

OPIOIDS & SUBSTANCE USE DISORDERS SECTION

Measuring Opioid Withdrawal in a Phase 3 Study of a New Analgesic, NKTR-181 (Oxycodogol), in Patients with Moderate to Severe Chronic Low Back Pain

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Abstract

Objective. To evaluate the SUMMIT-07 trial opioid withdrawal results of NKTR-181 (oxycodogol), a new molecular entity mu-opioid receptor agonist. **Design.** Phase 3, enriched-enrollment, double-blind, randomized-withdrawal study in patients with chronic low back pain (CLBP). **Setting.** Conducted in the United States at multiple sites. **Methods.** SUMMIT-07 was comprised of five periods: screening; NKTR-181 open-label titration (100 to 400 mg twice daily); 12-week randomized, double-blind study drug (NKTR-181 or placebo); one-week study drug taper; and two-week safety follow-up. Permitted rescue medication included hydrocodone 5 mg/acetaminophen 300 mg (two tablets daily) for two weeks after randomization, then acetaminophen 1.0 gm daily for the remainder of the trial. Signs and symptoms of drug withdrawal were evaluated using the Clinical Opiate Withdrawal Scale (COWS); Subjective Opiate Withdrawal Scale (SOWS); Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS); and withdrawal-related adverse events. **Results.** Of 1,190 patients entering titration, one patient had moderate withdrawal (COWS score 13/48 maximum) three days after discontinuing NKTR-181. Of 610 patients randomized (N = 309, NKTR-181; N = 301, placebo), no COWS scores indicating withdrawal at a moderate level or greater (i.e., score ≥ 13) were observed at any time point. At day 8 after randomization, week 12, and the end of tapering, COWS scores indicating mild withdrawal (< 13) were observed in seven (2.4%), one (0.4%), and one (0.5%) placebo patients, respectively, and three (1.0%), one (0.4%), and five (2.3%) NKTR-181 patients, respectively. Mean SOWS scores in both arms were ≤ 2.8 of 64 possible points at all time points. During the randomized period, of 35 events identified by MADDERS, adjudicators identified 20 possible “withdrawal” events (9 [2.9%] NKTR-181 and 11 [3.7%] placebo). **Conclusions.** NKTR-181 exhibited a low rate and severity of opioid withdrawal in SUMMIT-07 patients with CLBP.

Key Words: Opioid; NKTR-181; Oxycodogol; Clinical Opiate Withdrawal Scale (COWS); Subjective Opiate Withdrawal Scale (SOWS); MADDERS

Introduction

Chronic low back pain (CLBP) should initially be managed with nonpharmacologic strategies, followed by non-opioid pharmacologic agents in nonresponders [1]. Despite these measures, a subset of patients will continue to suffer pain and may be appropriate candidates for opioid analgesics [1–3]. However, limitations of opioid use include adverse effects, overdose, abuse, and diversion [4–7]. Conventional opioid analgesics can produce physical dependence; in this setting, cessation of chronic administration may lead to drug withdrawal symptoms [8,9]. Physical dependence and withdrawal are not necessarily indicative of substance use disorder (SUD), and many chronic pain patients discontinuing appropriately administered opioid maintenance therapy may require a gradual opioid taper to minimize withdrawal symptoms (i.e., physical dependence can occur separately from SUD) [10,11]. SUD is associated with compulsive behaviors and an inability to control use despite clinically significant impairment or distress with continued drug use [12]. Withdrawal symptoms may be severe and may vary according to the specific agent [9]. Withdrawal symptoms include restlessness, anxiety, insomnia, body aches and muscle cramps, yawning, tearing, rhinorrhea, mydriasis, perspiration, hot flushes, temperature elevation, goosebumps, nausea, vomiting, diarrhea, weight loss, and increased respiratory rate and systolic blood pressure [13]. Withdrawal symptoms contribute to negative affect and to drug cravings that are acutely relieved by re-administration of the drug, thus contributing to the perpetuation of opioid self-administration and opioid use disorder [8,14]. Therefore, appraisal and evaluation of withdrawal (in clinical trials) are critical elements of abuse potential assessment for drugs with reinforcing properties, as withdrawal may contribute to abuse [15]. For example, buprenorphine and tramadol are scheduled less restrictively under the Controlled Substances Act, in part because their withdrawal syndromes are less severe than those characteristic of Schedule II opioids such as morphine and oxycodone [16–18].

NKTR-181 (oxycodolol), a new molecular entity, is an orally administered mu-opioid receptor agonist designed to have an inherently slow rate of entry into the central nervous system (CNS) and slower receptor binding and activation compared with conventional opioids [19]. In addition, NKTR-181 has a prolonged duration of action due to a half-life of approximately 14 hours, which allows twice-daily dosing. In human abuse potential studies of recreational opioid users, drug-high and drug-liking scores for NKTR-181 administered across the therapeutic dose range of 100 mg to 400 mg were significantly lower than those for oral oxycodone 40 mg or 60 mg [20,21].

The efficacy and safety of NKTR-181 were assessed in a phase 3, enriched-enrollment, double-blind, randomized-withdrawal study of adult patients with CLBP

(SUMMIT-07 trial) [22]. NKTR-181 administered at 100 mg to 400 mg twice daily was associated with a significantly greater analgesic effect compared with placebo. Due to the physical–chemical properties and the long half-life of NKTR-181, it is hypothesized that NKTR-181 will have low withdrawal associated with discontinuation of dosing. Here we present measurements of opioid/drug withdrawal reported during SUMMIT-07 (NCT02362672).

Methods

Study Design

SUMMIT-07 was an enriched-enrollment, double-blind, randomized-withdrawal study. Enriched-enrollment randomized withdrawal is a trial design utilized commonly to evaluate the safety and efficacy of opioids in managing chronic pain. These trials are designed to select patients who respond to the analgesic agent being tested by demonstrating a defined level of pain relief and acceptable safety profile in each patient before randomization [23,24]. Consistent with this design, study periods consisted of screening, open-label NKTR-181 titration, 12-week placebo-controlled double-blind study drug, one-week study drug taper, and two-week safety follow-up (Figure 1). Detailed methods have been previously published [22]; methods pertaining to evaluating withdrawal are detailed here.

The study was conducted in accordance with the Declaration of Helsinki, Food and Drug Administration (FDA) regulations, and the Good Clinical Practice principles of the International Council for Harmonisation. All study participants provided written informed consent. The study protocol was approved by central and local ethics committees or institutional review boards before patient enrollment.

Patients

Eligible patients were opioid-naïve adults with moderate to severe, non-neuropathic CLBP of six or more months' duration, for which nonopioid analgesic therapies had been inadequate and for whom opioid analgesia was necessary. Patients defined by the protocol as "opioid-naïve" were either not taking opioids or were taking short-acting opioids at ≤ 10 mg/d of morphine-sulfate equivalents during the 14 days before the screening period. Diagnosis of non-neuropathic CLBP was made by the investigator, according to the Quebec Task Force Classification of Spinal Disorders [25]. Key exclusion criteria included a Clinical Opiate Withdrawal Scale (COWS) score > 12 at the start of the study, indicating at least moderate withdrawal.

Study Drugs

During open-label titration, NKTR-181 was initiated at 100 mg twice daily and adjusted to an effective and stable

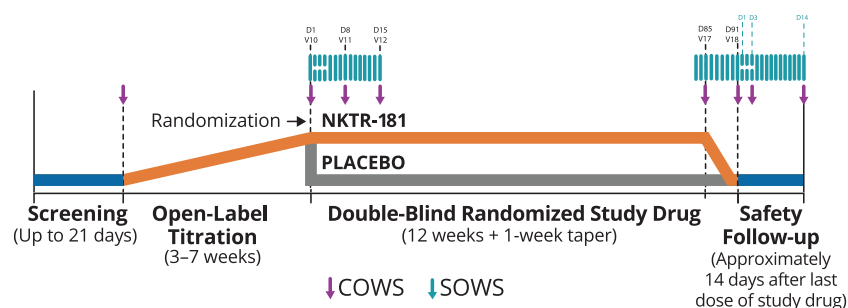


Figure 1. COWS and SOWS observation time points during each study period. COWS = Clinical Opiate Withdrawal Scale; SOWS = Subjective Opiate Withdrawal Scale.

analgesic dose, with a maximum allowed dose of 400 mg twice daily. Patients achieving adequate efficacy and tolerability with three to seven weeks of NKTR-181 dosing were randomized to continue the same dose or to receive placebo twice daily. Those who were randomized to placebo had their NKTR-181 dosing stopped abruptly without taper.

For two weeks after randomization, patients experiencing breakthrough pain were allowed hydrocodone 5 mg/acetaminophen 300 mg every six hours, up to two tablets per day. After two weeks, one dose of acetaminophen up to 1.0 gm per day was permitted. At the end of 12 weeks of randomized study drug, patients began a one-week taper of NKTR-181 or placebo, followed by a two-week safety follow-up period.

Assessments

Opioid withdrawal was assessed as a prespecified analysis by the COWS, the Subjective Opiate Withdrawal Scale (SOWS), and the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS) throughout the trial. The COWS is an 11-item investigator-administered scale used to assess clinical symptoms related to opiate withdrawal, with a maximum score of 48; the SOWS is a self-administered 64-point scale used by subjects to assess 16 symptoms of opioid withdrawal (Table 1). On each scale, greater scores correspond to increased perception of any of the symptoms. The COWS and SOWS scales were originally validated in patients with active opioid abuse [26,27]. MADDERS is a newly developed reporting system to identify potentially abuse-related events occurring in association with use of the study drug [28,29]. Evaluations were triggered by adverse events of interest and drug accountability discrepancies signaling potentially abuse-related events. Drug accountability discrepancies included missing pills (<80% of expected study drug was returned at the site visit) and evidence of tampering with recovered drugs. Events were defined in the MADDERS adjudication manual and assigned classifications by investigators and a blinded, independent committee of substance abuse experts [28–30].

Table 1. COWS and SOWS items and scoring

COWS		SOWS
Items Scored Variably from 0–5 Total Score Range: 0–48		Items Scored Variably from 0–4 Total Score Range: 0–64
1. Resting pulse rate (0–4)		1. I feel anxious
2. Sweating (0–4)		2. I feel like yawning
3. Restlessness (0–5)		3. I am perspiring
4. Pupil size (0–5)		4. My eyes are teary
5. Bone or joint aches (0–4)		5. My nose is running
6. Runny nose or tearing (0–4)		6. I have goosebumps
7. Gastrointestinal upset (0–5)		7. I am shaking
8. Tremor (0–4)		8. I have hot flushes
9. Yawning (0–4)		9. I have cold flushes
10. Anxiety or irritability (0–4)		10. My bones and muscles ache
11. Gooseflesh skin (0–5)		11. I feel restless
COWS Score	Withdrawal Severity	12. I feel nauseous
5–12	Mild	13. I feel like vomiting
13–24	Moderate	14. My muscles twitch
25–36	Moderately severe	15. I have stomach cramps
>36	Severe	16. I feel like using now

COWS = Clinical Opiate Withdrawal Scale; SOWS = Subjective Opiate Withdrawal Scale.

COWS and SOWS scores were obtained at prespecified time points during the trial or following early discontinuation from the study (Figure 1). Potential withdrawal symptoms were assessed during four phases of the study: 1) after abrupt cessation of NKTR-181 dosing during titration in patients terminating the study during this phase; 2) after randomization from NKTR-181 to placebo during the randomized study drug phase; 3) tapering from placebo or active drug at the end of randomized study drug; and 4) during safety follow-up. During the randomized period, COWS scores were obtained at days 1, 8, 15, and 85. For patients who completed the randomized study drug, COWS scores were also obtained at the end of the one-week study drug tapering and twice during the two-week safety follow-up period; however, COWS scores were obtained at the end of the two-week safety follow-up period only for patients who did not enter the long-term NKTR-181 safety study [31]. To evaluate if the hydrocodone-containing rescue medication could have tempered the withdrawal symptoms in the

placebo group following randomization, data were analyzed for the subset of patients who received no rescue medication during the first week of randomized study drug. During the randomized period, SOWS scores were obtained on day 1, twice daily for the next three days, and then daily through day 15. For patients who completed the randomized study drug, SOWS scores were also obtained twice daily for the first three days of the one-week study drug tapering and daily during the two-week safety follow-up period.

Potential withdrawal adverse events were also described in the prespecified analysis and were defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), and the Standardized MedDRA Query (SMQ) for drug withdrawal syndrome. These events included the following: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhea, pupillary dilation, piloerection, sweating, diarrhea, yawning, fever, or insomnia. Potential withdrawal adverse events were also captured by evaluating adverse events requiring use of concomitant medications typically used to manage withdrawal symptoms and MADDERS.

Statistical Analysis

The findings from COWS and SOWS were summarized descriptively. Continuous variables were compared using *t* tests, categorical variables were compared using chi-square tests, and ordinal variables were compared using the Cochran-Mantel-Haenszel test. COWS scores are categorized according to withdrawal severity as follows: 5–12, mild; 13–24, moderate; 25–36, moderately severe; and >36, severe [32]. The percentages of patients experiencing COWS scores are reported by severity category. The total scores from COWS and SOWS were summarized over time. Scores for COWS and SOWS were analyzed according to opioid rescue medication use. Adverse events were summarized descriptively.

Results

A total of 1,190 patients entered the open-label titration phase, and 1,189 patients received at least one dose of NKTR-181 (Supplementary Figure 1). Of these patients, 610 were randomized (N = 309, NKTR-181; N = 301, placebo) [22]. Of patients receiving NKTR-181, 153 patients (49.5%) were titrated to the 400-mg dose, 86 patients (27.8%) to 300 mg, 63 patients (20.3%) to 200 mg, and seven patients (2.3%) remained at 100 mg. The study drug was discontinued prematurely by 60 patients receiving NKTR-181 (N = 26 due to an adverse event) and by 59 patients receiving placebo (N = 9 due to an adverse event). The most common adverse events leading to NKTR-181 discontinuation were gastrointestinal disorders, occurring in nine patients (2.9%). Among placebo patients, the most common reasons for discontinuation were infection and gastrointestinal disorders

Table 2. Baseline characteristics of the randomized (ITT) population

Characteristic	NKTR-181 (N = 309)	Placebo (N = 301)	P
Age, y			
Mean (SD)	52.0 (12.7)	50.7 (12.5)	0.2032*
Range	20–74	20–75	
Female, No. (%)	187 (60.5)	170 (56.5)	0.3114 [†]
Race, No. (%)			
White	205 (66.3)	196 (65.1)	0.7607 [†]
Black	95 (30.7)	93 (30.9)	
Other	9 (2.9)	12 (4.0)	
Years since CLBP onset, mean (SD)	13.3 (10.0)	13.0 (9.8)	0.7252*
COWS score at screening, mean (SD) [‡]	0.5 (0.9)	0.5 (0.9)	0.6751 [§]
Withdrawal classification, No. (%)			
None	305 (99.0)	298 (99.3)	
Mild	3 (1.0)	2 (0.7)	
SOWS score at baseline, [¶] mean (SD)	1.8 (2.8)	1.9 (2.7)	0.3504*

CLBP = chronic low back pain; COWS = Clinical Opiate Withdrawal Scale; ITT = intention-to-treat; SOWS = Subjective Opiate Withdrawal Scale.

*Student *t* test.

[†]Chi-square test.

[‡]N = 308, NKTR-181; N = 300, placebo.

[§]Cochran-Mantel-Haenszel test.

[¶]Day 1 of randomization.

(two patients [0.7%] each). Full safety results are published with the report of the primary results of the study [22]. The baseline characteristics of the randomized patients (intention-to-treat population) were generally comparable between groups (Table 2). Patients had a mean (SD) age of 51.4 (12.6) years and CLBP duration of 13.2 (9.9) years; 58.5% were female.

COWS

At the end of the titration period, the mean (SD) total COWS score was 0.5 (0.9) among 1,138 patients who had COWS data available. Similar proportions of patients across dose groups experienced no withdrawal symptoms according to COWS scores (Table 3). One patient had a COWS score of 13 (the lowest end of the moderate range of 13–24), indicating moderate withdrawal, upon measurement three days after their last NKTR-181 dose. This patient abruptly discontinued the study during the titration phase.

Among the 610 patients randomized, COWS scores were available at randomization (day 1) for 599 patients; the mean (SD) COWS score was 0.4 (0.8) in the NKTR-181 group and 0.3 (0.6) in the placebo group. During the randomized period, no patients had moderate or worse withdrawal based on COWS scores. Mild withdrawal was recorded on day 8 in seven patients (2.4%) in the placebo group (all scores <8) and three patients (1.0%; *P* = 0.1948) in the NKTR-181 group (maximum score of

Table 3. COWS withdrawal classification at the end of the titration period by dose

Withdrawal Classification, COWS Score*	NKTR-181 Dose				Total (N = 1189)
	100 mg (N = 135)	200 mg (N = 199)	300 mg (N = 231)	400 mg (N = 624)	
	No. (%)				
No. patients evaluated	119	186	223	610	1138
None	116 (97.5)	185 (99.5)	222 (96.6)	606 (99.3)	1129 (99.2)
Mild	3 (2.5)	1 (0.5)	1 (0.4)	4 (0.6)	9 (0.8)

COWS = Clinical Opiate Withdrawal Scale.

*Mild, 5–12; moderate, 13–24; moderately severe, 25–36; severe, >36.

Table 4. COWS withdrawal classification at and after randomization (ITT population)

Time Point	Withdrawal Classification, COWS Score*	NKTR-181 (N = 309), No. (%)	Placebo (N = 301), No. (%)	P†
Randomization (day 1)	No. patients	301	298	0.3197
	None	300 (99.7)	298 (100)	
	Mild	1 (0.3)	0	
End of week 1 (day 8)	No. patients	295	291	0.1948
	None	292 (99.0)	284 (97.6)	
	Mild	3 (1.0)	7 (2.4)	
End of week 2 (day 15)	No. patients	291	273	0.2021
	None	287 (98.6)	272 (99.6)	
	Mild	4 (1.4)	1 (0.4)	
End of week 12 (day 85)	No. patients	265	264	0.9979
	None	264 (99.6)	263 (99.6)	
	Mild	1 (0.4)	1 (0.4)	
End of tapering (day 91)	No. patients	218	220	0.0982
	None	213 (97.7)	219 (99.5)	
	Mild	5 (2.3)	1 (0.5)	

COWS = Clinical Opiate Withdrawal Scale; ITT = intention-to-treat.

*Mild, 5–12; moderate, 13–24; moderately severe, 25–36; severe, >36.

†Cochran-Mantel-Haenszel test.

10); on day 15, mild withdrawal was seen in one patient (0.4%) in the placebo group (all scores ≤8) and four patients (1.4%; $P=0.2021$) in the NKTR-181 group (maximum score of 10) (Table 4).

At the end of the tapering period (i.e., one week after the end of randomized study drug dosing), COWS scores indicating mild withdrawal were recorded in one patient (0.5%) in the placebo group and five patients (2.3%) in the NKTR-181 group ($P=0.0982$). The maximum COWS scores were 8 in the NKTR-181 group and 5 in the placebo group during this period. COWS results for the two-week safety follow-up period are not reported due to the majority of SUMMIT-07 patients rolling over into the SUMMIT-08 long-term safety study.

Data were analyzed for the subset of patients who received no rescue medication during the first week of randomized study drug (N=166 [53.7%], NKTR-181; N=110 [36.5%], placebo). In this subgroup, no patients experienced a COWS score >6, and COWS scores indicating no withdrawal symptoms (COWS 0–5) were observed in 166 patients (100%) receiving NKTR-181 and 109 patients (99%) receiving placebo ($P=0.0545$) (Figure 2).

SOWS

Mean SOWS scores after randomization (abrupt discontinuation for patients randomized to placebo) and during and after the tapering period are presented in Figure 3, A and B, respectively. At randomization, the mean (SD) SOWS scores were 1.8 (2.8) in the NKTR-181 group and 1.9 (2.7) in the placebo group out of a total SOWS score of 64. In both groups, the mean SOWS scores remained low (<2.7), with no discernible increase at any time during this period. Similar results were seen during and after the tapering period, where NKTR-181 SOWS scores were low and similar to placebo. SOWS results are only reported until day 7 during the safety period because of rapid patient dropoff due to patients rolling over into the SUMMIT-08 trial.

Withdrawal Adverse Events

One or more potential withdrawal adverse events occurred in one patient (0.3%) in the NKTR-181 group and one patient (0.3%) in the placebo group after the last dose during the randomized period ($P=0.9852$). The patient who had received NKTR-181 experienced one event (vomiting). The patient who had received placebo

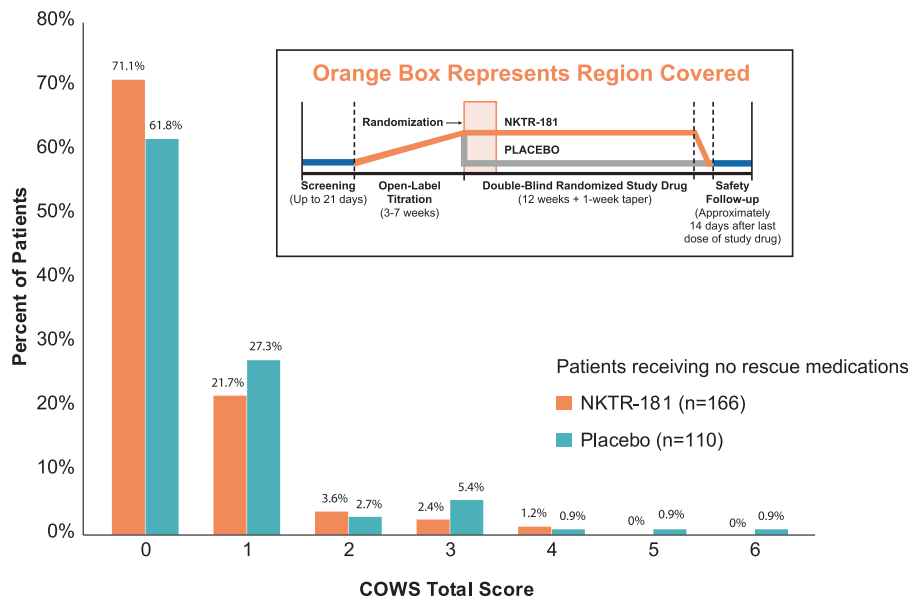


Figure 2. Distribution of COWS scores in patients who received no rescue medication in the first week after randomization; Cochran-Mantel-Haenszel $P=0.0545$ for NKTR-181 vs placebo. COWS = Clinical Opiate Withdrawal Scale.

experienced five events (increased lacrimation, rhinorrhea, diarrhea, nausea, and vomiting). Potential withdrawal adverse events, as defined by the Medical Dictionary for Regulatory Activities (MedDRA), version 17.1, Standardized MedDRA Queries (SMQ), occurred in 10 patients (3.2%) in the NKTR-181 group and 12 patients (4.0%) in the placebo group after the last randomized study drug dose ($P=0.6192$). Adverse events requiring medication administration to manage opioid withdrawal occurred in three patients (1.0%) in the NKTR-181 group and 10 patients (3.3%) in the placebo group ($P=0.0444$). MADDERS identified only a small number of potentially abuse-related events, including abuse, misuse, diversion, withdrawal, or addiction-related behaviors. Seventy-nine (6.6%) of 1,189 patients were associated with 86 events. Most events were attributed to “withdrawal,” “therapeutic error” (unintentional overuse), or “misuse” (intentional overuse for a therapeutic purpose) of study medication. During the titration period, MADDERS identified 24/1,189 (2.0%) cases of withdrawal. Thirty-five events were triggered during the randomized period; of those, adjudicators identified 20 possible “withdrawal” events (9 [2.9%] NKTR-181 and 11 [3.7%] placebo; $P=0.6070$). Full MADDERS results from SUMMIT-07 have been published separately [30].

Discussion

In this enriched-enrollment, double-blind, randomized-withdrawal study, patients with CLBP who received NKTR-181 exhibited a low rate and severity of opioid withdrawal, as rated by clinicians and the patients themselves. No substantial difference in withdrawal symptoms was observed between NKTR-181 and placebo

following abrupt NKTR-181 discontinuation (99% and 97.6% had a classification of no withdrawal per the COWS at the end of week 1 for NKTR-181 and placebo, respectively) or during a one-week study drug taper at the end of the 12-week double-blind study drug period (97.7% and 99.5% had a classification of no withdrawal per the COWS at the end of tapering for NKTR-181 and placebo, respectively).

The randomized, placebo-controlled design of SUMMIT-07 is particularly valuable when measuring withdrawal, as symptoms were at times reported by patients who were not discontinuing NKTR-181. This study helps quantify the background noise with withdrawal assessment using COWS and SOWS on day 8 and day 15 during the randomization period. A possible confounder in the evaluation of withdrawal symptoms in placebo patients who abruptly discontinued from NKTR-181 is the use of hydrocodone-containing rescue medication. Hydrocodone-containing rescue medication was allowed in the first two weeks following randomization specifically for breakthrough pain but may also have tempered withdrawal symptoms. The possibility of rescue medication use confounding the reporting of withdrawal symptoms was evaluated by analyzing COWS scores in the subgroup of patients who received no rescue hydrocodone during the first week of randomized study drug. Rates of withdrawal symptoms were similar between the NKTR-181 and placebo groups, suggesting that hydrocodone rescue medication use during this time period was not masking withdrawal symptoms in the placebo group.

Overall, there were relatively few MADDERS events reported in the SUMMIT-07 trial [30]. MADDERS showed low rates of opioid withdrawal and a low risk of abuse potential, diversion, or addiction.

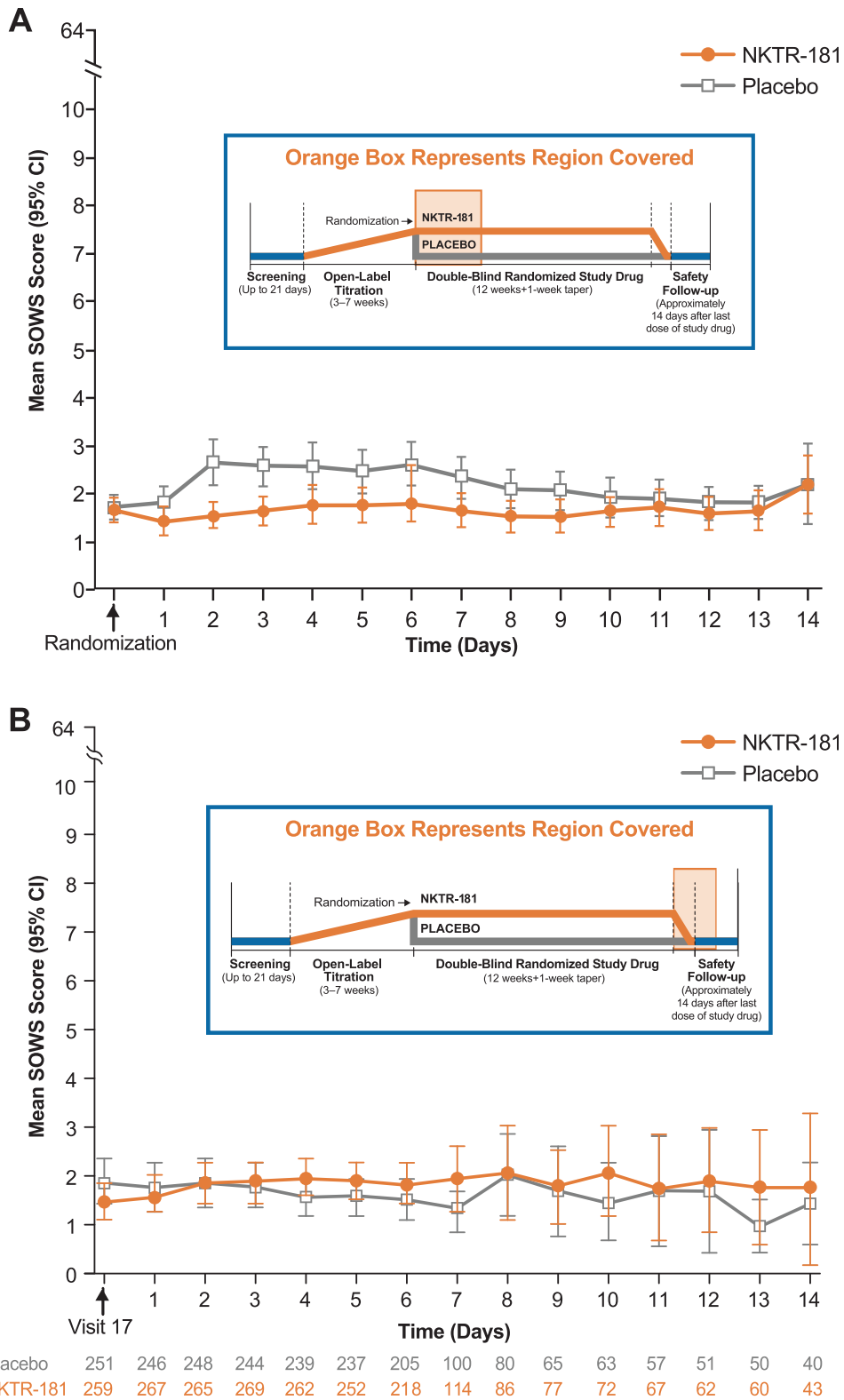


Figure 3. Mean SOWS scores after randomization (A) and mean SOWS scores during and after the tapering period (B). Vertical lines represent 95% CI. CI = confidence interval; SOWS = Subjective Opiate Withdrawal Scale.

“Withdrawal” events tended to occur when the active drug was discontinued abruptly or when the dose was reduced; however, the overall incidence of withdrawal was quite low [30].

The FDA issued a safety announcement that rapid discontinuation of opioid pain medicines can result in uncontrolled pain or withdrawal symptoms, which, in turn, can lead patients to seek other sources of opioid

pain medicines, or patients may attempt to manage their pain or withdrawal symptoms with illicit opioids [15]. Opioids associated with minimal drug discontinuation-associated withdrawal symptoms may be of clinical utility in helping to mitigate the risks associated with serious withdrawal symptoms (e.g., abuse, addiction, overdose, and death) when combined with gradual, individualized tapering schedules [15]. In the SUMMIT-07 trial, patients reported low subjective withdrawal symptoms independent of whether NKTR-181 was discontinued abruptly or during or after a gradual taper.

The strengths of this study include its large sample size and randomized placebo-controlled design. In addition, the trial provided a comprehensive evaluation of withdrawal symptoms from both the physician and patient perspectives and utilized validated measures of withdrawal symptoms [26,27]. The limitations of the present analysis include that the withdrawal symptom measurement was a secondary endpoint, that this study did not compare NKTR-181 with conventional mu opioid agonists, and that the 12-week duration of opioid administration for the pivotal efficacy study was a relatively short study period for a chronic pain condition. A 52-week duration of NKTR-181 was evaluated in the long-term open-label safety study 14-181-08 (SUMMIT-08; N = 638), which has been published separately [31]. In that study, low scores were observed on clinician-administered (COWS) and self-reported (SOWS) evaluations of withdrawal after study drug discontinuation at all time points. Seventy-two hours after discontinuation of NKTR-181, 487 patients completed the COWS assessment and had a mean COWS score of 1 ± 1.47 out of a maximum possible score of 48. At that time point, only nine patients exhibited mild opioid withdrawal (scoring between 5 and 12 points), and only one patient exhibited moderate opioid withdrawal (scoring of 17 points).

Conclusions

In SUMMIT-07, patients with CLBP administered NKTR-181 at 100 mg to 400 mg twice daily for 12 weeks exhibited a low rate and severity of opioid withdrawal, as rated by clinicians and patients. No differences in withdrawal symptoms were observed between NKTR-181 and placebo following abrupt NKTR-181 discontinuation in the placebo group during randomization, nor was a clinically meaningful incidence of withdrawal symptoms seen in the NKTR-181 group during a one-week study drug taper.

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Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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