Pain Medicine, 21(7), 2020, 1347–1356
doi: 10.1093/pm/pnz169
Advance Access Publication Date: 30 July 2019
Original Research Article

Long-term Safety and Tolerability of NKTR-181 in Patients with Moderate to Severe Chronic Low Back Pain or Chronic Noncancer Pain: A Phase 3 Multicenter, Open-Label, 52-Week Study (SUMMIT-08 LTS)

Jeffrey Gudin, MD,[*,†] Richard Rauck, MD,[‡] Charles Argoff, MD,[§] Eva Agaiby, PharmD,[¶] Joseph Gimbel, MD,[‖] Nathaniel Katz, MD,[|||,] Stephen K. Doberstein, PhD,[††] Mary Tagliaferri, MD,[††] Margit Tagliaferri, MD,[††] Jeffrey Potts, MD,[‡‡] James Wild, MD,[§§] Lin Lu, PhD,[††] Suresh Siddhanti, PhD,[††] Martin Hale, MD,[¶¶] and John Markman, MD[|||]**

[*]Department of Anesthesiology, Rutgers New Jersey Medical School, Newark, New Jersey; [†]Pain Management and Wellness Center, Englewood, New Jersey; [‡]Carolinas Pain Institute and The Center for Clinical Research, Winston-Salem, North Carolina; [§]Department of Neurology, Albany Medical Center, Albany, New York; [¶]Clinical Investigation Specialists Inc, Kenosha, Wisconsin; [‖]Arizona Research Center, Phoenix, Arizona; [|||]Tufts University School of Medicine, Boston, Massachusetts; [**]Analgesic Solutions, Wayland, Massachusetts; [††]Nektar Therapeutics, San Francisco, California; [‡‡]Great Lakes Research Group, Inc, Bay City, Michigan; [§§]Upstate Clinical Research Associates, Williamsville, New York; [¶¶]Gold Coast Research, LLC, Plantation, Florida; [|||]Department of Neurosurgery, Translational Pain Research Program, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA

Correspondence to: Jeffrey Gudin, MD, Pain Management Center, Englewood Hospital and Medical Center, 350 Engle Street, Englewood, NJ 07631, USA. Tel: 201-894-3595; E-mail: healthmd@optonline.net.

Funding sources: This study was funded by Nektar Therapeutics, San Francisco, California.

Conflicts of interest: JG in the past year, has served as a consultant for Averitas, Hisumitsu, Mallinckrodt, Nektar, Purdue and Quest Diagnostics; as an advisory board member for AcelRx Pharmaceuticals and GlaxoSmithKline; and as a consultant and part of a speakers bureau for BioDelivery Sciences International, DSI, Salix Pharmaceuticals, and Scilex Pharmaceuticals; RR received research funding from and is a consultant for Nektar Therapeutics; SKD, MT, MT, LL, and SS are employed by Nektar Therapeutics, and they are also stockholders; JM has participated in advisory boards for Editas Medicine, Flexion Therapeutics, Pfizer, Teva, Quark, Pacira, Inspirion, Delivery Sciences, Quartet, Pacira Egalet, Biogen, Nektar, Endo, Immune Pharma, Chromocell, Collegium, Purdue, Novartis, Sanofi, Convergence, Aptinyx, Daiichi Sankyo, Allergan, Plasmasurgical, and Grunenthal; received research funding from Depomed and Pfizer; and served on Data Safety Monitoring Boards for Allergan and Novartis; CA, EA, JG, NK, JP, JW, and MH declare no conflicts of interest.

Abstract

Objective. To evaluate the long-term safety of NKTR-181, a novel mu-opioid receptor agonist that may have reduced human abuse potential, in patients with moderate to severe chronic low back pain (CLBP) or other chronic noncancer pain (CNP). **Design.** Uncontrolled, multicenter, open-label, long-term study of NKTR-181 comprised of three periods: screening ($\leq$21 days), treatment (52 weeks), and safety follow-up ($\sim$14 days after the last dose of NKTR-181). **Setting.** Multicenter, long-term clinical research study. **Methods.** NKTR-181 administered at doses of 100–600 mg twice daily (BID) was evaluated in opioid-naïve and opioid-experienced patients. Patients were enrolled de novo or following completion of the randomized, placebo-controlled phase 3 efficacy study (SUMMIT-07). Safety assessments included adverse event documentation, measurements of opioid withdrawal, and clinical laboratory tests. Effectiveness was assessed using the modified Brief Pain Inventory Short Form (mBPI-SF). **Results.** The study enrolled 638 patients. The most frequently reported treatment-emergent adverse events (TEAEs) were constipation (26%) and nausea (12%). Serious TEAEs, reported in 5% of patients, were deemed by investigators to be unrelated to NKTR-181. There were no deaths or reported cases of respiratory depression. A sustained reduction in mBPI-SF pain intensity and pain interference from baseline to study termination was observed throughout treatment. Only 2% of patients discontinued NKTR-181 due to lack of efficacy, and 11% discontinued due to treatment-related AEs. NKTR-181 doses of up to 600 mg BID were generally well tolerated, and patients experienced low rates of opioid-

related adverse events. **Conclusions.** The study results support the premise that NKTR-181 is a safe and effective option for patients with moderate to severe CLBP or CNP.

Key Words: NKTR-181; Chronic Noncancer Pain; SUMMIT-08; Long-term Safety; Opioids; Chronic Pain; Low Back Pain; Oxycodegol

Introduction

An estimated 92 million adults in the United States use prescription opioids each year [1]. Although opioids can be an effective treatment for pain, complications related to diversion, abuse, misuse, and overdose hinder the usefulness of this drug class, leaving limited options for patients with chronic pain [2–4]. In 2016 alone, >11 million people in the United States misused (i.e., took in a manner or dose other than directed) prescription opioids [5]. The total yearly economic burden of prescription opioid misuse in the United States is estimated at $78.5 billion, including costs related to health care, lost productivity, addiction treatment, and criminal justice involvement [6].

As of January 2019, the Food and Drug Administration (FDA) had approved 10 oral opioids with abuse-deterrent formulations (ADFs) that contain physical or chemical barriers designed to make them more difficult to crush or dissolve to liberate the active moieties for nasal insufflation or intravenous use [7,8]. However, all ADFs can be defeated, and these formulations do not address abuse of the intact product [9–11]; therefore, novel treatments options are needed.

The pharmacokinetic profile of a drug plays a significant role in its potential for abuse. Nonclinical animal studies of drugs of abuse show that rapid uptake of the drug to the brain is more likely to potentiate the escalation of self-administration [12], psychomotor sensitization (i.e., effects of sensitization on psychomotor activation and reward measures) [13, 14], and changes in immediate early gene expression in brain reward pathways that moderate behaviors related to addiction [15]. In humans, faster rates of opioid administration are associated with greater feelings of euphoria and drug liking [16–19], as well as greater reinforcement effects [19]. Both nonclinical and clinical studies indicate that the more rapidly a drug enters the central nervous system (CNS), the higher its potential for abuse and addiction [12–19].

NKTR-181 is a novel mu-receptor agonist designed to have a reduced rate and extent of entry into the CNS when compared with conventional opioids. The reduced rate/extent of CNS entry is a feature of the molecular structure of NKTR-181, rather than due to any specific abuse-deterrent formulation technology [20]. Additionally, NKTR-181 exhibits delayed mu-receptor binding that is expected to attenuate the rapid onset of euphoria associated with conventional opioids. Further, its long duration of exposure permits sustained mu-receptor occupancy for prolonged pain relief. In nonclinical studies, NKTR-181 showed a markedly slower CNS entry rate compared with oxycodone while maintaining analgesic efficacy [20]. In a human abuse potential (HAP) study in recreational opioid users, when compared with oxycodone, therapeutic doses of NKTR-181 had significantly lower ratings for drug liking and drug high [21]. Also, NKTR-181 showed reduced incidence of CNS side effects in animals (e.g., less severe motor coordination deficits) [20] and in humans (reduced feelings of sleepiness and dizziness) when compared with oxycodone [21]. In the SUMMIT-07 (ClinicalTrials.gov ID: NCT02362672) randomized, double-blind, placebo-controlled 12-week phase 3 clinical trial, patients in the NKTR-181 group demonstrated significantly greater maintenance of pain reduction compared with placebo [22].

In the SUMMIT-08 long-term safety study (SUMMIT-08 LTS; ClinicalTrials.gov ID: NCT02367820), the safety and tolerability of NKTR-181 treatment were evaluated for 52 weeks in patients with moderate to severe chronic low back pain (CLBP) or chronic noncancer pain (CNP). As a secondary objective, the effectiveness of NKTR-181 in relieving pain throughout the 52-week study was evaluated.

Methods

Study Design

This uncontrolled, multicenter, open-label, long-term study of NKTR-181 comprised three periods: screening (≤21 days, visits 1 and 2), treatment (52 weeks, visits 3–22), and safety follow-up (∼14 days after the last dose of study drug, visits 23 and 24) (Figure 1).

The study complied with Good Clinical Practice as described in the International Council for Harmonisation, United States Code of Federal Regulations, and the Declaration of Helsinki. Patients provided written informed consent. An institutional review board and independent ethics committee approved the study protocol and the informed consent form.

Patients

Study participants were adults (age 18–75 years) with a clinical diagnosis of moderate to severe CLBP or CNP for three or more months before the start of the study and had received prior treatment for chronic pain. Eligibility was based on a patient's history of refractory pain, as well as complete examination of the patient and medical

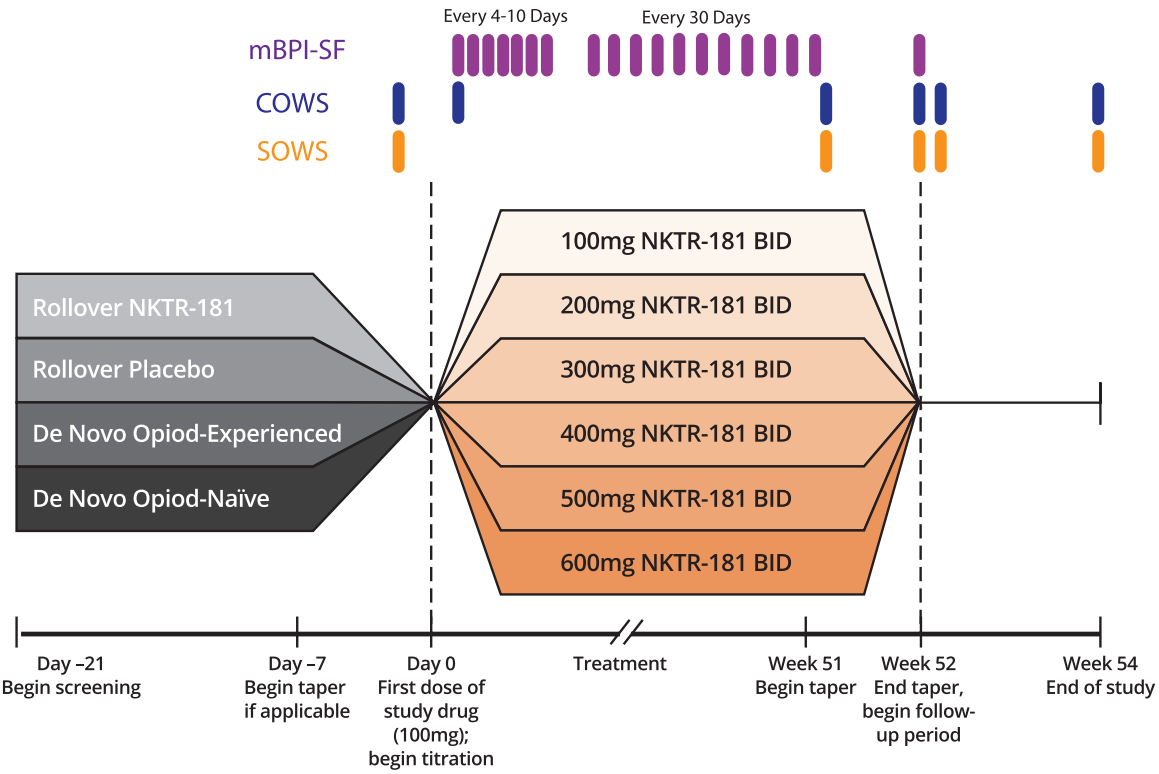

Figure 1. Study schematic.

history review by the investigator. Patients were enrolled to SUMMIT-08 LTS as two distinct study populations, "de novo" or "rollover," after completion of the SUMMIT-07 study (Figure 1). De novo patients were opioid-naïve (defined as taking <10 mg of morphine sulfate equivalents [MSE] per day for seven or more days before consent) or opioid-experienced and nontolerant (defined as taking ≥10 mg and ≤60 mg of MSE per day for seven or more days before consent). Rollover patients were enrolled from both the experimental (100 mg–400-mg NKTR-181 tablets twice daily [BID]) and placebo comparator arms after completing all SUMMIT-07 study visits without study treatment breaks (rollover patients in the NKTR-181 arm completed tapering to 100 mg of NKTR-181 twice daily). Patients were eligible for enrollment in SUMMIT-07 if they had received a clinical diagnosis of moderate to severe chronic non-neuropathic lower back pain for six or more months, had experienced inadequate pain relief with nonopioid analgesics, and were taking ≤10 mg MSE per day of short-acting opioids in the 14 days before study entry.

Patients were excluded from SUMMIT-08 LTS if they were pregnant or breastfeeding, if they had a history of substance use disorder within the past year, a score of ≥10 on the PHQ-8 at Visit 1 [23], clinically significant abnormalities in laboratory results or electrocardiogram, surgery four or fewer weeks before signing the informed consent form, or untreated moderate to severe sleep apnea. Patients were also excluded if they answered Yes to questions 4 or 5 on the screening version of the Electronic Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 12 months or scored >12 on the Clinical Opiate Withdrawal Scale (COWS). Women of childbearing potential and men with female partners of childbearing potential had to commit to using two forms of contraception during the study and for two weeks after receiving the last NKTR-181 dose.

Treatment

Rollover patients from the SUMMIT-07 NKTR-181 treatment arms were tapered down over the course of seven days to the 100-mg BID dose, as part of the study, before starting treatment in SUMMIT-08 LTS. Beginning with the second study visit, de novo patients taking opioids had their doses tapered over the course of seven to 14 days to ≤30 mg MSE per day. De novo patients were required to have been taking ≤30 mg MSE per day for three or more days before study entry, in order to reduce the potential for opioid withdrawal when transitioning onto NKTR-181.

Patients began treatment with NKTR-181 100-mg tablets BID. Patients unable to tolerate this dose were removed from the study. Over five weeks, patients returned to the clinic every four to 10 days (for a maximum of seven visits) for tolerability and effectiveness assessments. Patients who tolerated NKTR-181 but had inadequate pain relief underwent upward dose titration until they experienced adequate pain relief or reached the maximum allowed dosage of 600 mg BID. During the study, the

maximum NKTR-181 dosage was increased from 400 mg to 600 mg BID to allow inclusion of opioid-experienced subjects, who were expected to tolerate higher doses of NKTR-181. A stable dose was defined as one that was effective (i.e., provided adequate pain relief as defined by the patient) and was tolerated on two sequential clinic visits. Patients who did not achieve a stable dose were classified as nonresponders and were removed from the study. Patients were provided with over-the-counter analgesics (e.g., acetaminophen, aspirin, ibuprofen, and naproxen) and could use these nonopioid rescue medications, up to the maximum daily dose indicated on the label, at any point during the study.

After achieving a stable dose, patients were evaluated in the clinic monthly. Dosages were titrated up or down as deemed appropriate by the investigator or qualified subinvestigator based upon efficacy and safety. After 51 weeks of treatment, patient doses were tapered for one week, with all patients receiving NKTR-181 at 100 mg BID for two or more days during the final week of treatment. After the end-of-treatment visit, patients entered an approximately two-week-long safety follow-up period that included two clinic visits, during which patients were monitored for symptoms of opioid withdrawal.

Assessments

Safety assessments included treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Investigators graded all TEAEs as mild, moderate, or severe and determined their relationship to NKTR-181 treatment. Opioid withdrawal was measured using the 11-item COWS [24, 25] and the 16-item Subjective Opiate Withdrawal Scale (SOWS) [26]. The Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS) was used to identify potential abuse-, dependence-, or misuse-related events occurring in association with use of NKTR-181 [27, 28]. The electronic version of C-SSRS [29–31] was used to assess suicidal ideation and behaviors. Other scheduled assessments included clinical laboratory tests, vital signs, and 12-lead electrocardiograms.

Pain relief was assessed using the pain intensity and interference scores as part of the modified Brief Pain Inventory Short Form (mBPI-SF), a validated questionnaire that is widely used in the chronic pain setting [32–34]. Pain interference was defined to the patient as the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities (0 = "no interference" and 10 = "interfered completely").

Statistical Analysis

Sample size was based on regulatory requirements for safety evaluation, with the goal of obtaining a population of 200 patients treated with NKTR-181 for at least six months and 100 patients treated for one year. Continuous variables were summarized using descriptive statistics, and categorical data were summarized by the number and percentage of patients. Data analysis was performed using SAS, version 9.4 (SAS Institute Inc, Cary, NC, USA). The safety analysis set comprised all patients who received one or more doses of NKTR-181.

Results

Patients

The SUMMIT-08 LTS study enrolled 638 patients from 55 study centers in the United States. The study population that rolled over from SUMMIT-07 comprised 214 patients from the NKTR-181 treatment arm and 217 patients from the placebo arm (68%). The de novo enrolled population included 134 opioid-experienced patients and 73 opioid-naïve patients. Patients had a mean age of 52 ± 12 years and a mean BMI of 31 ± 6. Most patients (93%) had CLBP, and 7% had other chronic pain conditions such as osteoarthritis, rheumatoid arthritis, neck pain, and fibromyalgia. The mean duration of chronic pain before study entry was 13 ± 10 years (Table 1).

Disposition

Overall, 63% of enrolled patients completed the study, and 71% completed six or more months (Figure 2). The mean duration of treatment was 266 ± 135 days. Patients received 100 mg (10%), 200 mg (21%), 300 mg (24%), 400 mg (34%), 500 mg (6%), or 600 mg (5%) of NKTR-181 BID. The 500-mg and 600-mg groups had relatively fewer patients because these doses were permitted only after amendment of the protocol (January 25, 2016). The most common reasons for removal from the study were withdrawal from the study by the patient (11%) and adverse events (AEs; 11%). Withdrawal from the study by the patient was not related to AEs or lack of efficacy; the majority of these patients withdrew due to unforeseen personal circumstances (e.g., moving out of state, unable to come in for study visits, or no longer wanting to participate). Only 14 patients (2%) elected to discontinue the study due to lack of efficacy.

Safety

During the study, 72% of patients had one or more TEAEs, and 6% had a severe TEAE (Table 2). The most common TEAEs, constipation and nausea, occurred in 26% and 12% of patients, respectively. Patients treated with 500 mg or 600 mg of NKTR-181 were more likely to experience constipation compared with patients treated with lower doses. Forty-seven percent of patients experienced a drug-related TEAE (i.e., treatment-emergent adverse events related specifically to NKTR-181); of these, the most common drug-related TEAEs were constipation (24%) and nausea (9%). Fewer than

Table 1. Demographic and baseline characteristics (safety population)

	NKTR-181						
Characteristic	100 mg N = 65	200 mg N = 133	300 mg N = 154	400 mg N = 217	500 mg N = 39	600 mg N = 30	Total N = 638
Age, mean (SD), y	55 (12)	52 (11)	50 (13)	53 (11)	53 (11)	51 (14)	52 (12)
Women, No. (%)	37 (57)	78 (59)	97 (63)	122 (56)	29 (74)	12 (40)	375 (59)
Men, No. (%)	28 (43)	55 (41)	57 (37)	95 (44)	10 (26)	18 (60)	263 (41)
Race, No. (%)							
White	42 (65)	100 (75)	98 (64)	149 (69)	23 (59)	19 (63)	431 (68)
Black	20 (31)	28 (21)	48 (31)	65 (30)	14 (36)	9 (30)	184 (29)
Other*	0	5 (4)	5 (3)	2 (1)	0	0	12 (2)
Multiple	0	0	1 (1)	0	1 (3)	1 (3)	3 (0.5)
Not reported	3 (5)	0	2 (1)	1 (0.5)	1 (3)	1 (3)	8 (1)
BMI, mean (SD), kg/m^2	31 (6)	31 (6)	31 (6)	31 (6)	32 (6)	32 (4)	31 (6)
Opioid experienced, No. (%)							
Yes	11 (17)	23 (17)	36 (23)	50 (23)	8 (20)	6 (20)	134 (21)
No†	54 (83)	110 (83)	118 (77)	167 (77)	31 (80)	24 (80)	504 (79)
Type of chronic pain, No. (%)							
Low back pain	60 (92)	124 (93)	144 (94)	201 (93)	37 (95)	29 (97)	595 (93)
Non–low back pain	5 (8)	9 (7)	10 (6)	16 (7)	2 (5)	1 (3)	43 (7)
Duration of chronic pain, mean (SD), y	14 (10)	12 (10)	13 (9)	13 (10)	13 (8)	12 (10)	13 (10)
Musculoskeletal and connective tissue disorders occurring in >5% of patients, No. (%)							
Back pain	61 (94)	126 (95)	145 (94)	206 (95)	37 (95)	29 (97)	604 (95)
Osteoarthritis	25 (39)	24 (18)	30 (20)	65 (30)	8 (21)	7 (23)	159 (25)
Intervertebral disc degeneration	16 (25)	14 (11)	15 (10)	29 (13)	5 (13)	3 (10)	82 (13)
Muscle spasms	6 (9)	10 (8)	19 (12)	34 (16)	5 (13)	5 (17)	79 (12)
Intervertebral disc protrusion	10 (15)	17 (13)	17 (11)	22 (10)	3 (8)	4 (13)	73 (11)
Arthralgia	9 (14)	1 (11)	1 (11)	26 (12)	3 (8)	3 (10)	72 (11)
Neck pain	7 (11)	7 (5)	9 (6)	16 (7)	3 (8)	1 (3)	43 (7)
Spinal osteoarthritis	6 (9)	4 (3)	9 (6)	20 (9)	2 (5)	2 (7)	43 (7)
Arthritis	3 (5)	5 (4)	6 (4)	15 (7)	3 (8)	2 (7)	34 (5)

BMI = body mass index.

*Asian, Native American or Alaska Native, Native Hawaiian or other Pacific Islander.

†Includes the NKTR-181 rollover population.

5% of patients had drug-related CNS TEAEs (e.g., somnolence, dizziness, and insomnia).

A relatively high number of patients completed the 52-week treatment period, with only 10% of patients discontinuing treatment due to TEAEs. The most common events leading to discontinuation were constipation and headache, reported in 2% and 1% of patients, respectively. Serious TEAEs, reported in 5% of patients, were deemed unrelated to NKTR-181. The most common serious TEAEs were gastroenteritis and pneumonia; each occurred in 0.3% of patients. No cases of respiratory depression were observed in the study, and there were no deaths.

Withdrawal and Abuse Potential

Withdrawal was measured using the COWS and SOWS inventories. 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).

In the clinic, patients completed the SOWS assessment at Visit 2 (de novo subjects only), Visit 21, and Visit 22 (end of therapy visit), or at the early termination visit. Patients completed the SOWS twice a day for three days following the last dose of NKTR-181 and then once daily throughout the remainder of the safety follow-up period (i.e., through Visit 24). One hundred seventy-one patients completed the SOWS assessment 14 days after the end of therapy. The final mean total SOWS scores were 2.6 ± 2.6, 1.8 ± 2.7, 1.4 ± 2.3, 3.0 ± 5.8, 1.2 ± 2.2, and 9.3 ± 13.8 out of a possible 64 points for the NKTR-181 100-mg, 200-mg, 300-mg, 400-mg, 500-mg, and 600-mg groups, respectively. Figure 3 shows the mean total SOWS scores after the last dose over time by subgroup.

Analysis of C-SSRS data indicated low numbers of suicide-related TEAEs. Seventeen patients (2.7%) reported treatment-emergent suicidal ideation; however, no increase from baseline in suicide-related events was observed, and none of these patients reported treatment-emergent serious suicidal ideation. Although some patients displayed changes in clinical laboratory values, vital signs, and electrocardiograms, these changes were mild, transient, and not clinically meaningful. No clinically meaningful differences were observed between the different NKTR-181 dose groups.

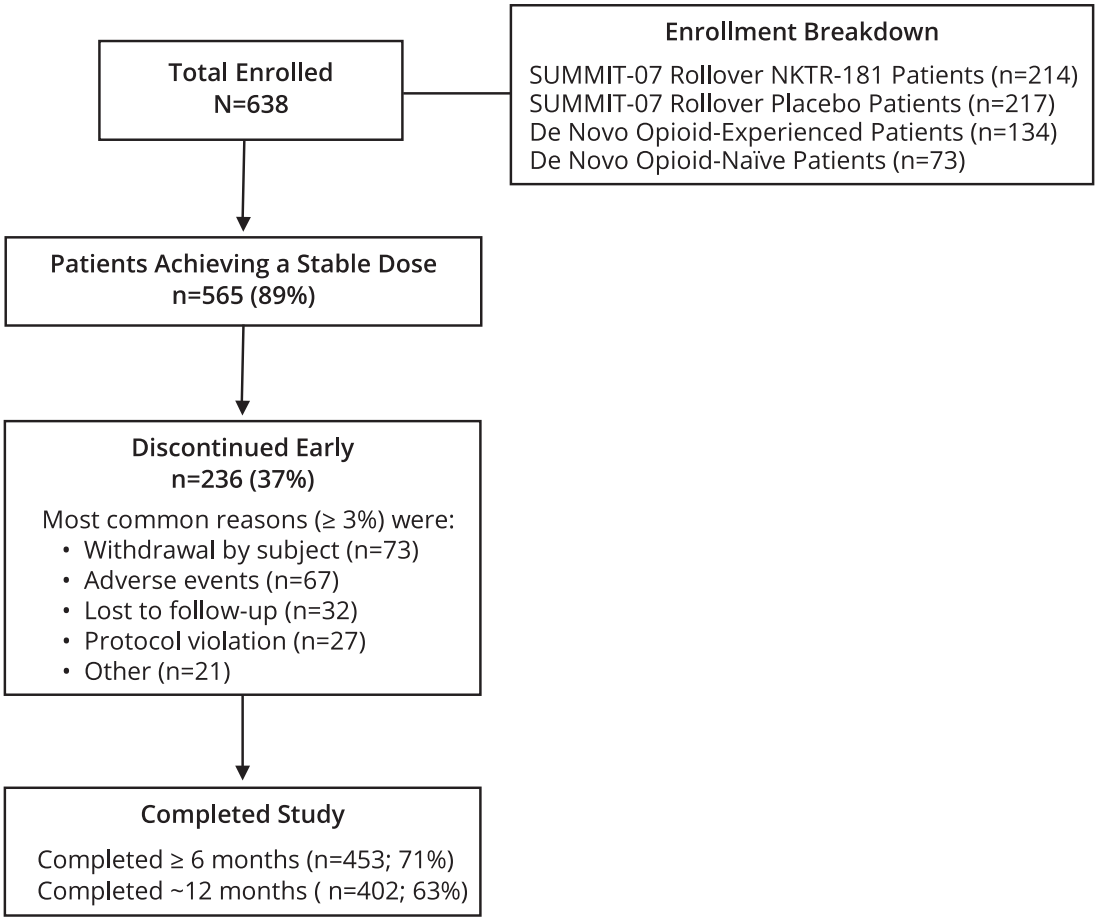

Figure 2. Disposition of patients.

Table 2. Summary of TEAEs (safety population)

	NKTR-181, No. (%)						
TEAEs	100 mg N = 65	200 mg N = 133	300 mg N = 154	400 mg N = 217	500 mg N = 39	600 mg N = 30	Total N = 638
Any	46 (71)	99 (74)	109 (71)	153 (70)	30 (77)	24 (80)	461 (72)
Drug-related	31 (48)	62 (47)	74 (48)	101 (46)	20 (51)	13 (43)	301 (47)
Reason for drug discontinuation	10 (15)	15 (11)	18 (12)	13 (6)	5 (13)	2 (7)	63 (10)
Serious	2 (3)	5 (4)	7 (4)	12 (6)	2 (5)	2 (7)	30 (5)
Deaths	0	0	0	0	0	0	0
Reported in >5% of patients overall							
Constipation	15 (23)	31 (23)	38 (25)	54 (25)	17 (44)	11 (37)	166 (26)
Nausea	7 (11)	23 (17)	18 (12)	20 (9)	3 (8)	5 (17)	76 (12)
Headache	6 (9)	13 (10)	17 (11)	20 (9)	0	1 (3)	57 (9)
URTI	4 (6)	10 (8)	12 (8)	19 (9)	1 (3)	2 (7)	48 (8)
Drug withdrawal syndrome	0	4 (3)	11 (7)	14 (6)	3 (8)	6 (20)	38 (6)
UTI	2 (3)	3 (2)	10 (6)	15 (7)	4 (10)	1 (3)	35 (6)
Vomiting	4 (6)	8 (6)	7 (4)	11 (5)	1 (3)	4 (13)	35 (6)

TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection.

MADDERS identified only a small number of potentially abuse-related events, including abuse, misuse, diversion, withdrawal, or addiction-related behaviors. Fifty-one (8.0%) of 638 subjects were associated with 59 events. Most events were attributed to "withdrawal," "therapeutic error (unintentional overuse)," or "misuse" (intentional overuse for a therapeutic purpose) of study medication. Adjudicators identified four possible "abuse" events. Full MADDERS results from SUMMIT-07 and SUMMIT-08 LTS have been published separately [28].

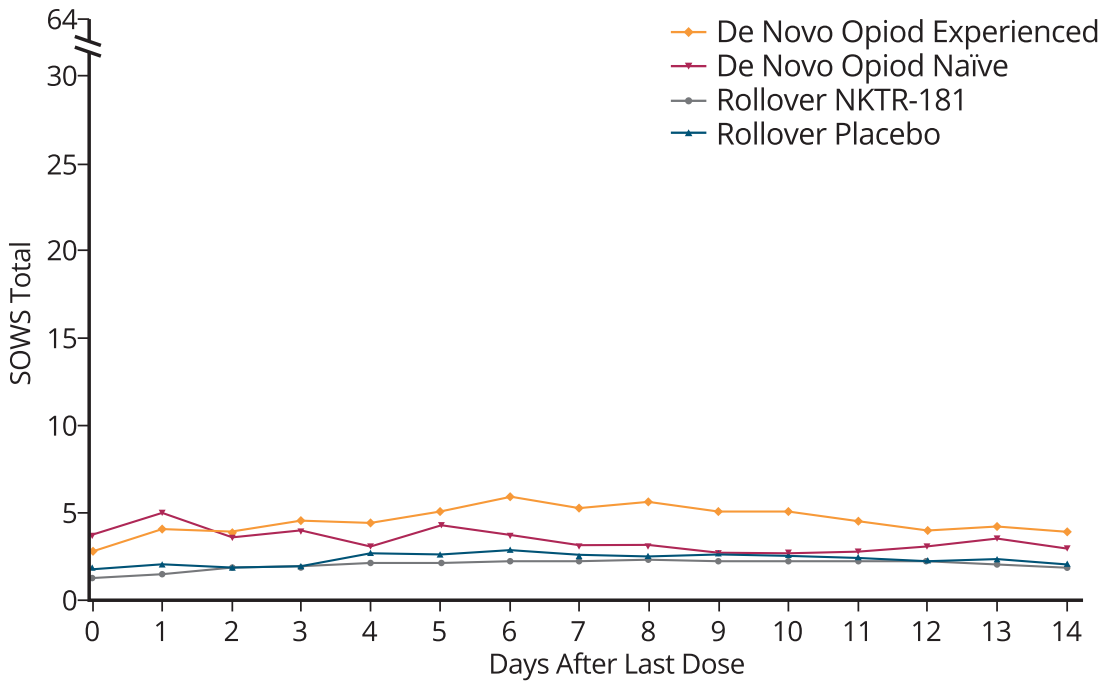

Figure 3. Mean total Subjective Opiate Withdrawal Scale (SOWS) scores after last dose over time by subgroup (patients completing the study). SOWS total scores could range from 0 to 64.

Analgesic Effectiveness

Figure 4 shows the mean mBPI-SF scores for the safety analysis population at each visit. The mean pain intensity decreased from 4.6 ± 2.2 at baseline to 2.7 ± 1.8 at the end of the dose titration period. Once a stable NKTR-181 dose was reached for each enrollment group, reduced pain intensity was maintained for the duration of treatment for both opioid-experienced and opioid-naïve patients (Figure 4A). Pain interference scores showed a similar pattern with patients experiencing an improvement from baseline, which was maintained throughout the duration of the study (Figure 4B). There was no substantial requirement for over-the-counter medication for breakthrough pain once a stable dose level of NKTR-181 was achieved; the mean number of occasions of rescue medication use per exposure days was 0.74 (sum of number of occasions of rescue medication post-titration)/(exposure duration of study drug in days).

Dose Escalation

Once a stable dose was reached over the first five weeks of the treatment period (N = 565; effective dose was defined by the patient), most patients (79%, 444/565) did not require further dose increases and maintained analgesia while on the stable dose until the end of the 52-week treatment period. Dose increases were required for 121 (21%) patients, whereas 37 (7%) patients required lower doses of NKTR-181 (Figure 5). The NKTR-181 rollover subjects self-titrated to a stable dose +/- one dose level relative to the dose level they titrated to in the SUMMIT-07 study.

Discussion

This study examined the safety of NKTR-181 over a longer period (52 weeks of treatment) and at higher doses (500 and 600 mg BID) than was previously tested in the phase 3 efficacy trial. Overall, NKTR-181 was well tolerated at doses from 100 to 600 mg BID, with TEAEs that were similar to the TEAEs observed in the randomized 12-week NKTR-181 phase 3 trial [22]. The most common TEAEs were constipation and nausea. TEAEs that led to study removal were uncommon, occurring in less than 10% of patients. Serious TEAEs occurred in less than 5% of patients and were deemed unrelated to study drug. TEAEs characteristic of CNS effects, abuse, or withdrawal were rare. Similarly, low scores were observed on clinician-administered (COWS) and self-reported (SOWS) evaluations of withdrawal after study drug discontinuation at all timepoints. There were no cases of respiratory depression or death. The NKTR-181 safety profile was generally consistent with results obtained in the SUMMIT-07 phase 3 clinical trial. A low rate of study mediation misuse and abuse related events were observed. This finding may reflect the success of the study design in excluding potential subjects at elevated risk for substance use disorder, investigator adherence to the exclusion criteria of the study protocol, or lower intrinsic abuse liability of NKT-181. MADDERS showed low rates of opioid withdrawal and a low risk of abuse potential, diversion, or addiction [28].

Overall, the observed reductions in pain intensity from baseline were maintained throughout the 52-week treatment period. After the initial five-week dose titration

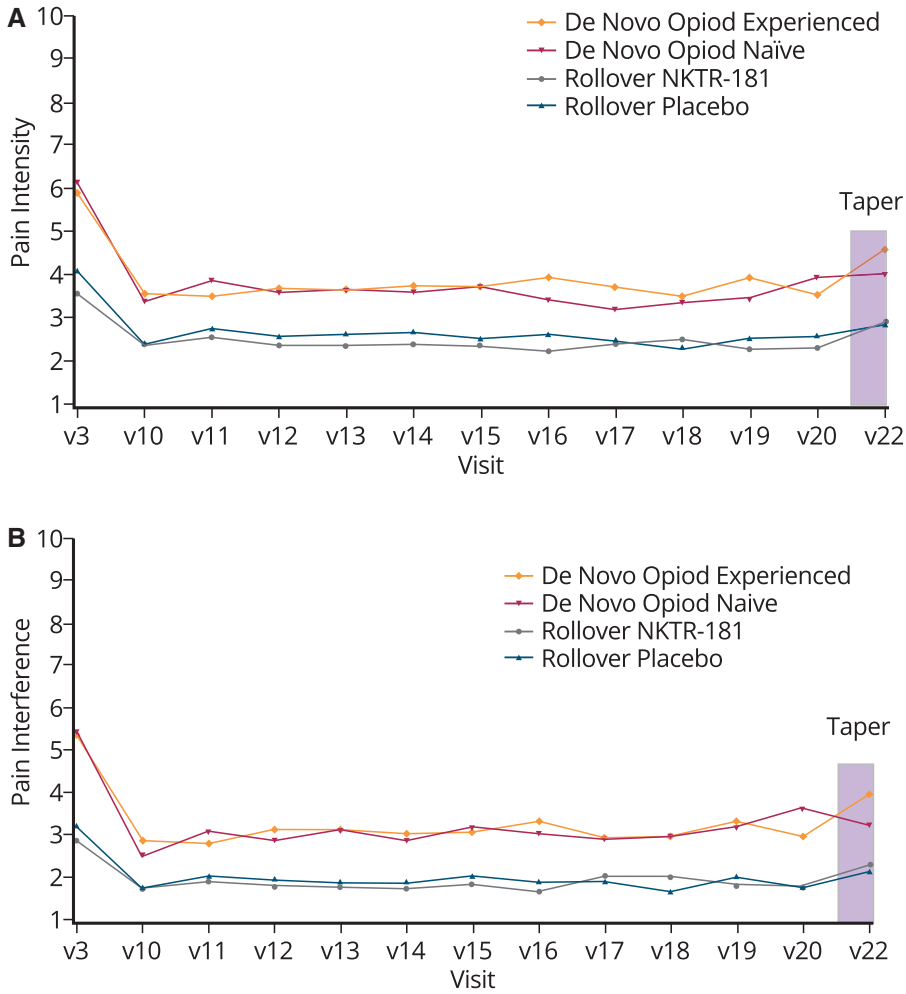

Figure 4. A) Mean pain intensity and (B) mean pain interference over each visit, as measured by the modified Brief Pain Inventory Short Form.

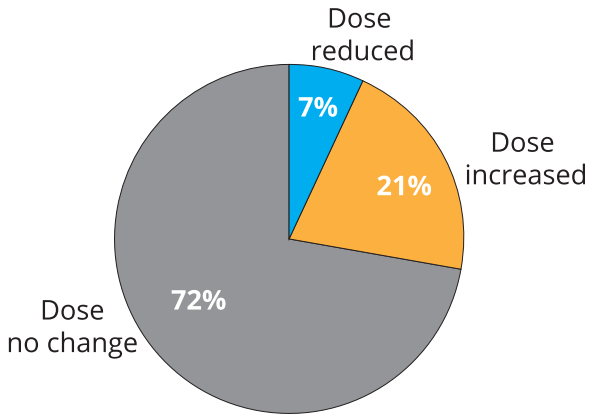

Figure 5. Percentage of patients in the safety population with NKTR-181 dose adjustments (+/- 100 mg twice daily) during the 52-week treatment period. Only the first dose change after a stable dose was achieved in the first five weeks of treatment was used for classifying dose decrease or increase. For subjects with tolerability issues, the dose of NKTR-181 may have been adjusted downwards, as necessary, based on the investigator's clinical judgment in stepwise 100-mg changes.

period, most patients (79%), both opioid-experienced and opioid-naïve, maintained a stable dose during the remainder of the study. Only 2% of patients discontinued the study due to lack of efficacy. In addition, there was no substantial requirement for rescue medication for breakthrough pain once a stable dose level of NKTR-181 was achieved. These findings may suggest that the emergence of tolerance to NKTR-181 was not commonly observed in this long-term safety study.

In the "real-world" setting, patients with chronic pain often receive opioids for an extended period. In this long-term safety study, the efficacy results are consistent with those observed in the randomized, double-blind, placebo-controlled SUMMIT-07 study [22]. Throughout the 12-week SUMMIT-07 study, patients randomized to the NKTR-181 group experienced statistically significantly greater maintenance of pain reduction compared with placebo, based on change in weekly pain score (scale 0–10) at 12 weeks ($P = 0.002$). In the present study (SUMMIT-08 LTS), a similar trend in reduced mBPI-SF pain intensity scores from baseline through the course of NKTR-181 treatment was observed.

In light of current concerns regarding opioid use, medical professionals have questioned whether long-term treatment with currently available opioids is appropriate considering the risks of addiction and overdose [3]. However, CLBP causes significant disability, and response to nonopioid treatments (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs, systemic corticosteroids, spinal manipulation, massage therapy, neuromodulation, or surgery) is often suboptimal for many patients [35–37]. Thus, a pressing need exists for effective opioids with acceptable tolerability and reduced potential for abuse.

NKTR-181 was developed in response to the unmet need for safer opioid therapy [38]. Unlike ADFs, which are reformulations of previously approved opioids that can be subverted to provide a fast-acting version of the opioid, NKTR-181 is a novel molecular entity designed to have a reduced rate of and extent of entry into the CNS when compared with conventional opioids [20]. NKTR-181 does not rely on a formulation approach to prevent its conversion into an abusable form of an opioid.

A strength of the current study is its long duration, providing 52 weeks of NKTR-181 safety, tolerability, and analgesic effectiveness data. The study also allowed patients to have their NKTR-181 doses adjusted, which reflects what is commonly done in clinical practice. However, this study has limitations related to its methodology, specifically the bias toward retention of patients with acceptable analgesic responses and acceptable safety and tolerability profiles, and lack of a control group (placebo) or active comparator arm. Also, the study excluded participants taking >60 mg of MSE per day for seven or more days before consent, a population more likely to develop tolerance.

Overall, NKTR-181 has a favorable safety profile with long-term use, and the results of this study, along with the results from the SUMMIT-07 study, support the conclusion that NKTR-181 is a safe and effective option for patients with CLBP.

Acknowledgments

The authors would like to thank Dr. Magdy Mikhail, MD, and Dr. Howard Rubenstein, MD, for their contributions to the study. Editorial support, funded by Nektar Therapeutics, was provided by Phillips Gilmore Oncology Communications, Inc.

References

1. Han B, Compton WM, Blanco C, et al. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 National Survey on Drug Use and Health. Ann Intern Med 2017;167(5):293–301.
2. Vowles KE, McEntee ML, Julnes PS, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. Pain 2015;156(4):569–76.
3. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015;162(4):276–86.
4. Middleton C, Harden J. Acquired pharmaco-dynamic opioid tolerance: A concept analysis. J Adv Nurs 2014;70(2):272–81.
5. Blendon RJ, Benson JM. The public and the opioid-abuse epidemic. N Engl J Med 2018;378(5):407–11.
6. Florence CS, Zhou C, Luo F, et al. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med Care 2016;54(10):901–6.
7. Litman RS, Pagan OH, Cicero TJ. Abuse-deterrent opioid formulations. Anesthesiology 2018;128(5):1015–26.
8. Adler JA, Mallick-Searle T. An overview of abuse-deterrent opioids and recommendations for practical patient care. J Multidiscip Healthc 2018;11:323–32.
9. Cicero TJ, Ellis MS. Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: Lessons learned from Oxycontin. JAMA Psychiatry 2015;72(5):424–30.
10. Coplan PM, Kale H, Sandstrom L, et al. Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. Pharmacoepidemiol Drug Saf 2013;22(12):1274–82.
11. Becker WC, Fiellin DA. Abuse-deterrent opioid formulations-putting the potential benefits into perspective. N Engl J Med 2017;376(22):2103–5.
12. Wakabayashi KT, Weiss MJ, Pickup KN, et al. Rats markedly escalate their intake and show a persistent susceptibility to reinstatement only when cocaine is injected rapidly. J Neurosci 2010;30(34):11346–55.
13. Samaha AN, Mallet N, Ferguson SM, Gonon F, Robinson TE. The rate of cocaine administration alters gene regulation and behavioral plasticity: Implications for addiction. J Neurosci 2004;24(28):6362–70.
14. Samaha AN, Yau WY, Yang P, Robinson TE. Rapid delivery of nicotine promotes behavioral sensitization and alters its neurobiological impact. Biol Psychiatry 2005;57(4):351–60.
15. Marsch LA, Bickel WK, Badger GJ, et al. Effects of infusion rate of intravenously administered morphine on physiological, psychomotor, and self-reported measures in humans. J Pharmacol Exp Ther 2001;299(3):1056–65.
16. Webster LR, Bath B, Medve RA, et al. Randomized, double-blind, placebo-controlled study of the abuse potential of different formulations of oral oxycodone. Pain Med 2012;13(6):790–801.

17. Shram MJ, Sathyan G, Khanna S, et al. Evaluation of the abuse potential of extended release hydromorphone versus immediate release hydromorphone. J Clin Psychopharmacol 2010;30(1):25–33.
18. Harris SC, Perrino PJ, Smith I, et al. Abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered crushed oxycodone HCl abuse-deterrent controlled-release tablets in recreational opioid users. J Clin Pharmacol 2014;54 (4):468–77.
19. Comer SD, Ashworth JB, Sullivan MA, Vosburg SK, Saccone PA, Foltin RW. Relationship between rate of infusion and reinforcing strength of oxycodone in humans. J Opioid Manag 2009;5(4):203–12.
20. Miyazaki T, Choi IY, Rubas W, et al. NKTR-181: A novel mu-opioid analgesic with inherently low abuse potential. J Pharmacol Exp Ther 2017;363 (1):104–13.
21. Webster L, Henningfield J, Buchhalter AR, et al. Human abuse potential of the new opioid analgesic molecule NKTR-181 compared with oxycodone. Pain Med 2018;19(2):307–18.
22. Markman J, Gudin J, Rauck R, et al. SUMMIT-07: A randomized trial of NKTR-181, a new molecular entity, for chronic low-back pain. Pain 2019;160 (6):1374–82.
23. Kroenke K, Strine TW, Spitzer RL, et al. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009;114(1–3):163–73.
24. Tompkins DA, Bigelow GE, Harrison JA, et al. Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument. Drug Alcohol Depend 2009;105(1–2):154–9.
25. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 2003;35(2):253–9.
26. Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse 1987;13(3):293–308.
27. Treister R, Trudeau JJ, Van Inwegen R, et al. Development and feasibility of the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS(R)). Am J Addict 2016;25(8):641–51.
28. Lanier RK, Henningfield JE, Gudin J, et al. Assessment of potentially abuse-related events in two phase 3 studies of NKTR-181, a novel opioid analgesic, using the MADDERS(R) system (Misuse, Abuse, and Diversion Drug Event Reporting System). Curr Med Res Opin. 2019:1–10 (doi: 10.1080/03007995.2019.1594744).
29. Mundt JC, Greist JH, Jefferson JW, et al. Prediction of suicidal behavior in clinical research by lifetime suicidal ideation and behavior ascertained by the electronic Columbia-Suicide Severity Rating Scale. J Clin Psychiatry 2013;74(09):887–93.
30. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168(12):1266–77.
31. Mundt JC, Greist JH, Gelenberg AJ, et al. Feasibility and validation of a computer-automated Columbia-suicide severity rating scale using interactive voice response technology. J Psychiatr Res 2010;44 (16):1224–8.
32. Mendoza T, Mayne T, Rublee D, et al. Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis. Eur J Pain 2006; 10(4):353–61.
33. Coats TL, Borenstein DG, Nangia NK, et al. Effects of valdecoxib in the treatment of chronic low back pain: Results of a randomized, placebo-controlled trial. Clin Ther 2004;26(8):1249–60.
34. Zheng Y, Kostenbader K, Barrett T, et al. Tolerability of biphasic-release hydrocodone bitartrate/acetaminophen tablets (MNK-155): A phase III, multicenter, open-label study in patients with osteoarthritis or chronic low back pain. Clin Ther 2015;37(6):1235–47.
35. Enthoven WTM, Roelofs PD, Koes BW. NSAIDs for chronic low back pain. JAMA 2017;317(22): 2327–8.
36. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic therapies for low back pain: A systematic review for an American College of Physicians clinical practice guideline. Ann Intern Med 2017;166(7):493–505.
37. Chou R, Deyo R, Friedly J, et al. Systemic pharmacologic therapies for low back pain: A systematic review for an American College of Physicians clinical practice guideline. Ann Intern Med 2017;166(7):480–92.
38. Center for Drug Evaluation and Research. Abuse-Deterrent Opioids-Evaluation and Labeling Guidance for Industry. Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research; 2015.