical Dictionary for Regulatory Activities version 17.1. Safety assessments also included vital signs, electrocardiographic findings, and clinical laboratory tests. Opioid withdrawal was assessed by COWS and by the Subjective Opiate Withdrawal Scale.[14] Aberrant drug behavior was assessed using the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS).[30,31] Suicidal ideation was assessed using the Columbia-Suicide Severity Rating Scale.[24]

2.6. Statistical analysis

A total of 416 randomized subjects were planned, along with an interim analysis of the primary endpoint for potential sample-size adjustment that was to be conducted by an independent group when 50% of patients completed the study. The sample size was increased to the protocol-mandated 600 based on the interim evaluation.

The primary endpoint was tested for a statistically significant difference between NKTR-181 and placebo in the intention-to-treat (ITT) population (defined as all randomized patients) by an analysis of covariance model with treatment group as a fixed effect and baseline pain score as a covariate. Missing scores were substituted through multiple imputation using the imputation rules: the screening score for patients who discontinued due to AEs, the baseline score for patients who discontinued due to opioid-withdrawal symptoms, the last mean carried forward for patients who discontinued due to lack of efficacy, and Markov Chain Monte Carlo (MCMC) methods assuming nonmonotone missing for all other cases. Change in pain score was also tested among patients who completed 12 weeks of randomized treatment. Proportions of pain score and PGIC responders were evaluated by the chi-square test. Safety and tolerability data were summarized descriptively in the safety population (defined as all study-drug recipients).

3. Results

3.1. Study participants

Of 1189 patients exposed to NKTR-181 during the titration period, 610 were randomized at 55 study sites in the United States. Reasons for withdrawal during the titration period are detailed in the CONSORT diagram (**Fig. 2**) and supplementary Table 1 (available at http://links.lww.com/PAIN/A754). Among

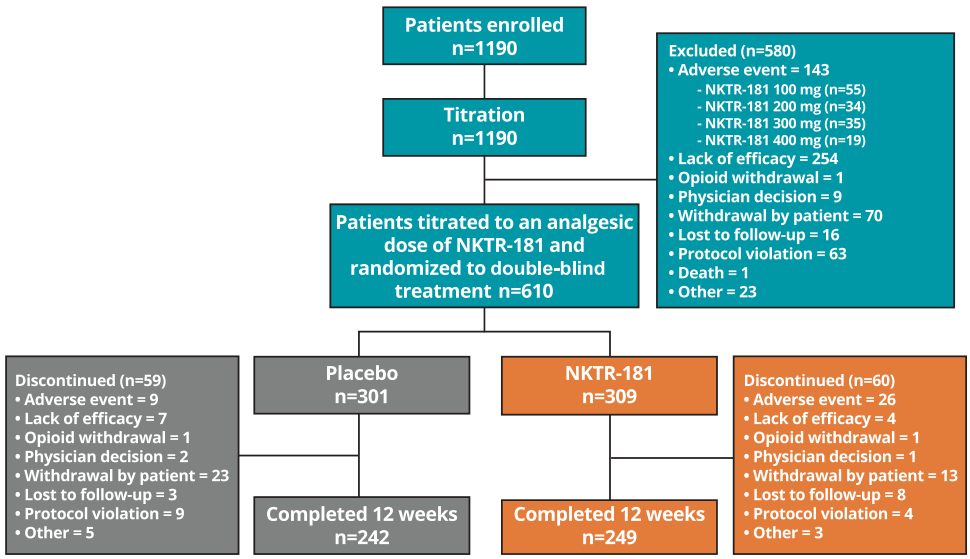

Figure 2. Patient disposition.

them, 309 patients were randomized to NKTR-181 and 301 to placebo. Of the patients randomized to NKTR-181, 2% received 100 mg, 20% received 200 mg, 28% received 300 mg, and 50% received 400 mg twice daily, and the average dose was 324.6 mg twice daily during randomization. Baseline characteristics showed no differences between the NKTR-181 group and the placebo group (**Table 1**), or between NKTR-181 dosage subgroups (data not shown). In both groups, 83% of patients completed 12 weeks of treatment.

3.2. Efficacy

During the titration period, the mean weekly pain score in the ITT population decreased from 6.73 at screening to 2.32 at double-blind baseline. From randomization baseline to the end of treatment, the score in the ITT population increased by a least-squares mean (±SE) of 1.46 ± 0.11 points in the placebo group compared with 0.92 ± 0.11 points in the NKTR-181 group. The difference between groups (primary efficacy analysis) was a significantly greater maintenance of pain reduction among patients continuing to take NKTR-181 than among patients switched to placebo (treatment difference, 0.55; 95% confidence interval [CI], 0.23-0.86; $P = 0.002$). Among 12-week completers, maintenance of pain reduction was also significantly greater in the NKTR-181 group (treatment difference, 0.69; 95% CI, 0.40-0.98; $P < 0.001$). The time course of mean weekly pain scores during treatment is displayed by treatment group in **Figure 3A**. Maintenance of pain reduction was significantly greater in the NKTR-181 group than in the placebo group at week 1 and in all subsequent weeks ($P < 0.001$).

The distribution of percent reduction in pain score at 12 weeks is presented in **Figure 3B**. A reduction ≥30% was reported by 71.2% of the NKTR-181 group vs 57.1% of the placebo group ($P < 0.001$), and a reduction ≥50% by 51.1% vs 37.9% of the 2 respective groups ($P = 0.001$). Among other secondary outcome measures (**Table 2**), the percentage of patients rating themselves on the PGIC as "better" or "a great deal better" at week 12 was significantly greater for NKTR-181 than for placebo (51.5% vs 33.2%, respectively; $P < 0.001$). On the Medical Outcomes Study Sleep Scale, treatment effects at week 12 showed reduced sleep disturbance ($P < 0.001$), reduced sleep problems ($P < 0.001$), and improved sleep adequacy ($P = 0.002$) in the NKTR-181 group, compared with placebo. The Roland–Morris Disability Questionnaire total score at week 12 was not statistically different between groups at a significance level of 0.05 (−4.2 NKT-181 vs −3.3 placebo, respectively; $P = 0.061$). When comparing rescue medication use during the titration period vs the randomized treatment period of the patients that were randomized to NKTR-181 or placebo, rescue medication use was similar between the NKTR-181 group and the placebo group during the titration period (0.429 vs 0.495 occasions per day, respectively), while the mean use of rescue medication was lower for subjects in the NKTR-181 group compared with the placebo group during the randomized treatment period (0.316 vs 0.484 occasions per day, respectively).

Table 1

Patients' characteristics by study period and treatment group (safety population).

Characteristic	Open-label titration	Double-blind, randomized treatment	
	NKTR-181 (N = 1189)	NKTR-181 (N = 309)	Placebo (N = 301)
Age, y			
Mean ± SD	51.0 ± 12.6	52.0 ± 12.7	50.7 ± 12.5
Median (range)	52.0 (19-75)	54.0 (20-74)	52.0 (20-75)
Sex, no (%)			
Male	495 (41.6%)	122 (39.5%)	131 (43.5%)
Female	694 (58.4%)	187 (60.5%)	170 (56.5%)
Race, no (%)			
White	792 (66.6%)	205 (66.3%)	196 (65.1%)
Black	357 (30.0%)	95 (30.7%)	93 (30.9%)
Other	40 (3.4%)	9 (2.9%)	12 (4.0%)
Body mass index*			
Mean ± SD	30.4 ± 5.2†	30.5 ± 5.4	30.5 ± 5.1‡
Median (range)	30.4 (18.4-51.9)	30.6 (18.6-39.1)	30.5 (18.4-40.7)
Time since low-back pain onset, y			
Mean ± SD	13.1 ± 0.1	13.3 ± 10.0	13.0 ± 9.8
Median (range)	10.5 (0.5-61.4)	10.7 (0.5-50.5)	10.4 (0.8-55.3)
Low-back pain classification, no (%)§			
Grade 1	762 (64.1%)	211 (68.3%)	196 (65.1%)
Grade 2	423 (35.6%)	98 (31.7%)	105 (34.9%)
Pain score‖ at screening			
Mean ± SD	6.78 ± 0.98	6.70 ± 0.98	6.76 ± 0.91
Median (range)	6.86 (3.0-9.1)	6.71 (5.0-9.0)	6.71 (5.0-9.0)
Pain score‖ at double-blind baseline¶			
Mean ± SD	—	2.29 ± 1.08	2.35 ± 1.09
Median (range)	—	2.40 (0.0-4.0)	2.43 (0.0-6.6)

* The body mass index is the weight in kilograms divided by the square of the height in meters.
† N = 1187.
‡ N = 300.
§ Quebec Task Force Classification for Spinal Disorders.
‖ From 0 ("no pain") to 10 ("pain as bad as you can imagine"), as 7-day average of daily scores.
¶ End of open-label NKTR-181 titration, immediately preceding randomization.

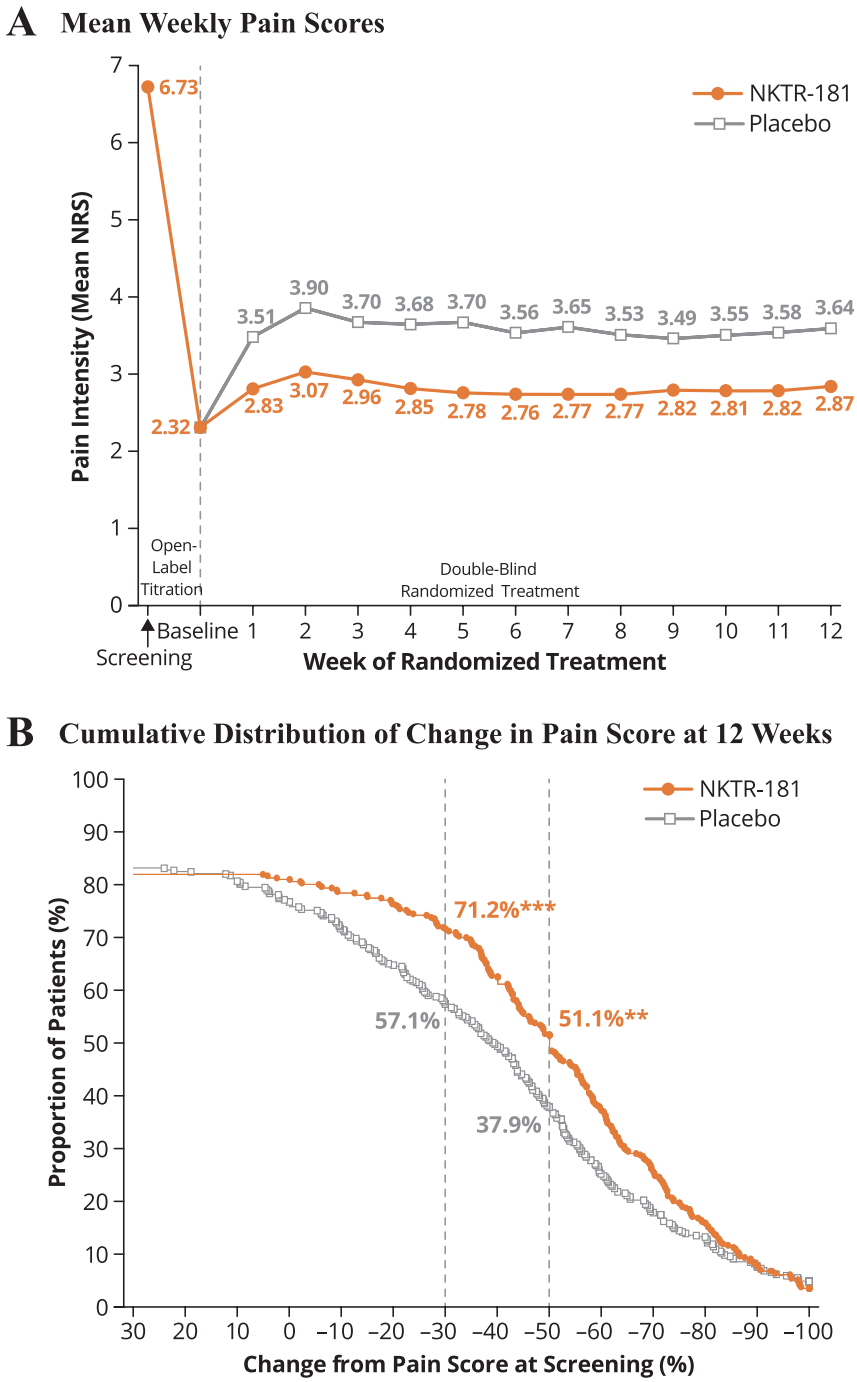

Figure 3. Primary and secondary efficacy outcomes in SUMMIT-07 (intent-to-treat population). (A) shows the mean weekly pain scores from screening through week 12 of the randomized treatment period, and (B) shows the cumulative distribution of change in pain score at week 12 (**$P = 0.01$, ***$P < 0.001$ vs placebo, respectively). Patients discontinued before 12 weeks were counted as nonresponders. NRS, numerical rating scale.

3.3. Safety and tolerability

Adverse events (AE) reported during each study period are summarized in **Table 3**. During open-label NKTR-181 titration, 803 patients (67.5%) reported at least 1 AE, most commonly constipation (35.7%), nausea (14.8%), or somnolence (9.0%). During titration, 151 patients (12.7%) discontinued because of AEs; the most common AEs were nausea (3.0%), constipation (2.1%), and somnolence (1.7%). During titration, 9 patients (0.8%) had a total of 11 serious AEs, which were generally unrelated to NKTR-181. Of the 11 serious AEs, 2 were reported as related to the study drug by the investigator but were then deemed unrelated by the sponsor due to confounding variables related to concomitant medications. These were angioedema confounded by the patient's use of tadalafil and left superior vision loss confounded by the patient's use of lisinopril. There was no relationship observed between adverse events and dose level (supplementary Table 2, available at http://links.lww.com/PAIN/A754).

During double-blind, randomized treatment, 168 patients (54.4%) in the NKTR-181 group and 150 patients (49.8%) in the placebo group reported at least 1 AE. In the NKTR-181 group, the most common AEs were nausea (10.4%, compared with 6.0% for placebo), constipation (8.7% vs 3.0%),

Table 2

Summary of secondary efficacy and safety measures at week 12 (except as noted).

	Treatment group		*P*
	NKTR-181	Placebo	
RMDQ*			
Total score, mean ± SD	6.2 ± 5.6	7.5 ± 6.4	—
LS mean change from screening baseline ± SE	−4.2 ± 0.32	−3.3 ± 0.33	$P = 0.0605$
PGIC†			
Responders, no (%)	159 (51.5)	100 (33.2)	$P < 0.0001$
MOS sleep scale—revised‡			
Negative change indicates improvement			
Sleep disturbance			
Mean ± SD	30.1 ± 22.3	37.7 ± 23.9	—
LS mean change ± SE	−16.8 ± 1.3	−9.4 ± 1.3	$P < 0.0001$
Sleep problems			
Mean ± SD	29.8 ± 18.4	35.5 ± 18.9	—
LS mean change ± SE	−11.9 ± 1.0	−6.7 ± 1.0	$P = 0.0004$
Positive change indicates improvement			
Sleep quantity			
Mean h/night ± SD	6.3 ± 1.3	6.0 ± 1.3	—
LS mean change ± SE	0.4 ± 0.1	0.2 ± 0.1	$P = 0.477$
Sleep adequacy			
Mean ± SD	57.9 ± 25.8	50.3 ± 24.2	—
LS mean change ± SE	9.8 ± 1.4	3.4 ± 1.4	$P = 0.0015$
Comparability to placebo is preferred			
Daytime sleepiness (somnolence)			
Mean ± SD	25.6 ± 21.2	26.0 ± 21.5	—
LS mean change ± SE	−6.5 ± 1.2	−7.0 ± 1.2	$P = 0.7983$
Respiratory impairments			
Mean ± SD	21.5 ± 21.1	24.9 ± 22.2	—
LS mean change (SE)	−3.9 ± 1.1	−1.8 ± 1.1	$P = 0.1649$

* The Roland–Morris Disability Questionnaire (RMDQ) is a 24-item scale to measure the functional impact of low-back pain (0 indicates no functional impairment, and 24 indicates maximal functional impairment).
† The Patient Global Impression of Change (PGIC) scale is a 7-point scale assessing the patient's perceived change in symptoms and function. A responder was classified as a patient self-rated at week 12 as "better" or "a great deal better."
‡ The Medical Outcomes Study (MOS) Sleep Scale–Revised measures 6 dimensions of sleep quantity and quality based on a retrospective assessment of the past 4 weeks. Sleep quantity is quantified as the mean hours per night. Sleep quality domains are scored from 0 to 100 with higher scores indicating a greater degree of sleep disturbance, quality, respiratory impairment, adequacy, or somnolence. LS mean change values denote change from screening baseline to week 12 of randomized treatment.

and vomiting (4.9% vs 1.7%). Central nervous system–related AEs, such as dizziness (2.3% vs 0.3%) and somnolence (2.6% vs 0.3%), occurred relatively infrequently in both NKTR-181 and placebo groups, respectively. Twenty-six patients (8.4%) in the NKTR-181 group and 9 patients (3.0%) in the placebo group discontinued because of AEs. In the NKTR-181 group, the most common of these events were constipation and vomiting, as well as drug-withdrawal syndrome. The only severe

Table 3

Adverse events by study period and treatment group (safety population).

Adverse event	Open-label titration	Double-blind, randomized treatment	
	NKTR-181 (N = 1189)	Continued NKTR-181 (N = 309)	Placebo (N = 301)
	No. of patients (%)		
Summary			
Any adverse event	803 (67.5%)	168 (54.4%)	150 (49.8%)
Any severe adverse event	25 (2.1%)	8 (2.6%)	5 (1.7%)
Any serious adverse event	9 (0.8%)	5 (1.6%)	6 (2.0%)
Any study-drug–related adverse event	659 (55.4%)	90 (29.1%)	55 (18.3%)
Adverse event leading to discontinuation of treatment	151 (12.7%)	22 (7.1%)	8 (2.7%)
By preferred term*			
Constipation	425 (35.7%)	27 (8.7%)	9 (3.0%)
Nausea	176 (14.8%)	32 (10.4%)	18 (6.0%)
Daytime 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%)

* Per Medical Dictionary for Regulatory Activities, version 17.1. The listing includes all preferred terms reported in ≥5.0% of patients during the open-label titration period or in either treatment group during the double-blind treatment period.

or serious AE reported in more than one patient per treatment group was drug-withdrawal syndrome, reported as a severe AE in 2 patients on NKTR-181 and no patients on placebo.

Throughout the study, COWS, Subjective Opiate Withdrawal Scale, and MADDERS findings for NKTR-181 showed a low potential for opioid withdrawal and an incidence of abuse or misuse events closely resembling that for placebo. Detailed results are to be reported in separate publications.

4. Discussion

In SUMMIT-07, an enriched-enrollment, double-blind, randomized-withdrawal study of adults with moderate-to-severe CLBP refractory to nonopioid analgesics, treatment with NKTR-181 was associated with significant maintenance in the reduction of average weekly pain scores during the 12 weeks of double-blind treatment when compared with placebo. A significantly larger proportion of patients in the NKTR-181 group met responder criteria (30% and 50% reduction in pretreatment pain score; patient-rated global improvement) compared with placebo. The study was powered to evaluate patients treated with NKTR-181 compared with placebo, and efficacy assessments at the individual lower dose levels were not meaningful due to the study design. In addition, NKTR-181 was associated with significant improvement in multiple facets of sleep (eg, sleep initiation, maintenance, quantity, somnolence, adequacy, and respiratory impairments). Disturbed sleep has a major impact on quality of life and is often a common accompanying symptom of CLBP. The Roland–Morris Disability Questionnaire is a tool used to quantify the impact of low-back pain on a subject's ability to perform daily activities, change in the RMDQ total score at week 12 trended towards favoring NKTR-181 over placebo, but did not show statistical significance at a significance level of 0.05 ($P = 0.061$). Patients taking analgesics tend to prioritize pain relief over functional gains.[17] Patient-reported outcomes reported in PGIC reflected the improvement in the quality of life of subjects with CLBP.

In a recent double-blind, crossover Human Abuse Potential study in recreational opioid users, the same NKTR-181 dose range administered in SUMMIT-07 (100-400 mg) showed significantly lower mean drug-liking E_{max} scores (primary endpoint) than 40-mg oxycodone, with a slower onset and shorter duration. Drug-liking scores for oxycodone increased rapidly within 15 minutes and peaked at approximately 1 hour after dose, whereas drug liking for all doses of NKTR-181 was comparable with placebo.[38]

Throughout SUMMIT-07, NKTR-181 exhibited a favorable safety profile and was generally well tolerated. Central nervous system–related AEs commonly associated with opioids were reported infrequently during double-blind treatment with NKTR-181 (eg, dizziness and somnolence) with rates comparable with or lower than those for drugs such as extended-release oxycodone in enriched-enrollment, double-blind, randomized-withdrawal studies.[20,23,25]

Efficacy assessments in the SUMMIT-07 trial were limited to 12 weeks. Hence, this study's findings do not directly address the long-term treatment of patients with moderate-to-severe CLBP, a population likely to require analgesia for many years.[13] Also, opioids have been shown to be effective in other pain conditions including neuropathic pain[27]; however, these conditions were not included in this study because the goal of this pivotal phase 3 trial was to evaluate NKTR-181's efficacy in a specific pain condition. Future research may investigate the efficacy of NKT-181 in CLBP syndromes with neuropathic clinical features. Patients who completed the trial were allowed to enter an extension trial, still in progress, of open-label NKTR-181 treatment for up to 52 weeks (ClinicalTrials.gov number NCT02367820). In contrast to patients with CLBP encountered in clinical practice, this study's randomized population consisted entirely of patients achieving an effective, tolerable NKTR-181 dosage at the time of randomization. Importantly, the randomized population also comprised patients with significant refractory pain, as indicated by a mean pain duration of 13.1 years and a mean pain score, preceding their NKTR-181 treatment, of 6.8.

This study has several limitations that must be acknowledged. The main purpose of an EERW study design is to evaluate the magnitude of the true treatment effect in subjects that can tolerate a drug once they endorse relief following an initial, open-label period of exposure. Clinicians treating patients with CLBP are keenly interested in understanding the extent of pain relief in the subgroup of patients who can tolerate and choose to continue a given course of therapy. Consequently, confirmation that an initial perceived benefit in subjects who find a therapy tolerable is due to specific drug effects is a vital clinical question, one this study design helps to answer. However, it is important to note that the opioid analgesic effect observed in the randomized phase of an EERW study such as this one is not directly comparable with a traditional study with a prospective, parallel design. The generalizability of the efficacy results is diminished because the double-blind phase includes only patients who could tolerate the study drug and endorsed a prespecified threshold of relief in the open-label phase. In addition, to facilitate the conduct of the study, potential subjects were excluded if they had significant risk factors for aberrant drug-taking behavior. Therefore, the safety profile as observed in this study with respect to aberrant drug-taking behavior cannot be extrapolated to patients at higher risk of substance use disorder.

In recent years, the FDA has encouraged the development of abuse-deterrent formulations of opioid analgesics.[2] To date, only formulations of "legacy" opioids using physical/chemical barriers or agonist/antagonist combinations as abuse-deterrent strategies have been approved. The use of these agents has been advocated as a way to impede drug tampering; however, most of the current strategies for abuse deterrence can be circumvented and have not succeeded in addressing the escalating opioid epidemic.[4] Efforts to convert NKTR-181 into a more active mu-opioid receptor agonist or one that crosses the BBB at a faster rate using known chemical or physical methods have been unsuccessful.[19] In summary, NKTR-181 provides effective analgesia in patients with moderate-to-severe CLBP, with low rate of CNS side effects.

Conflict of interest statement

J. Markman has participated in advisory boards or consultant (Editas Medicine, Flexion Therapeutics, Pfizer, Teva, Quark, Pacira, Inspirion, Delivery Sciences, Quartet, Pacira Egalet, Biogen, Nektar, Endo, Immune Pharma, Chromocell, Collegium, Purdue, Trigemina, Novartis, Sanofi, Convergence, Aptinyx, Daiichi Sankyo, Allergan, Plasmasurgical, and Grunenthal), received research funding (Depomed, Pfizer), and served on Data Safety Monitoring Boards (Allergan, Novartis). Jeffrey Gudin is a consultant to Nektar Therapeutics, R. Rauck received research funding from Nektar; S.K. Doberstein, M. Tagliaferri, L. Lu, and S. Siddhanti are employed by Nektar Therapeutics. The remaining authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

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