NEKTAR®

NKTR-181 (Oxycodegol) Oral Tablets for Chronic Low Back Pain

Nektar Therapeutics

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TABLE OF CONTENTS

List of Appendices

List of Tables

List of Figures

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADF	Abuse-deterrent formulation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
$AUC_{0\text{-inf}}$	Area under the plasma concentration time curve from time 0 to infinity
AUC_{tau}	Area under the plasma concentration time curve from time 0 to 12 hours at steady state
AUE	Area under the effect
BBB	Blood brain barrier
BCRP	Breast cancer resistance protein
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CI	Confidence interval
CLBP	Chronic low back pain
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
COWS	Clinical opiate withdrawal scale
CV	Coefficient of variation
CYP	Cytochrome P450
DEQ	Drug Effects Questionnaire
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision
ECG	Electrocardiogram
ED_{50}	Half-maximal effective dose
EERW	Enriched enrollment randomized withdrawal
E_{max}	Maximum effect

Abbreviation	Definition
ER	Extended-release
FDA	Food and Drug Administration
HAP	Human abuse potential
IR	Immediate-release
ITT	Intention-to-treat
IV	Intravenous
K_d	Equilibrium dissociation constant
K_i	Inhibitory constant
K_{in}	Transfer constant
k_{off}	Dissociation rate constant
k_{on}	Association rate constant
LMCF	Last mean carried forward
LS	Least-squares
MAD	Multiple ascending dose
MADDERS	Misuse, Abuse, and Diversion Drug Event Reporting System
MME	Morphine milligram equivalence
mBPI-SF	modified Brief Pain Inventory-Short Form
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MITT	Modified intention-to-treat
MMRM	Mixed-effect model with repeated measures
MOR	Mu-opioid receptor
MOS Sleep-R	Medical Outcomes Study Sleep Scale-Revised
MSE	Morphine sulfate equivalents
NaCMC	Sodium carboxymethylcellulose
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NME	New molecular entity
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis

Abbreviation	Definition
OATP	Organic-anion-transporting polypeptide
PBPK	Physiologically-based pharmacokinetic
PD	Pharmacodynamic
PEG	Polyethylene glycol
PGIC	Patients' Global Impression of Change
P-gp	Permeability glycoprotein
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PRN	As needed
q12h	Every 12 hours
QTc	Corrected QT interval
QTcF	Corrected QT interval, Fridericia's correction
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
RMDQ	Roland-Morris Disability Questionnaire
SAD	Single ascending dose
SAE	Serious adverse events
SD	Standard deviation
SE	Standard error
SMQ	Standardized MedDRA query
SOWS	Subjective opiate withdrawal scale
T_{max}	Time to maximum observed plasma concentration
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale

1 EXECUTIVE SUMMARY

1.1 Introduction

In May of 2018, the United States (US) Food and Drug Administration (FDA) Commissioner reassured patients and physicians that in addressing the opioid crisis, "we wouldn't lose sight of the needs of Americans living with chronic pain" (Gottlieb 2018). The Commissioner has since introduced the framework for a more modern assessment of new opioids, whereby the approval of a novel opioid should be considered "in the context of the overall therapeutic armamentarium […] available to patients and providers" and "relative to the comparative benefit and risks of other opioids already on the market" (FDA 2018). The modernized benefit-risk assessment would examine if a new opioid product "provides a significant advantage relative to an already-approved opioid or opioid-containing drug for the same general indication" where potential safety advantages could include "reduced abuse liability, reduced incidence or severity of serious adverse events, or greater tolerability in particular subpopulations" (FDA 2019a; FDA 2019b). These recent activities to modernize the framework for assessing the benefits and risks of opioid drugs underscore the fact that patients suffering from severe chronic pain conditions need safer and effective analgesics.

While existing opioids are effective analgesics, they have significant liabilities, including central nervous system (CNS) adverse effects and euphoric effects that can lead to misuse and abuse. Nektar Therapeutics (Nektar) has developed NKTR-181 (oxycodegol), a new full mu-opioid receptor (MOR) agonist to provide effective chronic pain relief with a lower potential for abuse. Nektar applied its proprietary polymer conjugation technology to design a new opioid molecule with both a slow rate of movement across the blood-brain barrier (BBB) and slow rate of MOR binding, features that will hereafter be referred to as "CNS kinetic properties." These CNS kinetic properties are inherent properties of the NKTR-181 molecule that were designed to reduce its euphoric and reinforcing effects, and thus provide a novel mechanism to address abuse potential different from the currently-marketed abuse-deterrent formulation-based approaches.

The proposed indication for NKTR-181 is for the management of chronic low back pain (CLBP) in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (hereafter referred to as "management of moderate to severe CLBP").

This document provides an overview of the evidence that supports the approval of NKTR-181 for the treatment of CLBP. Nektar believes that, consistent with the FDA proposed framework for opioid review (FDA 2019a), NKTR-181 should be evaluated both on its own merits, as well as the comparative benefit and risks versus other opioids already on the market. NKTR-181 has been shown to have a lower abuse potential than oxycodone and a low incidence of withdrawal symptoms and CNS-mediated side effects. The evidence for NKTR-181's robust analgesic effect and differentiated safety profile includes:

- Physicochemical and pharmacodynamic (PD) assessments showing that the NKTR-181 molecule has a slower rate of both movement across the BBB and MOR binding compared to oxycodone.
- Two oral human abuse potential (HAP) studies (Studies 05 and 15) demonstrating diminished Drug Liking, Drug High, and Take Drug Again ratings for NKTR-181 at therapeutic doses compared with oxycodone, accompanied by a more gradual rate of rise and longer time to peak Drug Liking that would be less attractive to recreational users seeking a rapid high.
- Nonclinical findings showing less abuse-related behavior with intravenous (IV) NKTR-181 compared with IV oxycodone.
- In vitro manipulation studies showing that when the NKTR-181 molecule is subjected to a range of chemical, enzymatic, liver homogenate, and thermal treatments, it resists conversion to more rapidly acting MOR agonists.
- Demonstration of substantial evidence for efficacy based on a single robust adequate and well-controlled pivotal study (Study 07) supported by confirmatory evidence consistent with the FDA's thinking on the use of 1 trial plus confirmatory evidence discussed in FDAMA 1997, Sasinowski 2019, and Stein 2019:
    - Efficacy data from a pivotal 12-week randomized placebo-controlled study (Study 07) in patients with CLBP showing robust analgesia ($p < 0.0019$).
    - Confirmatory efficacy evidence from well-accepted knowledge that mu-opioid agonists have robust analgesia supported by nonclinical data confirming that NKTR-181 is a MOR agonist with analgesic effects similar to other MOR agonists.
    - Further supportive evidence of maintenance of analgesic efficacy in an open-label 52-week long-term safety study (Study 08).
- Safety data in 1,691 patients with chronic pain conditions from the pivotal study (Study 07), the long-term safety study (Study 08), and a Phase 2 randomized, placebo-controlled study (Study 04), demonstrating an acceptable overall safety profile, with a low rate of CNS-mediated side effects and opioid withdrawal effects.

Overall, the data demonstrate that NKTR-181 is an efficacious analgesic for appropriately selected patients suffering from CLBP. It has a low rate of CNS-mediated side effects and withdrawal symptoms, and a lower abuse potential compared to oxycodone – all important features for providing safe and effective pain relief for patients, and having a distinct safety advantage compared to the risks of opioids already on the market.

1.2 Background on Chronic Low Back Pain and Treatment

Low back pain is one of the most common causes of chronic pain in the US. Approximately 25 million adults have CLBP, defined as pain in the lower back that occurs on a frequent or daily

basis over a period of 3 months or longer (Kennedy et al. 2014). Chronic back pain impairs patients' ability to perform basic activities of daily living and is the leading cause of years lived with disability and job-related disability (National Institute of Neurological Disorders and Stroke 2018; U. S. Burden of Disease Collaborators et al. 2018).

Treatment for CLBP focuses on an array of physical and behavioral interventions, such as ice, heat, acupuncture, exercise, and cognitive behavioral therapy, as well as pharmacologic therapy. Treatment guidelines support initiating opioid therapy in carefully selected patients only if expected benefits for both pain and function are anticipated to outweigh the risks and generally, when other treatment options have failed (Chou et al. 2009; Dowell et al. 2016). If opioids are used to treat CLBP, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (Dowell et al. 2016).

While opioids are an important component of multimodal pain management, they are often accompanied by side effects that may thwart the goal of functional improvement. These include CNS-mediated adverse events (AEs) such as sedation and cognitive impairment, as well as the potential for withdrawal effects (Noble et al. 2010; Sloot et al. 2015; Villars et al. 2007). Moreover, opioid analgesics pose significant public health risks including abuse, misuse, addiction, and overdose. Nearly 12 million Americans misused prescription opioid analgesics in 2016 (SAMHSA 2017), and more than 17,000 deaths in 2017 were attributed to the use of these medications (National Institute on Drug Abuse 2018).

Novel ways to provide safer opioids to patients and to deter prescription opioid abuse are needed. A new opioid that has a low incidence of CNS-mediated AEs, low rate of withdrawal, and a better abuse potential profile that does not rely on its formulation would be a meaningful step forward to provide a safer product for patients requiring opioid therapy. NKTR-181 with its inherent CNS kinetic properties, not relying on a formulation approach, is an important, incremental step to provide patients who need opioid analgesia for CLBP with a less abusable option.

1.3 Overview of NKTR-181

NKTR-181 (oxycodegol) is a new molecular entity (NME) and is not a prodrug, a reformulation, or a drug product formulated for sustained release of an existing opioid. NKTR-181 was designed as a full MOR agonist that inhibits the nociceptive pathways while reducing reinforcing or euphoric effects and other negative CNS-mediated side effects. The NKTR-181 molecule is composed of a morphinan pharmacophore (oxycodol) covalently attached to a 6-unit polyethylene glycol (PEG) chain. PEGylation of the NKTR-181 molecule results in a slower rate of both movement across the BBB and activation of the MORs compared to oxycodone. These properties contribute to NKTR-181's unique PD profile. The 14-hour half-life of NKTR-181 makes the drug inherently long-acting, obviating the need for an extended-release (ER) formulation.

NKTR-181 is supplied as immediate-release (IR) oral tablets in dosage strengths of 100 and 200 mg. It is to be administered at a starting dose of one 100 mg tablet every 12 hours (q12h). Individualized titration to a dose that provides adequate analgesia and tolerability should proceed in increments of 100 mg per dose. Dose increases should occur no more frequently than once every 4 days. A dose above 400 mg every 12 hours has not been studied in randomized controlled trials.

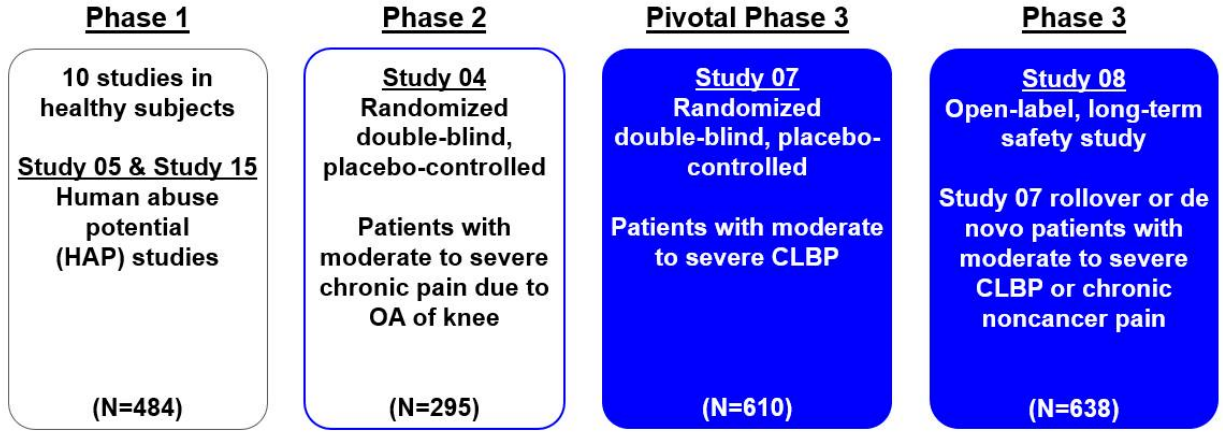
While no comparative clinical studies have been conducted to establish the equianalgesic dose ratio between NKTR-181 and oxycodone, in vitro pharmacology and nonclinical studies show that NKTR-181 exhibits equivalent analgesic efficacy to oxycodone at an estimated dose ratio of approximately 15 mg NKTR-181 to 1 mg oxycodone. Based on the morphine milligram equivalence (MME) conversion ratio from oxycodone to morphine of 1.5 (CDC 2016), NKTR-181 MME conversion factor is approximately 0.1.

NKTR-181 Development Program

The NKTR-181 clinical development program (Figure 1) consists of 12 Phase 1 studies; 1 Phase 2 study in chronic pain due to osteoarthritis (OA) of the knee (Study 04); 1 pivotal Phase 3 study in CLBP (Study 07); and 1 open-label, Phase 3 long-term safety study in CLBP or other chronic noncancer pain conditions (Study 08). The 2 Phase 1 HAP studies (Studies 05 and 15) and the pivotal Phase 3 trial (Study 07) were designed in consultation with the FDA.

Substantial evidence of efficacy for NKTR-181 comes from Study 07, a multicenter, double-blind, placebo-controlled, and adequately powered clinical trial, together with confirmatory evidence from the wealth of scientifically relevant data on MOR agonists. While NKTR-181 is a new opioid agent with novel CNS kinetic properties, comprehensive nonclinical studies have confirmed that it has the same mechanism of analgesic action as other MOR agonists. Given the well-accepted knowledge that mu-opioid agonists have robust analgesia, the efficacy data for the previously approved MOR agonist drugs serve as confirmatory evidence of NKTR-181's therapeutic effect. In addition, the Phase 3 long-term safety study (Study 08) provided evidence that the analgesic effect of NKTR-181 was maintained over 52 weeks.

Figure 1. Overview of NKTR-181 Clinical Development Program



Study 08 included 431 rollover patients from Study 07 and 207 de novo patients.
CLBP = chronic low back pain; OA = osteoarthritis

1.4 Clinical Pharmacology

Following oral administration, NKTR-181 exhibits linear plasma pharmacokinetics (PK), with a time to maximum observed plasma concentration (T_{max}) of 2-4 hours and an elimination half-life of approximately 14 hours. Following daily dosing of NKTR-181 q12h, steady-state is achieved after approximately 3 days, which provides the basis for the recommended 4-day interval between dose increases.

Slow transfer of NKTR-181 from systemic circulation across the BBB into the brain was confirmed by pupillary assessment in clinical studies. Pupillary constriction, a CNS-mediated physiological effect of mu-opioid agonism (Larson 2008) and PD measure, increased with increasing doses of NKTR-181. However, mean maximum pupil constriction occurred 4-5 hours following a single dose of 400 mg or 600 mg, or around 2 hours after T_{max}. In contrast, after administration of oxycodone, pupil constriction and plasma oxycodone concentration both achieved maximum values within approximately 0.5 hours of each other. Based on PK/PD modeling, the population mean half-life of NKTR-181 uptake by the brain from systemic circulation (3.7 hours) was 41-times longer than that for oxycodone (0.09 hours [5.4 minutes]). These data reflect NKTR-181's inherently slower rate of CNS entry and slower rate of MOR binding compared to oxycodone.

1.5 Abuse Potential Assessments

MOR activation stimulates the reward system, eliciting feelings of euphoria that can reinforce drug-seeking behavior. While many variables affect the abuse potential of a drug, factors that impart some of a drug's reinforcing properties include its speed of onset, potency, and route of

administration (Comer et al. 2009; de Wit et al. 1992; de Wit et al. 1993; Marsch et al. 2001; Mumford et al. 1995; Nelson et al. 2006; O'Brien 2011).

Recognizing that as a MOR agonist, NKTR-181 could be abused, Nektar designed a program to assess and characterize NKTR-181's abuse potential relative to that of other MOR agonists such as oxycodone or morphine. Assessments included in vitro testing, nonclinical studies, HAP studies, and in vitro drug manipulation studies.

As shown by the study results described below, the CNS kinetic properties of NKTR-181 reduces the speed of onset and the magnitude of euphoric effects leading to meaningful differences in abuse potential compared to oxycodone.

1.5.1 In Vitro Testing and Nonclinical Studies

The PEG chain on the NKTR-181 molecule slows the rate of movement across the BBB, renders NKTR-181 susceptible to active efflux from the CNS, and slows the association rate (k_{on}) of NKTR-181 at the MOR.

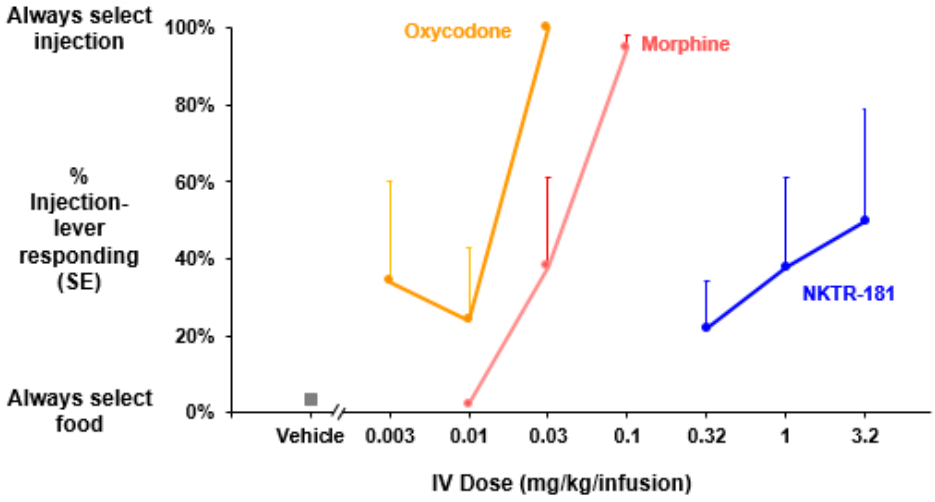
- In an in vitro system that serves as a surrogate for the BBB, NKTR-181 exhibited 38-fold slower overall permeability compared with oxycodone. When efflux transporters were inhibited in this model, NKTR-181 continued to maintain 11-fold lower passive permeability compared to oxycodone. Additionally, in situ and in vivo studies in rats found that the brain uptake of NKTR-181 was more than 25-times slower than that of oxycodone.
- In vitro testing showed that MOR binding was approximately 16-fold slower than oxycodone, indicating that NKTR-181 activates the MOR at a markedly slower rate than oxycodone.

Multiple behavioral nonclinical studies were conducted to evaluate the abuse and physical dependence potential of NKTR-181. These studies are detailed in Section 5.2; key findings are as follows:

- **Oral physical dependence study in rats:** Repeated oral dosing of NKTR-181 resulted in qualitatively milder withdrawal symptoms following abrupt cessation of treatment, relative to repeated doses of morphine.
- **Oral/Intraperitoneal drug discrimination study in rats:** Among animals trained to discriminate oxycodone from saline, discrimination between NKTR-181 and saline occurred only at 30-fold greater intraperitoneal doses and 50-fold greater oral doses than oxycodone.
- **IV self-administration study in rats – progressive ratio testing:** Animals trained to self-administer cocaine expended the same low level of effort to administer IV NKTR-181 as they did for saline. In contrast, animals performed 2-3 times more lever presses to receive a bolus of oxycodone at doses 100- to 300-fold lower than that of NKTR-181.

- **IV self-administration study in rats:** In animals trained to self-administer hydrocodone, NKTR-181 at doses 10-fold greater than oxycodone was associated with weak and inconsistent IV self-administration, whereas oxycodone resulted in stable self-administration over the test period.
- **IV self-administration study in monkeys:** Animals trained to self-administer morphine chose nearly exclusively to receive drug over food at the highest doses of oxycodone and morphine (Figure 2). In contrast, half of the animals chose food over NKTR-181 at the highest dose of NKTR-181 (a dose 100-fold and 30-fold greater than the highest dose of oxycodone and morphine, respectively).

Figure 2. Intravenous Self-Administration of NKTR-181 in Primates Trained to Administer Morphine in Substitution Study with Food Option



Each point represents the percentage of total lever presses observed in 4 animals over 90 minutes.
IV = intravenous; SE = standard error

Overall, these results demonstrate that NKTR-181 exhibits slower CNS entry and slower MOR activation compared with oxycodone and that animals administered NKTR-181 exhibit symptoms and behaviors consistent with lower abuse potential when compared with oxycodone and morphine.

1.5.2 Human Abuse Potential Studies

Two oral HAP studies (Studies 05 and 15) were conducted to evaluate the abuse potential of NKTR-181 compared with oxycodone HCl and placebo in healthy, non-dependent, recreational opioid users. Both were single-dose, active- and placebo-controlled, crossover studies that are consistent with the FDA guidance on HAP studies (FDA 2017).

Study 05 evaluated NKTR-181 at dose levels of 100, 200, and 400 mg and oxycodone 40 mg, all in oral solution; Study 15 evaluated NKTR-181 at 400, 600, and 1200 mg and oxycodone 40 and 60 mg in oral tablets/encapsulated tablets. Both studies included the 400 mg dose of NKTR-181, which is the maximum dose studied in the Phase 3 pivotal study (Study 07); NKTR-181 600 mg

was also studied, as this was the maximum dose evaluated in the Phase 3 open-label long-term safety study (Study 08). The 1200 mg dose level was included to assess the abuse potential of 2 to 3 times the highest doses tested in the Phase 3 studies.

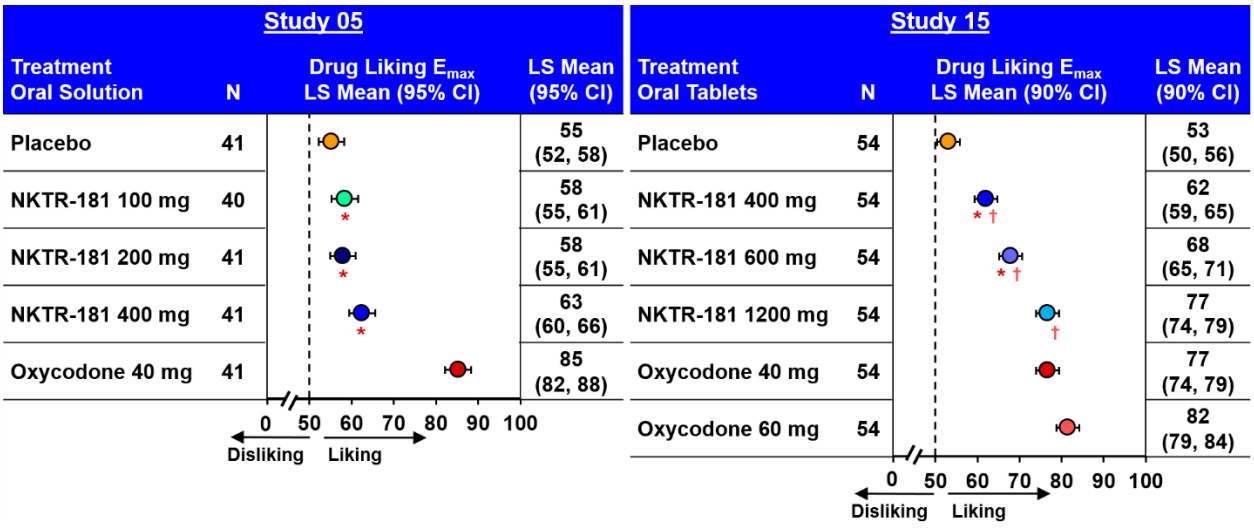
The primary endpoint measure was subject-reported Drug Liking "at this moment" as evaluated on a bipolar 100-mm visual analog scale (VAS) at multiple time points following administration of NKTR-181, oxycodone, or placebo. Additional VAS endpoint measures included Drug High, Take Drug Again, and Overall Drug Liking.

Key results from the 2 oral HAP studies are summarized below. Detailed results are provided in Section 5.3.

Drug Liking

Figure 3 shows the Drug Liking maximum effect (E_{max}) in both studies. In Study 05, NKTR-181 100 and 200 mg produced Drug Liking at a level similar to placebo. In Study 15, NKTR-181 400 and 600 mg produced lower Drug Liking than oxycodone 40 mg. NKTR-181 1200 mg produced similar Drug Liking E_{max} to oxycodone 40 mg, but lower Drug Liking E_{max} than oxycodone 60 mg. Importantly, the median time to Drug Liking E_{max} for NKTR-181 1200 mg (2.7 hours) was delayed compared to that of oxycodone 40 and 60 mg (2.0 and 1.7 hours, respectively). While the dose levels in the 2 HAP studies differed slightly, the oral dosage form (solution vs tablet) did not change the relative Drug Liking between NKTR-181 and oxycodone as seen by the consistent results across both studies for the 400 mg dose of NKTR-181.

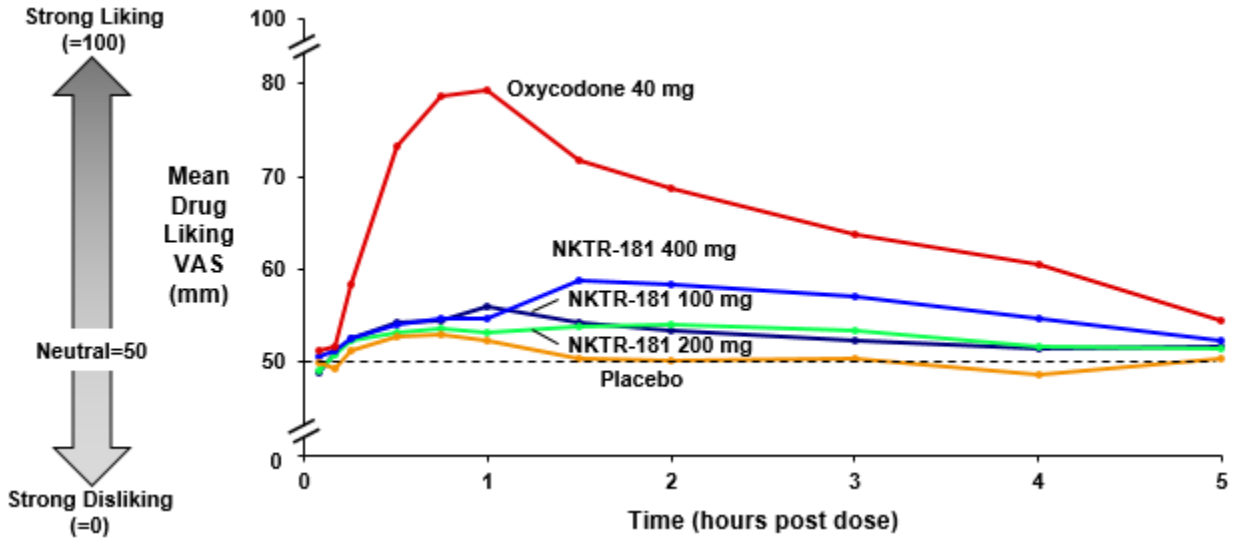
Figure 3. Drug Liking E_{max} in Study 05 and Study 15



Drug Liking question text: "At this moment, my liking for this drug is"; scale: 0 = strong disliking, 50 = neither like nor dislike, 100 = strong liking.
* $p < 0.05$ vs oxycodone 40 mg; † $p < 0.05$ vs oxycodone 60 mg
CI = confidence interval; E_{max} = maximum effect; LS = least squares

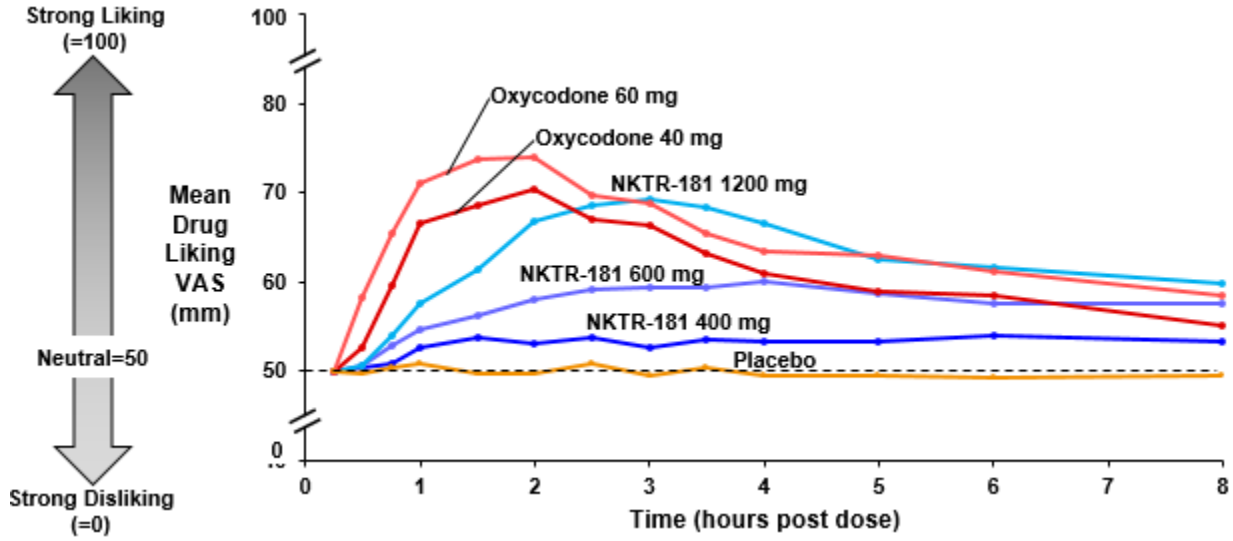
Figure 4 and Figure 5 show Drug Liking over time in Study 05 and Study 15, respectively, following a single oral dose of NKTR-181, oxycodone, and placebo. NKTR-181 was associated with a slower onset of Drug Liking within the first hour after dosing, consistent with the slower CNS kinetic properties of NKTR-181. The area under the effect (AUE) curve and the rate of rise of Drug Liking over the first 2 to 3 hours post-dose were lower for all dose levels of NKTR-181 than either dose of oxycodone (see Section 5.3.1.3, Table 12 and Section 5.3.2.3, Table 14 and Table 15). AUE and rate of rise are important PD markers linked to onset of effect and are important aspects of the reinforcing effects of a drug (Comer et al. 2009; Marsch et al. 2001). Oxycodone achieved peak Drug Liking within 1 to 2 hours. The more gradual effects of NKTR-181 may make NKTR-181 less attractive as a drug of abuse for individuals seeking a rapid onset of a "high."

Figure 4. Study 05 Mean Drug Liking



VAS = visual analog scale

Figure 5. Study 15 Mean Drug Liking



VAS = visual analog scale

Additional VAS Assessments

Other VAS assessments that have been correlated with abuse potential, Drug High (Eaton et al. 2012), Take Drug Again, and Overall Drug Liking (FDA 2015), showed results similar to the primary endpoint with lower E_{max} values observed for NKTR-181 400 and 600 mg compared to both oxycodone doses (40 and 60 mg), similar values between NKTR-181 1200 mg and oxycodone 40 mg, and lower values for NKTR-181 1200 mg compared to oxycodone 60 mg (see Section 5.3.2.4, Figure 23 and Section 5.3.2.4, Figure 24).

1.5.3 In Vitro Manipulation Testing

Because of its intrinsic CNS kinetic properties, NKTR-181 is formulated without tamper-resistant features or other formulation-based physical/chemical barriers. Accordingly, in vitro laboratory manipulation studies were conducted in order to assess the degree to which the chemical structure of NKTR-181 could be altered to form more active opioid derivatives that act on MORs more rapidly. None of the 193 experimental conditions across a range of chemical, enzymatic, liver homogenate, and thermal treatments was able to convert more than 1.3% of oxycodone or 6β-oxycodol, which are more active derivatives than NKTR-181. Based on these findings, it is reasonable to conclude that attempts to convert NKTR-181 to a more abusable opioid form are unlikely to be successful.

1.5.4 Abuse Potential Conclusions

As predicted by NKTR-181's inherent molecular CNS kinetic properties – and not due to a formulation that can be easily manipulated – NKTR-181 has a slower onset of abuse-related CNS effects and a lower overall abuse potential profile when compared to oxycodone. This was demonstrated across a wide range of in vitro, nonclinical, and clinical assessments aimed at

predicting real-world abuse potential. Data from animal behavioral studies show that NKTR-181 has a reduced abuse potential profile compared to oxycodone, when administered by multiple routes of administration including oral, IV, and intraperitoneal.

In the 2 oral HAP studies (Studies 05 and 15), therapeutic doses of NKTR-181 produced lower abuse-related effects than oxycodone. Administration of NKTR-181 at 1200 mg (2-3 times the highest doses tested in the Phase 3 studies) resulted in Drug Liking similar to that of 40 mg oxycodone, but with a slower onset. This would be expected to result in NKTR-181 being viewed as a less desirable drug for those individuals seeking a rapid high. Finally, in vitro manipulation studies demonstrated that NKTR-181 resists conversion to a more active opioid substance that would be of potential interest for abuse or diversion.

Overall, these data support that patients receiving NKTR-181, within the therapeutic dose range of 100 to 600 mg, are less likely to experience euphoric effects that may lead to misuse and abuse. While NKTR-181 is an opioid analgesic that could be abused, for those seeking a rapid onset of effects that are characteristic of oxycodone, morphine, and other conventional opioids, NKTR-181 is expected to be less attractive.

1.6 Clinical Efficacy

1.6.1 Phase 2 Placebo-Controlled Study 04

Study 04 was a Phase 2 multicenter, randomized, 3-week double-blind, placebo-controlled study evaluating the efficacy and safety of NKTR-181 in patients with moderate to severe chronic pain due to OA of the knee.

The study followed an enriched-enrollment, randomized withdrawal (EERW) design, consistent with draft FDA Guidance (2012). In this design, the initial open-label period identifies patients who respond to and tolerate the investigational medication. Responders are then randomized in a double-blind phase to continue study medication or placebo to confirm that efficacy is statistically superior to placebo (Katz 2009). EERW is commonly used for studies of chronic opioid treatments, including registrational studies of new opioid drugs, to characterize treatment benefit among patients who show an analgesic response to treatment.

In Study 04, there was no difference between NKTR-181 and placebo on the primary endpoint of change in pain intensity from randomization to the end of treatment (least squares [LS] mean, -0.04; standard error [SE], 0.22; p = 0.8404). A review of the study design and data identified the following factors, which may have contributed to not showing a difference between groups:

- Study 04 was an opioid add-on study in which the patients did not discontinue their current analgesic therapies. Approximately 91% of patients were taking non-steroidal anti-inflammatory drugs (NSAIDs), which may have contributed to maintenance of pain relief in patients switched to placebo during the double-blind Treatment Period. These

concurrent analgesic therapies may also have played a role in suppression of the expected rebound in pain score upon withdrawal of NKTR-181 in the placebo group.

- Patients were eligible to enter the double-blind Treatment Period if they achieved at least a 20% decrease in numeric rating scale (NRS) score from screening. Such a criterion resulted in a more modest reduction of pain required for those with lower screening NRS scores, which may have contributed to an inability to achieve significant separation from placebo in this group of patients.

The insights from Study 04 informed the study design for the subsequent pivotal Phase 3 clinical study (Study 07), in which background concomitant medications for pain were prohibited and an absolute, rather than relative, measure of pain reduction was applied for entry into the double-blind Treatment Period (see Section 6.2.4). Additional information on Study 04 is provided in Section 6.1 and Appendix 3.

1.6.2 Phase 3 Pivotal Placebo-Controlled Study 07

Study Design

Study 07 was a Phase 3 multicenter, randomized, 12-week double-blind, placebo-controlled EERW study in patients with moderate to severe CLBP who were previously taking ≤ 10 mg morphine sulfate equivalents (MSE) per day of short-acting opioids for the 14 days prior to screening.

All patients initiated NKTR-181 at a dose of 100 mg q12h. Those patients who were able to titrate to an effective and tolerable dose over the 3- to 7-week Titration Period were then randomized in a 1:1 ratio to continue treatment with NKTR-181 at the dose established during titration, or to receive placebo. Double-blind treatment with placebo or NKTR-181 was administered for 12 weeks, followed by a 1-week taper, and an additional 2 weeks of safety follow-up.

Rescue opioid medication (up to 2 tablets of 5 mg hydrocodone/300 mg acetaminophen per day) was allowed for breakthrough pain during the first 2 weeks of the double-blind Treatment Period only; opioid analgesics were otherwise prohibited. After Week 2, acetaminophen (up to two 500-mg tablets per day) was allowed as rescue medication.

The primary efficacy endpoint was the change in Weekly Pain Score from baseline (immediately prior to randomization) to Week 12. Patients rated their pain daily on a 11-point (0-10) NRS.

Patient Population

Patients enrolled in Study 07 were appropriate candidates for chronic opioid therapy, based on the following:

- Patients had a history of chronic non-neuropathic low back pain (ie, ≥ 6 months; mean [standard deviation (SD)], 13 [10] years) that was moderate to severe (ie, NRS score of 5-9; mean [SD], 6.7 [0.9]).

- Patients had received prior pain medications for an extended duration (mean [SD], 7.5 [7.7] years) and had an inadequate response. Therefore, consistent with current guidelines of treatment after failed medical therapy, opioid analgesia was deemed appropriate.

Of the 1,189 patients dosed with NKTR-181 during the Titration Period, 610 met the protocol-specified randomization criteria (Section 6.2.4) for entry to the double-blind Treatment Period, and 309 and 301 patients were randomized to receive continued dosing with NKTR-181 and placebo, respectively. The rate of randomization in Study 07 (610/1,189; approximately 51%) is consistent with those reported in other EERW opioid studies (Meske et al. 2018).

During the double-blind Treatment Period, approximately 80% of randomized patients completed the study, with similar discontinuation rates in each arm. The most common reason for discontinuation was AEs in the NKTR-181 group (8.4%) and withdrawal of consent in the placebo group (7.6%; see Section 6.2.7.1 for further details).

Overall, the demographics were similar between NKTR-181 and placebo arms and were typical of the patient population. Disease characteristics were also similar between treatment groups. The mean (SD) Screening Pain Score was 6.7 (1.0) and 6.8 (0.9) among patients who were eventually randomized to NKTR-181 and placebo, respectively. At the end of the open-label Titration Period with NKTR-181, the mean pain score fell to 2.3 (1.1) and 2.4 (1.1), respectively.

Among patients randomized to the NKTR-181 group, 2.3%, 20.4%, 27.8%, and 49.5% had titrated to a dose of 100, 200, 300, and 400 mg q12h, respectively.

Primary Endpoint Results

Patients treated with NKTR-181 showed a statistically significant difference in the change in Weekly Pain Score from Randomization Baseline to Week 12 when compared with those treated with placebo. The LS mean change (SE) in Weekly Pain Score favored NKTR-181 by a difference of -0.55 (0.16; p = 0.0019; Table 1). A separation between NKTR-181 and placebo was observed at Week 1 post-randomization and was maintained through Week 12. Multiple sensitivity analyses were conducted to evaluate the robustness of the primary endpoint analysis for missing data, and the results supported the robustness of the primary efficacy analysis.

Table 1. Primary Efficacy Endpoint Results in Study 07

Change from Baseline in Weekly Pain Score at Week 12	**NKTR-181 N = 309**	**Placebo N = 301**
LS Mean (SE)	0.92 (0.112)	1.46 (0.114)
Treatment difference, LS Mean (SE) **95% CI** **p-value**	-0.55 (0.160) (-0.86, -0.23) 0.0019	

CI = confidence interval; LS = least squares; SE = standard error

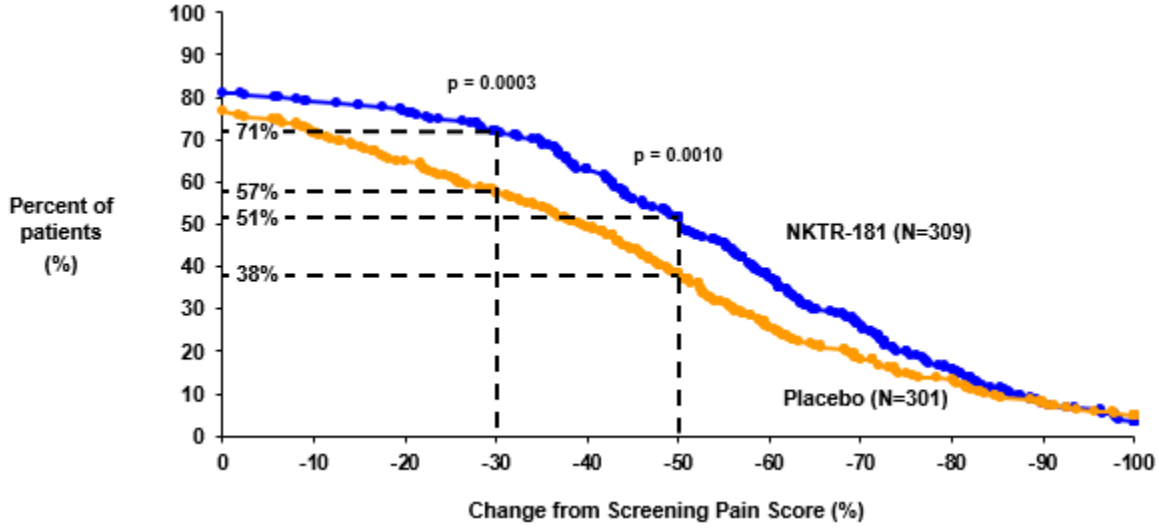
The magnitude of pain reduction attributed to NKTR-181 in Study 07 is similar to that of other opioids used for the treatment of chronic pain (see Section 6.2.8, Figure 30) (Meske et al. 2018).

Secondary Endpoint Results

At Week 12, patients treated with NKTR-181 had consistently higher response rates than those treated with placebo on the following measures:

- **Reductions in pain of ≥ 30% and ≥ 50%** are considered benchmarks of clinically important changes across chronic pain studies (Dworkin et al. 2008). The proportion of patients experiencing ≥ 30% improvement in Weekly Pain Score was 71.2% in the NKTR-181 group versus 57.1% in the placebo group (p = 0.0003; Figure 6). Moreover, 51.1% of the patients in the NKTR-181 group versus 37.9% of the patients in the placebo group achieved a ≥ 50% reduction in mean Weekly Pain Score (p = 0.0010).

Figure 6. Cumulative Distribution of Percent Reduction from Screening Pain Score at 12 Weeks in Study 07



- **Patients' Global Impression of Change (PGIC)** captures the importance of treatment-related improvement or worsening as judged by the patient and is recommended as a supportive measure of treatment response in chronic pain studies (Dworkin et al. 2008). At Week 12, 51.5% of NKTR-181 patients reported their overall status as being "better" or "a great deal better" since the beginning of treatment compared to 33.2% of patients in the placebo group (p < 0.0001).

Additional secondary efficacy measures also supported the primary efficacy endpoint:

- During the first 2 weeks of the double-blind Treatment Period, in which opioid rescue medication was permitted, a lower percentage of patients in the NKTR-181 group (44.3%

and 45.4% during Week 1 and Week 2, respectively) used rescue medication than did patients in the placebo group (62.8% and 60.6%, respectively).

- The Medical Outcomes Study Sleep Scale-Revised (MOS Sleep-R) assessment showed that patients in the NKTR-181 group experienced improvements in sleep disturbance, sleep problems, sleep adequacy, and hours slept per night from screening to Week 12, compared to placebo ($p \leq 0.0477$ for each). Furthermore, no worsening was observed with NKTR-181 treatment in terms of day time sleepiness (ie, somnolence) or respiratory impairment (ie, snoring and shortness of breath) in comparison to placebo, indicating overall improvements in quality of sleep with the absence of 2 important opioid-related side effects.
- Patients in the NKTR-181 group showed a numerically greater improvement in mean Roland-Morris Disability Questionnaire (RMDQ) score compared with placebo at Week 12 (LS mean [SE] difference from placebo, -0.9 [0.5]; unadjusted $p = 0.0605$).
- There was little difference in time to discontinuation during the Treatment Period for patients in the NKTR-181 versus the placebo group (hazard ratio [95% CI], 1.02 [0.7, 1.5]; $p = 0.9225$).

Section 6.2.9 provides additional details on the secondary endpoints.

1.6.3 Phase 3 Open-Label Long-Term Safety Study 08

Study Design

Study 08 was a Phase 3, open-label long-term (52-week) safety and tolerability study in adult patients with moderate to severe CLBP or chronic noncancer pain, who received treatment with NKTR-181 at doses of 100 to 600 mg q12h. Study 08 enrolled Study 07 rollover patients as well as de novo patients with CLBP or chronic noncancer pain.

All enrolled patients started with a dose of 100 mg q12h and were titrated to adequate analgesic response per the Investigator's judgment up to a maximum dose of 600 mg q12h. Dose adjustments were permitted during the course of the study based on the Investigator's assessment of effectiveness and tolerability. The 52-week treatment period ended with a 1-week taper period. The use of other opioids was prohibited in Study 08. Over-the-counter analgesics (ie, aspirin, acetaminophen, ibuprofen, and naproxen) were allowed to be used in accordance with their labels for breakthrough pain.

Pain intensity and the degree to which pain interfered with daily activities was assessed using the modified Brief Pain Inventory-Short Form (mBPI-SF).

Patient Population

Eligible patients were adults with moderate to severe CLBP or chronic noncancer pain of > 3 months' duration. De novo patients could have received up to 60 mg MSE per day in the 7 days prior to screening; prior opioids were tapered and discontinued prior to starting treatment with NKTR-181. Rollover patients from Study 07 were required to complete that study before

entering Study 08, without a break in study treatment. A clinical opiate withdrawal scale (COWS) score ≤ 12 was required for entry into Study 08.

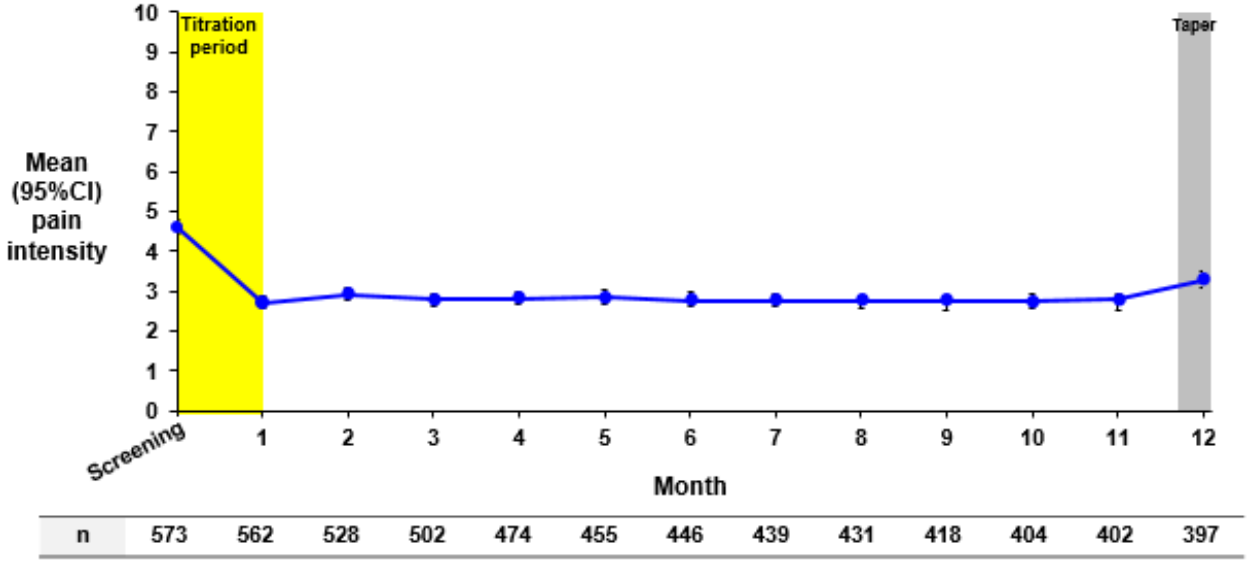
Of the 638 enrolled patients, 62.2% completed Study 08, which is similar to the study completion rates in other long-term opioid studies (Broglio et al. 2017; Friedmann et al. 2011; Hale et al. 2015). The most common reasons for study discontinuation were withdrawal of consent (11.4%), AEs (10.5%), and lost to follow-up (5.0%); 2.2% of patients discontinued the study due to lack of efficacy (see Section 6.3.5.1 for further details).

Demographics and baseline disease characteristics were generally similar between the different NKTR-181 dose groups and among rollover and de novo patient subgroups. The mean time since onset of chronic pain was approximately 13 years.

Results

Mean pain intensity scores decreased from 4.6 at screening to 2.7 at the end of titration. The reduction in pain was consistent throughout the duration of the study, with mean scores of 2.7 at Week 42 (last mBPI-SF measurement prior to tapering; Figure 7). Importantly, 72.0% of patients maintained the same dose of NKTR-181 for the duration of the study (ie, up to 52 weeks).

Figure 7. mBPI-SF Pain Intensity Scores Over Time in Study 08



1.6.4 Clinical Efficacy Conclusions

Study 07 demonstrated that NKTR-181 provides robust analgesic efficacy in patients with moderate or severe CLBP, and Study 08 showed that the effect is durable and consistent over long-term treatment. Study 07 showed a statistically significant improvement based on pain scores and responder analyses. The clinical meaningfulness of these pain reductions was

supported by the secondary endpoints of PGIC, as well as MOS Sleep-R showing improvements in night time sleep disturbances with no negative impact on day time sleepiness (ie, somnolence).

1.7 Clinical Safety

1.7.1 Exposure

The safety of NKTR-181 is supported by exposures in 2,175 individuals across the clinical development program who received at least 1 dose, including 1,691 patients with CLBP or other noncancer chronic pain from the Phase 2 and Phase 3 studies. The primary safety database from the placebo-controlled study (Study 07) includes data from 1,189 patients with CLBP who were exposed to at least 1 dose of NKTR-181 during the Titration Period and 309 patients who received NKTR-181 during the double-blind Treatment Period. The safety assessment of NKTR-181 is also supported by data from Phase 1 studies, Phase 2 Study 04, and the 52-week Phase 3 Study 08.

1.7.2 Overview of Adverse Events

Study 07

During the open-label Titration Period, 67.5% of patients had at least 1 AE, which decreased to 54.4% and 49.8% of NKTR-181- and placebo-treated patients, respectively, during the double-blind Treatment Period.

Types of AEs observed in Study 07 were consistent with opioid-type side effects, and most were mild or moderate in severity. The most common AEs (occurring in > 5% of patients) during the open-label Titration Period were constipation, nausea, somnolence, headache, vomiting, dry mouth, and fatigue (Table 2); nausea and constipation continued to be the most common AEs during the double-blind Treatment Period.

Table 2. Adverse Events Reported ≥ 3% of Patients in Study 07

	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301
Patients reporting ≥ 1 AE, n (%)	803 (67.5)	168 (54.4)	150 (49.8)
Constipation	425 (35.7)	27 (8.7)	9 (3.0)
Nausea	176 (14.8)	32 (10.4)	18 (6.0)
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)
Pruritus	52 (4.4)	2 (0.6)	0
Dizziness	47 (4.0)	7 (2.3)	1 (0.3)
Diarrhoea	35 (2.9)	8 (2.6)	17 (5.6)
Drug withdrawal syndrome	32 (2.7)	14 (4.5)	12 (4.0)
Nasopharyngitis	13 (1.1)	10 (3.2)	11 (3.7)
Upper respiratory tract infection	21 (1.8)	10 (3.2)	9 (3.0)

AEs leading to discontinuation occurred more frequently in the NKTR-181 group than the placebo group (7.1% vs 2.7%) during the double-blind Treatment Period. Those reported more frequently in the NKTR-181 group and by more than 1 patient during double-blind treatment were typical opioid-related AEs (ie, constipation and vomiting).

A low incidence of serious AEs (SAEs) occurred during the Titration Period (0.8%). In the double-blind Treatment Period, the incidence of SAEs was low and similar between treatment groups (1.6% for NKTR-181 vs 2.0% for placebo). No SAEs occurred in more than 1 patient (see Section 7.2.4 for details).

One death, due to a cerebrovascular accident, which was not considered by the Investigator to be related to NKTR-181, occurred across all clinical studies. The 66-year-old male patient had a history of hypertension and hypercholesterolemia and had been receiving 100 mg NKTR-181 q12h at the time of the fatal event. A narrative is provided in Appendix 9.

Study 08

No new safety signals were identified in the 52-week safety study (see Section 7.3.1, Table 31 for details) that were not previously observed in the clinical program or with other opioids. Most patients (72.3%) reported at least 1 AE, the majority of which were mild or moderate in severity. SAEs, none of which was assessed as related to study drug, were reported in 4.7% of patients. AEs leading to discontinuation occurred in 9.9% of patients; among these, constipation, headache, nausea, irritability, and vomiting were the most commonly reported.

Study 15

HAP Study 15 provides head-to-head safety data on NKTR-181 and oxycodone IR following single-oral-dose administration in healthy recreational opioid users. In this study, a dose-dependent incidence of AEs was observed for NKTR-181 and oxycodone, with a greater rate of AEs being reported following treatment with oxycodone 40 and 60 mg than with NKTR-181 400 and 600 mg (Section 7.4, Table 35). CNS-mediated AEs, including euphoric mood, somnolence, and dizziness, were reported approximately 2 times more frequently for oxycodone 40 or 60 mg than for NKTR-181 400 or 600 mg. Other common opioid-related side effects (pruritus, nausea, and vomiting) also occurred more frequently following a single dose of oxycodone (40 or 60 mg) than a single dose of NKTR-181 (400 or 600 mg). NKTR-181 1200 mg (2-3 times the highest doses tested in the Phase 3 studies) produced a similar rate of AEs as oxycodone 60 mg.

1.7.3 Adverse Events of Special Interest

Based on discussions with the FDA and the known pharmacology of NKTR-181, AEs of special interest (AESIs) were investigated; AESIs included hepatic and cardiac safety, CNS-mediated AEs, respiratory depression, opioid withdrawal, as well as misuse, abuse, and diversion. Additional details on AESIs are provided in Section 7.6.

1.7.3.1 Hepatic and Cardiac Safety

Throughout the development program, no AE was reported as drug-induced liver injury. No patient treated with NKTR-181 met the criteria for Hy's Law.

No clinically meaningful change in electrocardiogram (ECG) parameters was observed at any of the NKTR-181 doses studied.

Additional details on hepatic and cardiac safety are provided in Sections 7.6.1 and 7.6.2, respectively.

1.7.3.2 CNS-Mediated Events

It was hypothesized that the CNS kinetic properties of NKTR-181 may lessen the CNS-mediated side effects commonly associated with opioid therapy. CNS-mediated AEs, ie, those having a centrally-mediated etiology and representing opioid-related clinically important manifestations of CNS activation or suppression, were specifically investigated. In Study 07, the overall incidence of patients with at least 1 CNS-mediated AE was 26.2% and 17.6% for the NKTR-181

and placebo groups, respectively (see Table 37 in Section 7.6.3). The incidence of nausea (10.4%), vomiting (4.9%), somnolence (2.6%), dizziness, and dry mouth (both 2.3%) among NKTR-181-treated patients was higher than placebo by only 2 to 4 percentage points. In HAP Study 15, among recreational users, CNS-mediated AEs occurred at a greater incidence with oxycodone use than with the 2 highest NKTR-181 doses (400 and 600 mg) studied in the Phase 3 program. Euphoric mood, somnolence, and dizziness were reported approximately 2 times more frequently for oxycodone 40 and 60 mg than NKTR-181 400 and 600 mg.

1.7.3.3 Respiratory Depression

No AE of respiratory depression was reported across the clinical development program. However, decreased oxygen saturation was reported as an AE in the Phase 1 multiple ascending dose studies in 2 and 4 subjects receiving 400 and 500 mg of NKTR-181 q12h, respectively. Nadir oxygen saturation levels in these subjects ranged from 80 to 89%. The events of decreased oxygen saturation were transient and treated with 0.5 to 2 liters oxygen per nasal cannula. Notably, these earlier studies initiated NKTR-181 at doses higher than the starting dose recommended in the proposed label.

1.7.3.4 Opioid Withdrawal

COWS assessments were conducted 1 week following randomization in Study 07; prior to randomization all patients had received a stable dose of NKTR-181 for 2 weeks. One-week post-randomization, the incidence of withdrawal was similar for the placebo group, which had abruptly ceased NKTR-181, and the NKTR-181 group, which continued NKTR-181 treatment; 97.6% and 99.0% had no withdrawal symptoms, respectively (Table 3).

Subjective Opiate Withdrawal Scale (SOWS) assessments were also recorded by patients daily for 14 days following randomization. Following discontinuation of NKTR-181, placebo patients had a maximum mean increase of 1.1-points in SOWS scores from 1.9 (SD, 2.7) at randomization to 2.9 (4.6) on Day 3, suggesting a minimal change in symptoms of opioid withdrawal on this 64-point scale.

Table 3. Clinical Opiate Withdrawal Scale Assessments Following Randomization in Study 07

COWS 1-week post-randomization (Day 8)	**Double-Blind Treatment**	
	NKTR-181 N = 309	**Placebo N = 301**
N	295	291
No withdrawal symptoms, n (%)	292 (99.0)	284 (97.6)

COWS total scores range from 0 to 48, with higher scores indicating greater severity as follows: < 5: no withdrawal; 5 to 12: mild withdrawal; 13 to 24: moderate withdrawal; 25 to 36: moderately severe withdrawal; > 36: severe withdrawal.
COWS = Clinical Opiate Withdrawal Scale

Consistent with the COWS and SOWS results, analyses of drug-withdrawal-related AEs showed a low incidence of patients (5.4% or less) exhibiting withdrawal following their last dose of NKTR-181 (see Section 7.6.5.3, Table 39).

1.7.3.5 Misuse, Abuse, and Diversion

The Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS®) (Smith et al. 2013) is a methodology for systematically identifying, evaluating, and classifying potentially abuse-related events in clinical trials. In Study 07, the incidence of overall MADDERS events was low and similar for the NKTR-181 and placebo groups, as were the events adjudicated as misuse or abuse (see Section 7.6.6.1, Table 40).

In the Phase 2 and 3 studies, standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) for AEs related to misuse, diversion, abuse, and dependence were performed and identified a total of 4 AEs. Accidental overdose, toxicity to various agents, drug abuse, and drug dependence were each reported by 1 patient in Study 07 or Study 08. All events resolved and are detailed in Section 7.6.6.2.

1.7.4 Clinical Safety Conclusions

Overall, NKTR-181 has a favorable safety profile, with expected typical opioid-type AEs. Its unique physicochemical properties support a low risk for withdrawal symptoms at a rate similar to placebo and a low rate of CNS-mediated AEs, with only a 2 to 4-percentage point difference versus placebo in the incidence of nausea, somnolence, vomiting, dry mouth, and dizziness.

1.8 Risk Mitigation Plan

Nektar will participate in the opioid analgesic Risk Evaluation and Mitigation Strategy (REMS) programs to reduce and mitigate serious risks resulting from inappropriate prescribing, misuse, and abuse of NKTR-181. In addition to participation in the opioid analgesic REMS programs and standard pharmacovigilance activities, Nektar has proposed further post-marketing activities to ensure the safe use of NKTR-181. These plans, which will be discussed and finalized in collaboration with the FDA, potentially include the use of real-world evidence (eg, patient registry), existing data collection systems (eg, Researched Abuse, Diversion and Addiction-Related Surveillance [RADARS] System, National Addictions Vigilance Intervention and Prevention Program [NAVIPPRO]), and systematic surveillance of social media to characterize prescribing practices, identify patterns of abuse and misuse in real-world scenarios, and further assess risks of abuse, misuse, withdrawal symptoms, and overdose. Further details are provided in Section 8.

1.9 Benefit and Risk Conclusions

NKTR-181, an NME novel MOR agonist, has unique physicochemical properties inherent to the molecule, resulting in slower CNS penetration and slower MOR binding compared to oxycodone. Clinical studies have demonstrated that NKTR-181 provides clinically meaningful and durable analgesia with a favorable safety profile for patients with CLBP for whom

alternative treatment options are inadequate. A battery of nonclinical and clinical studies have demonstrated that NKTR-181 has a lower potential for abuse compared to oxycodone within the therapeutic dose range. The long half-life (14 hours) of NKTR-181 allows twice-daily dosing without an extended-release formulation and also contributes to the low rate of withdrawal symptoms. No chemical, physical and enzymatic method applied has been able to efficiently convert NKTR-181 into a more rapidly-acting opioid substance. NKTR-181 uses excipients commonly used for currently marketed immediate-release opioid tablet formulations and is not expected to result in increased safety risk from alternative route of administration in comparison to other oral opioid tablets (eg, oxycodone tablets).

In addition to participating in the opioid analgesic REMS programs, Nektar is working with the FDA to develop additional post-marketing plans to monitor the use of NKTR-181 and to confirm that the risk mitigations put in place to minimize inappropriate prescribing, misuse, and abuse of NKTR-181 have their intended effect in real-world settings.

FDA's recently issued Draft Guidance for Industry, *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework Guidance for Industry* (FDA 2019a), provides a framework to assess the benefit and risk profile for a new molecular opioid, such as NKTR-181. Following this guidance, the structured, qualitative benefit and risk assessment for NKTR-181 concludes that NKTR-181 has a favorable benefit-risk profile in patients with CLBP who received inadequate pain control on other treatment options and provides an incremental improvement over existing opioid medications. A summary of the analyses is provided in Section 9.4, Table 42.

1) NKTR-181 is a full MOR agonist, demonstrating sustained and clinically meaningful analgesia consistent with other mu-opioid products.
2) NKTR-181, at therapeutic doses, demonstrates lower abuse potential compared to oxycodone.
3) NKTR-181 has a low rate of CNS-mediated AEs.
4) NKTR-181 has a low rate of opioid withdrawal symptoms.

In conclusion, for appropriately selected patients with CLBP for whom alternative treatment options are inadequate, the totality of evidence supports that NKTR-181 is an efficacious analgesic with an acceptable safety profile. Importantly, the inherent physicochemical properties of NKTR-181 result in a slower CNS entry and slower MOR activation with a long half-life, which contribute to its lower potential for abuse versus oxycodone. Patients receiving NKTR-181 are less likely to experience the euphoric and withdrawal effects that may lead to misuse and abuse. Furthermore, because of the inherent properties of the NKTR-181 molecule and its resistance to alteration, its availability may help limit access to opioid products that are susceptible to manipulation or prone to abuse within the community.

Overall, NKTR-181 is an effective opioid analgesic treatment option for patients with CLBP in critical need of pain relief and provides an incremental comparative benefit over existing opioids due to NKTR-181's inherent lower abuse potential properties.

2 BACKGROUND ON CHRONIC LOW BACK PAIN

Key Points

- An estimated 25 million patients in the US suffer from CLBP (Kennedy et al. 2014).
- Persistent pain is associated with poor quality of life, anxiety, depression, and fatigue; chronic back pain limits activities of daily living and is the leading cause of disability, including job-related disability (National Institute of Neurological Disorders and Stroke 2018; U.S. Burden of Disease Collaborators et al. 2018).
- Despite their risks of dependence, abuse, and addiction, opioids remain an important analgesic option for patients who are unresponsive to nonopioid therapies.
  - Current guidelines maintain that opioid therapy is appropriate if the expected benefits are anticipated to outweigh the risks (Dowell et al. 2016).
- While several opioid abuse-deterrent formulations (ADFs) have been approved, their abuse-deterrent features can be compromised. No new opioid molecular entity with intrinsic properties to reduce the potential for abuse has been approved for chronic pain since tramadol (in 1995).
- Therapeutic use of opioid analgesics is limited by opiate-type side effects, including CNS-mediated AEs such as sedation, cognitive impairment, and opioid withdrawal syndrome (Pergolizzi et al. 2017).
- For patients who require chronic opioid analgesia, a new treatment approach is needed to provide pain relief similar to today's opioids but with a lower potential for abuse and other CNS-mediated side effects.

2.1 Overview of Chronic Low Back Pain

Back pain is a common reason for seeking medical care (Deyo et al. 2015; Institute of Medicine 2011; Shmagel et al. 2016) and a leading cause of disability (U.S. Burden of Disease Collaborators et al. 2018) including job-related disability (National Institute of Neurological Disorders and Stroke 2018). It is estimated that approximately 25 million adults in the US experience CLBP, defined as constant or frequent pain in the lower back that persists for at least 3 months (Kennedy et al. 2014).

In addition to imparting a sense of suffering, chronic pain can negatively impact daily functioning and health-related quality of life, contributing to anxiety, depression, and fatigue (Kennedy et al. 2014). When undertreated, it is associated with lost productivity, illicit drug-seeking, and even increased rates of suicide (Alford et al. 2016; Fishbain et al. 2014; Petrosky et al. 2018).

There remains a significant unmet medical need for novel, safe, and effective therapies to treat pain and improve the lives of those suffering from CLBP.

2.2 Current Treatment Options

The management of chronic pain including CLBP is complex and integrative, with an emphasis on multimodal and multidisciplinary treatment (Dowell et al. 2016).

2.2.1 Non-Pharmacologic and Non-Opioid Treatment Options

Non-pharmacologic interventions include ice, heat, cognitive therapy, exercise or physical therapy, acupuncture, yoga, swim therapy, minimally invasive procedures (eg, epidural glucocorticoids, nerve block), and open or minimally invasive procedures requiring anesthesia (eg, surgery) (Institute of Medicine 2011). These alternatives have been shown to be effective in minimizing pain, disability, and improving quality of life in studies lasting 2 weeks to 6 months; however, magnitudes of effect vary, and some options are associated with risks (eg, post-procedure complications of surgery and epidural injection) (Dowell et al. 2016; Hayden et al. 2005).

Non-opioid pharmacotherapy options for treating CLBP include nonprescription analgesics such as acetaminophen or NSAIDs; corticosteroids (short-term use); and antidepressants or gabapentinoid drugs (Chaparro et al. 2013; Dowell et al. 2016; Institute of Medicine 2011; Roelofs et al. 2008; Salerno et al. 2002). While many of these treatments effectively reduce pain, they carry their own contraindications and risks, some of which are infrequent but potentially serious (eg, gastrointestinal bleeding for NSAIDs), thus limiting their long-term use.

2.2.2 Opioid Treatment Options

Opioids continue to be an important option in the armamentarium of pain therapies, providing effective analgesia in subgroups of patients (Chaparro et al. 2013; Herndon et al. 2015). Chronic pain management guidelines state that opioid therapy is appropriate if the benefits of treatment outweigh the risks and when a favorable benefit-risk ratio is not achievable with other treatment options (Chou et al. 2009; Dowell et al. 2016). Carefully selected patients with CLBP who have not achieved adequate pain control with other treatment options would qualify as appropriate candidates for opioid therapy.

Opioid products for the treatment of CLBP include a variety of chemical entities and formulations:

- IR oral tablets containing oxycodone, morphine, hydrocodone, and others, are often prescribed for initiation of opioid therapy and used additionally for breakthrough pain.
- ER oral tablets and capsules containing higher doses of morphine, oxycodone, oxymorphone, tapentadol, hydrocodone, hydromorphone, and others, are prescribed to control chronic pain.
- Partial mu-opioid agonist buprenorphine in dosage forms for transdermal and buccal administration are indicated for chronic pain.

- Oral tablets and/or solutions containing methadone and levorphanol, inherently long-acting opioids, are also used to treat chronic pain.

2.3 Opioid Treatment Limitations and Unmet Medical Need

Opioid-Related CNS-Mediated Side Effects

Opioid analgesia is often accompanied by drug-related side effects, which can negatively impact optimization of pain control, activities of daily living, and quality of life (Noble et al. 2010; Sloot et al. 2015; Villars et al. 2007). In addition to gastrointestinal AEs, common side effects include CNS-mediated AEs such as sedation and cognitive impairment. At high doses, opioid analgesics may also cause respiratory depression. Furthermore, even appropriate use of opioids can lead to withdrawal symptoms if patients discontinue therapy, run out of medications, or delay taking their next scheduled dose.

Opioids and Public Health

Opioid abuse, addiction, and associated morbidity and mortality in the US currently constitute a public health emergency with significant social, economic, and quality of life consequences. In 2016, nearly 12 million Americans misused prescription opioid analgesics and 2 million Americans met the criteria for having an opioid use disorder (SAMHSA 2017). According to the Centers for Disease Control and Prevention, in 2017, more than 17,000 deaths in the US were attributed to prescription opioid analgesics (National Institute on Drug Abuse 2018).

It is estimated that approximately 20 to 30% of patients who are prescribed traditional opioids for chronic pain will misuse them (Vowles et al. 2015). ER products are associated with a high potential for abuse and potentially dangerous consequences as they generally contain higher quantities of active pharmaceutical ingredient (API), and legacy non-ADF opioid formulations can be easily manipulated to enable alternative means of administration such as snorting, chewing, or injection.

Abuse-Deterrent Opioid Formulations

Substantial effort has been undertaken to develop abuse-deterrent opioid formulations in order to create safer opioid analgesics. Opioid ADFs, which are primarily ER formulations, contain properties expected to reduce abuse (FDA 2015; Smith et al. 2013). They are designed to achieve this benefit typically by reducing the ability to tamper with the product to alter the release of the API and making it more difficult to administer manipulated product by non-oral routes that would produce a faster onset of and higher peak CNS effects. The most common abuse-deterrent technologies are physical or chemical barriers, agonist/antagonist combinations, and aversion technologies (FDA 2015). However, ADF opioids are still susceptible to tampering (Cicero and Ellis 2015) and all contain legacy opioid entities with inherently abuseable properties. A novel opioid molecular entity with a lower intrinsic abuse potential has the potential to reduce the risk of abuse. Since tramadol was approved in 1995, there have been no new opioid products that minimize abuse through their inherent molecular structure.

An effective analgesic agent with a reduced potential for abuse and low incidence of withdrawal symptoms and CNS-mediated side effects is needed for patients with CLBP to provide a safer option in the context of the prescription opioid abuse crisis.

3 PRODUCT DESCRIPTION AND DEVELOPMENT HISTORY

Key Points

- NKTR-181 (oxycodegol) is an NME long-acting full MOR agonist developed as an oral IR tablet.
- The proposed indication of NKTR-181 is for the management of CLBP in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for whom alternative treatment options are inadequate.
- NKTR-181 consists of a 6-unit PEG chain attached to a morphinan pharmacophore structure (oxycodol).
  - NKTR-181 crosses the BBB and binds to MORs at a slower rate than oxycodone. These CNS kinetic properties are inherent to NKTR-181's molecular structure and are independent of formulation, dosage form, or route of administration.
  - NKTR-181 exhibits a long half-life (14-hours), which is ideal for providing around-the-clock analgesia.
  - NKTR-181's CNS kinetic properties are expected to lead to attenuation of typical opioid-related CNS-mediated side effects and confer a lower potential for abuse.
  - NKTR-181 is not a prodrug and does not contain excipients or substances that extend release or deter abuse.
- NKTR-181 is to be administered at a starting dose of 100 mg q12h and titrated in increments of 100 mg q12h no more frequently than every 4 days.
- The clinical development program for NKTR-181 includes 15 completed studies:
  - 1 pivotal Phase 3 placebo-controlled study in patients with CLBP (N = 610);
  - 1 Phase 3 open-label, long-term safety study in patients with CLBP or chronic noncancer pain (N = 638);
  - 1 Phase 2 study evaluating the efficacy and safety of NKTR-181 in patients with chronic pain due to OA of the knee;
  - 2 HAP studies comparing NKTR-181 to oxycodone in healthy non-dependent recreational opioid users; and
  - 10 Phase 1 clinical pharmacology studies in healthy volunteers.

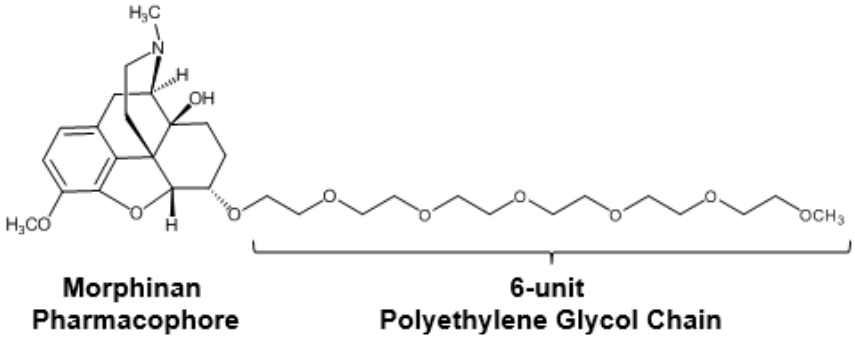
3.1 Product Overview

NKTR-181 (oxycodegol) oral tablet is an IR, long-acting MOR agonist containing 100 or 200 mg of the active ingredient. NKTR-181 is an NME composed of a morphinan pharmacophore (oxycodol) with a covalently attached methoxy-capped 6-unit PEG chain (Figure 8). This design provides a chemically stable molecule with unique physicochemical

properties that allow for effective long-acting analgesia, while reducing CNS-mediated side effects and abuse potential.

NKTR-181 tablets are formulated with excipients commonly used in immediate release tablets and supplied in round film-coated tablets. NKTR-181 is not a prodrug, a reformulation to add excipients or active ingredients to deter abuse, nor an ER formulation of an existing opioid.

Figure 8. Chemical Structure of NKTR-181



3.1.1 Proposed Indication

NKTR-181 is indicated for the management of CLBP in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

For simplicity, the proposed indication is hereafter referred to as "management of moderate to severe CLBP."

3.1.2 Mechanism of Analgesia Action

NKTR-181 is a full MOR agonist and exhibits low binding affinity to delta and kappa opioid receptors (Table 4). NKTR-181 activates signal transduction pathways downstream of the MOR similarly to oxycodone, acting as a full agonist for classical G-protein-coupled receptor signaling (adenylyl cyclase inhibition) and partial agonist for β-arrestin recruitment.

Table 4. Receptor Binding Affinity of NKTR-181 at Human Opioid Receptors

K_i (nM), Mean ± SD	**Mu (μ)**	**Delta (Δ)**	**Kappa (K)**
NKTR-181	237 ± 31	4,150 ± 870	> 100,000

K_i = inhibitory constant; SD = standard deviation

3.1.3 Dosing

NKTR-181 is to be administered at a starting dose of one 100 mg tablet orally q12h with or without food.

Individualized titration to a dose that provides adequate analgesia and minimizes adverse drug reactions should proceed in increments of 100 mg per dose. Dose increases should occur no more frequently than once every 4 days. A dose above 400 mg every 12 hours has not been studied in randomized controlled trials.

3.1.3.1 Approximation of NKTR-181 to Oxycodone Dose Ratio

To date, no clinical studies have directly compared the analgesic effects of NKTR-181 to oxycodone to guide equianalgesic dose conversions. Recognizing the scientific limitations involved with approximating a dose ratio between different opioid entities in the absence of comparative data from a randomized controlled study, Nektar derived a working dose conversion ratio of approximately 15 mg NKTR-181 to 1 mg oxycodone based on in vitro and animal studies:

- Across MOR binding, GTPγS binding, cyclic adenosine monophosphate (cAMP) signaling, and β-arrestin recruitment studies, the potency of oxycodone was 8- to 26-fold higher than NKTR-181.
- In 3 different rodent models of visceral and thermal pain, NKTR-181 produced similar analgesic control to oxycodone at doses 3- to 30-fold higher, depending on the pain model and species.

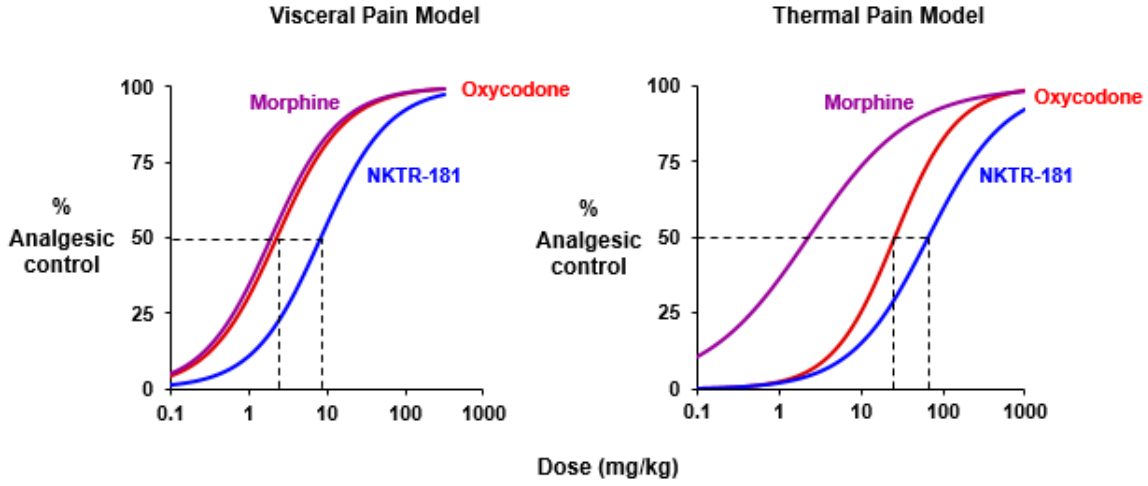
These studies, which reflect different aspects of receptor pharmacology leading to analgesia, together suggest that NKTR-181 and oxycodone produce equivalent levels of analgesia with an estimated dose ratio of approximately 15:1 (NKTR-181:oxycodone). While this derivation has limitations and is not intended to inform clinical decision-making, the estimated dose ratio may serve as a point of reference when interpreting the results of nonclinical and clinical studies that include different doses of NKTR-181 and oxycodone.

3.1.4 Overview of Nonclinical Findings

3.1.4.1 Analgesia

NKTR-181 achieved maximal analgesic effect similar to oxycodone and morphine in several nonclinical models of pain. NKTR-181 demonstrated dose-dependent analgesic control in mice and rats in models of visceral and thermal pain. As shown in Figure 9, the maximal analgesic effect at saturating dose levels was similar for NKTR-181 and the comparators; however, the half-maximal effective dose (ED_{50}; mg/kg) was 3- to 30-fold higher for NKTR-181 compared with oxycodone, depending on the pain model and species.

Figure 9. Analgesic Effect Following Oral Administration of NKTR-181, Oxycodone, and Morphine in Mice



In time-course studies, NKTR-181 produced antinociception with delayed peak activity relative to morphine and oxycodone and a long duration of effect, consistent with its slow penetration into the CNS and slow rate of association with its target receptor, a profile suitable for chronic pain therapy.

3.1.4.2 Abuse Potential

Nonclinical abuse potential studies included an in vitro receptor-ligand binding screen to assess NKTR-181's interaction at various abuse-related targets, a drug dependence/withdrawal assessment in rats, and abuse potential assessments by drug discrimination and self-administration in rats and/or non-human primates, in accordance with FDA Guidance (2017). NKTR-181 displayed a lower abuse potential relative to oxycodone in in vitro studies and nonclinical studies in rats and monkeys. Nonclinical test results showed that NKTR-181 was associated with lower dopamine release in the nucleus accumbens, fewer signs of physical dependence, less potent generalization in drug discrimination, and reduced reinforcing effects compared to oxycodone or morphine. Section 5.2 provides a description of the nonclinical studies conducted to assess the abuse potential of NKTR-181.

3.1.4.3 Nonclinical Safety

The nonclinical safety assessment of NKTR-181 included a comprehensive range of safety, secondary pharmacology, and toxicity studies, in accordance with regulatory guidelines. Key findings are summarized below:

- In an assessment of sedation using a rotarod test in rats, NKTR-181, at a 10-fold higher dose than oxycodone, induced modest loss of motor coordination relative to oxycodone.

- Safety pharmacology studies showed no adverse changes in respiratory or neurobehavioral parameters in rats at the highest dose tested (estimated to result in NKTR-181 maximum observed plasma concentration [C_{max}] exposures 10-fold higher than those associated with the highest dose tested in Phase 3 studies [600 mg q12h; 1200 mg/day].
- Major findings in oral repeat dose toxicity studies in rodents and dogs were consistent with the pharmacology of a MOR agonist, including suppression of body weight gain in both species, emesis and symptoms of opioid overdose in dogs. At the maximum doses tested in dogs (≥ 600 mg/kg/day), symptoms of opioid overdose, including recumbency, minimal response to stimuli, shallow respiration, and/or nonresponsive pupillary reflex, occurred in 2 out of 18 dogs. The NKTR-181 C_{max} exposures in the affected animals were estimated to be at least 10-fold higher than those at the highest dose tested in Phase 3 studies [600 mg q12h; 1200 mg/day]. Both animals recovered after administration of naloxone. Exposures (area under the plasma concentration time curve [AUC]) in the chronic oral toxicity studies at the no-observed-adverse-effect levels were 0.8-, 1.5-, and 2.6-fold the highest dose tested in Phase 3 studies [600 mg q12h; 1200 mg/day], depending on the species and study duration.
- NKTR-181 was not genotoxic or carcinogenic and had minimal effects on reproductive and developmental function.

3.2 Regulatory History and Clinical Development

3.2.1 Regulatory History

Nektar received Fast Track Designation for NKTR-181 based on its potentially better safety profile to address an unmet medical need in chronic pain conditions, including a lower abuse potential versus conventional opioids. Notable FDA advice and agreements relevant to the development of NKTR-181 include the study design of the pivotal Phase 3 study (Study 07) and the 2 HAP studies (Studies 05 and 15), full waiver for pediatric studies in CLBP, and a waiver for conducting a stand-alone thorough QT study. In addition, overall agreement was reached regarding components needed for the New Drug Application submission.

3.2.2 Clinical Development Program

The NKTR-181 clinical development program included 2 Phase 3 studies (Study 07 and Study 08) in patients with moderate to severe CLBP and chronic noncancer pain, 1 Phase 2 study in OA of the knee (Study 04), and 12 Phase 1 studies, including 2 HAP studies (Study 05 and Study 15), as listed below. The key clinical efficacy and safety studies and HAP studies are detailed in Table 5.

The efficacy of NKTR-181 is primarily supported by Study 07, a pivotal, double-blind, placebo-controlled, EERW study that evaluated the efficacy and safety of NKTR-181 compared to placebo in 610 patients with CLBP. This single multicenter clinical trial, together with confirmatory evidence from the wealth of scientifically relevant data on MOR agonists, provides

substantial evidence of efficacy for NKTR-181. Given the well-accepted knowledge that mu-opioid agonists have robust analgesia, the efficacy data for previously approved MOR analgesics serve as confirmatory evidence of NKTR-181's therapeutic effect.

Study 08 was a long-term (52-week), open-label safety study in 638 patients with CLBP or chronic noncancer pain, including rollover patients from Study 07 and de novo patients.

A Phase 2, placebo-controlled EERW study (Study 04) evaluated the efficacy and safety of NKTR-181 in patients with moderate to severe chronic pain due to OA of the knee.

Two Phase 1 oral HAP studies (Studies 05 and 15) were conducted in healthy, non-dependent recreational opioid users to assess the abuse potential of NKTR-181 (100 to 1200 mg) and oxycodone (40 and 60 mg).

In addition, 10 Phase 1 studies in healthy subjects evaluated the PK, relative bioavailability, food effect, formulation, and drug-drug interactions of NKTR-181.

A listing of all 15 studies in the NKTR-181 clinical development program is presented in Appendix 1.

Table 5. Overview of Key Clinical Studies

	Efficacy and Safety		Human Abuse Potential	
	Pivotal Study 07	**Supportive Study 08**	**Study 05**	**Study 15**
Study design	Double-blind, randomized, controlled, EERW	Open-label	Randomized, crossover	Randomized, crossover
Population	Patients with moderate to severe CLBP[ac]	Patients with moderate to severe CLBP or chronic noncancer pain[bc]	Healthy, non-dependent recreational opioid users	Healthy, non-dependent recreational opioid users
N	610	638[d]	42	69
Treatment	NKTR-181 100-400 mg q12h Placebo q12h	NKTR-181 100-600 mg q12h	NKTR-181 100 mg NKTR-181 200 mg NKTR-181 400 mg Placebo Oxycodone IR 40 mg (oral solutions)	NKTR-181 400 mg NKTR-181 600 mg NKTR-181 1200 mg Placebo Oxycodone IR 40 mg Oxycodone IR 60 mg (oral tablets or encapsulated tablets)
Duration	Titration Period: 3-7 weeks Treatment Period: 12 weeks Taper: 1 week	Treatment Period: 52 weeks including titration and 1-week taper	1 dose of each treatment, with 3-day washout period between treatments	1 dose of each treatment, with 5-day washout period between treatments
Primary endpoint	Change in Weekly Pain Score at 12 weeks from Randomization Baseline	Responses on mBPI-SF throughout Treatment Period	Drug Liking	Maximum Drug Liking

a. Patients taking ≤ 10 mg MSE/day of short-acting opioids during the 14 days prior to screening.
b. Patients taking ≤ 60 mg MSE/day of short-acting opioids during the 7 days prior to screening.
c. Moderate to severe CLBP for ≥ 6 months (Study 07) and moderate to severe CLBP or noncancer pain for > 3 months (Study 08).
d. Includes 431 rollover patients from Study 07 and 207 de novo patients.
CLBP = chronic low back pain; EERW = enriched enrollment randomized withdrawal; IR = immediate release; mBPI-SF = modified Brief Pain Inventory-Short Form; MSE = morphine sulfate equivalents; q12h = every 12 hours

4 CLINICAL PHARMACOLOGY

Key Points

- In PK studies, NKTR-181 C_{max} and AUC increased in a dose-proportional manner across the dose range of 10 to 1200 mg.
- C_{max} was achieved at 2 to 4 hours following oral administration. Steady-state plasma concentrations were reached after 3 days of dosing q12h, supporting a 4-day interval between incremental dose titrations.
- The elimination half-life of NKTR-181 was approximately 14 hours, supporting a dosing frequency of every 12 hours and reduced likelihood for acute withdrawal signs or symptoms.
- The major elimination pathway for NKTR-181 was hepatic metabolism by cytochrome P450 (CYP) 3A4.
- NKTR-181 is metabolized to 27 metabolites, each representing < 10% of the total drug-related exposure; fractions of the non-pegylated metabolites, oxycodol and oxycodone, were about 2.3% and 1.4% of NKTR-181 in plasma, respectively.
- NKTR-181 is a substrate of efflux transporter permeability glycoprotein (P-gp), but is expected to saturate transport in the gastrointestinal tract. The oral bioavailability of NKTR-181 was predicted to be approximately 70% based on physiologically-based pharmacokinetic (PBPK) modeling. Administration with food had no effect on absorption.
- No dose adjustments are required for age, body weight, sex, or race. Monitoring and dose adjustments may be warranted in patients taking CYP3A4 inhibitors or inducers.
- The maximum CNS effect of NKTR-181, as measured by pupil constriction, was observed approximately 2 hours later than plasma C_{max}, consistent with the molecule's CNS kinetic properties.
- NKTR-181's inherent physicochemical properties result in 41-times slower plasma-to-CNS equilibrium half-life compared with oxycodone.

4.1 Pharmacokinetics

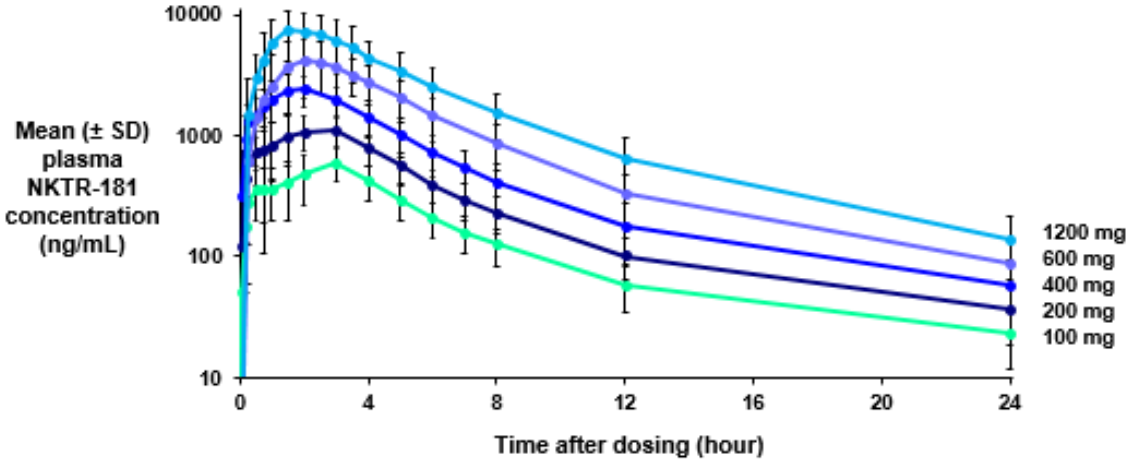
Characterization of the PK of NKTR-181 was based on PK assessments from 12 Phase 1, 1 Phase 2, and 2 Phase 3 clinical studies. A listing of the studies is provided in Appendix 1. In addition, a population PK (PopPK) model was developed to characterize the disposition of NKTR-181 and assess the impact of intrinsic covariates on drug exposure. This modeling dataset included plasma concentration data obtained from 1,557 patients and healthy volunteers who received NKTR-181.

4.1.1 Pharmacokinetic Profile

In clinical studies, NKTR-181 was absorbed with C_{max} achieved at 2 to 4 hours following oral administration. At the therapeutic dose range of 100-600 mg, C_{max} was achieved between 2 to 3 hours post-dose (Table 6). Across the range of doses evaluated (10-1200 mg), C_{max} and AUC increased in a dose proportional manner. Figure 10 shows the PK profile following single dose oral administration of NKTR-181.

Following repeat dosing q12h, NKTR-181 reached steady-state after 3 days of dosing with an accumulation ratio of approximately 1.6-fold, thus supporting the recommended 4-day interval between incremental dose titrations.

Figure 10. PK Profile Following Single Dose Oral Administration of NKTR-181



SD = standard deviation

Table 6. PK Parameters Following Single-Dose and Repeat-Dose Oral Administration of NKTR-181

	PK Parameter	Mean (%CV)			
		NKTR-181 100 mg	**NKTR-181 200 mg**	**NKTR-181 400 mg**	**NKTR-181 600 mg**
Single-Dose	C_{max} (ng/mL)	666 (32.9)	1,307 (26.7)	3,390 (53.6)	5,390 (44.4)
	T_{max} (hour)	2.5	2.4	2.8	2.2
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	3,561 (25.7)	6,934 (24.2)	17,500 (30.7)	25,100 (32.7)
Multiple-Dose	C_{max} (ng/mL)	793 (36.9)	2,072 (61.8)	4,015 (32.5)	6,032 (44.4)
	T_{max} (hour)	2.5	2.0	2.9	2.0
	AUC_{tau} (ng*hr/mL)	4542 (8.7)	13,560 (96.0)	25,340 (36.8)	38,220 (53.4)

$AUC_{0\text{-}inf}$ = area under the plasma concentration time curve from time 0 to infinity; AUC_{tau} = area under the plasma concentration time curve from time 0 to 12 hours at steady state; CV = coefficient of variation

The absolute bioavailability of NKTR-181 was predicted to be approximately 70% based on PBPK modeling. A food effect study demonstrated the absence of any meaningful food effect on NKTR-181 PK.

Based on PopPK analyses, NKTR-181 apparent plasma clearance was estimated to be 21.5 L/h. The estimated elimination half-life of NKTR-181 was 14 hours, supporting a dosing frequency of q12h.

In vitro studies have indicated that NKTR-181 is metabolized primarily by the CYP3A4 enzyme. In a mass balance study in humans, approximately 17% and 2% of the dose was excreted as unchanged NKTR-181 in urine and feces, respectively; approximately 60% of the dose was excreted as metabolites. Twenty-seven metabolites of low abundance were identified in plasma, urine, and feces, each representing < 10% of the total drug-related exposure. Oxycodol and oxycodone are formed through minor metabolic pathways of NKTR-181; their formation was consistent across dose levels, dosing duration, and studies, with metabolite to parent molar ratios averaging 2.3% (range: < 0.1 to 7.9%) and 1.4% (range: < 0.1 to 4.3%), respectively, and coefficient of variation (CV) of approximately 50%.

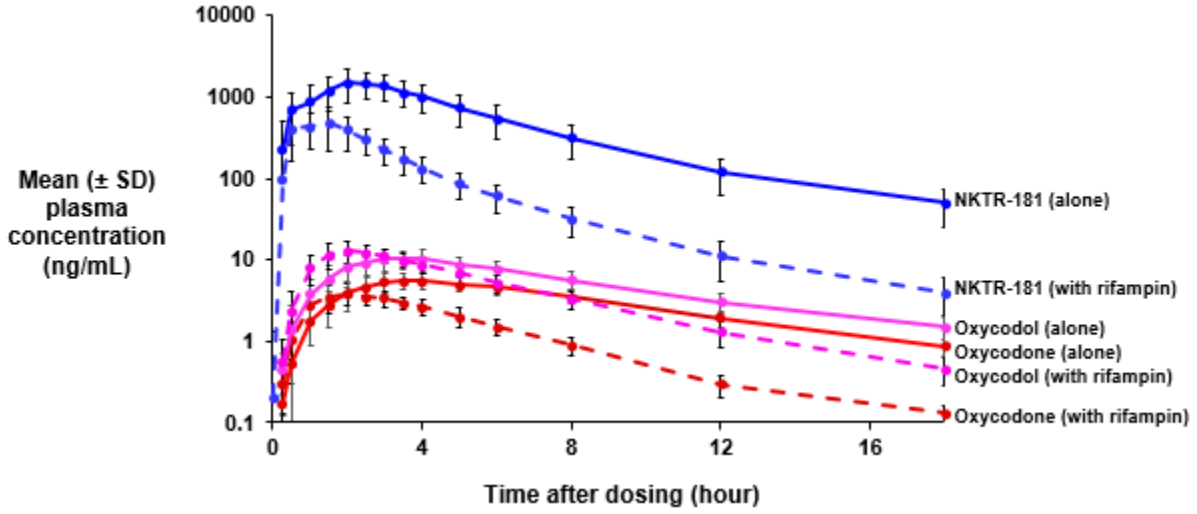
In the PopPK analyses, NKTR-181 exposure (steady-state AUC and C_{max}) was not impacted in a clinically relevant manner by the intrinsic factors of body weight, age, sex, and race, nor was it impacted by prior opioid use (≤ 10 mg MSE/day vs 10-60 mg MSE/day).

4.1.2 Drug-Drug Interactions

Because NKTR-181 is predominantly metabolized by CYP3A4, 2 clinical studies (Study 13, n = 29 and Study 19, n = 30) were conducted with concomitant administration of NKTR-181 with itraconazole, a strong CYP3A4 inhibitor, or with rifampin, a strong CYP3A4 inducer, respectively:

- Administration of NKTR-181 with itraconazole resulted in 1.7-fold and 3.7-fold greater mean NKTR-181 C_{max} and $AUC_{0\text{-}inf}$ (AUC from time 0 extrapolated to infinity) values, respectively, compared with the administration of NKTR-181 alone.
- Administration of NKTR-181 with rifampin decreased NKTR-181 C_{max} and AUC by 68% and 81%, respectively. Changes in plasma concentration-time profiles for NKTR-181 and metabolites, oxycodol and oxycodone, in the presence of rifampin are illustrated in Figure 11. When coadministered with rifampin, the formation of oxycodol and oxycodone remained low; the C_{max} and AUC of oxycodone decreased by 29% and 65%, respectively, while oxycodol C_{max} increased 124% (1.2-fold) and AUC decreased 26%.

Figure 11. PK Profile Following Single Dose Oral Administration of NKTR-181 Alone and with Rifampin



PK = pharmacokinetic; SD = standard deviation

A PBPK model was used to evaluate the impact of moderate and weak CYP3A4 inhibitors and inducers. The proposed prescribing information for NKTR-181 instructs the physician to consider NKTR-181 dosage adjustments when administered with strong and moderate CYP3A4 inhibitors or inducers.

In vitro studies showed that NKTR-181 was not a substrate of BCRP, OATP1B1, or OATP1B3. Therefore, inhibitors of these transporters are not expected to have an effect on the PK of NKTR-181. Conversely, NKTR-181 was observed to be a substrate of P-gp in vitro. Concurrent

administration of P-gp inhibitors are not expected to affect NKTR-181 absorption as P-gp active efflux in the gastrointestinal tract is predicted to be saturated after oral administration of NKTR-181 at clinically efficacious doses. Currently marketed P-gp inhibitors are also not expected to affect the rate of brain uptake of NKTR-181 as these drugs have not been associated with appreciable changes in the BBB crossing of P-gp substrates in a broad range of investigations (Kalvass et al. 2013).

In vivo brain uptake studies were conducted in wild-type mice, in the presence or absence of quinidine (a P-gp inhibitor), and P-gp knock-out mice. Across these animal models, the brain uptake rate of NKTR-181 was slower than that of oxycodone by 18-, 93-, and 115-fold in P-gp knock-out, wild-type mice, and wild-type mice pretreated with quinidine, respectively. These data confirm that NKTR-181's intrinsic permeability at the BBB is substantially lower than that of oxycodone with or without P-gp efflux. In addition, the results demonstrate that the P-gp inhibitor, quinidine, at the highest tolerated dose in wild-type mice has minimal effect on the rate of brain uptake of NKTR-181.

4.2 Pharmacodynamics

Since opioid-induced pupil constriction is a PD marker of CNS entry and receptor-binding of the opioid substance (Larson 2008), pupillometry was assessed following NKTR-181 administration.

In single ascending dose studies, pupil constriction increased with increasing doses of NKTR-181 in the range of 10 to 1200 mg. Following multiple doses of NKTR-181 administered q12h, pupil constriction continued to increase until after PK steady-state was achieved.

In HAP Study 15, pupil constriction peaked between 4 and 5 hours following a single dose of NKTR-181 at 400 and 600 mg and at 3.4 hours following a single dose of NKTR-181 1200 mg (Figure 12); across all doses, pupil diameters returned to baseline by 24 to 30 hours post-dose. Moreover, NKTR-181 and oxycodone exhibited a different PK to PD relationship (Figure 13). While oxycodone exhibited little delay between the rise in plasma concentrations and onset of CNS effects, pupil constriction occurs more slowly with NKTR-181 relative to the increase in plasma concentrations, resulting in a delay in time to maximum pupillary effects.

Figure 12. Pupil Diameter Change from Baseline Over Time in Study 15 (Completer Analysis Population)

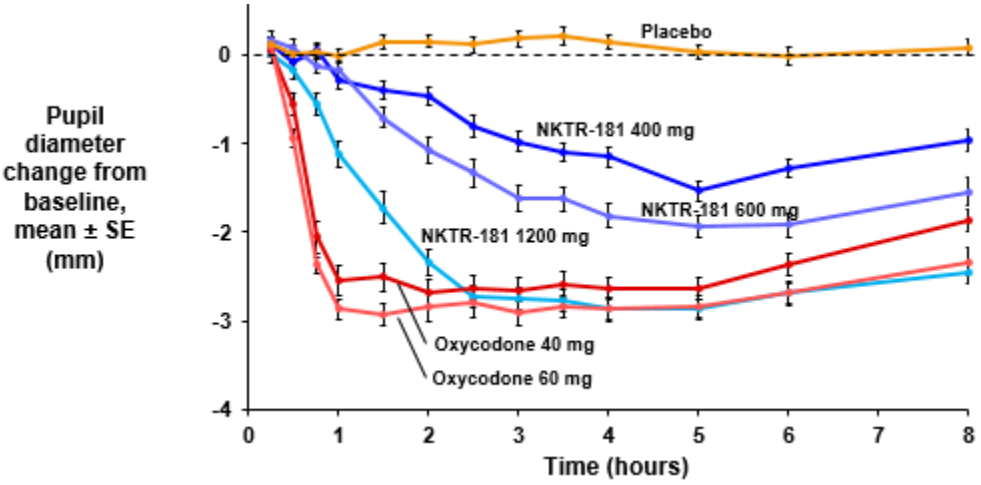
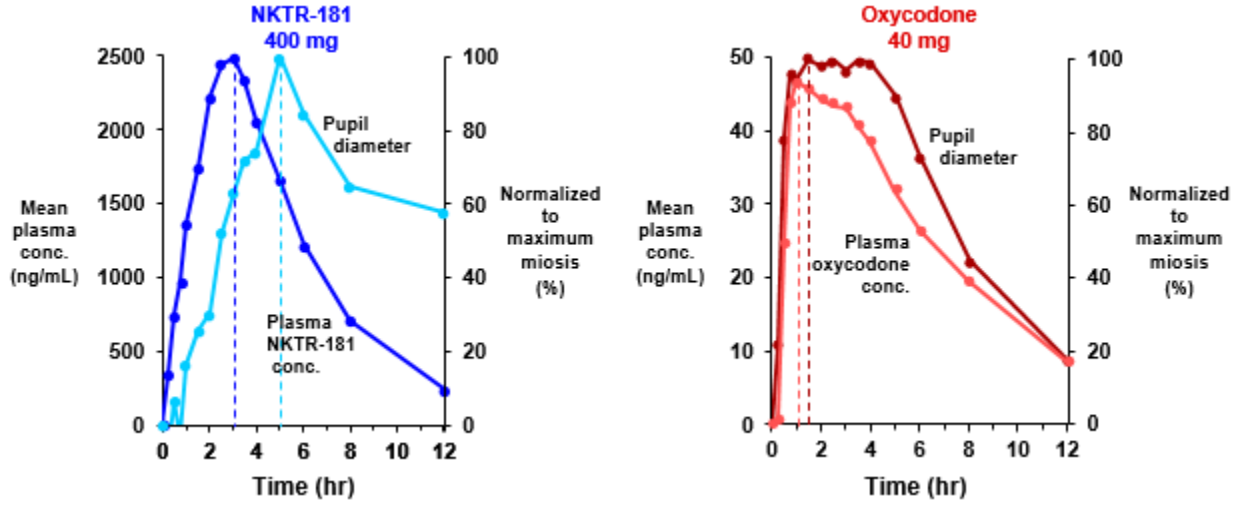


Figure 13. Observed Plasma Drug Levels and Pupil Diameter in Study 15



In order to assess the relationship between systemic exposure and CNS effects, PK/PD models were developed that linked plasma concentrations to pupillary measurements after administration of NKTR-181 or oxycodone. Across dose levels and studies, the population mean plasma-to-CNS equilibrium half-life, which reflects the rate of transport across the BBB and the rate of MOR binding, was 3.7 hours for NKTR-181 compared to 0.09 hours [5.4 minutes]) for oxycodone, a 41-fold difference. These results highlight the unique CNS kinetic properties resulting from NKTR's intrinsic physicochemical properties.

5 POTENTIAL FOR ABUSE

Key Points

- The abuse potential of a psychoactive drug is affected in part by the speed of onset of euphoric effects (Comer et al. 2009; de Wit et al. 1992; de Wit et al. 1993; FDA 2015; Marsch et al. 2001; Mumford et al. 1995; Nelson et al. 2006; O'Brien 2011).
- NKTR-181 was designed with intrinsic physicochemical properties that leads to a gradual onset of MOR action, and lower abuse potential.
  - Compared to oxycodone, the NKTR-181 molecule crosses the BBB and binds to the MOR at a slower rate in nonclinical studies.
- Animal studies showed that NKTR-181 was associated with lower dopamine release in the nucleus accumbens, fewer signs of physical dependence, less potent generalization in drug discrimination, and reduced reinforcing effects compared to oxycodone and morphine.
- Oral HAP Studies 05 and 15 demonstrated that NKTR-181 100 to 600 mg had a lower abuse potential than oxycodone with a slower onset of and lower peak abuse-related effects:
  - Drug Liking E_{max} for NKTR-181 400 and 600 mg was statistically significantly lower than oxycodone 40 mg. The 2 lowest therapeutic doses of NKTR-181 (100 and 200 mg) produced Drug Liking at a level similar to placebo.
  - Take Drug Again and Overall Drug Liking ratings for NKTR-181 100 and 200 mg and placebo were similar; scores were lower for NKTR-181 400 and 600 mg than oxycodone 40 mg.
  - Drug High ratings mirrored those of Drug Liking, with 100 to 600 mg doses of NKTR-181 producing lower effects compared to oxycodone 40 mg.
- At 2 to 3 times the highest doses studied in Phase 3 studies, NKTR-181 1200 mg produced Drug Liking at a peak level similar to oxycodone 40 mg but statistically significantly lower than oxycodone 60 mg. The rate of rise in Drug Liking over the first 2 hours was slower for NKTR-181 1200 mg than both doses of oxycodone. Assessments of Drug High, Take Drug Again, and Overall Drug Liking also resulted in peak levels similar to oxycodone 40 mg and lower than oxycodone 60 mg.
- Extensive chemical, enzymatic, liver homogenate, and heat treatments were unsuccessful in efficiently converting NKTR-181 to a more active opioid derivative (i.e., < 1.3% oxycodone or 6β-oxycodol).
- NKTR-181 is a non-ADF IR formulation. While NKTR-181 can be snorted and syringed to an extent, the rate of NKTR-181 uptake by the brain is expected to remain similar to the oral route and independent of route of administration.

5.1 Lower Abuse Potential Properties of NKTR-181

Drug products that provide faster onset of CNS effects are known to have a higher abuse potential than drugs that provide slower delivering effects (Comer et al. 2009; de Wit et al. 1992; de Wit et al. 1993; FDA 2015; Marsch et al. 2001; Mumford et al. 1995; Nelson et al. 2006; O'Brien 2011). Researchers have identified a "direct relationship between a drug's PK profile (i.e. the speed with which it enters and leaves the brain) and its reinforcing effects. Specifically, the faster a drug reaches peak levels in the brain the more intense the 'high'" (Volkow and Baler 2014; Volkow et al. 2009).

The speed at which a drug produces psychoactive effects is significant for prescription opioid abuse, as opioid products with a faster onset of effect are believed to be associated with a higher potential for abuse (Comer et al. 2009; de Wit et al. 1992; de Wit et al. 1993; FDA 2015; Marsch et al. 2001; Mumford et al. 1995; Nelson et al. 2006; O'Brien 2011).

NKTR-181 modulates CNS effects by achieving slower and lower CNS penetration and a slower rate of MOR activation compared with oxycodone.

In Vitro BBB Permeability

The inclusion of a single 6-unit PEG chain on NKTR-181 leads to a higher molecular weight, lower partition and distribution coefficients, increased number of rotational bonds, increased polar surface area, and increased number of hydrogen bond acceptors, compared with oxycodone. These chemical characteristics contribute to NKTR-181's lower passive BBB permeability and susceptibility to active efflux by P-gp.

Transport of NKTR-181 and oxycodone across the BBB was evaluated in vitro using Caco-2 cells, endothelial cells expressing P-gp in the luminal membrane, as a surrogate for the BBB. NKTR-181 had 38-fold lower permeability compared to oxycodone when P-gp efflux was uninhibited (Table 7). When P-gp efflux was inhibited, NKTR-181's passive permeability was still 11-fold lower than that of oxycodone.

Table 7. Membrane Permeability of NKTR-181 and Oxycodone

	Membrane Permeability	
	Without P-gp Efflux (Passive)	**With P-gp Efflux**
NKTR-181	3×10^{-6} cm/s	0.9×10^{-6} cm/s
Oxycodone	33×10^{-6} cm/s	33×10^{-6} cm/s

In Vitro Mu-Opioid Receptor Binding Kinetics

As described in Section 3.1.2, NKTR-181 binds selectively to the human MOR. In in vitro studies of cell lines and membranes expressing human MORs, NKTR-181 demonstrated

approximately 16-fold slower association rate constant (k_{on}) compared with oxycodone (Table 8).

Table 8. Mu-Opioid Receptor Binding Kinetics of NKTR-181 and Oxycodone

Mu-Opioid Receptor Affinity	k_{on} ($M^{-1}min^{-1}$)	k_{off} (min^{-1})	K_d (nM)
NKTR-181	5.45×10^5	0.443	813
Oxycodone	86.8×10^5	0.554	63.8

k_{on} = association rate constant; k_{off} = dissociation rate constant; K_d = equilibrium dissociation constant

5.2 Nonclinical Studies

5.2.1 Brain Uptake Studies

In Situ Brain Penetration

In an in situ rat brain perfusion model, the unidirectional brain transfer constant (K_{in}) values were determined at 2 concentrations of NKTR-181 and oxycodone. As shown in Table 9, the K_{in} for each compound was relatively independent of concentration. NKTR-181 K_{in} values were approximately 70-fold lower than those of oxycodone, which had K_{in} results comparable to those of antipyrine (0.417 to 0.475 mL/g/min), the positive control that readily permeates the brain. These K_{in} results support that NKTR-181's PEGylated structure significantly reduces the rate of brain penetration relative to oxycodone.

Table 9. Brain Penetration Rates in In Situ Rat Study

	Perfusate Concentration	K_{in} (mL/g/min) Mean (SD)
NKTR-181	10 µM	0.007 (0.005)
	100 µM	0.008 (0.005)
Oxycodone	10 µM	0.497 (0.121)
	100 µM	0.560 (0.056)

K_{in} = transfer constant; SD = standard deviation

In Vivo Brain Uptake after IV Administration of NKTR-181

To determine the in vivo brain uptake rate of NKTR-181 and oxycodone, Sprague-Dawley rats were administered 1 mg/kg of oxycodone or 10 mg/kg of NKTR-181 via IV injection. Blood and brain tissue were collected after 10 minutes, and the brain uptake rates (K_{in}) were calculated. The K_{in} of NKTR-181 was 25-fold slower than that of oxycodone (Table 10), consistent with the results from the in situ study.

Table 10. Brain Uptake Rate (K_{in}) After IV Administration of NKTR-181 and Oxycodone in Rats

	Single IV Dose	K_{in} (mL/min)
NKTR-181	10 mg/kg	0.020
Oxycodone	1 mg/kg	0.500

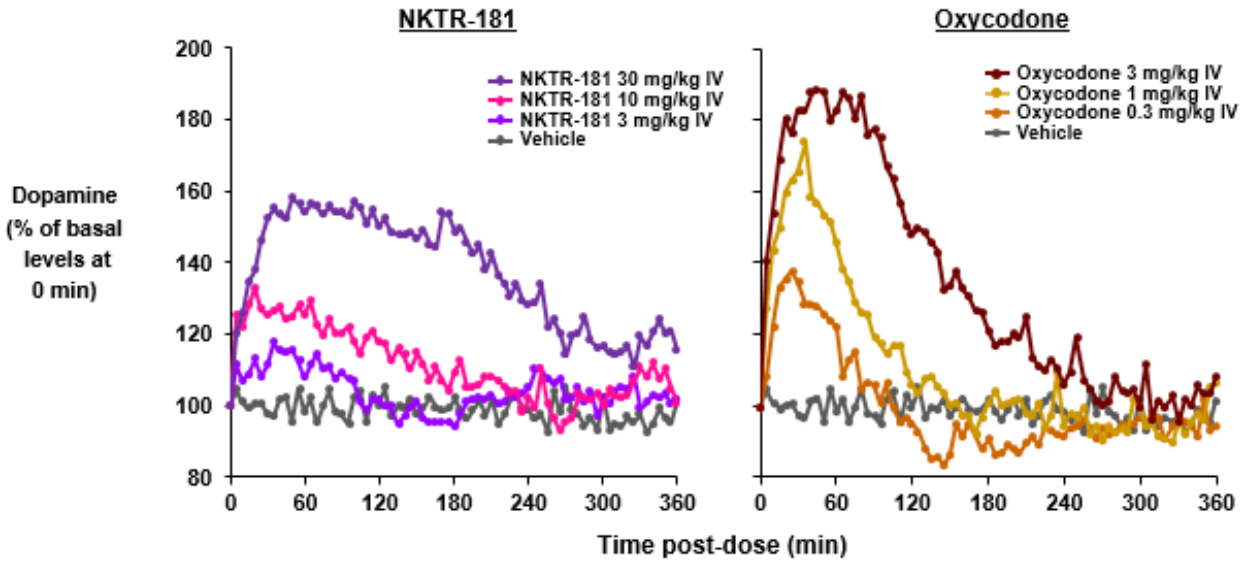
K_{in} was calculated based on $A_{brain,\ 10\ min}/AUC_{0\text{-}10\ min,\ plasma}$ where $A_{brain,\ 10\ min}$ is the amount (ng) in the brain at 10 minutes post-dose and $AUC_{0\text{-}10\ min,\ plasma}$ (min*ng/mL) is the area under the plasma concentration-time curve from 0 to 10 minutes post-dose.
IV = intravenous; K_{in} = brain uptake rate

Dopamine Release

Mu opioid receptor activation triggers the release of dopamine in the reward centers of the brain, and the speed and magnitude of release is positively correlated with abuse potential (Volkow and Baler 2014). The effect of IV NKTR-181 (3, 10, or 30 mg/kg) and oxycodone (0.3, 1, or 3 mg/kg) on dopamine release was measured in an in vivo rat study.

NKTR-181 and oxycodone both produced dose-dependent increases in dopamine levels (Figure 14). However, the highest dose of NKTR-181 (30 mg/kg) produced lower peak dopamine levels than the highest dose of oxycodone (3 mg/kg), with increases of 158% and 189% relative to baseline levels, respectively. These findings demonstrate that NKTR-181 produces more gradual and blunted peak dopamine levels compared with oxycodone, consistent with NKTR-181's CNS kinetic properties. The PD profile exhibited by NKTR-181 in the rat dopamine model may contribute to and help explain the lower abuse potential of NKTR-181 as compared to oxycodone that was demonstrated in nonclinical studies discussed below.

Figure 14. Dopamine Levels in the Nucleus Accumbens Shell of Rats Following IV Administration of NKTR-181 and Oxycodone



IV = intravenous

5.2.2 Behavioral Studies

Physical Dependence

The ability of a drug to induce physical dependence may influence its overall abuse potential if aversive withdrawal symptoms occur upon discontinuation (FDA 2017).

The potential of NKTR-181 to produce a physical dependence/withdrawal syndrome was assessed following abrupt cessation in male and female Sprague-Dawley rats dosed with vehicle, NKTR-181 (100, 200, and 400 mg/kg/day), or morphine (escalating doses from 40 to 300 mg/kg/day) orally q12h for 30 consecutive days. NKTR-181 C_{max} and AUC values at the highest dose tested in this study were 4- to 5-fold higher than exposures at the highest dose tested in Phase 3 studies [600 mg q12h; 1200 mg/day]. The morphine dose regimen used was previously shown to generate a dependence syndrome in rats (Gauvin et al. 2015).

Abrupt cessation of morphine produced prototypical symptoms of a dependence syndrome of the opiate-type (Cicero et al. 2002; Craft et al. 1999), such as motor excitation, hyper-responsiveness to touch or stimuli, poor grooming, weight loss, ptosis, and malaise. Following cessation of treatment with NKTR-181, withdrawal symptoms consisted of weight loss, changes in the frequency of urination and defecation, and poor grooming; the overall incidence and severity of abnormal observations were reduced relative to those seen following discontinuation of morphine.

Drug Discrimination

Drug discrimination studies are routinely performed in animals to compare a new drug with a well-characterized drug of abuse. In a drug discrimination study, male Sprague-Dawley rats were trained to differentiate between a subcutaneous injection of oxycodone and saline and then administered NKTR-181 or oxycodone via the oral or intraperitoneal route.

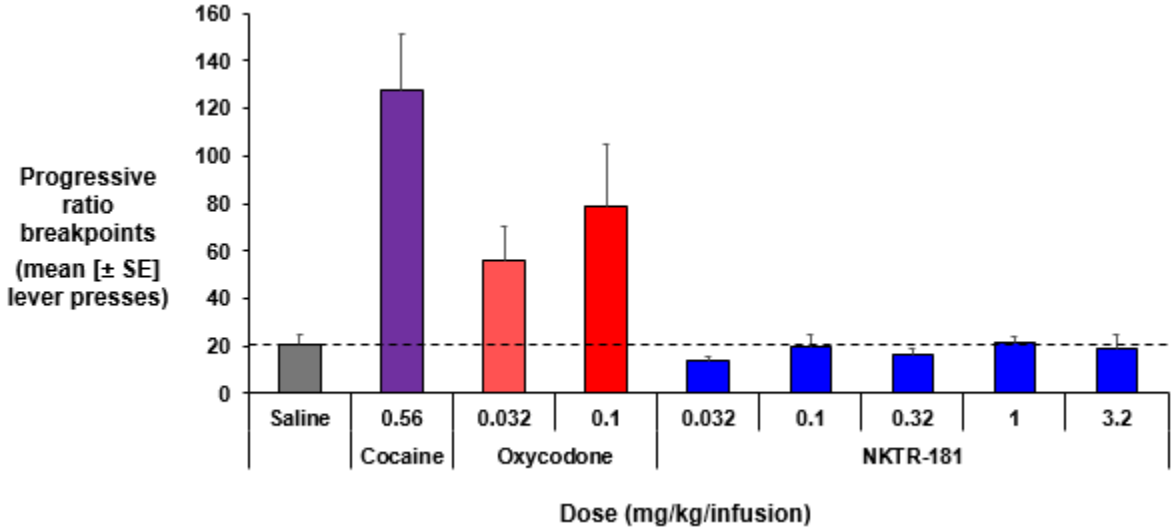
NKTR-181 showed a substantial difference from oxycodone, requiring high doses to be identified as oxycodone-like. Specifically, NKTR-181 caused animals to respond predominantly (> 80% of the time) with the oxycodone-trained behavior only at oral and intraperitoneal doses of 500 and 100 mg/kg, respectively. In contrast, complete generalization to the oxycodone cue was observed with oxycodone at doses of 10 and 3.2 mg/kg. Thus, the minimal discriminable dose of NKTR-181 was 50- (oral) and 30-fold (intraperitoneal) greater than the minimal discriminable dose of oxycodone.

Self-Administration

To assess the reinforcing properties of NKTR-181 in rodents, Sprague-Dawley rats were trained to self-administer cocaine, whereby IV injection of drug was delivered following a fixed number of lever presses. These rats were then evaluated in a progressive ratio study during which the number of lever presses required to deliver an IV injection of test drug was progressively increased until the breakpoint was reached (ie, the number of lever presses above which the animal no longer seeks the drug).

Figure 15 shows the results for saline, cocaine, oxycodone, and NKTR-181. All doses of NKTR-181 generated progressive ratio breakpoints that were similar to those generated by saline. In contrast, cocaine at the maintenance dose engendered a breakpoint of 128 lever presses for the delivery of a single bolus of drug, and oxycodone produced mean breakpoints in between those of saline and cocaine.

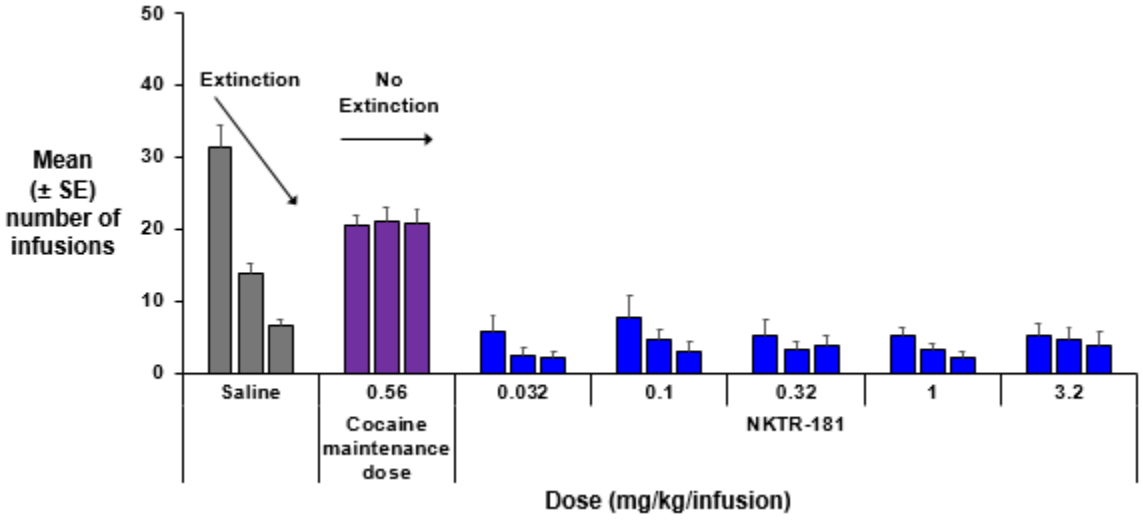
Figure 15. Self-Administration of NKTR-181 in Rats Trained to Administer Cocaine in Progressive Ratio Study



Each bar represents the mean of ≥ 6 rats.

In another study in rats, animals trained to self-administer IV cocaine were subjected to 3-day substitution tests during which saline, cocaine, or NKTR-181 (0.032-3.2 mg/kg/injection) was delivered after a fixed number of lever presses. Rats receiving saline exhibited a characteristic extinction pattern over the 3-day test period, while cocaine resulted in day-to-day stability over the 3-day test period, characteristic of reinforcing behavior (Figure 16). Substitution with NKTR-181 failed to maintain stable lever presses over the 3-day period at any of the doses tested, showing a decline in the trained behavior.

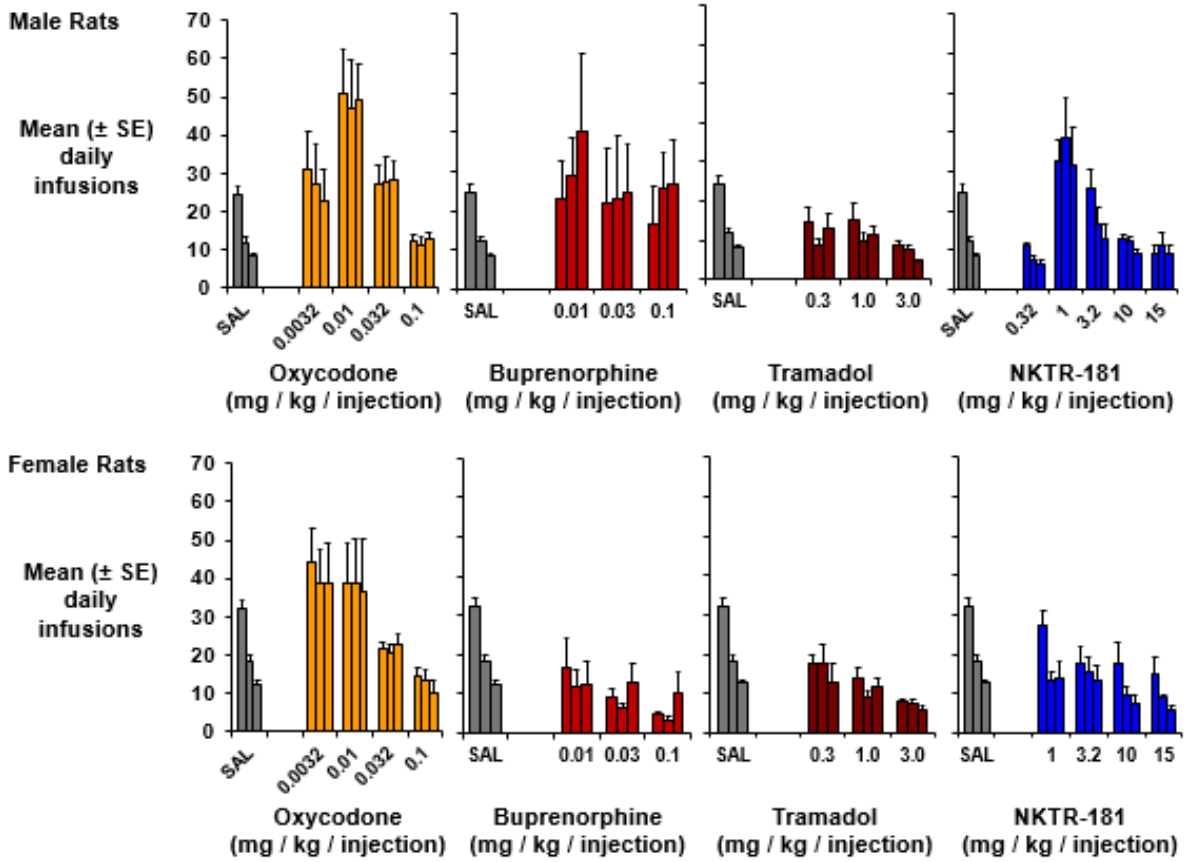
Figure 16. Self-Administration of NKTR-181 in Rats Trained to Administer Cocaine in 3-Day Substitution Study



Each group of 3 bars represents the results for Days 1, 2, and 3. Each bar represents the mean of ≥ 6 rats.

In another study, rats trained to self-administer hydrocodone were subjected to 3-day substitution tests during which IV saline, NKTR-181 (0.32-15 mg/kg/injection), oxycodone (0.0032-0.1 mg/kg/injection), buprenorphine (0.01-0.1 mg/kg/injection), or tramadol (0.3-3.0 mg/kg/injection) was delivered after a fixed number of lever presses. As expected, saline engendered a characteristic extinction pattern over the 3-day test period. Rats receiving oxycodone consistently performed the same reinforced behavior. NKTR-181 failed to demonstrate robust reinforcing effects in male and female rats. Although NKTR-181 engendered voluntary intake of a single test dose (1.0 mg/kg/injection) in male rats, a lower dose of 0.32 mg/kg/injection failed to elicit robust lever-press responding, consistent with low reinforcing behavior. As shown in Figure 17, the relative reinforcing efficacies of the comparator articles tested were saline ≡ tramadol < NKTR-181 < buprenorphine < oxycodone.

Figure 17. Self-Administration of NKTR-181 in Rats Trained to Administer Hydrocodone in 3-Day Substitution Study

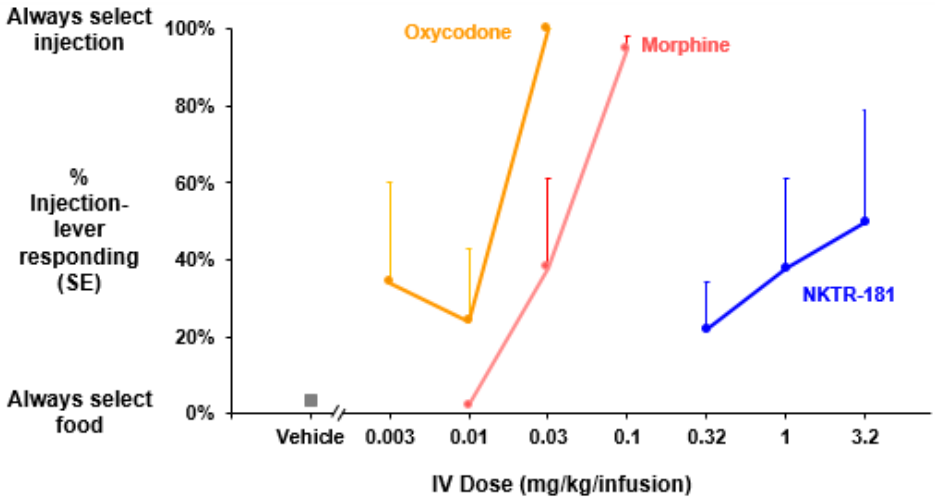


Each group of 3 bars represents the results for Days 1, 2, and 3. Each bar represents the mean of ≥ 6 rats.

In another animal study, squirrel monkeys trained to self-administer IV morphine were given the option to either self-administer food or an IV injection of drug by pressing 1 of 2 levers a fixed number of times. NKTR-181, oxycodone, or morphine (each at a low, middle, and high dose) were tested. As shown in Figure 18, the low and middle doses of the 3 drugs all received fewer

injection-lever presses on average than food. However, the high doses of oxycodone and morphine (0.03 mg/kg/injection and 0.1 mg/kg/injection, respectively) produced nearly exclusive injection-lever responses in all 4 animals. In contrast, at the high dose of NKTR-181 (3.2 mg/kg/injection), 2 out of 4 animals opted for the food lever over the injection lever, resulting in an average drug administration rate of 50%.

Figure 18. Intravenous Self-Administration of NKTR-181 in Primates Trained to Administer Morphine in Substitution Study with Food Option



Each point represents the percentage of total lever presses observed in 4 animals over 90 minutes.
SE = standard error

5.3 Human Abuse Potential Studies

Two oral HAP studies were conducted to assess the abuse potential of NKTR-181 compared with oxycodone HCl in recreational opioid users. Both studies were designed and conducted in accordance with FDA guidance (2017). The first study (Study 05) evaluated NKTR-181 and oxycodone in oral solution and the second study (Study 15) evaluated NKTR-181 and oxycodone oral tablets. Both studies collected PK, pupillometry (an objective measure of PD), and various subjective PD outcomes.

5.3.1 Study 05

5.3.1.1 Study Design

Study 05 was a Phase 1, randomized, double-blind, single-dose, active- and placebo-controlled, 5-period crossover study that evaluated the subjective drug effects indicative of abuse potential of NKTR-181 100, 200, and 400 mg compared with oxycodone 40 mg when administered as oral solutions or placebo in 42 healthy, non-dependent, recreational opioid users. Study 05 provides information on the abuse potential of NKTR-181 tablets if dissolved in solution or chewed and swallowed.

The study consisted of a Screening Stage; a Qualifying Stage which comprised a Naloxone Challenge Test and a Drug Discrimination Test; a Treatment Stage; and a Follow-up Telephone Contact. The purpose of the Qualifying Stage was to confirm that subjects were not opioid dependent and that they were able to perceive a difference between opioid and placebo in the subjective measures to be used in the Treatment Stage.

The in-patient Treatment Stage consisted of 5 treatment periods each separated by a washout period of at least 3 days (modified Williams Latin square design). Subjects were randomized in a 1:1:1:1:1 ratio to a treatment sequence to receive the following treatments in a double-blind fashion:

- NKTR-181 100 mg in solution
- NKTR-181 200 mg in solution
- NKTR-181 400 mg in solution
- Oxycodone HCl 40 mg in solution
- Placebo in solution (denatonium benzoate, to simulate the expected bitter taste of NKTR-181 in solution)

The doses of NKTR-181 selected for this study (100-400 mg) represent the doses tested in the pivotal Phase 3 study (Study 07). The 40 mg of oxycodone was selected as a moderate dose of oxycodone that has been shown to reliably differentiate from placebo on subjective abuse potential assessments among recreational opioid users to serve as a positive control (Setnik et al. 2017). While no comparative clinical studies have been conducted to establish the equianalgesic dose ratio between NKTR-181 and oxycodone, in vitro pharmacology and nonclinical studies have demonstrated that both drugs produce similar efficacy at an estimated dose ratio of 10 to 15 mg NKTR-181 to 1 mg oxycodone (Section 3.1.3.1).

The primary endpoint was the Drug Liking “at this moment” measured on a bipolar 0 to 100 mm VAS, which was analyzed for the modified intention-to-treat (MITT) population. Additional PD assessments included the following: Drug Effects Questionnaire (DEQ) for Drug High, Any Effects, Good Effects, Bad Effects, Nausea, Sick, Dizzy, and Sleepy VASs assessed “at this moment”; Addiction Research Center Inventory/Morphine Benzedrine Group subscale; Take Drug Again VAS assessed at 24 hours; Global Assessment of Overall Drug Liking VAS assessed at 24 hours; price value assessment questionnaire assessed at 24 hours; and pupillometry. PK and safety were also assessed.

5.3.1.2 Study Participants

Study enrollment criteria are listed in Appendix 2.1. After completion of the Naloxone Challenge Test and the Drug Discrimination Test, 42 non-dependent recreational opioid users entered the Treatment Stage. Forty subjects completed study treatment. Of the 2 subjects who did not complete study treatment, 1 discontinued after 3 periods, while the other discontinued after

1 period. The mean (SD) age of participants was 25.1 (5.3) years. Thirty-one (74%) of the subjects were male and 34 (81%) were white.

5.3.1.3 Primary Endpoint – Drug Liking

Maximum Drug Liking effects with NKTR-181 at doses of 100, 200, and 400 mg were lower than 40 mg oxycodone ($p < 0.0001$; Table 11). The 2 lower therapeutic doses of NKTR-181 (100 and 200 mg) were similar to placebo.

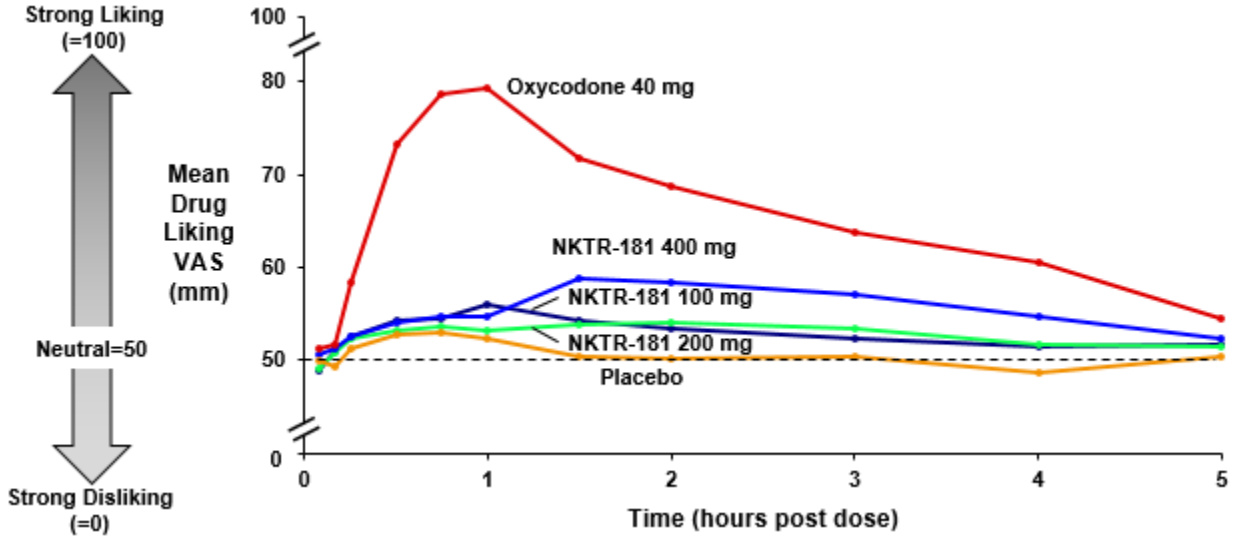
Table 11. Drug Liking E_{max} in Study 05 (MITT Population)

Drug Liking E_{max}	NKTR-181 100 mg N = 40	NKTR-181 200 mg N = 41	NKTR-181 400 mg N = 41	Oxycodone 40 mg N = 41	Placebo N = 41
LS mean (SE)	58.4 (1.6)	57.9 (1.5)	62.5 (1.5)	85.3 (1.5)	55.3 (1.5)
LS mean difference vs placebo	3.1 (2.2) p = 0.1601	2.6 (2.2) p = 0.2356	7.3 (2.2) p = 0.0011	30.0 (2.2) p < 0.0001	-
LS mean difference vs oxycodone 40 mg	-26.9 (2.2) p < 0.0001	-27.4 (2.2) p < 0.0001	-22.7 (2.2) p < 0.0001	-	-

LS = least squares; MITT = modified intention-to-treat; SE = standard error

A separation between oxycodone and placebo in Drug Liking was observed starting at 15 minutes post-dose (Figure 19). In contrast, the 400 mg dose of NKTR-181 did not separate from placebo until the 90-minute time point. NKTR-181 100 and 200 mg produced similar Drug Liking to placebo at all but the 1-hour time point (100 mg dose).

Figure 19. Mean Drug Liking Over Time in Study 05 (MITT Population)



MITT = modified intention-to-treat; VAS = visual analog scale

All NKTR-181 dose levels were associated with lower Drug Liking AUE than oxycodone, with the highest NKTR-181 dose (400 mg) achieving only one third the AUE of oxycodone in the 3-hour post-dose period (Table 12).

Table 12. AUE for Drug Liking in Study 05 (MITT Population)

LS Mean (SE)	NKTR-181 100 mg N = 40	NKTR-181 200 mg N = 41	NKTR-181 400 mg N = 41	Oxycodone 40 mg N = 41
$AUE_{0\text{-}1h}$ (mm*h)	3.43 (0.885)	2.49 (0.873)	3.30 (0.873)	17.85 (0.873)
Difference vs oxycodone 40 mg	-14.4 (1.2) p < 0.0001	-15.4 (1.2) p < 0.0001	-14.6 (1.2) p < 0.0001	-
$AUE_{0\text{-}2h}$ (mm*h)	8.15 (2.315)	6.33 (2.285)	11.14 (2.285)	40.97 (2.285)
Difference vs oxycodone 40 mg	-32.8 (3.2) p < 0.0001	-34.7 (3.2) p < 0.0001	-29.8 (3.2) p < 0.0001	-
$AUE_{0\text{-}3h}$ (mm*h)	11.31 (3.802)	10.22 (3.753)	18.99 (3.753)	57.53 (3.753)
Difference vs oxycodone 40 mg	-46.2 (5.3) p < 0.0001	-47.3 (5.3) p < 0.0001	-38.6 (5.3) p < 0.0001	-

AUE = area under the effect curve; LS = least squares; MITT = modified intention-to-treat; SE = standard error

5.3.1.4 Additional Endpoints

The VAS assessments that have been correlated with abuse potential, Drug High (Eaton et al. 2012), as well as Take Drug Again and Overall Drug Liking (FDA 2015), which are of particular interest to the FDA, are presented below. Results for other PD endpoints evaluated in the study can be found in Appendix 2.2.

The Drug Liking results were corroborated by all other measures of abuse potential in Study 05 including Drug High and Take Drug Again (Figure 20 and Figure 21).

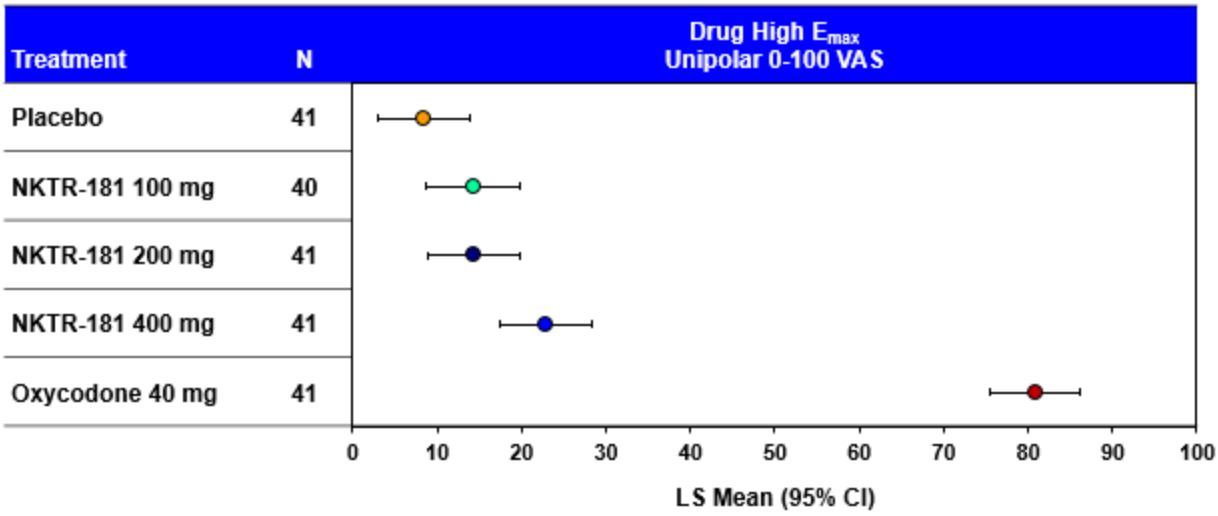
Findings on the Drug High VAS mirrored those of Drug Liking, with all doses of NKTR-181 producing meaningfully lower effects compared to oxycodone 40 mg when 10-point difference in Drug High rating predicts the clinically important difference (Eaton et al. 2012). In addition, each of the 2 lower therapeutic doses yielded effects similar to placebo.

The Take Drug Again VAS (where 0 = definitely would not take the drug again and 100 = definitely would take the drug again) was completed at 24 hours after drug administration. While the different dose levels of NKTR-181 were not consistently statistically different from oxycodone, they were also not different from placebo. Numerically, mean Take Drug Again ratings for NTKR-181 fell between that of oxycodone and placebo.

The Global Assessment of Overall Drug Liking is a measure of the subject's global perception of drug liking over the entire drug experience and was assessed at 24 hours post-drug

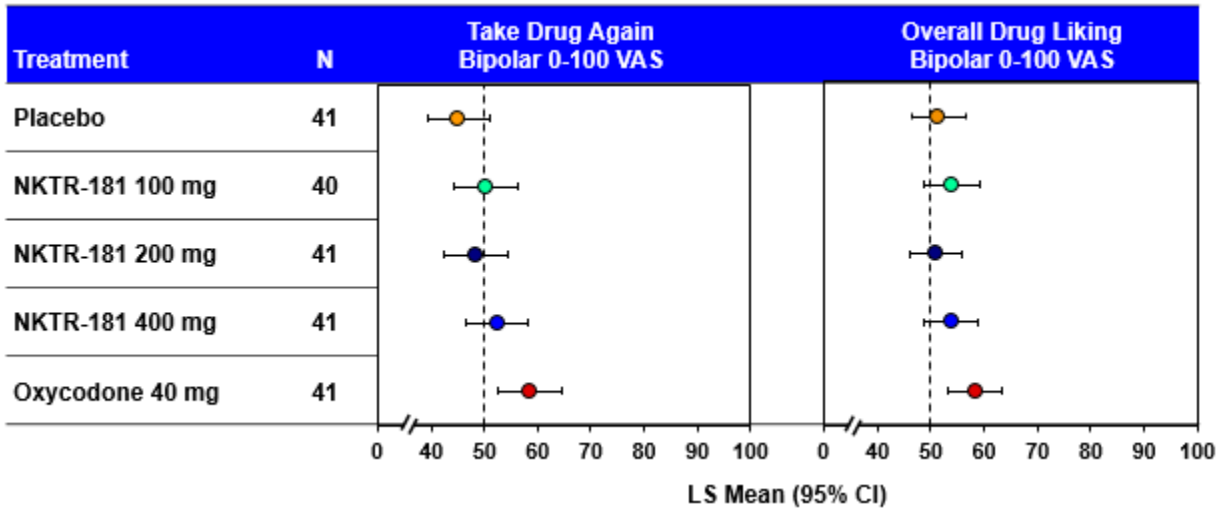
administration. Oxycodone did not differentiate from placebo on this measure (p = 0.0525), nor did any of the NKTR-181 doses.

Figure 20. Drug High E_{max} in Study 05 (MITT Population)



Drug High question text: "At this moment, I am feeling high"; scale: 0 = not at all, 100 = extremely.
CI = confidence interval; E_{max} = maximum effect; LS = least squares; MITT = modified intention-to-treat; VAS = visual analog scale

Figure 21. Take Drug Again and Overall Drug Liking at 24 Hours in Study 05 (MITT Population)



Take Drug Again question text: "Overall, I would take this drug again"; scale: 0 = definitely would not, 50 = don't care either way, 100 = definitely would.
Overall Drug Liking question text: "Overall, my liking for this drug is"; scale: 0 = strong disliking, 50 = neither like nor dislike, 100 = strong liking.
CI = confidence interval; LS = least squares; MITT = modified intention-to-treat; VAS = visual analog scale

5.3.2 Study 15

5.3.2.1 Study Design

Study 15, the second HAP study, enrolled 69 subjects and compared higher doses of NKTR-181 with 2 dose levels of oxycodone. It was also a randomized, double-blind, double-dummy, single-dose, active- and placebo-controlled, crossover study designed to evaluate the abuse potential of NKTR-181 (in tablet form) compared with oxycodone and placebo in healthy, non-dependent, recreational opioid users.

Subjects participated in screening procedures, including a Naloxone Challenge Test, a Qualification Phase, and a single in-patient Treatment Phase, consisting of 6 back-to-back treatment periods, each separated by a washout period of at least 5 days (Williams Latin square design). Study participants who qualified for study treatment were randomly assigned to a treatment sequence to receive the following treatments:

- NKTR-181 400 mg oral tablet + oxycodone placebo
- NKTR-181 600 mg oral tablet + oxycodone placebo
- NKTR-181 1200 mg oral tablet + oxycodone placebo
- Oxycodone HCl 40 mg oral tablet with over-encapsulation + NKTR-181 placebo
- Oxycodone HCl 60 mg oral tablet with over-encapsulation + NKTR-181 placebo
- Oxycodone placebo + NKTR-181 placebo

The dose selection for this study is consistent with FDA guidance (FDA 2017) and included the 2 highest clinical doses of NKTR-181 evaluated in the Phase 3 studies as well as a dose 2 to 3 times greater. Specific considerations were as follows:

- NKTR-181 400 mg is the highest dose studied in the pivotal Study 07 for the treatment of moderate to severe CLBP. This dose was also evaluated in Study 05 and allows for comparison of the consistency between the results of the 2 HAP studies.
- NKTR-181 600 mg is the highest dose studied in the long-term safety study (Study 08).
- NKTR-181 1200 mg is 2 to 3 times the highest doses tested in the Phase 3 studies. This dose is a reasonable representation of what would be taken by someone seeking to abuse opioids who has access to, and a desire to use, twelve 100 mg tablets or six 200 mg tablets at once. It should be noted that in a Phase 1 single-ascending dose study in 60 healthy subjects (Study 10), severe adverse effects were reported in 5 subjects, all of whom were receiving 1200 mg (severe vomiting in 3 subjects, severe nausea in 1 subject, and severe syncope in 1 subject).
- Oxycodone 40 and 60 mg were selected to serve as positive controls. These dose levels are representative of a moderate to high dose of oxycodone that have been shown to

reliably differentiate from placebo on subjective measures of abuse potential when tested in HAP studies of recreational opioid users (Setnik et al. 2017).

The primary endpoint was the E_{max} for Drug Liking based on VAS assessments taken "at this moment." Additional PD assessments included the following: DEQ for Drug High, Any Effects, Good Effects, Bad Effects, Nausea, and Alertness/Drowsiness VASs "at this moment"; Take Drug Again VAS assessed at 12 and 24 hours; Overall Drug Liking VAS assessed at 12 and 24 hours; and pupillometry. PK and safety were also assessed.

The primary endpoint analysis was performed with the completer population and used a linear mixed effects model to compare the mean difference of Drug Liking E_{max} among treatment groups. LS means and 2-sided 90% confidence intervals (CIs) for treatment groups and treatment differences among NKTR-181, oxycodone, and placebo were reported, as specified in FDA guidance (FDA 2017), along with the p-values of treatment comparison hypothesis tests for the primary endpoint. All statistical tests were 1-sided with a significance level of 5% in accordance with feedback from the FDA. No adjustments for multiplicity were made for these comparisons. The treatment comparisons between oxycodone and placebo were for study validation. Comparisons between NKTR-181 and placebo were for absolute abuse potential, and comparisons between NKTR-181 and oxycodone were for relative abuse potential.

5.3.2.2 Study Participants

Study enrollment criteria are listed in Appendix 2.3. A total of 69 subjects received study drug during the treatment phase. The mean (SD) age of participants was 31.7 (7.6) years; nearly all subjects were male (n = 66; 95.7%); and most were black or African American (n = 45; 65.2%). Of the 69 subjects who started receiving study treatment, 54 (78.3%) completed the study; 15 discontinued the study for the following reasons: AEs (4 subjects), withdrawal of consent (1 subject), and "other" reasons (10 subjects).

5.3.2.3 Primary Endpoint – Drug Liking

Oxycodone and NKTR-181 differed in both their magnitude and time course of Drug Liking.

With respect to the magnitude of Drug Liking (Table 13), NKTR-181 400 and 600 mg elicited lower peak values (E_{max}) compared with both doses of oxycodone (all $p < 0.0001$). In addition, NKTR-181 1200 mg also showed statistically significantly lower E_{max} (76.7) compared with oxycodone 60 mg (81.5; $p = 0.0071$), but a similar E_{max} compared with oxycodone 40 mg (76.6; $p = 0.5154$). However, the median time to Drug Liking E_{max} was longer for NKTR-181 1200 mg at 2.7 hours, compared to 2.0 and 1.7 hours for oxycodone 40 and 60 mg, respectively.

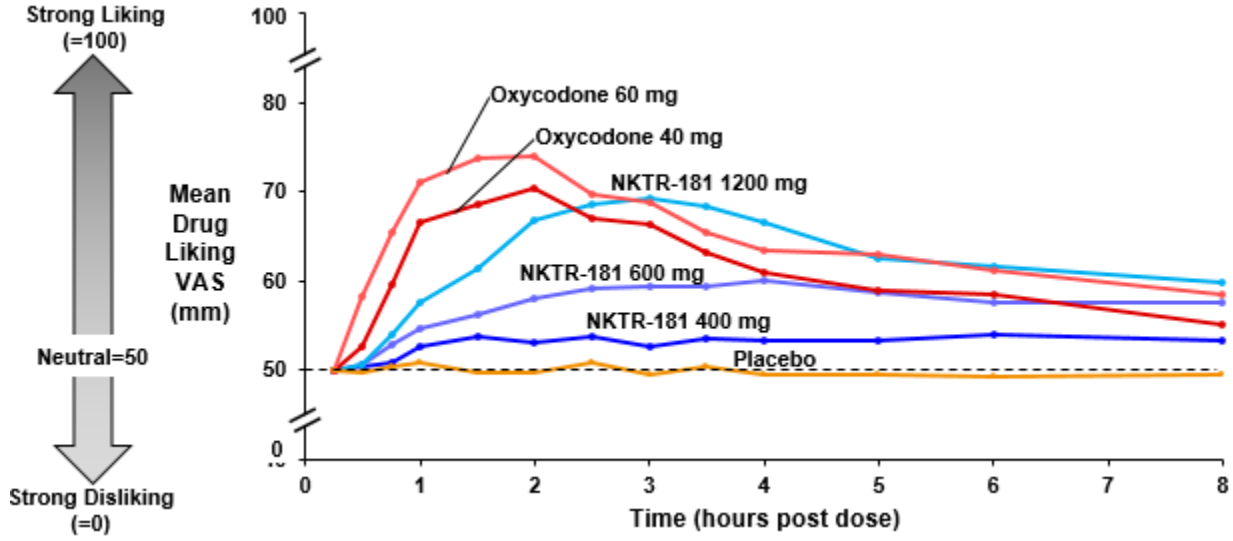
Table 13. Drug Liking E_{max} in Study 15 (Completer Analysis Population)

Drug Liking E_{max}	NKTR-181 400 mg N = 54	NKTR-181 600 mg N = 54	NKTR-181 1200 mg N = 54	Oxycodone 40 mg N = 54	Oxycodone 60 mg N = 54	Placebo N = 54
LS mean (SE)	62.0 (1.6)	67.9 (1.6)	76.7 (1.7)	76.6 (1.7)	81.5 (1.6)	53.2 (1.7)
LS mean difference vs oxycodone 40 mg	-14.6 (2.0) p < 0.0001	-8.7 (2.0) p < 0.0001	0.1 (2.0) p = 0.5154	-	-	-
LS mean difference vs oxycodone 60 mg	-19.5 (2.0) p < 0.0001	-13.6 (2.0) p < 0.0001	-4.8 (2.0) p = 0.0071	-	-	-

E_{max} = maximum effect; LS = least squares; SE = standard error

As can be seen in Figure 22, oxycodone 40 and 60 mg separated from placebo on Drug Liking as early as 45 and 30 minutes post-dose, respectively, whereas NKTR-181 separated from placebo at 1 hour (1200 mg) and 1.5 hours (400 and 600 mg).

Figure 22. Mean Drug Liking Over Time in Study 15 (Completer Analysis Population)



VAS = visual analog scale

Slower rates of rise were observed over the 1- and 2-hour post-dose periods for all doses of NKTR-181 compared to either dose of oxycodone (Table 14).

Table 14. Rate of Rise in Drug Liking in Study 15 (Completer Analysis Population)

Rate of Rise (mm/h), LS Mean (SE)	NKTR-181 400 mg N = 54	NKTR-181 600 mg N = 54	NKTR-181 1200 mg N = 54	Oxycodone 40 mg N = 54	Oxycodone 60 mg N = 54
0-1.0 hours	1.6 (1.5)	4.5 (1.5)	6.1 (1.5)	14.2 (1.5)	20.5 (1.5)
Difference vs oxycodone 40 mg[a]	-12.6 (1.9) p < 0.0001	-9.6 (1.9) p < 0.0001	-8.1 (1.9) p = 0.0001	-	-
0-2.0 hours	1.8 (1.0)	4.3 (1.0)	7.6 (1.0)	11.9 (1.0)	15.1 (1.0)
Difference vs oxycodone 40 mg[a]	-10.1 (1.2) p < 0.0001	-7.6 (1.2) p < 0.0001	-4.3 (1.2) p = 0.0032	-	-

a. p < 0.0001 for all comparisons of NKTR-181 to oxycodone 60 mg.
LS = least squares; SE = standard error

During the first 3 hours post-dose, all NKTR-181 dose levels were associated with lower Drug Liking AUE than oxycodone at either dose level (Table 15).

Table 15. AUE for Drug Liking in Study 15 (Completer Analysis Population)

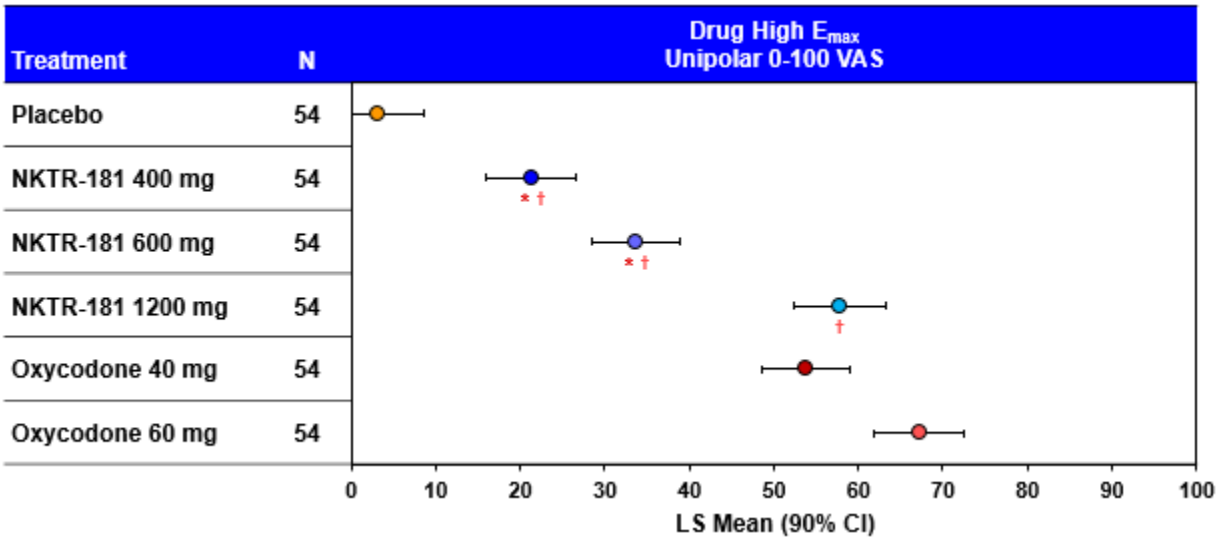
LS Mean (SE)	NKTR-181 400 mg N = 54	NKTR-181 600 mg N = 54	NKTR-181 1200 mg N = 54	Oxycodone 40 mg N = 54	Oxycodone 60 mg N = 54
$AUE_{0\text{-}1h}$ (mm*h)	0.8 (0.7)	1.7 (0.7)	2.4 (0.7)	5.8 (0.7)	9.5 (0.7)
Difference vs oxycodone 40 mg[a]	-5.1 (0.9) p < 0.0001	-4.2 (0.9) p < 0.0001	-3.4 (0.9) p = 0.0002	-	-
$AUE_{0\text{-}2h}$ (mm*h)	3.7 (2.1)	8.5 (2.1)	14.2 (2.1)	24.5 (2.1)	32.3 (2.1)
Difference vs oxycodone 40 mg[a]	-20.8 (2.7) p < 0.0001	-16.0 (2.6) p < 0.0001	-10.2 (2.7) p = 0.0010	-	-
$AUE_{0\text{-}3h}$ (mm*h)	7.0 (3.5)	17.6 (3.5)	32.4 (3.5)	41.8 (3.5)	52.6 (3.5)
Difference vs oxycodone 40 mg[a]	-34.8 (4.4) p < 0.0001	-24.2 (4.4) p < 0.0001	-9.4 (4.4) p = 0.0396	-	-

a. p ≤ 0.0003 for all comparisons of NKTR-181 to oxycodone 60 mg.
AUE = area under the effect curve; LS = least squares; SE = standard error

5.3.2.4 Additional Endpoints

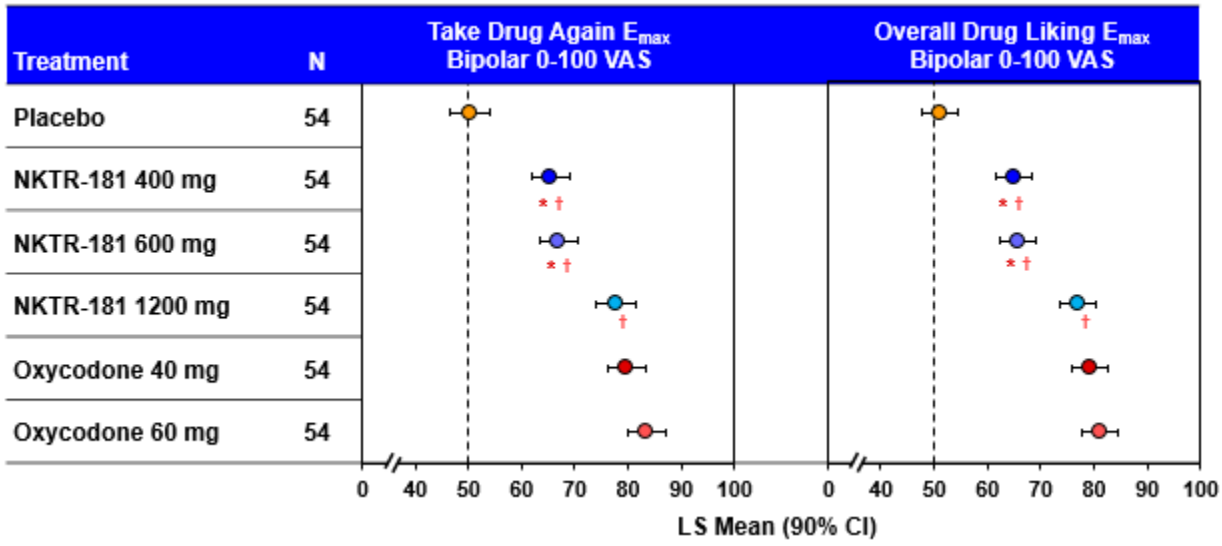
Drug High, Take Drug Again, and Overall Drug Liking scores mirrored those of Drug Liking across the different NKTR-181 and oxycodone arms. As shown in Figure 23 and Figure 24, the two highest clinical doses of NKTR-181 (400 and 600 mg) produced lower ratings in each of these assessments compared to either dose of oxycodone; the 1200 mg dose of NKTR-181 produced lower scores than oxycodone 60 mg.

Figure 23. Drug High E_{max} in Study 15 (Completer Analysis Population)



Drug High question text: "At this moment, I am feeling high"; scale: 0 = not at all, 100 = extremely.
* $p < 0.05$ vs oxycodone 40 mg; † $p < 0.05$ vs oxycodone 60 mg
CI = confidence interval; E_{max} = maximum effect; LS = least squares; VAS = visual analog scale

Figure 24. Take Drug Again E_{max} and Overall Drug Liking E_{max} in Study 15 (Completer Analysis Population)



Take Drug Again question text: "Overall, I would take this drug again"; scale: 0 = definitely would not, 50 = don't care either way, 100 = definitely would.
Overall Drug Liking question text: "Overall, my liking for this drug is"; scale: 0 = strong disliking, 50 = neither like nor dislike, 100 = strong liking.
* $p < 0.05$ vs oxycodone 40 mg; † $p < 0.05$ vs oxycodone 60 mg
CI = confidence interval; E_{max} = maximum effect; LS = least squares; VAS = visual analog scale

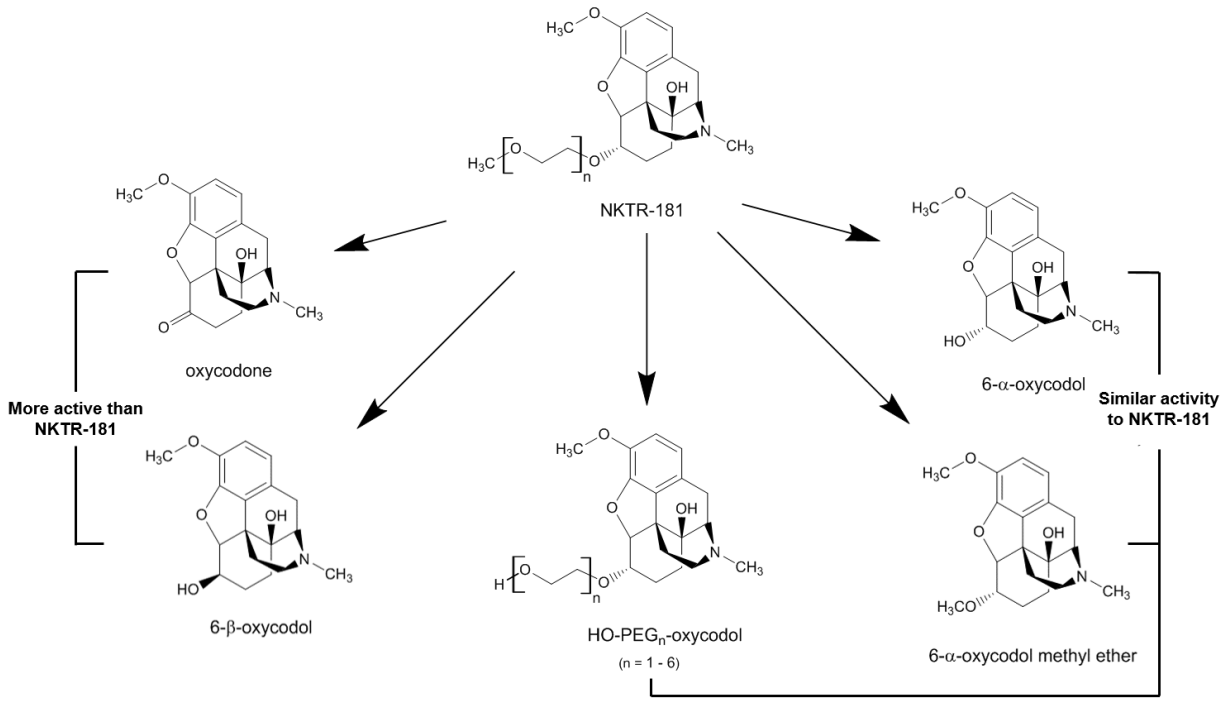
Results for other PD endpoints evaluated in Study 15 can be found in Appendix 2.4.

5.4 In Vitro Testing to Convert NKTR-181 to Other Opioid Derivatives

In vitro laboratory manipulation studies were performed to evaluate the extent to which NKTR-181 could be converted into other potential pharmacologically active opioid derivatives. NKTR-181 API and drug product were subjected to various chemical, enzymatic, liver homogenate, and thermal treatments that could plausibly be attempted by reasonably skilled and resourceful individuals (ie, individuals with chemical training and/or a detailed laboratory protocol and access to glassware and chemicals).

Prior to conducting the in vitro studies, 10 potential derivatives were identified as either known metabolites of NKTR-181 or theoretical products from chemical or enzymatic manipulation; all contain the morphinan (oxycodol) structure (Figure 25). Of the 10 derivatives, oxycodone and 6β-oxycodol are more active than NKTR-181, based on receptor binding affinity (Lalovic et al. 2006). The remaining 8 derivatives, including the 6 containing the PEG moiety (represented by HO-PEG$_n$-oxycodol [n = 1-6]), 6α-oxycodol, and 6α-oxycodol methyl ether, are expected to have similar activity to NKTR-181.

Figure 25. Structure of Potentially Active Derivatives of NKTR-181 Molecule



Activity based on receptor-binding affinity.

5.4.1 Methodology

Chemical Treatment of NKTR-181

Based on chemical considerations of the molecular nature of NKTR-181, 25 chemical reagents were selected including common household solvents and reagents, strong acids and bases,

oxidants, reducing reagents, and reagents that could potentially cleave the PEG-morphinan ether bond. Chemical manipulation experiments were conducted with NKTR-181 API, intact NKTR-181 tablets, and crushed NKTR-181 tablets in solvent and reagents under different temperatures and with or without heat pretreatment.

Enzymatic Treatment of NKTR-181

A total of 14 enzymes in various preparations were used to challenge the molecular integrity of NKTR-181. Enzymatic manipulation experiments were conducted with 30 mg of NKTR-181 API in 30 mL of enzyme-free simulated gastric fluid and enzyme-free simulated intestinal fluid, incubated for 8 hours.

Liver Homogenate Treatments

NKTR-181 API and tablets were incubated with liver homogenates of cow, pig, chicken, and rat origin to evaluate if such homogenates could effectively convert NKTR-181 into more active opioid derivatives. A total of 74 different experimental conditions that involved kitchen chemistry conditions and more highly advanced laboratory preparations were tested. Midazolam, which is readily metabolized by animal liver homogenates, was utilized as a control throughout all studies.

Thermal Treatment of NKTR-181

NKTR-181 API, free base, intact tablets, and crushed tablets were heated at various controlled temperatures and over an open flame. The residue in the apparatus and any volatilized compounds were measured for NKTR-181 and the 10 potential derivatives described above.

5.4.2 Results

Of the 193 experimental conditions tested, none were able to efficiently convert NKTR-181 to a more abusable opioid compound that can more rapidly activate MORs (Table 16). The most oxycodone or oxycodol that could be detected was no more than 1.3% of the active compound. Based on these findings, it is reasonable to conclude that attempts to convert NKTR-181 to a more abusable opioid form are unlikely to be successful.

Table 16. Summary of In Vitro Manipulation Studies Designed to Alter the Molecular Structure of NKTR-181

Type of Treatment	Conditions Tested	Results
Chemical	**NKTR-181 API** Incubation with 22 aqueous liquids, solvents, and chemical reagents, at different temperatures. N = 38 total chemical/temperature combinations.	< 1.3% conversion to oxycodone or oxycodol.
	NKTR-181 tablets (intact and crushed) Incubation with 6 solvents and chemical reagents, with and without heat pretreatment. N = 36 total different conditions.	
Enzymatic	**NKTR-181 API** Incubation with 14 enzymes, in different media. N = 25 different preparations.	Levels of oxycodone or oxycodol produced were below or near the limit of quantitation (0.00025%).
Liver Homogenate	**NKTR-181 API and tablets** Incubation with liver homogenates from 4 animal species (cow, pig, chicken, rat) under laboratory and "kitchen chemistry" conditions. N = 74 different conditions.	< 0.5% conversion to oxycodone or oxycodol.
Heat	**NKTR-181 API and NKTR-181 free base** Heated over a range of temperatures. N = 15 conditions.	< 0.8% conversion to oxycodone or oxycodol in residue or vapor.
	NKTR-181 tablets (intact and crushed) Heated over a range of temperatures. N = 5 conditions.	

API = active pharmaceutical ingredient

5.5 In Vitro Manipulation of NKTR-181 Tablet for Alternative Routes of Administration

Because of its intrinsic slow onset and offset of effects relative to conventional opioids, NKTR-181 is formulated without any ER properties, tamper-resistant features, or other formulation-based physical/chemical barriers. Nevertheless, in vitro drug manipulation studies were designed and conducted in accordance with the FDA's guidance document, "Abuse-Deterrent Opioids – Evaluation and Labeling "(FDA 2015), to characterize the potential for NKTR-181 to be abused by non-intended routes of administration.

5.5.1 Physical Manipulation for Swallowing or Intranasal Insufflation

Some ER products can be chewed or crushed and swallowed to bypass the sustained release formulation, providing the user with immediate access to higher levels of API. While NKTR-181 does not contain crush-resistant properties, the slow entry of NKTR-181 into the brain and slow

rate of MOR binding, which are intrinsic to the molecule and not the tablet formulation, are maintained. Therefore, the rewarding effects of NKTR-181 would not be enhanced by oral administration of chewed or crushed tablets. Liquid solutions of NKTR-181 up to 400 mg showed lower Drug Liking compared to an oral solution of 40 mg oxycodone in HAP Study 05.

More than 88% of the powdered material produced by grinding NKTR-181 tablets was smaller than 500 µm, a particle size suitable for nasal insufflation. However, NKTR-181 tablets have a high total mass to API ratio, with only 24% of the total mass being active drug. Therefore, a large volume of crushed NKTR-181 is needed to produce a dose of active drug which might be sought by abusers. For example, to access 600 mg of NKTR-181, one would need to insufflate approximately 2500 mg of powder material (Figure 26). For context, 1000 mg represents a high volume of material reported by experienced intranasal cocaine users (Bluelight.org 2002; Levy-Cooperman et al. 2016). In comparison, a single tablet of OxyContin® has a total mass of 133 mg (Lofwall et al. 2012). Given the high total mass to API ratio and considering that the rate of NKTR-181 uptake by the brain is expected to remain similar independent of route of administration, the insufflation route of abuse is unlikely to be attractive to an abuser seeking immediate euphoria.

Figure 26. Intact and Crushed NKTR-181 Tablet

API = active pharmaceutical ingredient

5.5.2 Large Volume Solvent Extraction

With other ER opioid formulations including ADFs, large volume extraction provides a means for individuals to circumvent the tablet's sustained-release mechanism and extract higher levels of API. As an IR tablet, NKTR-181 is readily soluble and extractable in many solvents. However, the inherent physicochemical properties attributed to NKTR-181's molecular structure result in similar exposures being delivered by oral administration of NKTR-181 in solution and intact tablets; this is supported by bioequivalence data from a study of NKTR-181 in solution and in tablet form. Further, the oral dosage form (solution vs tablet) did not change the relative Drug Liking between NKTR-181 and oxycodone in the 2 HAP studies, as seen by the consistent results across both studies for the 400 mg dose of NKTR-181 (Figure 3). Hence, there may be no perceived benefit from abuse of large volume extractions of NKTR-181. As demonstrated in

HAP Study 05, NKTR-181 in oral solution produced lower Drug Liking and Drug High compared to an oral solution of oxycodone (see Section 5.3.1).

5.5.3 Syringeability for IV Injection

A broad range of syringeability conditions were examined in order to assess how much NKTR-181 API could be extracted and syringed for IV injection. Solutions for injection were prepared using single 200 mg tablets of NKTR-181 ground into powder with the 2 most frequently used solvents. The solutions were syringed using 4 sizes of needles.

Regardless of the conditions used to dissolve the crushed NKTR-181 tablet, all solutions prepared exhibited a thick, gritty consistency, which impaired syringe loading. Depending on the needle size and whether filtration was employed, extraction of NKTR-181 API with small volumes (2-10 mL) produced variable results. Without filtration, 40% to nearly the full dose could be loaded into syringes fitted with the larger needles, and up to 45% could be drawn up through the smaller size needles preferred for IV administration (Harm Reduction Coalition 2012; Patterson and Strike 2009; Victorian Department of Human Services 2008). However, particulates containing undissolved drug were present in the unfiltered syringed solution. To avoid the possibility of injecting particulates, drug abusers routinely use filtration when preparing drugs for injection (eg, drawing solution through cotton ball or cigarette filter). In tests with filtration through a cotton ball, less than 30% of the dose could be loaded into syringes fitted across the different size needles.

Importantly, while IV administration is expected to alter the rate at which NKTR-181 enters systemic circulation, it is not expected to alter NKTR-181's BBB permeability and MOR binding kinetics. This was shown in the nonclinical abuse potential studies in which IV injections of NKTR-181 produced less behavioral reinforcement than IV injections of oxycodone (Section 5.2.2). Thus, the biochemical steps required to achieve the euphoric effects sought by abusers are not hastened by injection of NKTR-181.

5.5.4 Simulated Smoking

A simulated smoking study measured the amount of NKTR-181 that could be vaporized from intact and crushed tablets. Heating at controlled temperatures and over an open flame relinquished minimal amounts of NKTR-181 vapor (< 0.1%), demonstrating that smoking would not be an effective means of abuse.

5.6 Events Associated with Abuse Potential from NKTR-181 Clinical Program

Data on abuse-related events and opioid withdrawal symptoms were collected in the Phase 3 studies. Results from these investigations showed a low incidence of both categories of events (analyses are detailed in Sections 7.6.6 and 7.6.5, respectively).

Across the Phase 1 and 2 studies, no AEs related to abuse, misuse, or diversion of NKTR-181 have been reported.

5.7 Abuse Potential Conclusions

As with any opioid analgesic, NKTR-181 can be abused by individuals with access to a large supply of tablets. However, for persons seeking the rapid onset of effects that are characteristic of oxycodone, morphine, and other conventional opioids, NKTR-181 would be expected to be less attractive.

The physicochemical properties of NKTR-181 that confer its slower rate of CNS entry, slower rate of MOR activation, and prolonged systemic half-life result in a lower overall abuse potential profile as compared to oxycodone, as demonstrated through in vitro chemistry, nonclinical, and clinical studies. Nonclinical data including dopamine response, physical dependence, drug discrimination, and behavioral reinforcement in rats or monkeys all demonstrated that NKTR-181 had lower abuse potential as compared to oxycodone or morphine when administered via the oral, IV, or intraperitoneal route. The oral HAP data showed substantially reduced levels of Drug-Liking for NKTR-181 at the therapeutic dose range of 100 to 600 mg compared to oxycodone (40 and 60 mg). Administration of NKTR-181 at 1200 mg (2-3 times the highest doses studied in Phase 3 studies) resulted in Drug Liking similar to that of oxycodone 40 mg, but with a slower onset. These results are consistent with NKTR-181's lower BBB permeability and MOR kinetics and would be expected to result in NKTR-181 being viewed as a less desirable drug by individuals seeking a rapid high.

Furthermore, in vitro manipulation studies demonstrated that NKTR-181 resists conversion to a more active opioid substance that would be of potential interest for abuse or diversion. Attempts to chemically, enzymatically, or thermally alter the NKTR-181 molecular entity under 193 unique conditions resulted in mixtures containing less than 1.3% of more active derivatives (i.e., oxycodone or 6β-oxycodol). The physicochemical properties intrinsic to the NKTR-181 molecule are not expected to be defeated by administration via non-intended routes of abuse, thus limiting NKTR-181's attractiveness to recreational drug users seeking a rapid and concentrated opioid effect.

6 CLINICAL EFFICACY

Key Points

- The efficacy of NKTR-181 was evaluated in Study 07, a prospective, placebo-controlled, EERW study that assessed pain (using an 11-point NRS) in patients with CLBP who had inadequate pain relief with more conservative treatments.
- Study 07 demonstrated statistically significant reductions in Weekly Pain Scores after 12 weeks of treatment with NKTR-181 compared with placebo.
  - On the primary endpoint, the LS mean change in Weekly Pain Score from baseline to Week 12 favored NKTR-181 with a treatment difference of -0.55 ($p = 0.0019$).
  - Sensitivity analyses yielded similar results as the primary endpoint analysis.
- Secondary endpoint results showed greater improvement with NKTR-181 at different thresholds of pain reduction and in PGIC, demonstrating that the change in pain was clinically meaningful.
  - The cumulative distributions of percent reduction in pain scores showed consistent benefit over placebo across almost all pain reduction thresholds, including the $\geq 30\%$ and $\geq 50\%$ reduction benchmarks reported in the literature (Dworkin et al. 2008).
  - On the PGIC assessment, the proportion of patients reporting their status at Week 12 as "better" or "a great deal better" was statistically significantly greater in the NKTR-181 group compared with the placebo group (51.5% vs 33.2%; $p < 0.0001$).
  - Patients in the NKTR-181 group reported better overall quality of sleep on the MOS Sleep-R score assessment than patients in the placebo group, with improvements in sleep disturbance, sleep problems, sleep adequacy, and hours slept.
- Study 08 was an open-label safety study that evaluated pain in roll-over patients from Study 07 and de novo patients with chronic noncancer pain who received NKTR-181 at doses up to 600 mg q12h.
  - Sustained reductions in mBPI-SF pain intensity scores were observed during the open-label Treatment Period, with mean scores of 2.72 at the end of the Titration Period and at Week 42.

6.1 Phase 2 Placebo-Controlled Study 04

Study 04 was a Phase 2 multicenter, double-blind, placebo-controlled EERW study in patients with moderate to severe chronic pain due to OA of the knee who were not taking opioid-containing medications.

The EERW study design is consistent with draft FDA guidance (2012) and is commonly used for studies of chronic opioid therapies to characterize treatment benefit among patients who show an analgesic response to treatment. EERW studies are designed to utilize study medication as it would be used in clinical practice in an initial open-label titration phase, then randomize responders in a double-blind phase to either continue study medication or receive placebo to confirm that efficacy is statistically superior to placebo (Katz 2009).

In Study 04, patients were initially titrated to an effective dose of NKTR-181 and then randomized in a 1:1 ratio to receive either NKTR-181 (at the dose established during the open-label Titration Period) or matching placebo; the double-blind Treatment Period lasted 21 days.

There was no difference between NKTR-181 and placebo on the primary endpoint, change in pain intensity from randomization to the end of treatment, with a treatment difference of -0.04 (LS mean; SE, 0.22; p = 0.8404). However, larger treatment effects were detected in certain patient subgroups and positive trends in the general study population showed evidence of a treatment benefit in secondary efficacy endpoints.

Further analysis of the study results led to the conclusion that the following factors may have contributed to the lack of a difference between treatment groups:

- Study 04 was an opioid add-on study in which the patients did not discontinue their current analgesic therapies. Approximately 91% of patients were taking NSAIDs, which may have contributed to maintenance of pain relief in patients switched to placebo during the double-blind Treatment Period. These concurrent analgesic therapies may also have played a role in suppression of the expected rebound in pain score upon withdrawal of NKTR-181 in the placebo group.
- Patients were eligible to enter the Treatment Period if they achieved at least a 20% decrease in NRS score from screening. Such a criterion resulted in a more modest reduction of pain required for those with lower screening NRS scores, which may have contributed to an inability to achieve significant separation from placebo in this group of patients.

The learnings from Study 04 were used to inform study design parameters for Study 07:

- Background concomitant medications for pain were prohibited.
- An absolute, rather than relative, measure of pain reduction was applied for entry into the double-blind Treatment Period (see Section 6.2.4).
- Patients were required to have a minimum Screening Pain Score of 5.

Additional information on Study 04 is provided in Appendix 3.

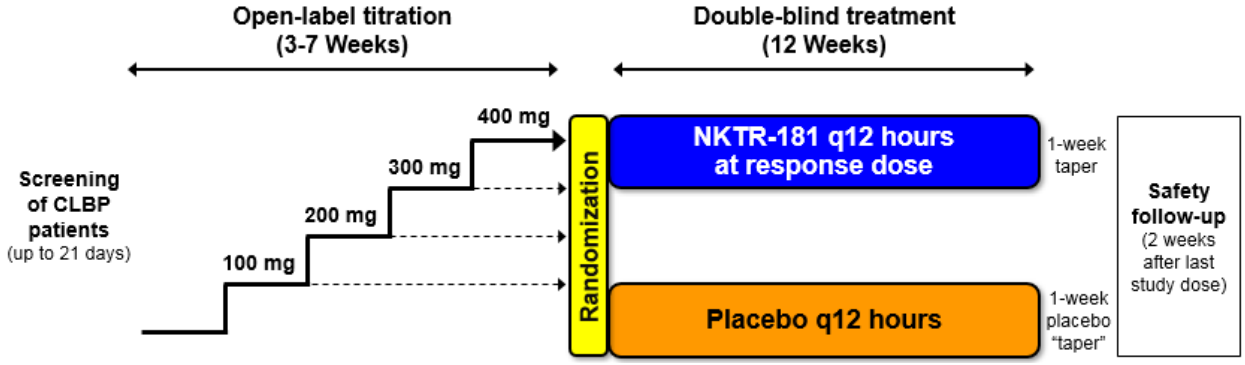
6.2 Pivotal Placebo-Controlled Study 07

6.2.1 Study Design

Study 07 was a multicenter, pivotal, Phase 3, randomized, double-blind, placebo-controlled EERW study that assessed the efficacy, safety, and tolerability of NKTR-181 in patients with moderate to severe CLBP and who were taking no more than 10 mg MSE per day.

Study 07 utilized an EERW design consistent with FDA guidance (2012) and consisted of a 3- to 7-week open-label Titration Period, a 12-week double-blind Treatment Period, followed by a 1-week taper and 2-week safety follow-up. A schematic of the study design is shown in Figure 27. Patients who completed the end of treatment visit were given the option to enroll in Study 08, the open-label long-term safety study.

Figure 27. Study Design for Study 07



CLBP = chronic low back pain; q12 hours = every 12 hours

6.2.2 Study Drug, Concomitant, and Rescue Analgesics

Study Treatment

Study drug consisted of NKTR-181 at doses of 100 to 400 mg or placebo administered q12h.

During the open-label Titration Period, all patients began dosing with NKTR-181 100 mg q12h. The dose was increased in 100 mg increments until the patient met the randomization criteria (see Section 6.2.4) or could not tolerate the given dose. Patients who tolerated and responded to NKTR-181 (ie, met the randomization criteria) were randomized. Patients who could not tolerate NKTR-181 or meet any other randomization criteria during the Titration Period were discontinued. Details on the titration procedure are provided in Appendix 4.

Patients randomized to the NKTR-181 treatment group continued to take the dose established during the Titration Period. In patients randomized to placebo, NKTR-181 was withdrawn and placebo was administered throughout the double-blind Treatment Period (12 weeks) and 1-week taper.

Following the 12-week Treatment Period, the NKTR 181 dose was decreased over a 1-week period until all patients were receiving 100 mg q12h (or placebo) for at least 2 days, at which time dosing was discontinued.

Concomitant/Prior Opioid Treatment

Concomitant use of opioids or NSAIDs with NKTR-181 was prohibited throughout the study.

Patients who were taking opioid-containing medications prior to study start (up to 10 mg MSE per day) were required to discontinue prior to starting NKTR-181.

Rescue Medication for Breakthrough Pain

During the Titration Period, acetaminophen was allowed (1-2 500-mg tablets every 6 hours as needed [PRN] and not to exceed 3 grams [ie, 6 tablets] per day).

During the first 2 weeks of the double-blind Treatment Period, 5 mg hydrocodone/300 mg acetaminophen tablets were allowed (1 tablet every 6 hours PRN and up to 2 tablets per day). No other opioid medications were permitted throughout the duration of the study.

Following the first 2 weeks of the double-blind Treatment Period, acetaminophen was allowed (1 dose not to exceed 1 gram [ie, 2 tablets] per day).

6.2.3 Enrollment Criteria

Eligible patients were adults, 18-75 years of age, with moderate to severe CLBP. Key inclusion criteria included the following:

- Clinical diagnosis of moderate to severe chronic (≥ 6 months) non-neuropathic low back pain, consistent with Quebec Task Force Classification for Spinal Disorders Grade I-II.
- Patients who had not experienced adequate pain relief or failed treatment with non-opioid analgesics (eg, NSAIDs, cyclooxygenase-2 inhibitors) and for whom opioid analgesics were necessary.
- Taking ≤ 10 mg MSE/day of short-acting opioids for the 14 days prior to screening.
- Had a Screening Pain Score (ie, weekly mean pain score over the last 7 days of the Screening Period) of ≥ 5 and ≤ 9 and an average daily pain score of ≥ 5 and ≤ 9 for at least 5 of those 7 days.
- Had COWS score ≤ 12 to enter the open-label Titration Period.

Full inclusion and exclusion criteria can be found in Appendix 5.

6.2.4 Randomization Criteria

To proceed to the Treatment Period, patients had to meet the following criteria:

- Patient must have tolerated NKTR-181, based on Investigator's clinical judgment.

- The Randomization Baseline Pain Score (as defined in Section 6.2.5) was reduced by ≥ 2 points from the Screening Pain Score.
- The Randomization Baseline Pain Score was ≤ 4.
- The patient's Average Daily Pain was ≤ 4 for 5 out of the 7 days immediately prior to randomization.
- The patient had not used rescue medication on more than 2 out of those 7 days.

6.2.5 Efficacy Endpoints

The primary efficacy endpoint was change in Weekly Pain Score at the end of the double-blind Treatment Period (Week 12) relative to the Weekly Pain Score immediately prior to randomization (Randomization Baseline Pain Score).

Weekly Pain Score was defined as the mean of Daily Pain Scores over 7 days, as measured by patients' electronic Diary records. The Daily Pain Score was the patient-reported average pain over the last 24 hours (recorded at bedtime) or the pain score immediately prior to taking rescue medication on a 0 to 10-point NRS.

Secondary efficacy endpoints were as follows:

- Response rate, where a responder was defined as a randomized patient who completed the double-blind Treatment Period (Week 12) and experienced ≥ 30% or ≥ 50% improvement in the Week 12 Weekly Pain Score from Screening Pain Score
- Patients' PGIC score at Week 12
- Average use of rescue medication
- Physical function based on the RMDQ, a validated tool used to quantify the impact of low back pain on a patient's ability to perform daily activities including mobility and self-care, mood, and sleep (Roland and Morris 1983).
- Sleep based on the MOS Sleep-R, a patient-reported measure that assesses the extent of sleep problems due to low back pain as measured by 6 dimensions of sleep (Hays et al. 2005). Disturbed sleep has a major impact on quality of life and is often a common accompanying symptom of chronic pain.
- Time to discontinuation due to any reason

The first 2 listed secondary endpoints were considered important measures of treatment benefit in chronic pain studies (Dworkin et al. 2008).

6.2.6 Statistical Considerations

Primary Endpoint Analysis

The principal efficacy analysis population consisted of the intention-to-treat (ITT) analysis set, defined as all randomized patients. The principal analysis method for the primary efficacy endpoint used an analysis of covariance (ANCOVA) model that included treatment group as a fixed effect and Randomization Baseline Pain Score as a covariate. For the primary endpoint ANCOVA model, multiple imputation (MI) was used to handle missing values, as described in Appendix 6.

Study Power

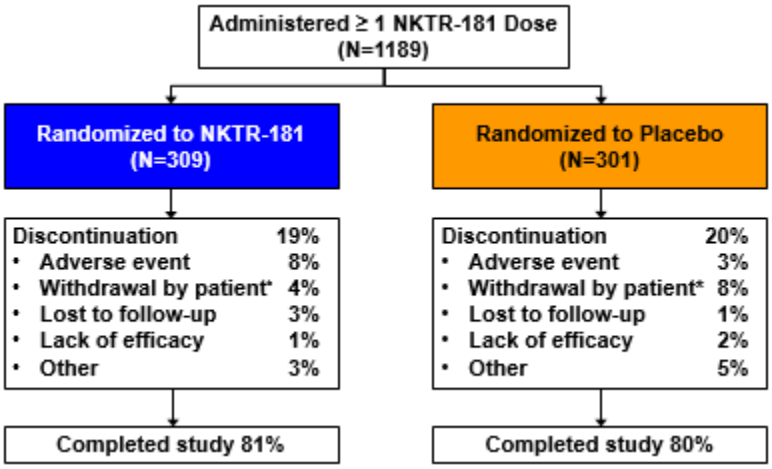
A total sample size of 416 patients (208 per treatment arm) would provide 90% power to detect a relative effect size of 0.32 at a 0.05 significance level (2-sided). This corresponded to an anticipated absolute treatment difference of 0.7 and a standard deviation of 2.2. Based on the prespecified sample size adaptation strategy and the outcome of the planned interim analysis, the sample size was increased to 600 randomized patients to maintain statistical power for the primary endpoint.

6.2.7 Patient Population

6.2.7.1 Patient Disposition

In Study 07, 1,189 patients received at least 1 dose of study drug during the open-label Titration Period (Figure 28). Six hundred and ten patients (309 in the NKTR-181 group and 301 in the placebo group) were subsequently randomized into the double-blind Treatment Period, and 491 patients (80.5%) completed the study. The most common reason for discontinuation during the Treatment Period was AE in the NKTR-181 group and withdrawal of consent in the placebo group. Most patients (n = 430; 87.6%) who completed Study 07 enrolled into Study 08 to receive open-label treatment.

Figure 28. Patient Disposition in Study 07



* The majority of patients in the "withdrawal by patient" category withdrew for non-drug-related reasons (eg, relocation, job, etc.).

As expected, approximately half the initially enrolled patients were responders on both efficacy and tolerability, which is similar to results from other EERW opioid studies (Meske et al. 2018). Reasons for patients not proceeding to the double-blind Treatment Period are summarized in Table 17; the most common reasons were nonresponder per protocol definition (see Section 6.2.4; 21.3%) and AEs (12.0%). For patients who completed the Titration Period and were randomized to treatment with NKTR-181, the majority titrated to either the 300 mg (27.8%) or 400 mg (49.5%) dose.

Table 17. Patients Who Discontinued Prior to Randomization in Study 07

	Patients, n (%)
Enrolled	1,190
Began titration	1,189
Randomized	610 (51.3%)
Not randomized	579 (48.7%)
Reasons for discontinuation	
Adverse event	143 (12.0%)
Opioid withdrawal	1 (<0.1%)
Physician decision	9 (0.8%)
Lost to follow-up	16 (1.3%)
Nonresponder per protocol definition	254 (21.3%)
Death	1 (<0.1%)
Protocol violation	63 (5.3%)
Withdrawal of consent	70 (5.9%)
Other	23 (1.9%)

6.2.7.2 Demographics and Baseline Characteristics

Patients enrolled in Study 07 were appropriate candidates for chronic opioid therapy, consistent with current treatment guidelines (Chou et al. 2007; Dowell et al. 2016). Patients entering Study 07 had endured pain for an extensive period of time and continued to have moderate to severe pain despite prior pharmacotherapies. The average duration of CLBP was approximately 13 years (median, 10.5 years) (Table 19). Based on chart review, among the 1,190 patients who enrolled in the study, 1,154 (97.0%) had been using prior analgesics for CLBP at study entry; 307 (25.8%) patients had used opioids. For patients with prior pain medication recorded in the database, 1,083 patients had been using prior analgesics for an average (SD) of 7.5 (7.7) years, and 405 had received multiple medications. The history of extensive, extended prior pain therapy combined with the elevated pain intensity scores at screening (mean [SD], 6.8 [1.0]) indicate that treatment with conservative pharmacotherapy was unsuccessful (Table 19). Overall, there were no relevant differences in medical history between treatment groups.

Patient demographics were typical of the patient population and were balanced between the NKTR-181 and placebo groups (Table 18). Of the patients randomized, 58.5% were female, and 65.7% were white; their mean age was 51.4 years (range, 20-75 years). The mean Body Mass Index (BMI) was 30.5 kg/m^2.

Among patients randomized to the NKTR-181 group, 2.3%, 20.4%, 27.8%, and 49.5% had titrated to a dose of 100, 200, 300, and 400 mg q12h, respectively.

Table 18. Patient Demographics in Study 07

	NKTR-181 N = 309	**Placebo N = 301**
Age, years, mean (SD)	52 (12.7)	51 (12.5)
Female, n (%)	187 (61%)	170 (56%)
Race, n (%)		
White	205 (66%)	196 (65%)
Black or African American	95 (31%)	93 (31%)
Ethnicity, n (%)		
Non-Hispanic	282 (91%)	280 (93%)
BMI, kg/m^2, mean (SD)	31 (5.4)	30 (5.1)

BMI = body mass index; SD = standard deviation

Table 19. Patient Baseline Characteristics in Study 07

	NKTR-181 N = 309	**Placebo N = 301**
Time from onset of low back pain, years **Mean (SD)** **Median (range)**	 13.3 (10.0) 10.7 (0.5, 50.5)	 13.0 (9.8) 10.4 (0.8, 55.3)
Screening Pain Score **Mean (SD)**	 6.7 (1.0)	 6.8 (0.9)
Randomization Baseline Pain Score **Mean (SD) after Titration** **Range**	 2.3 (1.1) 0-4.0	 2.4 (1.1) 0-6.6

SD = standard deviation

6.2.8 Primary Endpoint – Change in Weekly Pain Score at Week 12

NKTR-181 demonstrated a statistically significant improvement on the primary endpoint; the LS mean change in Weekly Pain Score from baseline (randomization) to Week 12 favored NKTR-181 with a treatment difference of -0.55 (p = 0.0019; Table 20).

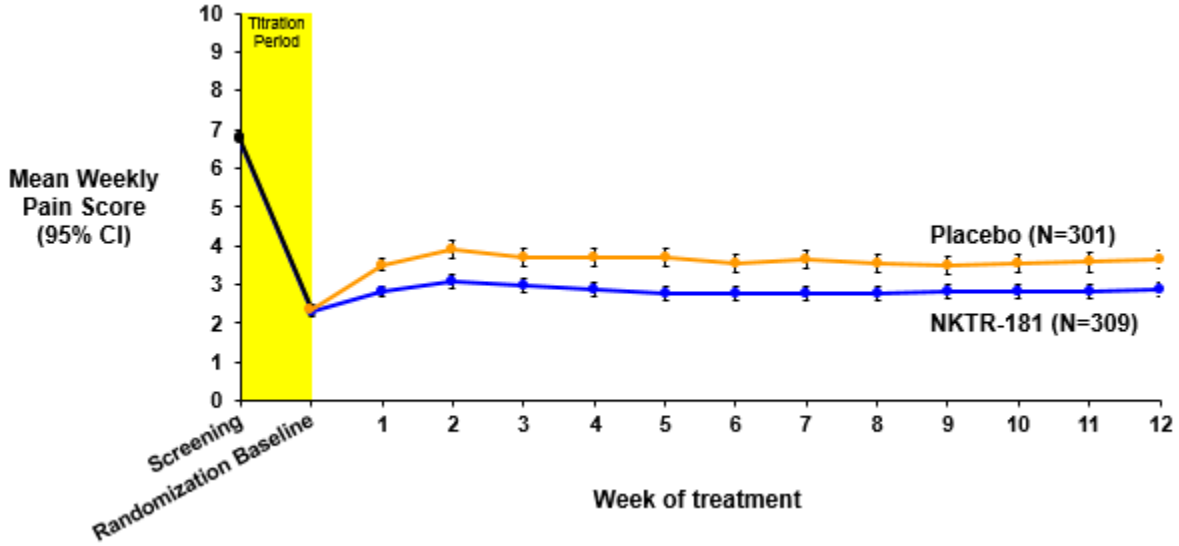
Table 20. Primary Efficacy Endpoint Results in Study 07

Change from Baseline in Weekly Pain Score at Week 12	NKTR-181 N = 309	Placebo N = 301
LS mean (SE)	0.92 (0.112)	1.46 (0.114)
Treatment difference, LS mean (SE) 95% CI p-value	-0.55 (0.160) (-0.86, -0.23) 0.0019	

CI = confidence interval; LS = least squares; SE = standard error

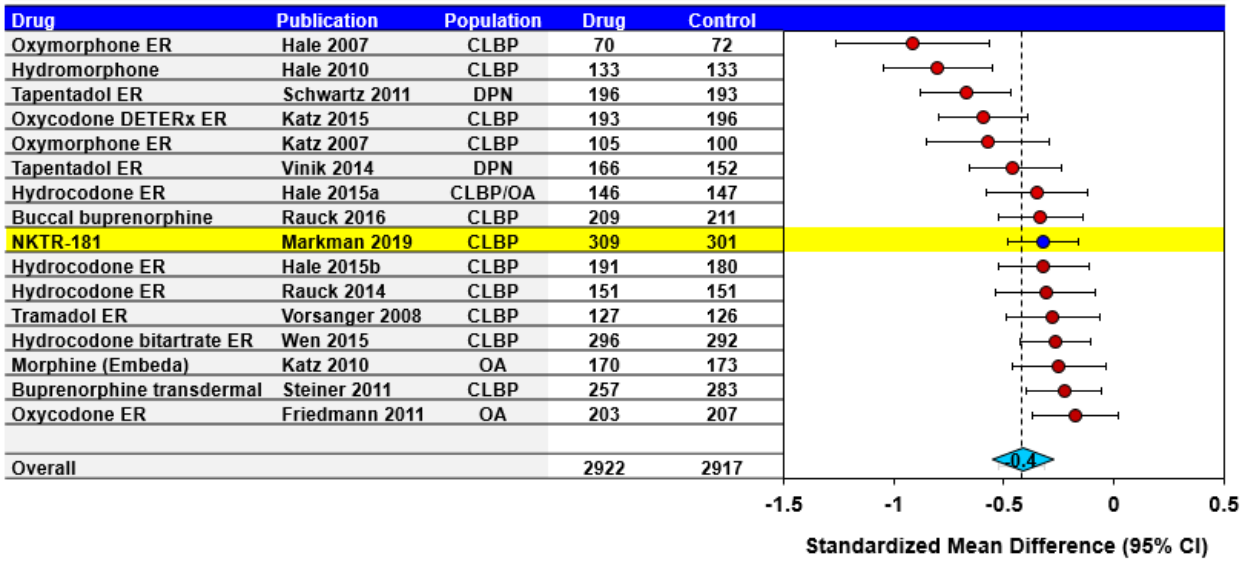
At screening, the mean (SD) Weekly Pain Score among patients eventually randomized to NKTR-181 and placebo was 6.7 (1.0) and 6.8 (0.9), respectively, which decreased during the open-label Titration Period. Both NKTR-181 and placebo groups had a similar Randomization Baseline Pain Score at the beginning of the Treatment Period (2.3 [1.1] and 2.4 [1.1]) (Table 19). Following randomization, patients in the placebo group experienced less improvement in Weekly Pain Scores compared with patients in the NKTR-181 group as early as 1 week following discontinuation of NKTR-181 (Figure 29).

Figure 29. Weekly Pain Scores over Time in Study 07



The level of pain reduction observed in Study 07 is consistent with the treatment effect observed in other chronic pain studies of approved opioid analgesics. Figure 30 shows the standardized effect size calculated for Study 07 compared with the results from the 12-week placebo-controlled EERW trials of opioids analyzed in a meta-analysis by Meske et al. (2018).

Figure 30. Change in Pain Intensity for NKTR-181 Compared with Other Opioids in 12-Week Placebo-Controlled EERW Studies (Meske et al. 2018)



Standardized mean difference effect size for pain score change in primary endpoint from Randomization to Week 12.
Among the studies that reported screening pain scores, the mean scores ranged from 6.3 to 7.3. The exception was 1 study in which the mean score was 8.2.
CLBP = chronic low back pain; OA = osteoarthritis; DPN = diabetic neuropathy

6.2.8.1 Sensitivity Analyses

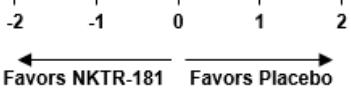
All prespecified and additional ad-hoc sensitivity analyses that Nektar performed consistently supported the robustness of the primary endpoint findings (Figure A-3). The sensitivity analyses are described in Appendix 6.

6.2.8.2 Subgroup Analyses

The primary efficacy endpoint was analyzed by age (< 65 and ≥ 65 years), gender, race (white and non-white), Screening Pain Score (< 6.71 and ≥ 6.71), and duration of CLBP (< 10.51 and ≥ 10.51 years) (Figure 31). Based on these analyses, treatment effect was not affected by gender or Screening Pain Score. These subgroup analyses demonstrated consistent treatment advantages across all subgroups investigated.

Figure 31. Primary Efficacy Endpoint for Patient Subgroups in Study 07

Subgroup		N (NKTR-181, Placebo)	Change in Pain Score	LS Mean Difference (95% CI)	p-value
Age[a]	< 65 Years	251, 262		-0.68 (-1.01, -0.35)	<0.0001
	≥ 65 years	58, 39		-0.10 (-1.01, 0.81)	0.8279
Sex	Male	122, 131		-0.68 (-1.15, -0.22)	0.0043
	Female	187, 170		-0.46 (-0.88, -0.05)	0.0279
Race	White	205, 196		-0.64 (-1.03, -0.24)	0.0016
	Nonwhite	104, 105		-0.39 (-0.90, 0.13)	0.1389
Screening Pain Score	< 6.71[b]	149, 143		-0.49 (-0.92, -0.07)	0.0236
	≥ 6.71[b]	160, 158		-0.57 (-1.03, -0.11)	0.0143
Time from CLBP onset	< 10.51[b]	153, 152		-0.70 (-1.14, -0.27)	0.0015
	≥ 10.51[b]	156, 149		-0.45 (-0.91, 0.01)	0.0528



a. The p-value for interaction coefficient of age group and treatment is 0.2657.
b. 6.71 and 10.51 are median Screening Pain Score and median time (years) to onset of CLBP at screening, respectively.
CI = confidence interval; CLBP = chronic low back pain; LS = least squares

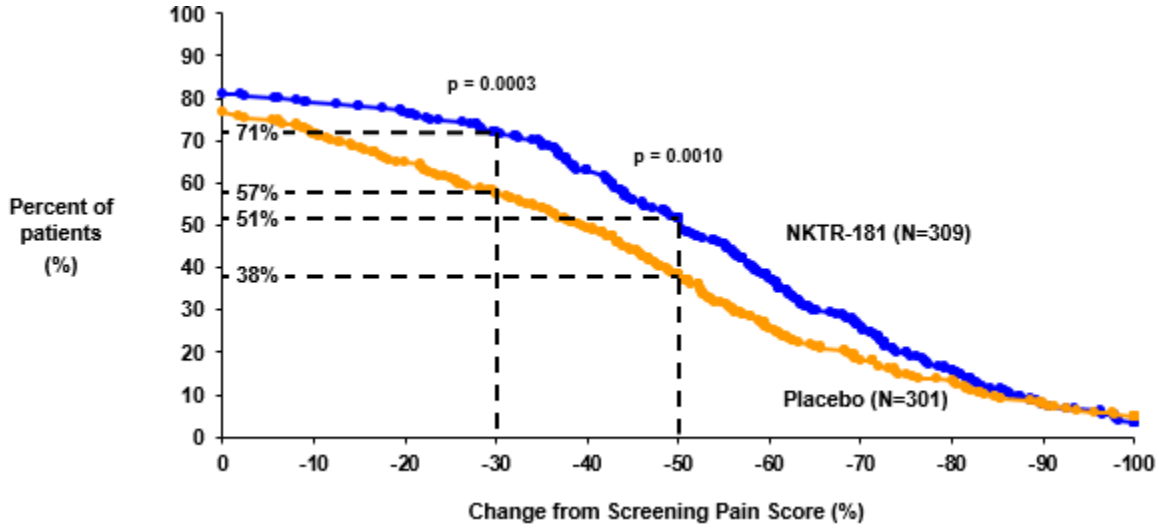
6.2.9 Secondary Endpoints

Results for the primary efficacy endpoint were supported by secondary efficacy endpoints analyses.

6.2.9.1 Proportion of Responders Based on Percent Reduction in Weekly Pain Scores

A pain intensity reduction of 30% and 50% have been proposed as benchmarks for identifying clinically important changes in studies of chronic pain therapies, indicating at least moderate and substantial improvements, respectively (Dworkin et al. 2008). In Study 07, the proportion of responders achieving these thresholds was greater in the NKTR-181 group compared with the placebo group. At Week 12, 71.2% of the patients in the NKTR-181 group versus 57.1% of the patients in the placebo group achieved a ≥ 30% reduction in mean Weekly Pain Score ($p = 0.0003$). Moreover, 51.1% of the patients in the NKTR-181 group versus 37.9% of the patients in the placebo group achieved a ≥ 50% reduction in mean Weekly Pain Score ($p = 0.0010$). As shown in Figure 32, differences between NKTR-181 and placebo were evident at multiple pain reduction thresholds and not just at the prespecified ≥ 30% and ≥ 50% responder thresholds.

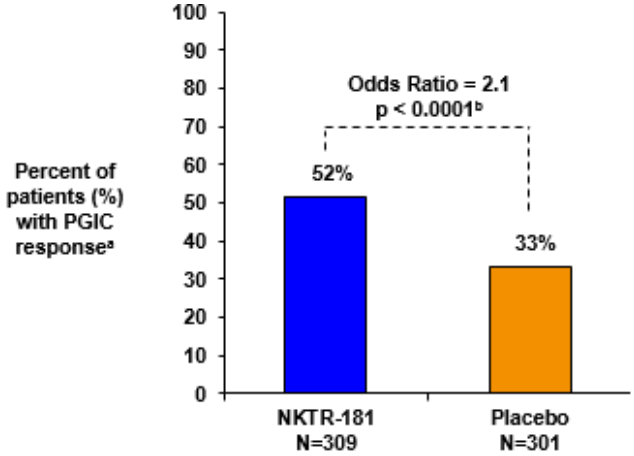
Figure 32. Cumulative Distribution of Percent Reduction from Screening Pain Score at 12 Weeks in Study 07



6.2.9.2 Patient Global Impression of Change

Patients who reported their overall status as being "better" or "a great deal better" on the PGIC assessment were defined as PGIC responders. The proportion of PGIC responders at Week 12 was greater in the NKTR-181 group compared with the placebo group (51.5% vs 33.2%, $p < 0.0001$; Figure 33). The PGIC results also indicate greater improvement for patients in the NKTR-181 group relative to patients in the placebo group based on the proportion who reported "moderately better," "better," or "a great deal better" in their overall status since beginning treatment.

Figure 33. PGIC Responders at Week 12 in Study 07



a. Patients without Week 12 data were treated as nonresponders. Responders were those reporting "better" or "a great deal better."
b. Based on Chi-square test; 95% confidence interval = 1.5, 3.0.

6.2.9.3 Use of Rescue Medication

The use of rescue medication and patient-reported quality of life measures further supported the results from the primary endpoint analysis.

During the first 2 weeks of the Treatment Period, patients were allowed to take up to 2 tablets of 5 mg hydrocodone/300 mg acetaminophen per day. Opioid rescue medications were used by a lower percentage of patients in the NKTR-181 group (44.3% and 45.4% in Week 1 and Week 2, respectively) than in the placebo group (62.8% and 60.6%, respectively; Table 21). Patients in the NKTR-181 group used an average of 2.4 and 2.7 tablets per week during Weeks 1 and 2, respectively, while the placebo group used an average of 3.8 and 4.6 tablets per week.

Table 21. Rescue Medication Usage in Study 07

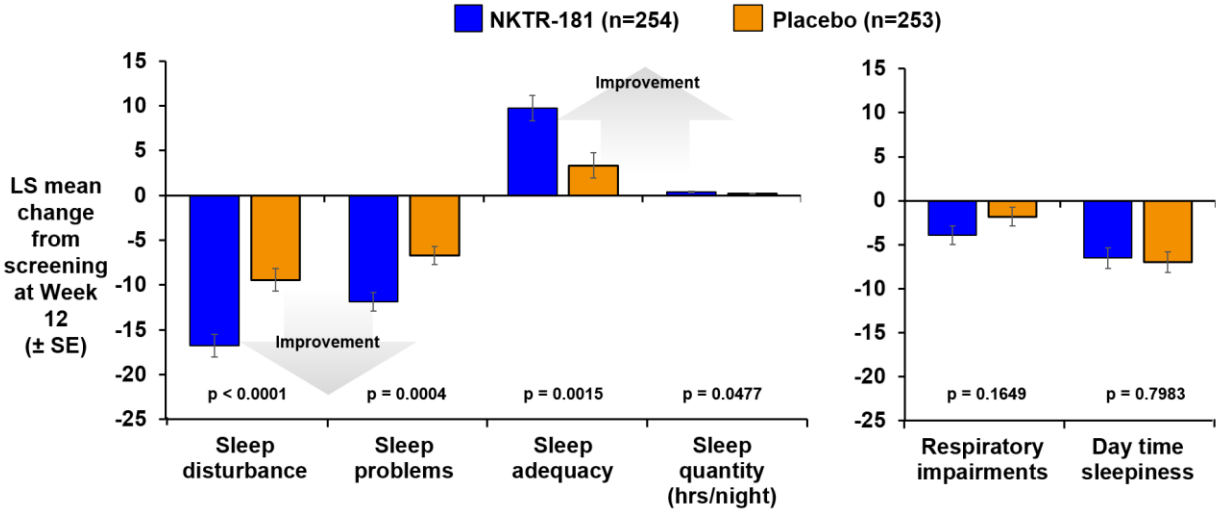
Use of Opioid Rescue Medications During Treatment Period[a]	**NKTR-181 N = 309**	**Placebo N = 301**
Tablets/week, mean (SD)		
Week 1	2.4 (4.14)	3.8 (4.56)
Week 2	2.7 (4.48)	4.6 (5.78)
Patients using rescue medication, n (%)		
Week 1	137 (44.3%)	189 (62.8%)
Week 2	139 (45.4%)	180 (60.6%)

a. Up to 2 tablets per day of 5 mg hydrocodone/300 mg acetaminophen during the first 2 weeks of the Treatment Period.
SD = standard deviation

6.2.9.4 MOS Sleep-R Assessment

Based on the MOS Sleep-R questionnaire, patients in the NKTR-181 group reported better overall quality of sleep, with fewer sleep disturbances and fewer sleep problems, compared with patients in the placebo group. At Week 12, patients in the NKTR-181 group showed improvement compared with patients in the placebo group in the following 4 sleep domains: sleep disturbance (LS mean [SE] treatment difference, -7.4 [1.8]; $p < 0.0001$), sleep problems (-5.2 [1.4]; $p = 0.0004$), sleep adequacy (6.4 [2.0]; $p = 0.0015$), and hours slept (0.2 [0.1]; $p = 0.0477$). In addition, NKTR-181-treated patients showed no worsening in respiratory impairment and day time sleepiness compared with placebo (Figure 34).

Figure 34. MOS Sleep-R Results in Study 07



n = number of patients with data at both screening baseline and Week 12
LS = least squares; SE = standard error

6.2.9.5 Roland-Morris Disability Questionnaire

The RMDQ quantifies the impact of low back pain on a person's ability to perform daily activities, mood, and sleep on a scale of 0 (no disability) to 24 (maximum disability). At Week 12, patients in the NKTR-181 group showed numerically greater improvements in scores on the RMDQ compared with patients in the placebo group (Table 22).

Table 22. RMDQ Results in Study 07

Roland-Morris Disability Questionnaire Score	**NKTR-181 N = 309**	**Placebo N = 301**
Screening score, Mean (SD)	10.2 (5.4)	11.0 (5.2)
Change from baseline at Week 12, LS mean (SE)	-4.2 (0.3)	-3.3 (0.3)
Treatment difference, LS mean (SE) **95% confidence interval** **p-value**	-0.9 (0.5) (-1.8, 0.0) 0.0605	

LS = least-squares; SD = standard deviation; SE = standard error

6.2.9.6 Time to Discontinuation

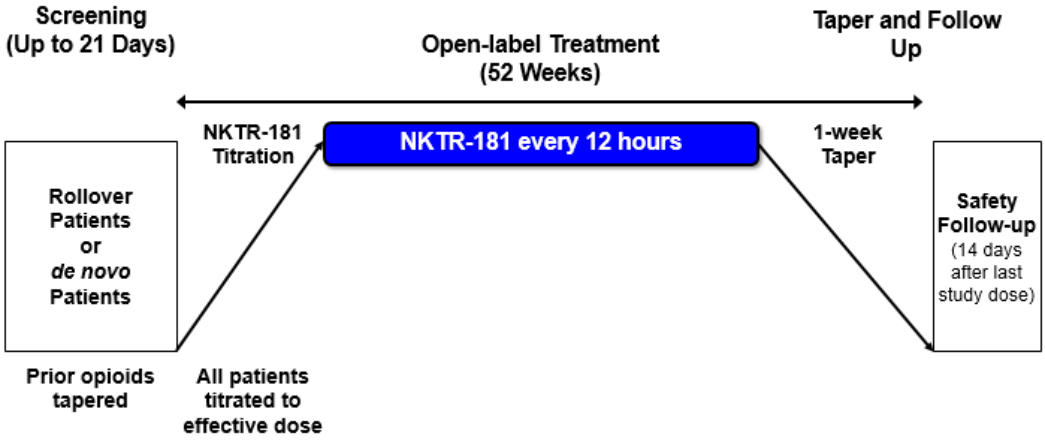
During the Treatment Period, there was little difference in time to discontinuation due to any reason for patients in the NKTR-181 versus the placebo group (hazard ratio [95% CI], 1.02 [0.7, 1.5]; p=0.9225).

6.3 Open-Label Long-Term Safety Study 08

6.3.1 Study Design

Study 08 was a multicenter, Phase 3, open-label, safety and tolerability study in which adult patients with moderate to severe CLBP or chronic noncancer pain received NKTR-181 at doses of 100 to 600 mg q12h for up to 12 months (52 weeks). The study included de novo (ie, newly enrolled) patients in addition to rollover patients who completed Study 07. Approximately 600 patients were planned for enrollment, including approximately 250 de novo patients who were not part of Study 07.

Figure 35. Study Design for Study 08



6.3.2 Study Drug, Concomitant, and Rescue Analgesics

Study Treatment

Study drug consisted of NKTR-181 at doses of 100 to 600 mg administered q12h.

All patients began dosing with 100 mg NKTR-181 q12h with dose escalation proceeding in stepwise increments of 100 mg q12h, no more frequently than every 4 days. All dose escalations occurred over a 5-week period. Implementation of dose escalations was based on Investigator assessment of tolerability and effectiveness until a dose was not tolerated – at which point the patient was discontinued – or until a stable dose was achieved. A stable dose was a dose that was effective and tolerated on 2 sequential visits (ie, at least 8 days of continuous treatment).

During the Treatment Period, doses of NKTR-181 were adjusted upward (up to a maximum dose of 600 mg q12h) or downward in 100 mg increments as needed, based on the Investigator's assessment of effectiveness and tolerability.

Following 51 weeks of NKTR-181 treatment, patients began a 1-week taper from study drug, during which the NKTR-181 dose was decreased until all patients were receiving 100 mg q12h for at least 2 days.

Rescue Medication

Nektar provided over-the-counter analgesics (ie, aspirin, acetaminophen, ibuprofen, and naproxen) for patients who experienced breakthrough pain. Rescue medications were taken in accordance with their labels.

Concomitant use of opioids with NKTR-181 was prohibited.

6.3.3 Enrollment Criteria

Eligible patients were adults, 18-75 years of age, with moderate to severe CLBP or chronic noncancer pain.

The key inclusion criteria included the following:

- Clinical diagnosis of moderate to severe CLBP or chronic noncancer pain for > 3 months.
- De novo patients were non-tolerant to opioid analgesics (ie, were taking ≤ 60 mg MSE/day for at least the 7 days prior to screening). De novo patients included 2 groups of patients: 1) taking 10 to 60 mg MSE/day in the 7 days prior, and 2) taking < 10 mg MSE/day in the 7 days prior.
- Rollover NKTR-181 and placebo patients were required to complete Study 07 before entering Study 08. These patients had no break in treatment with study drug. The end of treatment visit in Study 07 was the first visit of the Study 08 Treatment Period.
- All patients were required to have COWS score ≤ 12 to enter the Treatment Period.

6.3.4 Efficacy Endpoints

The primary objective of Study 08 was to evaluate the long-term safety and tolerability of NKTR-181 in patients with moderate to severe CLBP or chronic noncancer pain. The secondary objective was to evaluate the effectiveness of NKTR-181 as measured by the mBPI-SF at each study visit (approximately every week for 6 weeks, and then every 30 days until the end of the study).

The mBPI-SF collects patient-reported assessments of pain intensity and the degree to which pain interferes with patient functioning (Mendoza et al. 2006). Using a 0-10 scale, patients rated their pain at the time of responding to the questionnaire (Pain Now), and also at its worst, least, and average over the previous 24 hours. Interference in 7 areas (mood, walking and other physical activity, work, social activity, relations with others, and sleep) was rated using a 0-10 scale, with 0 being "no interference" and 10 being "interferes completely."

Efficacy measures included the following:

- Change from baseline in mean mBPI-SF pain intensity scores (ie, the mean of the 4 pain intensity items on the mBPI-SF) over time

- Change from baseline in mean mBPI-SF pain interference (ie, the mean of the 7 pain interference items on the mBPI-SF) over time
- Time to dose level increase after the Titration Period
- Time to treatment discontinuation
- Average use of rescue medication

6.3.5 Patient Population

6.3.5.1 Patient Disposition

A total of 638 patients were enrolled in the study including 431 rollover patients from Study 07 (214, NKTR-181; 217, placebo) and 207 de novo patients (134 patients taking 10 to 60 mg MSE/day; 73 patients taking < 10 mg MSE/day). Of the 638 patients enrolled, 62.2% completed the 52-week study (Table 23), which is comparable to the rate of study completers across long-term opioid studies (Broglio et al. 2017; Friedmann et al. 2011; Hale et al. 2015). The most common reasons (≥ 3%) for study discontinuation were withdrawal of consent (11.4%), AEs (10.5%), lost to follow-up (5.0%), protocol violation (4.2%), and other (3.3%). Few cases in the category, "withdrawal of consent" were related to lack of efficacy or to AEs. Ten de novo patients (10/207; 4.8%) and 4 rollover patients (4/431; 0.9%) discontinued due to lack of efficacy.

Table 23. Patient Disposition in Study 08

	Patients, n (%)
Began titration	638
Completed study	397 (62.2%)
Discontinued study	241 (37.8%)
Reasons for discontinuation	
AE	67 (10.5%)
Physician decision	7 (1.1%)
Lost to follow-up	32 (5.0%)
Lack of efficacy	14 (2.2%)
Protocol violation	27 (4.2%)
Withdrawal of consent[a]	73 (11.4%)
Other	21 (3.3%)

a. The majority of patients who withdrew from the study did so for non-drug-related reasons (eg, relocation, job, etc.).

6.3.5.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics were generally similar among the subgroups with respect to age, gender, race, ethnicity, and BMI (Table 24). The majority of de novo patients had CLBP, with 43 patients having non-low back pain; the duration of chronic pain across subgroups was similar.

Table 24. Patient Demographics and Baseline Characteristics in Study 08

	All N = 638	**Rollover NKTR-181 N = 214**	**Rollover Placebo N = 217**	**De Novo Prior MSE < 10 mg/Day N = 73**	**De Novo Prior MSE 10-60 mg/Day N = 134**
Age, years, mean (SD)	52 (11.9)	52 (12.0)	51 (12.3)	52 (10.4)	56 (11.1)
Female, n (%)	375 (59%)	123 (57%)	126 (58%)	44 (60%)	82 (61%)
Race, n (%)					
White	431 (68%)	136 (64%)	138 (64%)	51 (70%)	106 (79%)
Black or African American	184 (29%)	71 (33%)	70 (32%)	19 (26%)	24 (18%)
Ethnicity, n (%)					
Non-Hispanic	585 (92%)	197 (92%)	199 (92%)	61 (84%)	128 (96%)
BMI, kg/m^2, mean (SD)	31 (5.9)	31 (5.7)	31 (5.7)	34 (6.4)	31 (6.0)
Chronic low back pain, n (%)	595 (93%)	214 (100%)	217 (100%)	44 (60%)	120 (90%)
Chronic non-low back pain, n (%)	43 (7%)	0	0	29 (40%)	14 (10%)
Time since onset, years, mean (SD)	13 (9.6)	13 (9.2)	12 (9.4)	12 (9.6)	14 (10.4)

BMI = body mass index; SD = standard deviation

Prior to study initiation, 201 (97.1%) de novo patients had taken prior medications for analgesia, including 134 who were taking 10 to 60 mg MSE/day of opioid analgesics at screening.

6.3.6 Efficacy Endpoints – Modified Brief Pain Inventory-Short Form

The results of Study 08 showed that the analgesic effect of NKTR-181 is durable and maintained over a 52-week period in patients with chronic pain.

The mean mBPI-SF pain intensity score for all patients was 4.60 at screening and 2.72 at the end of the Titration Period (Figure 36). Sustained reductions in mBPI-SF pain intensity scores were observed during the open-label Treatment Period, with mean scores of 2.72 at Week 42 (last

mBPI-SF measurement prior to tapering) and 3.28 at Week 52 (end of tapering). Similar trends were observed for mBPI-SF pain interference scores with mean scores of 3.90 at screening, 2.05 at the end of the Titration Period, 2.10 at Week 42 (last mBPI-SF measurement prior to tapering), and 2.64 at Week 52 (end of tapering; Figure 37).

Figure 36. mBPI-SF Pain Intensity Scores Over Time in Study 08

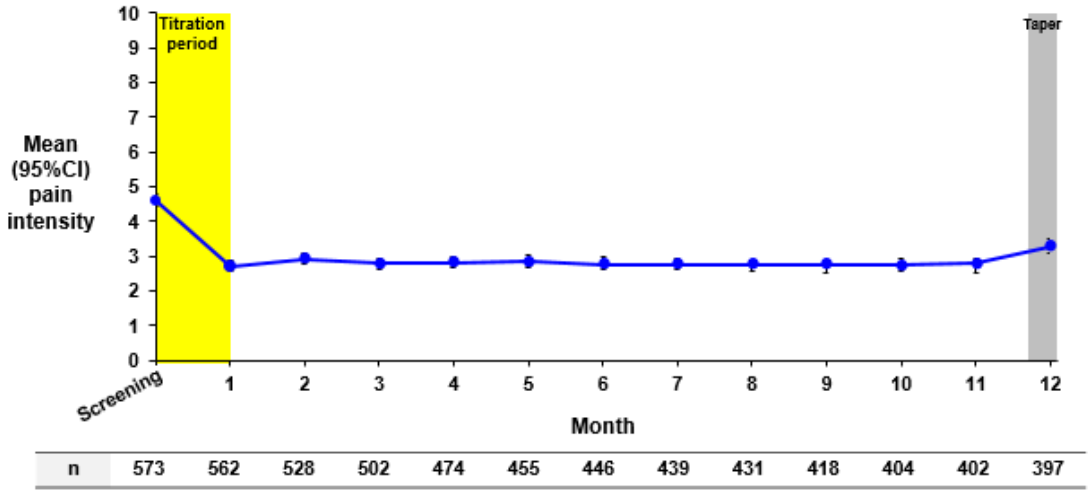
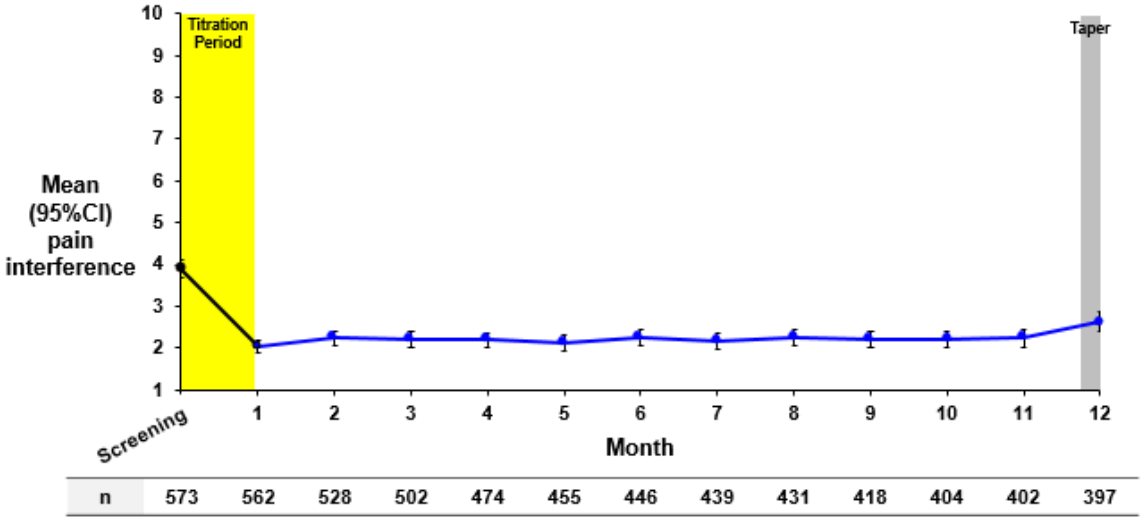


Figure 37. mBPI-SF Pain Interference Scores Over Time in Study 08



The majority of patients (72.0%) ended the study with the same dose of NKTR-181 that was established during the Titration Period, suggesting a lack of tolerance to the analgesic effect of NKTR-181.

6.4 Efficacy Conclusions

Overall, NKTR-181 was an effective analgesic in the management of moderate or severe CLBP for patients whose pain was not well controlled using non-opioid pharmacotherapies, as demonstrated by the results for the primary and secondary endpoints in the 12-week double-blind placebo-controlled pivotal Phase 3 study (Study 07). Statistically significant and clinically meaningful improvements were shown with respect to pain reduction and response rates, with consistent and robust results on patient-reported pain and quality of life measures as well as in sensitivity and subgroup analyses. The long-term (52-week) safety study (Study 08) demonstrated that pain reduction was maintained, generally without the need for a change in dose, further supporting the efficacy of NKTR-181 for the treatment of CLBP.

7 CLINICAL SAFETY

Key Points

- NKTR-181's clinical development program comprises 2,175 individuals who received ≥ 1 dose of NKTR-181, including 1,691 patients with CLBP or other noncancer chronic pain from the Phase 2 and Phase 3 studies; 412 patients had approximately 1 year of exposure.
- No safety signals were identified in the pivotal, placebo-controlled study (Study 07) beyond those AEs typically seen for opioids.
  - NKTR-181 produced a higher rate of AEs and AEs leading to treatment discontinuation compared with placebo. AEs reported in >5% of patients and more frequently for NKTR-181 were typical opioid-related AEs (nausea and constipation).
  - SAEs were reported by 0.8% of patients during the open-label Titration Period and at similar rates in the NKTR-181 and placebo groups during the double-blind Treatment Period (1.6% vs 2.0%, respectively). One patient died of an SAE of cerebrovascular accident that was considered unrelated to NKTR-181; no other deaths were reported in the NKTR-181 clinical program.
  - The proportion of patients with the most notable CNS-mediated AEs impacting daily functions, such as somnolence and dizziness, was 9.0% and 4.0%, respectively during the Titration Period. Following randomization, the incidence of these events was even lower.
  - Symptoms of opioid withdrawal upon cessation of NKTR-181 were minimal on both COWS and SOWS assessments; 98% of patients had no withdrawal symptoms following abrupt cessation of NKTR-181.
- No new safety signals were identified in the 52-week long-term safety study (Study 08), which included Study 07 rollover patients and de novo patients who were previously taking < 10 mg MSE/day of opioids or transitioning from another opioid analgesic (taking 10 to 60 mg MSE/day of opioids).
- In the oral HAP Study 15, a lower incidence of AEs was observed following exposure to a single dose of NKTR-181 400 and 600 mg (44.1% and 56.5%, respectively) compared with oxycodone 40 and 60 mg (71.7% and 79.0%, respectively). Euphoric mood, somnolence, and dizziness were reported approximately 2-fold lower with NKTR-181 than with oxycodone.
- Abuse-potential related events were reported at a similar rate for NKTR-181 (5.5%) and placebo (4.7%) in Study 07; events adjudicated as abuse or misuse were observed in <1% of patients on NKTR-181 during the long-term safety study (Study 08).
- Overall, NKTR-181 has a safety profile similar to other opioids, with a low rate of CNS-mediated side effects and withdrawal symptoms.

7.1 Treatment Exposure

During the clinical development program for NKTR-181, 2,175 individuals received at least 1 dose of NKTR-181, including 1,691 patients with CLBP or other noncancer chronic pain from the Phase 2 and Phase 3 studies (Table 25).

Since the proposed indication for NKTR-181 is for treatment of CLBP, Study 07 served as the primary safety dataset. During the open-label Titration Period of Study 07, 1,189 patients were treated with NKTR-181 for a mean of 29.4 days. During the double-blind Treatment Period, 309 patients were dosed with NKTR-181 for a mean of 76.0 days. Integrated safety data for the Phase 2 and 3 placebo-controlled studies (Study 04 in OA of the knee and Study 07) are provided in Appendix 7.

Of the 638 patients enrolled in the 52-week long-term Phase 3 safety study (Study 08), 453 were exposed to NKTR-181 for ≥ 26 weeks (180 days) and 402 were exposed to NKTR-181 for ≥ 50 weeks.

Table 25. Exposure to NKTR-181 in Phase 2 and Phase 3 Studies

	Study 04	Study 07	Study 08	Total
Patients Dosed with NKTR-181, N				
During open-label titration/treatment	295	1,189	638[a]	1,691
During double-blind treatment	107	309	-	416
For ≥ 26 weeks	-	-	453	483
For ≥ 50 weeks	-	-	402	412[b]
Exposure[c], days, mean (SD)	20 (4)	76 (24)	266 (135)	-

a. Includes 207 newly enrolled patients, 214 rollover NKTR-181 patients from Study 07, and 217 rollover placebo patients from Study 07.
b. 412 patients dosed for ≥ 51 weeks.
c. During double-blind Treatment Period for Study 04 and Study 07 and open-label Treatment Period for Study 08.

7.2 Placebo-Controlled Safety (Study 07)

7.2.1 Adverse Events

An overview of AEs that occurred during the open-label Titration Period and double-blind Treatment Period of Study 07 is provided in Table 26. A majority of patients treated with NKTR-181 experienced AEs (67.5% during the Titration Period, and 54.4% during the Treatment Period vs 49.8% for placebo), which were predominantly mild to moderate in severity. A total of 151 (12.7%) patients experienced AEs during the Titration Period that led to study drug discontinuation, and a higher proportion did so during treatment with NKTR-181 than placebo (7.1% vs 2.7%, respectively) in the Treatment Period. Serious AEs were infrequent and generally unrelated to NKTR-181; SAEs occurred at a similar rate in the NKTR-181 and placebo

groups during the Treatment Period (1.6% vs 2.0%, respectively). One patient died of an unrelated SAE (cerebrovascular accident; described in Section 7.5).

Table 26. Overview of Adverse Events Reported in Study 07

	Patients, n (%)		
	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301
Patients reporting ≥ 1:			
AE	803 (67.5)	168 (54.4)	150 (49.8)
Severe AE	25 (2.1)	8 (2.6)	5 (1.7)
AE leading to study drug discontinuation	151 (12.7)	22 (7.1)	8 (2.7)
SAE	9 (0.8)	5 (1.6)	6 (2.0)
Death	1 (<0.1)	0	0

The most frequently reported AEs during Study 07 are summarized in Table 27. During the Titration Period, the most common AEs were constipation (35.7%), nausea (14.8%), somnolence (9.0%), headache (7.0%), vomiting (5.6%), dry mouth (5.6%), and fatigue (5.1%). During the Treatment Period, AEs that were reported in more than 5% of patients on NKTR-181 and more frequently compared to placebo were nausea and constipation, consistent with AEs commonly associated with opioids.

Table 27. Adverse Events Reported ≥ 3% of Patients in Study 07

	Patients, n (%)		
	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301
Patients reporting ≥ 1 AE	803 (67.5)	168 (54.4)	150 (49.8)
Constipation	425 (35.7)	27 (8.7)	9 (3.0)
Nausea	176 (14.8)	32 (10.4)	18 (6.0)
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)
Pruritus	52 (4.4)	2 (0.6)	0
Dizziness	47 (4.0)	7 (2.3)	1 (0.3)
Diarrhoea	35 (2.9)	8 (2.6)	17 (5.6)
Drug withdrawal syndrome	32 (2.7)	14 (4.5)	12 (4.0)
Nasopharyngitis	13 (1.1)	10 (3.2)	11 (3.7)
Upper respiratory tract infection	21 (1.8)	10 (3.2)	9 (3.0)

7.2.2 Adverse Events by Severity

The majority of AEs during both the Titration and Treatment Periods were mild or moderate in severity, with a similar incidence of severe AEs occurring in the NKTR-181 and placebo groups. Severe AEs were also similar to those commonly reported for opioids; those that occurred in at least 2 patients are listed in Table 28.

Table 28. Severe Adverse Events in ≥ 2 Patients in Any Treatment Group in Study 07

	Patients, n (%)		
	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301
Patients with ≥ 1 severe AE	25 (2.1)	8 (2.6)	5 (1.7)
Abdominal Pain	2 (0.2)	1 (0.3)	0
Constipation	4 (0.3)	1 (0.3)	0
Headache	3 (0.3)	0	0
Migraine	2 (0.2)	0	0
Nausea	1 (<0.1)	2 (0.6)	0
Sedation	2 (0.2)	0	0
Somnolence	2 (0.2)	0	0
Drug withdrawal syndrome	0	2 (0.6)	0

7.2.3 Adverse Events Leading to Discontinuation

A summary of AEs that led to discontinuation of study drug in Study 07 is provided in Table 29. As expected with initiating opioid therapy and owing to the EERW design of the study, a greater proportion of patients discontinued treatment with NKTR-181 because of AEs during the Titration Period (12.7%) than did during the Treatment Period (7.1%). While the rate of discontinuation due to AEs was higher for NKTR-181 compared with placebo during the Treatment Period, the majority of events leading to discontinuation are common opioid-related AEs.

Table 29. Adverse Events that Led to Withdrawal of Study Drug in ≥ 0.5% Patients in Study 07

	Patients, n (%)		
	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301
Patients reporting ≥ 1 AE	151 (12.7)	22 (7.1)	8 (2.7)
Nausea	36 (3.0)	1 (0.3)	1 (0.3)
Constipation	25 (2.1)	3 (1.0)	0
Somnolence	20 (1.7)	1 (0.3)	0
Vomiting	19 (1.6)	3 (1.0)	0
Dizziness	17 (1.4)	1 (0.3)	0
Fatigue	13 (1.1)	1 (0.3)	0
Headache	11 (0.9)	0	1 (0.3)
Diarrhoea	6 (0.5)	0	1 (0.3)
Hyperhidrosis	6 (0.5)	0	0
Migraine	6 (0.5)	0	0
Pruritus	6 (0.5)	0	0

7.2.4 Serious Adverse Events

During the open-label Titration Period, 9 (0.8%) patients reported SAEs (Table 30). None of the SAEs reported during the Titration Period occurred in more than 1 patient. With the exception of the reported cases of angioedema and transient blindness, none was considered related to study drug. One patient treated with NKTR-181 at 200 mg q12h developed angioedema on Day 15, which resolved within 2 days. This SAE was confounded by the patient's use of lisinopril, an angiotensin-converting enzyme inhibitor with a known risk of angioedema. Another patient, this one treated with NKTR-181 at 100 mg q12h, reported left superior vision loss, coded as transient blindness, on Day 4 of the Titration Period, which resolved on the same day. This SAE was confounded by the patient's use of tadalafil, which is known to carry the risk of transient blindness via optic nerve ischemia.

During the double-blind Treatment Period, a similar percentage of patients had SAEs in each treatment group. None of the SAEs was reported in more than 1 patient in either treatment group, and none of the SAEs was considered drug-related by the Investigator.

Table 30. Serious Adverse Events in Study 07

	Patients, n (%)		
	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301
Patients reporting ≥ 1 SAE	9 (0.8)	5 (1.6)	6 (2.0)
Angioedema	1 (<0.1)	0	0
Atrial fibrillation	1 (<0.1)	0	0
Blindness transient	1 (<0.1)	0	0
Cellulitis	1 (<0.1)	0	0
Cerebrovascular accident	1 (<0.1)	0	0
Gastrointestinal infection	1 (<0.1)	0	0
Herpes virus infection	1 (<0.1)	0	0
Infective exacerbation of chronic obstructive airways disease	1 (<0.1)	0	0
Large intestine perforation	1 (<0.1)	0	0
Pneumonia	1 (<0.1)	0	0
Pulmonary embolism	1 (<0.1)	0	0
Chest pain	0	1 (0.3)	0
Diverticulitis	0	1 (0.3)	0
Hypertension	0	1 (0.3)	0
Renal failure	0	1 (0.3)	0
Rib fracture	0	1 (0.3)	0
Bacterial infection	0	0	1 (0.3)
Bladder cancer	0	0	1 (0.3)
Diverticulum intestinal	0	0	1 (0.3)
Dysarthria	0	0	1 (0.3)
Gastroenteritis	0	0	1 (0.3)
Malignant hypertension	0	0	1 (0.3)
Skin abrasion	0	0	1 (0.3)

7.3 Long-Term Safety (Study 08)

7.3.1 Adverse Events

Table 31 shows an overview of AEs in Study 08 for the overall study population as well as groups based on previous opioid treatment: 1) rollover patients who received NKTR-181 in Study 07; 2) rollover patients who received placebo in Study 07; 3) de novo patients previously taking < 10 mg MSE/day; and 4) de novo patients previously taking 10 to 60 mg MSE/day. In Study 08, 461 (72.3%) patients reported at least 1 AE. The incidence of AEs was higher in the de novo groups than the rollover groups, which may be a result of the previously enriched enrollment in Study 07. Most AEs were mild or moderate in severity; AEs that led to study drug discontinuation (9.9%) and SAEs (4.7%) were reported in a small percentage of patients. No deaths were reported in the study.

Table 31. Overview of Adverse Events in Long-Term Safety Study 08

	Patients, n (%)				
	All N = 638	**Rollover NKTR-181 N = 214**	**Rollover Placebo N = 217**	**De Novo Prior MSE < 10 mg/Day N = 73**	**De Novo Prior MSE 10-60 mg/Day N = 134**
Patients reporting ≥ 1:					
AE	461 (72.3)	138 (64.5)	151 (69.6)	62 (84.9)	110 (82.1)
Severe AE	41 (6.4)	11 (5.1)	7 (3.2)	8 (11.0)	15 (11.2)
AE leading to treatment discontinuation	63 (9.9)	9 (4.2)	18 (8.3)	16 (21.9)	20 (14.9)
SAE	30 (4.7)	10 (4.7)	8 (3.7)	4 (5.5)	8 (6.0)
Deaths	0	0	0	0	0

The types of AEs observed during Study 08 (Table 32) were similar to those seen in Study 07. CNS-mediated AEs such as somnolence, lethargy, and dizziness were each reported in fewer than 5% of patients overall.

Table 32. Adverse Events Reported in ≥ 3% of Patients in Study 08

	Patients, n (%)				
	All N = 638	**Rollover NKTR-181 N = 214**	**Rollover Placebo N = 217**	**De Novo Prior MSE < 10 mg/Day N = 73**	**De Novo Prior MSE 10-60 mg/Day N = 134**
Patients reporting ≥ 1 AE	461 (72.3)	138 (64.5)	151 (69.6)	62 (84.9)	110 (82.1)
Constipation	166 (26.0)	28 (13.1)	41 (18.9)	41 (56.2)	56 (41.8)
Nausea	76 (11.9)	17 (7.9)	21 (9.7)	21 (28.8)	17 (12.7)
Headache	57 (8.9)	9 (4.2)	21 (9.7)	6 (8.2)	21 (15.7)
Upper respiratory tract infection	48 (7.5)	12 (5.6)	19 (8.8)	7 (9.6)	10 (7.5)
Drug withdrawal syndrome	38 (6.0)	10 (4.7)	16 (7.4)	2 (2.7)	10 (7.5)
Urinary tract infection	35 (5.5)	10 (4.7)	14 (6.5)	6 (8.2)	5 (3.7)
Vomiting	35 (5.5)	13 (6.1)	10 (4.6)	9 (12.3)	3 (2.2)
Somnolence	31 (4.9)	6 (2.8)	13 (6.0)	3 (4.1)	9 (6.7)
Diarrhoea	29 (4.5)	6 (2.8)	11 (5.1)	8 (11.0)	4 (3.0)
Influenza	24 (3.8)	5 (2.3)	10 (4.6)	5 (6.8)	4 (3.0)
Arthralgia	23 (3.6)	6 (2.8)	7 (3.2)	3 (4.1)	7 (5.2)
Nasopharyngitis	23 (3.6)	9 (4.2)	6 (2.8)	2 (2.7)	6 (4.5)
Sinusitis	23 (3.6)	8 (3.7)	8 (3.7)	1 (1.4)	6 (4.5)
Pruritus	21 (3.3)	4 (1.9)	5 (2.3)	6 (8.2)	6 (4.5)
Bronchitis	19 (3.0)	5 (2.3)	7 (3.2)	3 (4.1)	4 (3.0)
Dizziness	19 (3.0)	5 (2.3)	3 (1.4)	5 (6.8)	6 (4.5)

7.3.2 Adverse Events by Severity

While the majority of AEs reported in Study 08 were mild or moderate in severity, severe AEs were reported by 41 (6.4%) patients in Study 08 (Table 33). The only severe AE that occurred in more than 2 patients was back pain in 3 patients (0.5%).

Table 33. Severe Adverse Events in ≥ 2 Patients in Study 08

	Patients, n (%)				
	All N = 638	**Rollover NKTR-181 N = 214**	**Rollover Placebo N = 217**	**De Novo Prior MSE < 10 mg/Day N = 73**	**De Novo Prior MSE 10-60 mg/Day N = 134**
Patients reporting ≥ 1 severe AE	41 (6.4)	11 (5.1)	7 (3.2)	8 (11.0)	15 (11.2)
Back pain	3 (0.5)	2 (0.9)	0	0	1 (0.7)
Gastroenteritis	2 (0.3)	1 (0.5)	0	0	1 (0.7)
Influenza	2 (0.3)	0	1 (0.5)	0	1 (0.7)
Somnolence	2 (0.3)	0	1 (0.5)	1 (1.4)	0
Migraine	2 (0.3)	0	0	1 (1.4)	1 (0.7)
Duodenal ulcer	2 (0.3)	0	0	1 (1.4)	1 (0.7)

7.3.3 Adverse Events Leading to Discontinuation

In Study 08, AEs that led to study drug discontinuation were reported in 9.9% of patients (Table 34). Again, a higher incidence was observed in the de novo groups compared with the rollover groups, likely as a result of the Study 07 enriched enrollment design.

Table 34. Adverse Events Leading to Discontinuation in ≥ 0.5% of Patients in Study 08

	Patients, n (%)				
	All N = 638	**Rollover NKTR-181 N = 214**	**Rollover Placebo N = 217**	**De Novo Prior MSE < 10 mg/Day N = 73**	**De Novo Prior MSE 10-60 mg/Day N = 134**
Patients reporting ≥ 1 AE leading to treatment discontinuation	63 (9.9)	9 (4.2)	18 (8.3)	16 (21.9)	20 (14.9)
Constipation	10 (1.6)	0	2 (0.9)	4 (5.5)	4 (3.0)
Headache	7 (1.1)	0	0	1 (1.4)	6 (4.5)
Nausea	5 (0.8)	0	0	3 (4.1)	2 (1.5)
Irritability	4 (0.6)	1 (0.5)	2 (0.9)	0	1 (0.7)
Vomiting	4 (0.6)	1 (0.5)	0	2 (2.7)	1 (0.7)
Dizziness	3 (0.5)	1 (0.5)	0	1 (1.4)	1 (0.7)
Hepatic enzyme increased	3 (0.5)	0	1 (0.5)	2 (2.7)	0

7.3.4 Serious Adverse Events

In Study 08, SAEs were reported in 4.7% of patients. Only gastroenteritis and pneumonia were reported in more than 1 patient (both occurred in 2 patients). Of the 30 patients with SAEs, 11 discontinued the study because of the SAEs. None of the SAEs were deemed related to NKTR-181 and there was no apparent relationship between the incidence of SAEs and NKTR-181 dose.

7.4 Safety in Human Abuse Potential Studies

The HAP studies (Study 05 and Study 15) provide safety data on NKTR-181 and oxycodone IR following single-dose administration in healthy recreational opioid users. Study 15 is summarized below as it included higher doses of NKTR-181 than Study 05.

In Study 15, a dose-dependent relationship was observed for both NKTR-181 and oxycodone. A higher incidence of AEs was reported following treatment with oxycodone (40 and 60 mg) and NKTR-181 1200 mg than with NKTR-181 400 and 600 mg (Table 35). Euphoric mood, somnolence, and dizziness were reported approximately 2 times more frequently for oxycodone 40 and 60 mg than NKTR-181 400 and 600 mg. Similarly, pruritus, nausea, and vomiting were reported more frequently following exposure to oxycodone 40 and 60 mg than to NKTR-181 400 and 600 mg.

Of note, euphoric mood, an AE indicative of abuse potential, was the most frequently reported AE in Study 15. While the incidence of euphoric mood with the 1200 mg dose of NKTR-181 (2-3 times the highest doses studied in Phase 3 studies) was similar to the incidence with oxycodone 40 and 60 mg, the time to onset was longer for NKTR-181 1200 mg; the mean time from drug administration to the appearance of euphoric mood was 1.2 hours following NKTR-181 1200 mg compared with 0.6 and 0.7 hours for oxycodone 40 and 60 mg, respectively (Table 36).

Table 35. Adverse Events Experienced by ≥ 5% of Subjects in Any Treatment Group in Study 15

	Patients, n (%)					
	NKTR-181			Oxycodone		Placebo N = 61
	400 mg N = 59	600 mg N = 62	1200 mg N = 62	40 mg N = 60	60 mg N = 62	
Subjects reporting ≥ 1 AE	26 (44.1)	35 (56.5)	50 (80.6)	43 (71.7)	49 (79.0)	13 (21.3)
Euphoric mood	10 (16.9)	17 (27.4)	31 (50.0)	33 (55.0)	29 (46.8)	2 (3.3)
Pruritus	1 (1.7)	8 (12.9)	19 (30.6)	13 (21.7)	24 (38.7)	0
Nausea	5 (8.5)	3 (4.8)	12 (19.4)	8 (13.3)	9 (14.5)	2 (3.3)
Headache	5 (8.5)	3 (4.8)	6 (9.7)	3 (5.0)	7 (11.3)	4 (6.6)
Somnolence	3 (5.1)	3 (4.8)	6 (9.7)	7 (11.7)	10 (16.1)	1 (1.6)
Vomiting	3 (5.1)	0	9 (14.5)	4 (6.7)	6 (9.7)	0
Feeling abnormal	2 (3.4)	4 (6.5)	0	0	0	0
Dry mouth	0	1 (1.6)	4 (6.5)	1 (1.7)	1 (1.6)	0
Pruritus generalized	1 (1.7)	0	3 (4.8)	4 (6.7)	3 (4.8)	0
Dizziness	1 (1.7)	0	1 (1.6)	3 (5.0)	2 (3.2)	0

Table 36. Time to Onset of Euphoric Mood in Study 15

Onset of Euphoric Mood (hours post-dose)	NKTR-181			Oxycodone		Placebo N = 61
	400 mg N = 59	600 mg N = 62	1200 mg N = 62	40 mg N = 60	60 mg N = 62	
n	10	17	31	33	29	2
Mean (SD)	1.7 (1.4)	1.7 (1.4)	1.2 (0.7)	0.6 (0.3)	0.7 (0.5)	0.6 (0.2)

7.5 Deaths

One patient in Study 07, a 66-year-old male, died during the open-label Titration Period (Day 6) from a cerebrovascular accident; the patient had initiated study treatment on 100 mg NKTR-181 q12h. The time of last dose before the fatal event is unknown. The patient had a history of hypertension and hypercholesterolemia and was a non-smoker. The Investigator considered the event to be unlikely related to study drug. A narrative for this patient is provided in Appendix 9.

No other fatality occurred during the NKTR-181 clinical development program.

7.6 Adverse Events of Special Interest (Study 04, Study 07, and/or Study 08)

7.6.1 Hepatic Safety

In Studies 04 and 07, 1.0% of patients receiving at least 1 dose of NKTR-181 experienced an alanine aminotransferase (ALT) value ≥ 3 × upper limit of normal (ULN); 1.6% of patients in Study 08 experienced an ALT value ≥ 3 × ULN. Inspection of the data confirmed that none of the cases met the criteria of Hy's Law for drug-induced liver injury. One patient in Study 08, who was in the placebo group of Study 07, had biochemical abnormalities consistent with Hy's Law but did not fulfill the criteria for Hy's Law because acute hepatitis B was serologically proven as the cause of the liver function test abnormalities. The patient discontinued from the study because of the hepatitis B prior to complete resolution of the associated laboratory abnormalities.

Importantly, in all cases, the liver function test abnormalities occurred relatively early during dosing, principally while doses were being titrated to achieve optimal pain control. The ALT increases were generally transient and returned towards baseline whether drug was stopped or continued. This suggests that NKTR-181's effects on liver function, if any, are transient.

An independent review of liver function abnormalities was conducted by an external hepatologist with expertise in drug-induced liver injury to determine whether there was a pattern to the liver test abnormalities or evidence of apparent drug effect from NKTR-181. Patient profiles (including medical history, concomitant medications, AEs, and key laboratory and safety data) for patients in the Phase 2 or 3 studies who had 1 or more elevations in ALT or aspartate aminotransferase (AST) to ≥ 5 × ULN or repeated (ie, 2 or more) elevations in ALT or AST to ≥ 3 × ULN were reviewed. The reviewer concluded that the elevations likely represent an acute effect of hepatic adaptation to the drug load.

7.6.2 Cardiac Safety

Cardiac safety was monitored throughout the clinical studies. The results consistently showed that ECG parameters including PR, QRS, and corrected QT intervals, Fridericia's correction (QTcF) intervals, and heart rate were not significantly impacted by NKTR-181 administered at therapeutic doses.

In Study 04 and Study 07, overall changes from baseline were minimal and not clinically relevant for any ECG parameter assessed at the end of titration and the end of treatment time points (Appendix 8, Table A-9). No safety signal was apparent for NKTR-181 with regards to cardiac rate or rhythm. Notably, QTcF > 500 msec and increases in QTcF > 60 msec occurred in only 1 patient during open-label titration and no patients during double-blind treatment.

Similar to the controlled studies, in the long-term safety study (Study 08), overall changes from baseline were minimal and not clinically relevant for all ECG parameters. NKTR-181 was shown to have no potential to prolong corrected QT (QTc) interval to a significant extent at therapeutically relevant plasma concentrations. Two patients had QTcF interval > 500 msec, and 4 patients had increases of > 60 msec.

Cardiac safety is also supported by data from HAP Study 15 (Section 5.3.2), in which no significant change in QTcF or other ECG parameters was observed following administration of up to 1200 mg of NKTR-181 (2-3 times the highest doses studied in Phase 3 studies) in concurrence with C_{max}. Upon review of the data from Study 15, the FDA confirmed that a thorough QT study was not required based on the currently known worst case scenario of a drug-drug interaction with strong CYP3A4 inhibitors.

Overall, clinical experience with NKTR-181 indicates a minimal risk for QTc prolongation, torsade de pointes, and other cardiac AEs.

7.6.3 CNS-Mediated Adverse Events

Because the CNS kinetic properties of NKTR-181 were hypothesized to reduce the risk of CNS-mediated side effects, these types of AEs were investigated. A list of 84 AEs that could be described as having a CNS-mediated etiology and representing clinically important manifestations of opioid-related CNS activation or suppression were identified by consensus among 3 independent reviewers from the clinical database. The most common CNS-mediated AEs (occurring in > 0.5% of any treatment group) in Study 07 and Study 08 are shown in Table 37; a complete list can be found in Appendix 8, Table A-10.

During the Treatment Period in Study 07, the incidence of CNS-mediated AEs was 26.2% for NKTR-181 and 17.6% for placebo, with a greater incidence of nausea, vomiting, somnolence, dizziness, and dry mouth being reported for NKTR-181. However, these events occurred in 2 to 10% of patients treated with NKTR-181, only 2 to 4 percentage points higher than the incidence in the placebo group. In Study 08, CNS-mediated AEs were reported in approximately 37.3% of patients.

Table 37. CNS-Mediated Adverse Events in > 0.5% of Patients Receiving NKTR-181 in Study 07 and Study 08

	Patients, n (%)			
	Study 07			Study 08
	Open-Label Titration	Double-Blind Treatment		
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301	NKTR-181 N = 638
Patients with ≥ 1 CNS-mediated AE	469 (39.4)	81 (26.2)	53 (17.6)	238 (37.3)
Nausea	176 (14.8)	32 (10.4)	18 (6.0)	76 (11.9)
Somnolence	107 (9.0)	8 (2.6)	1 (0.3)	31 (4.9)
Vomiting	67 (5.6)	15 (4.9)	5 (1.7)	35 (5.5)
Dry mouth	66 (5.6)	7 (2.3)	1 (0.3)	18 (2.8)
Fatigue	61 (5.1)	4 (1.3)	1 (0.3)	13 (2.0)
Pruritus	52 (4.4)	2 (0.6)	0	21 (3.3)
Dizziness	47 (4.0)	7 (2.3)	1 (0.3)	19 (3.0)
Drug withdrawal syndrome	32 (2.7)	14 (4.5)	12 (4.0)	38 (6.0)
Sedation	20 (1.7)	0	1 (0.3)	4 (0.6)
Insomnia	19 (1.6)	4 (1.3)	5 (1.7)	17 (2.7)
Hyperhidrosis	15 (1.3)	0	1 (0.3)	2 (0.3)
Decreased appetite	13 (1.1)	4 (1.3)	1 (0.3)	8 (1.3)
Hot flush	12 (1.0)	3 (1.0)	3 (1.0)	8 (1.3)
Feeling abnormal	12 (1.0)	0	0	3 (0.5)
Pruritus generalised	12 (1.0)	0	0	5 (0.8)
Irritability	10 (0.8)	2 (0.6)	1 (0.3)	9 (1.4)
Anxiety	9 (0.8)	1 (0.3)	4 (1.3)	12 (1.9)
Euphoric mood	8 (0.7)	0	1 (0.3)	2 (0.3)
Lethargy	7 (0.6)	0	0	6 (0.9)
Vertigo	2 (0.2)	0	1 (0.3)	4 (0.6)
Depression	1 (<0.1)	4 (1.3)	2 (0.7)	12 (1.9)
Libido decreased	1 (<0.1)	0	1 (0.3)	4 (0.6)
Syncope	0	2 (0.6)	0	1 (0.2)

7.6.4 Respiratory Depression

Respiratory depression is a known opioid-related AE. Notably, there were no AEs of respiratory depression observed across the entire NKTR-181 clinical development program with doses up to 1200 mg.

Across the clinical development program, oxygen saturation monitoring was conducted during 11 Phase 1 studies. Among these studies, AEs of oxygen saturation decreased were reported in 6 subjects who received NKTR-181 in the multiple ascending dose studies.

One subject in Study 02, who received 400 mg NKTR-181 q12h, experienced a transient AE of mild oxygen saturation decreased on Day 4. No corresponding oxygen saturation value was available.

In Study 11, AEs of oxygen saturation decreased were reported in 5 subjects (1 subject in the 400 mg cohort and 4 subjects in the 500 mg cohort). Nadir oxygen saturation levels in these subjects ranged from 80 to 89%. The events were transient and were treated with 0.5 to 2 liters oxygen per nasal cannula.

It is important to note that subjects in these studies were not titrated in 100 mg increments to their assigned dose, as recommended in the proposed label. Rather, dosing for the 400 mg cohort was at first initiated at 400 mg q12h with no titration. Based on opioid-type AEs experienced with such dosing, NKTR-181 200 mg q12h was given for 2 days prior to administration of 500 mg q12h. For the 4 subjects in the 500 mg cohort, the oxygen desaturation events occurred during administration of the 500 mg dose, not the 200 mg dose.

In line with opioid class labeling, the proposed NKTR-181 label will contain the following statement: Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase.

7.6.5 Opioid Withdrawal Assessment

In the Phase 3 studies, COWS and SOWS assessments were conducted as prospective evaluations of the severity of withdrawal signs and symptoms associated with cessation of NKTR-181; AEs and medications related to withdrawal symptoms were also evaluated.

7.6.5.1 COWS

The COWS is a clinician-reported assessment of 11 physical components of withdrawal, evaluated through observations and questions (Appendix 10). Total COWS scores range from 0 to 48, with higher scores indicating greater severity of withdrawal.

In Study 07, the COWS assessment was performed 1 week following randomization (Day 8). As shown in Table 38, nearly all placebo patients (97.6%) were free from withdrawal symptoms 1 week following abrupt discontinuation of NKTR-181, a similar proportion to NKTR-181 patients (99.0%) who continued to receive active drug. The 7 placebo patients who had withdrawal symptoms had mild symptoms. COWS was administered again following the

12-week double-blind Treatment Period and the 1-week taper (Day 91), during which all patients in the NKTR-181 group received a dose of 100 mg q12h. There was little indication of withdrawal symptoms following the reduction in NKTR-181 dose, as the proportion of NKTR-181 patients who were symptom-free was 97.7% at the end of the 1-week taper.

Table 38. Clinical Opiate Withdrawal Scale Assessments in Study 07

Patients with Withdrawal Symptoms		Patients, n (%)	
		Double-Blind Treatment	
		NKTR-181 N = 309	Placebo N = 301
1-week post-randomization (Day 8)	N	295	291
	None	292 (99.0)	284 (97.6)
	Mild	3 (1.0)	7 (2.4)
	Moderate/Moderately severe/Severe	0	0
End of taper (Day 91)	N	218	220
	None	213 (97.7)	219 (99.5)
	Mild	5 (2.3)	1 (0.5)
	Moderate/Moderately severe/Severe	0	0

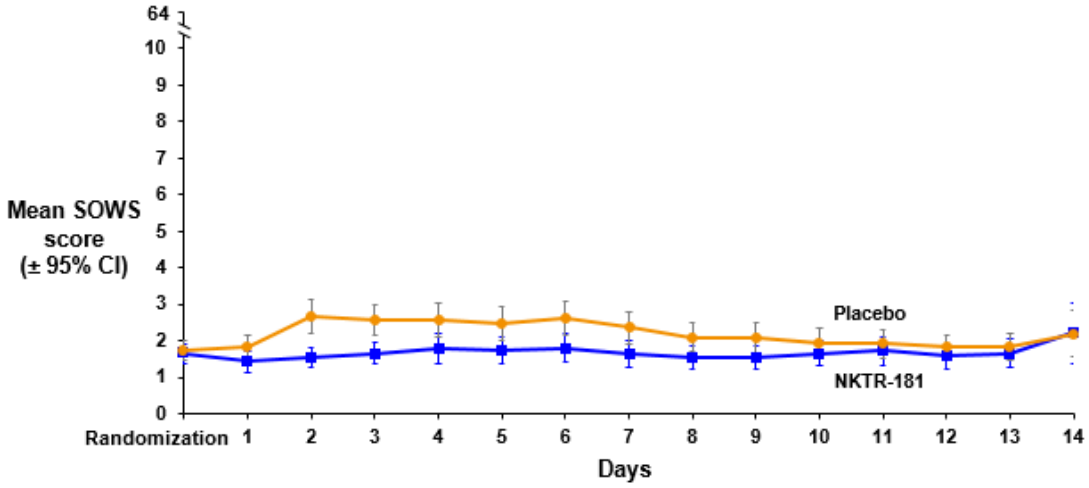
COWS total scores range from 0 to 48, with higher scores indicating greater severity as follows: < 5: no withdrawal; 5-12: mild withdrawal; 13-24: moderate withdrawal; 25-36: moderately severe withdrawal; > 36: severe withdrawal.
COWS = Clinical Opiate Withdrawal Scale

7.6.5.2 SOWS

The SOWS is a self-administered, patient-reported assessment of 16 opiate withdrawal symptoms (Appendix 11). Total SOWS scores range from 0 to 64, where 0 indicates no symptoms across all items and 64 indicates extreme symptoms on all items.

SOWS assessments were recorded by patients at randomization (Day 1) and the days immediately following through Day 15. Placebo patients had a maximal mean 1.1-point increase in SOWS score following withdrawal of NKTR-181, suggesting a minimal change in symptoms of opioid withdrawal (Figure 38). At the end of the Treatment Period, NKTR-181 patients exhibited ≤ 0.7-point change in SOWS during treatment taper.

Figure 38. Subjective Opiate Withdrawal Scores Following Randomization in Study 07



SOWS total score ranges from 0 to 64 where 0 indicates no symptoms across all items and 64 indicates extreme symptoms on all items.
CI = confidence interval; SOWS = Subjective Opiate Withdrawal Scale

7.6.5.3 Investigation of AEs and Medications Related to Withdrawal Symptoms

Two additional analyses were conducted to investigate opioid withdrawal in Study 07 and Study 08; the first used an SMQ to search for drug-withdrawal-related AEs reported after the last dose of NKTR-181, and the second investigated the use of medication for the treatment of withdrawal symptoms after NKTR-181 discontinuation.

As shown in Table 39, the incidence of patients exhibiting withdrawal in both of these analyses was low. Among the 10 withdrawal-related Preferred Terms queried, drug withdrawal syndrome was the only Preferred Term reported, occurring in < 6% of patients. An even lower percentage of patients used medications, primarily for diarrhea, headache, and drug withdrawal syndrome; drug withdrawal syndrome was the reason for medication use for 1 patient in the open-label Titration Period and 2 placebo-treated patients in the double-blind Treatment Period of Study 07 and 2 patients in Study 08.

Table 39. Opioid-Withdrawal Related AEs and Medication Use in Study 07 and Study 08

	Patients, n (%)			
	Study 07			
	Open-Label Titration	Double-Blind Treatment		Study 08
	NKTR-181 N = 579	NKTR-181 N = 309	Placebo N = 301	NKTR-181 N = 638
Reporting ≥ 1 AE in opioid withdrawal SMQ[a]	31 (5.4)	10 (3.2)	12 (4.0)	37 (5.8)
Using medication for treatment of withdrawal symptoms[b]	12 (2.1)	3 (1.0)	11 (3.7)	15 (2.4)

a. AE occurred after last dose of NKTR-181.
b. Use of medications was within 12 days after cessation of NKTR-181 treatment.
SMQ = standardized MedDRA query

Overall, the Phase 3 study data suggest that the long half-life of NKTR-181 and its CNS kinetic properties provide a safety margin for patients who discontinue treatment.

7.6.6 Events Potentially Associated with Opioid Abuse, Misuse, or Diversion in Patients with Chronic Pain

7.6.6.1 Misuse, Abuse, and Diversion Drug Event Reporting System

In Study 07 and Study 08, potentially aberrant drug behavior was identified, assessed, and quantified using MADDERS® to specifically monitor those events that could be associated with opioid abuse, misuse, or diversion (Smith et al. 2013). MADDERS® is a methodology for systematically identifying, evaluating, and classifying potentially abuse-related events in clinical trials. Investigators were trained to identify and report any potentially abuse-related event at the time the event is identified throughout the duration of the study. All reported events were reviewed by an independent adjudication committee for final classification into 1 of 6 subcategories (abuse, misuse, suicide-related, therapeutic error, none of the above, or unknown) and supplemental classification (Tampering, Withdrawal, Addiction-related Behavior, Diversion, or Overdose).

The incidence of total MADDERS events was similar during both Titration and Treatment Periods of Study 07 and higher during Study 08 (Table 40). The majority of events across the 2 studies were adjudicated as none of the above, meaning that sufficient information was provided for each of these events to rule out misuse, abuse, suicide-related, and therapeutic error as the cause of the event. Importantly, during the double-blind Treatment Period of Study 07, the rates of total MADDERS events and those adjudicated as related to abuse or misuse were similar between NKTR-181 and placebo.

Table 40. Adjudicated MADDERS Events in Study 07 and Study 08

	Study 07			Study 08
	Open-Label Titration	Double-Blind Treatment		
	NKTR-181 N = 1189	NKTR-181 N = 309	Placebo N = 301	NKTR-181 N = 638
Number of adjudicated events, n	51	19	16	59
Patients with adjudicated events, n (%)	48 (4.0)	17 (5.5)	14 (4.7)	51 (8.0)
Abuse	3 (0.3)	0	2 (0.7)	4 (0.6)
Misuse	9 (0.8)	3 (1.0)	3 (1.0)	1 (0.2)
Suicide-related	0	0	0	0
Therapeutic error	6 (0.5)	3 (1.0)	0	3 (0.5)
None of the above[a]	28 (2.4)	9 (2.9)	9 (3.0)	39 (6.1)
Unknown	3 (0.3)	3 (1.0)	1 (0.3)	6 (0.9)

a. Sufficient information was provided to determine that the event did not meet the primary classification listed above, ie, abuse, misuse, suicide-related, or therapeutic error.

7.6.6.2 Adverse Events Associated with Opioid Abuse

Targeted safety analyses were conducted to describe the incidence of AESIs associated with opioid abuse, misuse, or diversion. No AEs of intentional product misuse (the only Preferred Term associated with the topic of Misuse) or drug diversion (the only Preferred Term associated with the topic of Diversion) occurred at any time during the Phase 2 and 3 studies. Four patients reported a total of 4 AEs relating to abuse and dependence (defined on the basis of an SMQ, inclusive of 34 Preferred Terms) – accidental overdose, toxicity to various agents, drug abuse, and drug dependence. All 4 events resolved and are summarized below. A narrative for the accidental overdose is provided in Appendix 9.

- Accidental overdose was reported in a 21-year-old female patient during the Titration Period of Study 07. She was instructed to take 1 tablet from each of 2 study medication cards (NKTR-181 and placebo) every 12 hours, but took 2 tablets from the same card, using the cards in succession. Thus, she either received double the dose for 5 days and 3 days of placebo or vice versa instead of the intended 100 mg q12h. The site reported the accidental misuse as an overdose as the dose she received was higher than intended for that period although within the protocol defined range of study doses. The "overdose" was considered mild, non-serious, and unrelated to study drug. The event was considered resolved with no action taken. No other sign or symptom associated with the overdose was reported. The MADDERS adjudication committee assessed the event with a primary

classification of "therapeutic error" and a supplemental classification of "overdose." This case is consistent with a medication error and not a clinical AE of overdose.

- Toxicity to various agents was reported for a 64-year-old female who enrolled in Study 07 with a history of CLBP, osteopenia, migraines, and hypothyroidism. Concomitant medications included ibuprofen, cyclobenzaprine, alendronate, Imitrex, topiramate, and levothyroxine. She initiated NKTR-181 100 mg q12h on 31-Mar-2016. Laboratory results that day showed an ALT of 334 U/L (normal range 0-48), AST 288 U/L (normal range 0-42), total bilirubin 6 µmol/L (normal range 0-22), and alkaline phosphatase 139 U/L (normal range 20-125). On 04-Apr-2016, she had an ALT of 179 U/L, AST 77 U/L, total bilirubin 8 µmol/L, and alkaline phosphatase 137 U/L and was diagnosed with acetaminophen toxicity (coded to "toxicity to various agents") of moderate severity, which was considered not related to study drug. The event reportedly resolved on 14-Apr-2016. NKTR-181 was continued and titrated to 400 mg q12h; the patient did not qualify for entry into the double-blind Treatment Period. The dose and duration of acetaminophen treatment were unknown.
- Drug abuse was reported for a 57-year-old female who enrolled in Study 08 after rolling over from prior participation in Study 07. Her medical history included CLBP, anxiety, and depression. Concomitant medications included lorazepam and sertraline. She began treatment in Study 08 on 07-Jul-2016 and was titrated to a stable dose of 400 mg q12h. On 30-Oct-2016, she was reported to have used cocaine and THC, which was coded to drug abuse. As the abuse involved cocaine and marijuana, it was considered unrelated to NKTR-181. However, treatment with NKTR-181 was discontinued on 03-Nov-2016 because of the abuse of cocaine and marijuana.
- Drug dependence was reported in a 39-year-old male patient who enrolled in Study 08. His medical history included CLBP, anxiety, depression, and hyperlipidemia. Prior treatment for CLBP included hydrocodone/acetaminophen, which was discontinued 4 days prior to the first dose of NKTR-181. He began treatment with NKTR-181 on 16-Mar-2016 and was titrated to a stable dose of 600 mg q12h. On 04-Apr-2016 and 10-Apr-2016, he reported mild euphoria and mild feelings of craving, respectively. The craving was coded to drug dependence and considered related to study drug. The dose of study drug was not changed. The AE of craving persisted until he withdrew from the study. His last dose of study drug was on 13-Jul-2016, at which time the feeling of craving was resolving (euphoria resolved by 15-Jun-2016). The same day as the last dose of study drug, he reported moderate anxiety, muscle aches, and craving which were interpreted as opioid withdrawal. Treatment was initiated 14-Jul-2016 with ibuprofen 800 mg q12h, and the opioid withdrawal resolved on 27-Jul-2016.

7.6.7 Overdose

There is no clinical experience with NKTR-181 overdosage in humans. As detailed in Section 7.6.6.2, a site reported an AE of "accidental overdose"; however, the event was adjudicated as consistent with a medication error and not a clinical AE of overdose.

While there are no clinical data evaluating overdose in humans, the effects of high doses of NKTR-181 (ranging from 800 to 1200 mg) were evaluated in a Phase 1 single-ascending dose study (Study 10) in 36 healthy subjects. Severe AEs were reported in 5 subjects, all of whom were receiving the 1200 mg dose: severe vomiting in 3 subjects, severe nausea in 1 subject, and severe syncope in 1 subject. In terms of AEs typically associated with opioid overdose, 5 AEs of hypotension (2 in the 800 mg group and 3 in the 1000 mg group) were observed. All events were mild, lasted 1 or 2 days, and resolved. In terms of other AEs typically associated with opioid overdose, there were no AEs of respiratory depression, pupil constriction, bradycardia, pulmonary edema, or airway obstruction.

7.7 Safety Conclusions

In summary, NKTR-181 has a favorable safety profile, with a low rate of CNS-mediated AEs and withdrawal symptoms in patients with CLBP. In the pivotal 12-week double-blind placebo-controlled Phase 3 study (Study 07), most AEs were mild to moderate in severity and consistent with the types of AEs commonly associated with opioids. Serious AEs were infrequent and generally unrelated to NKTR-181. The safety of NKTR-181 is supported by the 52-week long-term exposure study, Study 08. No cases of respiratory depression occurred in the clinical program, and no clinically meaningful hepatic or cardiac safety signals were observed.

The incidence of CNS-mediated AEs was low in the Phase 3 studies. Additionally, there was minimal evidence of opioid withdrawal and minimal evidence of abuse or misuse of NKTR-181. Overall, the unique physicochemical properties of NKTR-181 demonstrated the potential for a low incidence of CNS-mediated AEs and low risk for opioid withdrawal symptoms.

8 RISK MANAGEMENT PLAN

8.1 Opioid Analgesic Risk Evaluation and Mitigation Strategy

As with any MOR agonist, NKTR-181 has risks of misuse, addiction, and abuse. Nektar will participate in the opioid analgesic REMS programs to reduce and mitigate the risk for serious adverse outcomes resulting from inappropriate prescribing, misuse, or abuse of NKTR-181.

8.2 Post-Marketing Activities

Beyond involvement in the opioid analgesic REMS programs, Nektar proposes to initiate additional activities to understand the use of NKTR-181:

- Use of "real-world evidence" sources, such as a patient registry, to characterize prescribing practices and risks associated with NKTR-181.
- Conduct broadened surveillance monitoring from existing data collection systems (eg, RADARS, NAVIPPRO) to enable early detection of attempts in the community to manipulate NKTR-181 for misuse or abuse and to distinguish risks associated with NKTR-181 from other opioid agonists.
- Identify additional educational needs of the healthcare community not presently addressed by the current opioid analgesic REMS programs (eg, tools for prescribers, patients, and communities to identify addiction and abuse behavior in patients).
- Systematic surveillance of social media (Facebook, Twitter, Bluelight.nu etc.) as another tool to understand any potential misuse abuse and diversion activity that may arise post-approval

Summaries of the above surveillance activities will be reported to the FDA. In addition, Nektar will perform routine pharmacovigilance activities in the post-marketing setting to collect, assess, and report AEs of new safety signals based on spontaneous reports received from patients, caregivers, and healthcare providers; AEs and SAEs from clinical studies; and new safety findings from literature monitoring.

9 BENEFIT-RISK SUMMARY

9.1 Clinical Context of Chronic Low Back Pain

CLBP is a common debilitating condition that affects millions of patients in the US. The ubiquity of CLBP and the paucity of new treatment options for effective pain management underscores the need for new therapies to improve the care of patients affected by CLBP. As stated by the Institute of Medicine, "overcoming the barriers to improved pain care" requires "a greater commitment to assessing and treating pain effectively, and enhanced recognition of the highly individual ways in which people experience pain and respond to treatment" (Institute of Medicine 2011). For patients who do not receive sufficient relief with non-opioid interventions, opioid analgesics represent an important treatment option. The availability of a novel opioid medicine that relies on physicochemical structure and not formulation to provide effective analgesia with a reduced potential for abuse and misuse and has a low incidence of CNS-mediated side effects and opioid withdrawal, would provide an incremental improvement in the management of CLBP and clinically meaningful pain relief for appropriately selected patients.

9.2 Summary of Benefits

NKTR-181 has demonstrated the following benefits for patients with CLBP:

- *Effective analgesia*: In Phase 3 studies, NKTR-181 provided meaningful and sustained analgesia in patients with CLBP with significant improvement on primary and key secondary efficacy endpoints. Pain reduction with NKTR-181 was accompanied by favorable findings on patient assessment of global change and quality of sleep, as well as reduced use of rescue medications. Analgesia was maintained in patients in the long-term safety study with no need for dose increases in most patients, suggesting a lack of analgesic tolerance to NKTR-181. When NKTR-181 was taken with or without food, there was no impact on drug exposure PK profile.
- *Lower potential for abuse than oxycodone*: Although any MOR agonist involves the risk of abuse, NKTR-181 has a slower rate of entry into the brain and slower MOR binding in comparison to oxycodone, which makes NKTR-181 less attractive for abuse. Overall, the data from the studies to assess abuse potential demonstrated that NKTR-181 has a lower abuse potential profile when compared to oxycodone. The 2 oral HAP studies showed that maximum Drug Liking was statistically significantly lower for therapeutic doses of NKTR-181 (100 to 600 mg) than for oxycodone (40 and 60 mg), and the onset of Drug Liking was more gradual for all doses of NKTR-181 than for oxycodone over the first 3 hours post-dose. The time profile of Drug Liking correlates with the unique CNS kinetic properties inherent to the NKTR-181 molecule. In the NKTR-181 clinical studies, a low incidence of potentially aberrant drug behavior and abuse-related AEs was observed with up to 52 weeks of treatment.

For individuals seeking the rapid and powerful euphoric state induced by opioids and enhanced by product manipulation and non-oral administration, NKTR-181 would be expected to be less attractive owing to its slower rate of entry into the brain and slower MOR binding relative to oxycodone. Because NKTR-181's CNS kinetic properties are inherent to the molecule rather than the tablet formulation, they are expected to be maintained even when the tablet is manipulated via crushing or extraction. To date, Nektar has not identified any chemical, enzymatic, or thermal method that is effective in converting NKTR-181 into a more active opioid derivative.

- *Low incidence of CNS-mediated AEs*: The unique physicochemical properties of NKTR-181 results in low rates of CNS-mediated AEs, as demonstrated in the Phase 3 clinical studies.

  In the oral HAP Study 15, NKTR-181 at dose levels of 400 and 600 mg was associated with a 50% reduction in AEs of euphoric mood, somnolence, and dizziness compared with 40 and 60 mg oxycodone.

- *Low incidence of withdrawal symptoms*: Withdrawal symptoms associated with NKTR-181 were infrequent and mild as demonstrated in the Phase 3 clinical studies.

The benefits of NKTR-181 and their potential impact on public health are outlined in Table 41. The lower abuse potential of NKTR-181 compared with oxycodone and the low incidence of withdrawal symptoms and CNS-mediated AEs represent distinct safety advantages over currently marketed opioids – an important consideration in FDA's guidance on comparative benefit-risk framework for assessment of new opioids (FDA 2019a).

Table 41. Summary of Public Health Considerations on the Benefits of NKTR-181

Key Properties of NKTR-181	Key Considerations for Public Health
Effective Analgesia • In Phase 3 studies in patients with CLBP, NKTR-181 showed meaningful and sustained analgesia in CLBP, supported by positive analyses on primary endpoints, with supportive evidence from secondary efficacy endpoints of pain and quality of life. • Phase 1 PK study has shown NKTR-181 can be taken with or without food with no impact on drug exposure.	Effective Analgesia • Chronic pain is challenging to treat, in part because of the limitations in all existing treatment options. • NKTR-181 provides durable analgesia and improved quality of life for patients with CLBP who are unable to gain adequate pain relief with alternative therapies
Lower Potential for Abuse than Oxycodone • Nonclinical studies demonstrated that NKTR-181 has a slower rate of brain uptake and slower MOR activation. compared to oxycodone and a lower degree of drug-discrimination and self-administration in animals compared with oxycodone and morphine. • On multiple measures of abuse potential in 2 oral HAP studies of recreational opioid users, NKTR-181 therapeutic doses of 100 to 600 mg have shown a lower risk for abuse compared with oxycodone (40 and 60 mg). • All methods applied to date were incapable of efficiently converting NKTR-181 to more active MOR agonist derivatives. • NKTR-181 has shown a low incidence of events relating to abuse, misuse, and diversion in clinical studies of patients with chronic pain.	Lower Potential for Abuse than Oxycodone • Approximately 20-30% of those prescribed opioids for chronic pain misuse them; 8-12% develop an opioid use disorder, which has been reported in nearly 2 million US adults (Han et al. 2017; SAMHSA 2017; Vowles et al. 2015). • NKTR-181 could provide an improvement for patients with CLBP by reducing the risk for abuse by lessening the CNS side effects, such as euphoric affects, that may lead to the transition from safe use to opioid misuse and opioid use disorder. • Because of NKTR-181's inherent physicochemical properties, having NKTR-181 available in the community may substitute for other opioid products which are more susceptible to abuse, misuse, and addiction.
Low Incidence of CNS-mediated AEs • NKTR-181 has a slower rate of entry into the brain than oxycodone, designed to delay the onset of CNS side effects and make it less attractive for abuse. • A low rate of CNS-mediated AEs was found in Phase 3 clinical studies and remained low in the 52-week long term safety study.	Low Incidence of CNS-mediated AEs • Available MOR opioids carry risk for CNS-mediated AEs that can negatively affect functionality and productivity (Noble et al. 2010; Sloot et al. 2015; Villars et al. 2007), leading to discontinuation of effective analgesic therapy. • Low rate of CNS-mediated AEs with NKTR-181 may lessen the risk for negative effects on cognition and activities of daily living.
Low Incidence of Dependence and Withdrawal • In a nonclinical rat study, there was evidence of lower withdrawal/dependence symptoms with NKTR-181 than morphine. • A low rate of withdrawal symptoms was found in Phase 3 clinical studies. • Results from the 52-week long-term clinical safety study suggest that patients do not develop tolerance to NKTR-181 over time.	Low Incidence of Dependence and Withdrawal • With conventional opioids, drug tolerance can develop rapidly with escalating dose requirements accompanied by withdrawal symptoms upon discontinuation. • NKTR-181 has shown a differentiated safety profile in terms of low dependence and withdrawal effects (ie, low frequency and mild to moderate severity) and a reduced need for continued dose increases in a chronic setting that could help to fill an important medical need.

9.3 Summary of Risks

While NKTR-181 is characterized by a lower abuse potential profile as compared with oxycodone, since it is a MOR agonist, NKTR-181 carries the risk of misuse, abuse, and opioid use disorder (addiction). As such, Nektar proposes black box warnings for NKTR-181 in line with other opioid analgesics until further data demonstrate otherwise.

Although NKTR-181 resulted in a low incidence of some opioid AE class effects in Phase 3 studies, such as CNS-mediated side effects and abuse or misuse, it has several known or anticipated risks inherent to all opioids. These include life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; CYP3A4 interaction; and risks from concomitant use with benzodiazepines or other CNS depressants. Other potential risks include addiction, abuse, and misuse, which may lead to overdose and death. However, the physicochemical properties of NKTR-181 are inherent to its molecular structure and are expected to be retained regardless of route of administration or product manipulation. Importantly, no AEs of respiratory depression were reported in any NKTR-181 study, and no evidence of cardiac signals or QT interval prolongation-related safety concerns were identified. NKTR-181 uses excipients commonly used for currently marketed immediate-release tablet formulations and is not expected to result in increased safety risk from alternative route of administration in comparison to other oral opioid tablets (eg, oxycodone tablets).

Key risk management measures planned include the following:

- Clear warnings and precautions will be outlined in the prescribing information for opioid use disorder (addiction), abuse, and misuse (including abuse by non-intended routes), life-threatening respiratory depression, accidental ingestion, neonatal opioid withdrawal syndrome, CYP3A4 interaction, and risks for concomitant use with benzodiazepines or other CNS depressants.
- Nektar will participate in the opioid analgesic REMS programs and conduct routine pharmacovigilance activities.
- Additionally, Nektar will work with the FDA to develop additional post-marketing plans to monitor the use of NKTR-181 and to confirm that the risk mitigations put in place to minimize inappropriate prescribing, misuse, and abuse of NKTR-181 have their intended effect in real-world settings.

9.4 Overall Conclusion

Overall, NKTR-181 (oxycodegol) is an NME novel opioid therapy for the management of moderate to severe CLBP for which alternative treatment options are inadequate. NKTR-181 provides opioid-level analgesia together with a lower potential for abuse compared to oxycodone and a low incidence of CNS-mediated side effects and withdrawal symptoms due to its unique inherent physicochemical properties. Due to its unique CNS kinetic properties, patients receiving NKTR-181 at the therapeutic dose range (100 to 600 mg) are less likely to experience euphoric and withdrawal effects, which place individuals at risk for misuse and abuse. NKTR-181 is an

effective opioid analgesic treatment option for patients with CLBP in critical need of pain relief, and thereby provides an incremental comparative benefit over currently marketed opioids due to NKTR-181's inherent properties associated with lower abuse potential and low withdrawal symptoms (Table 42).

Table 42. Benefit and Risk Assessment of NKTR-181 for Treating CLBP

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Uncontrolled CLBP is a leading cause of disability • Long-term benefit-risk of opioids for treating CLBP derived from short-term blinded and controlled studies	• Patients with CLBP who fail other therapies need effective analgesics that diminish barriers and liabilities of current opioids
Current Treatment Options	• Multi-factorial therapies should be used to control pain • Opioids are a treatment option when unable to achieve acceptable analgesia with alternative therapies • Approved opioid products can be manipulated to accelerate and increase drug liking	• Guidelines support conservative opioid use when other treatments are ineffective • Manufacturers have focused on formulation to delay the rate of rise and deter abuse

Benefit	• NKTR-181 provides MOR agonist analgesia with inherent physicochemical properties that produce slower CNS penetration and slower MOR activation
	  • Analgesic effect of full mu-opioid agonist with or without food
	  • Lower abuse potential than oxycodone
	  • Decreased rate of rise of drug liking inherent to the molecule, not dependent on formulation
	  • Less drug liking than oxycodone
	  • Cannot be efficiently converted to more abusable opioid derivatives via chemical, enzymatic, or thermal methods
	  • Low rate of CNS-mediated AEs, but not compared head-to-head
	  • Low rate of withdrawal symptoms, but not compared head-to-head
		• Incremental improvement over currently available extended-release/long-acting and ADF opioids
		  • Clinical efficacy data demonstrate efficacy in CLBP adult patients with effectiveness observed in long-term safety study; PK data conclude no food effect
		  • NKTR-181's attractiveness to recreational drug users seeking a rapid and concentrated opioid effect via non-intended route of abuse is likely to be limited because of slow CNS penetration and receptor uptake
		  • Resistant to tampering
		  • Inherent physicochemical properties result in slower CNS penetration and slower receptor activation, which lead to reduced abuse potential and low rate of CNS-mediated AEs
		  • Long elimination half-life results in the low rate of withdrawal symptoms

Risk and Risk Management	• Clear warnings and precautions for potential post-marketing safety risks applicable to the opioid class • Participation in opioid analgesic REMS programs • Work with FDA on pharmacovigilance surveillance plan to promptly identify new safety signals and monitor for abuse and misuse	• Potential risks of misuse, abuse, opioid use disorder, accidental exposure, and overdose not observed in the clinical studies • NKTR-181 is not expected to result in increased safety risk from alternative route of administration

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APPENDIX 1: LIST OF PHASE 1–3 CLINICAL STUDIES OF NKTR-181

Table A-1. List of Studies of NKTR-181

Study	Objective(s) of the Study	Study Design	Treatment Groups Randomization	N	Study Population	Duration of Treatment
01	To assess the safety, tolerability, and PK/PD profile of NKTR-181	Phase 1, first-in-human, double-blind, placebo-controlled, SAD study	Oral solutions NKTR-181 10, 20, 40, 80, 160, 320, and 500 mg Placebo 4:1 randomization ratio per cohort	N = 104: n = 83 total in NKTR-181 n = 21 placebo	Healthy Subjects	Single dose on Day 1
10	To assess the safety, tolerability, maximal tolerated single dose level, and PK/PD profile of oral doses of NKTR-181	Phase 1, double-blind, randomized, placebo-controlled, SAD study	Oral solutions NKTR-181 400, 600, 800, 1000, and 1200 mg Placebo 4:1 randomization ratio per cohort	N = 75: n = 60 total in NKTR-181 n = 15 placebo	Healthy Subjects	Single dose on Day 1
02	To assess the safety, tolerability, and PK/PD profile of NKTR-181 administered in multiple oral doses	Phase 1, double-blind, randomized, placebo-controlled MAD study	Oral solutions NKTR-181 100, 200, 300, and 400 mg q12h Placebo 4:1 randomization ratio per cohort	N = 61: n = 48 total in NKTR-181 n = 13 placebo	Healthy male subjects	8-day treatment period
11	To assess the safety, tolerability, and PK/PD profile of NKTR-181 administered in multiple oral doses	Phase 1, double-blind, randomized, placebo-controlled MAD study	Oral solutions NKTR-181 400 and 500 mg q12h Placebo 4:1 randomization ratio per cohort	N = 29 n = 23 total in NKTR-181 n = 6 placebo	Healthy subjects	14-day treatment period

Study	Objective(s) of the Study	Study Design	Treatment Groups Randomization	N	Study Population	Duration of Treatment
03	To determine the bioavailability, effect of administration with food, and safety and tolerability of NKTR-181 tablets relative to NKTR-181 oral solution	Phase 1, open-label, randomized, 4-treatment, crossover study	Oral solutions and tablets NKTR-181 oral solution 200 mg (fasted and fed) NKTR-181 oral tablet 200 mg (fasted and fed) Randomization treatment sequence	N = 24	Healthy subjects	4 treatment periods of 3 days each, with a 7-10 day washout between periods
06	To assess the PK profile of NKTR-181 and its metabolites, determine whole blood and plasma concentrations, and assess mass balance following a single dose of NKTR-181	Phase 1, open-label study	Oral solution ^{14}C-NKTR-181 400 mg No randomization	N = 8	Healthy male subjects	Single dose on Day 1
13	To assess the effect of itraconazole on the PK of a single oral dose of NKTR-181 and to assess the safety and tolerability of NKTR-181	Phase 1, open-label, 2-treatment, fixed-sequence, crossover study	Oral tablets NKTR-181 200 mg as a single dose on Day 1 Itraconazole 200 mg oral solution once daily on Days 1-8, with a single dose of NKTR-181 200 mg on Day 5 No randomization	N = 30	Healthy subjects	7-day washout between 2 treatments

Study	Objective(s) of the Study	Study Design	Treatment Groups Randomization	N	Study Population	Duration of Treatment
19	To assess the effect of rifampin on the PK of a single oral dose of NKTR-181	Phase 1, open-label, 2-treatment, fixed-sequence, crossover study	Oral tablets NKTR-181 200 mg as a single dose on Day 1 Rifampin 600 mg once daily on Days 4-16, with a single dose of NKTR-181 200 mg on Day 14 No randomization	N = 30	Healthy subjects	3-day washout between 2 treatments
14	To evaluate the PK profile of NKTR-181 after administration of different prototype formulations compared to the NKTR-181 Phase 3 formulation	Phase 1, open-label, randomized, crossover study	Oral tablets NKTR-181 200 mg prototype formulations 1, 2, and 3, Phase 3 formulation Randomized treatment sequence	N = 29	Healthy subjects	4 study periods, each from Day 1 to Day 4, followed by a 7-day washout period
16	To evaluate the PK and safety of 2 prototype formulations of NKTR-181 containing NaCMC versus the Phase 3 formulation	Phase 1, open-label, randomized, crossover study	Oral tablets NKTR-181 200 mg in the following formulations: 10% NaCMC, 7.5% NaCMC, Phase 3 formulation Randomization treatment sequence	N = 42	Healthy subjects	3 dosing periods, each with 72-hr evaluation period and a 7-day washout period

Study	Objective(s) of the Study	Study Design	Treatment Groups Randomization	N	Study Population	Duration of Treatment
05	To assess the abuse potential, safety, and tolerability of NKTR-181 compared with oxycodone IR and placebo	Phase 1, randomized, double-blind, active and placebo-controlled, crossover study	Oral solutions NKTR-181 100, 200, and 400 mg, oxycodone 40 mg, and placebo solution, each administered as a single dose Randomized treatment sequence	N = 42	Healthy, non-dependent recreational opioid users	5 dosing days, each with a single treatment followed by a 72-hr washout period
15	To assess the abuse potential, safety, and tolerability of NKTR-181 compared with oxycodone IR and placebo and assess the PK/PD of NKTR-181	Phase 1, randomized, double-blind, active and placebo-controlled, crossover study	Oral tablets NKTR-181 400, 600, and 1200 mg, oxycodone IR 40 and 60 mg, and placebo, each administered as a single dose Randomized treatment sequence	N = 69	Healthy, non-dependent recreational opioid users	6 dosing days, each with a single treatment followed by a 5-day washout period
04	To assess the analgesic effect, safety, and tolerability of NKTR-181	Phase 2, EERW, double-blind, placebo-controlled, multicenter study	Oral tablets NKTR-181 100, 200, 300, or 400 mg q12h Placebo 1:1 randomization ratio	N = 295 (Titration Period) N = 213 randomized: n = 107 NKTR-181 n = 106 placebo	Patients with moderate to severe pain due to OA of the knee, previously taking no opioid analgesics 6 months prior to screening	Open-label Titration Period of up to 30 days 21-day double-blind Treatment Period

Study	Objective(s) of the Study	Study Design	Treatment Groups Randomization	N	Study Population	Duration of Treatment
07	To assess the analgesic effect, safety, and tolerability of NKTR-181	Pivotal Phase 3, double-blind, placebo-controlled, EERW study	Oral tablets NKTR-181 100, 200, 300, or 400 mg q12h Placebo 1:1 randomization ratio	N = 1,189 (Titration Period) N = 610 randomized: n = 309 NKTR-181 n = 301 placebo	Patients with moderate to severe CLBP, previously taking ≤ 10 mg MSE/day 14 days prior to screening	Open-label Titration Period of 3-7 weeks 13-week double-blind Treatment Period (inclusive of a 1-week taper)
08	To evaluate the long-term safety, tolerability, and analgesic effect of NKTR-181	Phase 3, multicenter, open-label, 52-week study	Oral tablets NKTR-181 100, 200, 300, 400, 500, and 600 mg q12h No randomization	N = 638: n = 431 rollover patients from Study 07 n = 207 de novo patients	Rollover patients from Study 07 and de novo patients with moderate to severe CLBP or chronic noncancer pain previously taking ≤ 60 mg MSE/day 7 days prior to screening	Open-label Titration Period of ≤ 5 weeks 52-week Treatment Period (inclusive of a 1-week taper)

CLBP = chronic low back pain; EERW = enriched-enrollment, randomized-withdrawal; MAD = multiple ascending dose; NaCMC = sodium carboxymethylcellulose; OA = osteoarthritis; PD = Pharmacodynamic; PK = Pharmacokinetic; q12h = every 12 hours; SAD = single ascending dose

APPENDIX 2: ADDITIONAL INFORMATION ON HUMAN ABUSE POTENTIAL STUDIES

Appendix 2.1 Study 05 Enrollment Criteria

Inclusion Criteria:

1. Male or female subjects, 18 to 55 years of age.
2. Opioid or heroin users who were:
   - not physically dependent on opioids (based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision [DSM-IV-TR] criteria), but
   - experienced users of opioids for non-therapeutic purposes, defined as ≥ 10 occasions within the last year and at least once in the 12 weeks prior to the Screening Stage.
3. Women of childbearing potential and men agreed to use highly effective methods of birth control during the time of participation in this trial and for at least 2 months after the last dose of study drug.
4. Subjects were in good health as indicated by medical history, physical exam, vital signs, oxygen saturation, clinical laboratory tests, and 12-lead ECG. ALT/ AST were within normal limits, and creatinine clearance was ≥ 60 ml/min.
5. BMI of 19.0-33.0 kg/m^2 and weight > 55 kg.
6. Subject was able to speak, read, and understand English, and voluntarily provided written informed consent to participate in the study.

Exclusion Criteria:

1. Females who were pregnant or lactating.
2. History or current diagnosis of substance dependence (except nicotine and caffeine) or alcohol abuse, according to the criteria of DSM-IV-TR.
3. Consumption of the following drugs within 72 hours prior to Day 0: opioids of any type, including morphine-containing drugs, long-acting or sustained-release antihistamines; tranquilizers, muscle relaxants, hypnotics, anticonvulsants, monoamine oxidase inhibitors, tricyclic antidepressants, neuroleptics, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors.
4. Consumption of any substance that inhibited or induced CYP3A4 or CYP2D6 within 14 days prior to Day 0.
5. Subjects with ECG screening abnormalities deemed clinically significant by the Investigator. ECGs were repeated once to confirm eligibility.
6. Subjects with oxygen saturation value < 90% at Screening. Pulse oximetry was repeated once after the initial scheduled measurement to confirm eligibility.

7. Clinically significant abnormalities of vital signs or clinical laboratory results (including hematology, chemistry, and urinalysis).
8. Subjects with positive test results for human immunodeficiency virus, hepatitis B, or hepatitis C at Screening.
9. Subjects with a positive alcohol breathalyzer test at Screening or admission to the clinic on Day 0.
10. Subjects with a positive urine drug screen at Screening or admission to the clinic on Day 0 with the following exceptions:
    - positive urine drug screen for tetrahydrocannabinol at Screening and/or Day 0 were allowed
    - positive urine drug screen for opiates, cocaine, amphetamines, cannabinoids, and benzodiazepines at Screening were allowed
11. Subjects who did not refrain from using prohibited tobacco-containing products or nicotine-containing products during the Qualification and Treatment Stages of the study (including, but not limited to, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) and did not refrain from cigarettes within 1 hour prior to dosing and within 5 hours following dosing.
12. History of any drug allergy, hypersensitivity, or intolerance, including any opioid drug product, which, in the opinion of the Investigator, placed the subject at particular risk and compromised the safety of the subject in the study.
13. Subjects from vulnerable populations as defined by Code of Federal Regulations Title 45, Part 46, Section 46.111(b), including employees of the Sponsor and clinical site.
14. Subjects who planned to participate in another clinical trial while enrolled in this study and/or received an investigational drug and/or device within 30 days prior to Day 0.
15. Subjects who donated or had significant loss of whole blood (480 mL or more) within 30 days or plasma within 14 days prior to Day 0.
16. Subjects who took any prescription drugs, except for hormonal contraception or hormone replacement therapy, or over-the-counter medications including nutritional supplements, vitamins and herbal therapies, histamine 2 blockers, proton pump inhibitors, or antacids within 72 hours prior to Day 0, as well as those subjects who needed medications during the course of the study.
17. Acute illness within 14 days prior to Day 0.
18. History of anxiety, tension, agitation, psychiatric disorders, psychosis, or depression requiring hospitalization, psychotherapy, and/or medication within 3 years prior to Day 0.

19. History of malignancy (other than basal cell carcinoma or adequately treated carcinoma-in situ of the cervix), stroke, diabetes, or cardiac, renal, liver, or chronic pulmonary disease.

Qualification Stage Exclusion Criteria:

1. Physical dependence on opioids, as determined by the Naloxone Challenge Test (ie, a COWS score of ≥ 5).
2. Intolerance to study treatments in Drug Discrimination Test (eg, emesis within first 2 hours after dosing).
3. Inability to discriminate between opioid (15 mg oxycodone HCl) and placebo during the Drug Discrimination Test. Ability to discriminate was defined for the Drug Liking and Drug High as follows:
    - Drug Liking (bipolar VAS 0 to 100 mm scale) during the first 2 hours following drug administration: ≥ 65 mm response to active treatment; placebo response ≥ 40 mm and ≤ 60 mm; and ≥ 15 mm difference between active and placebo treatments
    - Drug High (unipolar VAS 0 to 100 mm scale) during the first 2 hours following drug administration: ≥ 30 mm difference between active and placebo treatments and placebo response ≥ 0 mm and ≤ 10 mm

Appendix 2.2 Study 05 Additional Endpoints

VAS scores for Any Drug Effects and Good Effects were higher for oxycodone 40 mg compared with placebo starting at 0.25 or 0.5 hours and continuing to 6 or 8 hours (most $p < 0.0001$). Compared with oxycodone, all NKTR-181 doses had lower scores at these time points (all $p < 0.0001$). Placebo and NKTR-181 100 and 200 mg resulted in similar scores. A similar trend was observed for the mean change from baseline in Addiction Research Center Inventory/Morphine Benzedrine Group assessment.

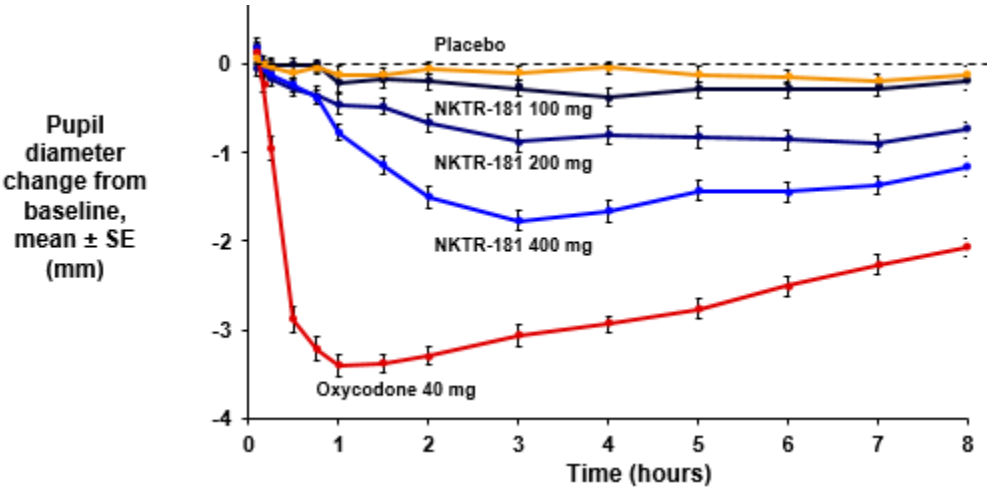
VAS scores for Bad Effects, Nausea, Feel Sick, Dizzy, and Sleepy were higher for oxycodone compared with placebo starting around 0.5 to 1.5 hours and continuing until 8 to 24 hours (most $p < 0.0001$). Separation between NKTR-181 and placebo was only observed for Sleepy at 3, 4, and 6 hours post-dose for NKTR-181 400 mg.

On the price value assessment questionnaire evaluated at 24 hours post-dose, oxycodone scored higher than placebo and all doses of NKTR-181. The 100 and 200 mg dose of NKTR-181 and placebo received similar scores.

The change in pupil diameter following administration of NKTR-181 and oxycodone are shown in Figure A-1. After administration of oxycodone, pupillary changes were immediate and reached maximum constriction at approximately 1.4 hours. In contrast, administration of NKTR-181 was followed by more gradual decreases in pupil diameter will smaller and flatter drops. The time to maximum pupil constriction for NKTR-181 400 mg was 4.3 hours post-dose (Table A-2).

This delay is attributed to NKTR-181's slow entry into the CNS coupled with its slow rate of activation at MORs.

Figure A-1. Pupil Diameter Change from Baseline Over Time in Study 05 (MITT Population)



SE = standard error

Table A-2. Time to Maximum Pupil Constriction Following Single Oral Doses of NKTR-181 and Oxycodone in Study 05 (MITT Population)

Mean (SD)	NKTR-181 400 mg N = 41	Oxycodone 40 mg N = 41
Time to maximum pupil constriction (hours)	4.3 (3.4)	1.4 (1.2)

SD = standard deviation

Appendix 2.3 Study 15 Enrollment Criteria

Key Inclusion Criteria:

1. Males or females, 18 to 55 years of age.
2. Recreational opioid user, who was not currently physically dependent on opioids (based on the Naloxone Challenge Test) but had experience in the use of opioids for non-therapeutic purposes (ie, for psychoactive effects) on at least 10 occasions within the last year and at least once in the 8 weeks prior to the screening visit.
3. BMI of 19.0-34.0 kg/m^2, and weight of ≥ 60.0 kg.
4. No clinically significant diseases in the medical history or evidence of clinically significant findings on physical examination, vital signs, clinical laboratory evaluations (hematology, chemistry, urinalysis) or 12-lead ECG as judged by the Investigator.
5. Was able to pass the Qualification Phase eligibility criteria.

Key Exclusion Criteria:

1. History or presence of drug or alcohol dependence (except nicotine or caffeine) as defined by the DSM-IV-TR, including subjects who had ever been in a drug rehabilitation program (other than treatment for smoking cessation).
2. History of acute asthma or other obstructive airway disease or any condition that may have increased the risk for respiratory depression (eg, sleep apnea), judged as clinically significant jointly by the Investigator and Sponsor.
3. History of neurologic conditions such as convulsive disorders or severe head injury, judged as clinically significant jointly by the Investigator and Sponsor.
4. Known contraindication, hypersensitivity, or allergy to naloxone, oxycodone, or other opioids.

Qualification Phase Exclusion Criteria:

1. Physical dependence on opioids, as determined by the Naloxone Challenge Test (ie, a COWS score of ≥ 5).
2. Intolerance to study treatments in Drug Discrimination Test (eg, emesis within first 2 hours after dosing).
3. Inability to discriminate between opioid (40 mg oxycodone HCl) and placebo during the Drug Discrimination Test. Ability to discriminate was defined as follows:
    - Drug Liking (bipolar VAS 0 to 100 mm scale) during the first 4 hours following drug administration: ≥ 65 mm response to active treatment; ≥ 40 mm and ≤ 60 mm response to placebo treatment; and ≥ 15 mm difference between active and placebo treatments; and
    - Acceptable overall responses to oxycodone for all other subjective measures, as judged by the Investigator or designee.

Appendix 2.4 Study 15 Additional Endpoints

In the VAS measurements for Any Drug Effects, Good Effects, and Alertness/Drowsiness, both the 400 and 600 mg doses of NKTR-181 had markedly lower maximum scores than both the 40 and 60 mg doses of oxycodone. The 1200 mg dose of NKTR-181 had maximum scores for Any Drug Effects and Good Effects that were similar to oxycodone 40 mg, but lower than oxycodone 60 mg. The 1200 mg dose of NKTR-181 did not differ from either dose of oxycodone on maximum scores for Alertness/Drowsiness.

For the VAS assessments of Nausea and Bad Effects, all doses of NKTR-181 had maximum scores similar to those of either dose of oxycodone, with the exception of NKTR-181 400 mg and 600 mg, which scored lower than oxycodone 60 mg for Nausea (400 mg only) and Bad Effects (400 and 600 mg).

Changes in pupil diameter following administration of NKTR-181 and oxycodone are shown in Figure 12. The 400 and 600 mg doses of NKTR-181 resulted in smaller and later maximal pupillary constriction compared to either dose of oxycodone. The 1200 mg dose of NKTR-181 resulted in pupillary constriction comparable to both doses of oxycodone; however, the time to maximum pupil constriction was longer for NKTR-181 1200 mg compared to oxycodone (Table A-3), consistent with the slow entry of NKTR-181 into the brain and slow binding to MORs.

Table A-3. Time to Maximum Pupil Constriction Following Single Oral Doses of NKTR-181 and Oxycodone in Study 15 (Completer Analysis Population)

LS Mean (SE)	**NKTR-181 400 mg N = 54**	**NKTR-181 600 mg N = 54**	**NKTR-181 1200 mg N = 54**	**Oxycodone 40 mg N = 54**	**Oxycodone 60 mg N = 54**
Time to maximum pupil constriction (hours)	5.4 (0.5)	4.5 (0.5)	3.4 (0.5)	2.5 (0.5)	2.2 (0.5)

LS = least squares; SE = standard error

APPENDIX 3: STUDY 04

Study Design

Study 04 was a Phase 2 multicenter, double-blind, placebo-controlled study that used an EERW design, encompassing an open-label Titration Period followed by a double-blind Treatment Period. Patients with OA were initially titrated to an effective dose of NKTR-181 and then were randomized in a 1:1 ratio to receive either NKTR-181 (at the dose established during the open-label Titration Period) or matching placebo; the double-blind treatment lasted 21 days.

Inclusion Criteria

1. Was willing and able to give written informed consent;
2. Was willing and able to understand the study procedures, complete the pain evaluation scales and questionnaires presented on an electronic patient-reported outcome device, and comply with all study procedures, including swallowing oral medications;
3. Was a male or a female, age ≥ 18 years old;
4. Had a BMI 18-41 kg/m^2, inclusive;
5. In good general health as determined by medical history and physical examination: clinical laboratory tests and vital signs (respiratory rate, heart rate, blood pressure, temperature) were not indicative of ongoing medical illness, ALT and AST were within normal limits, and creatinine clearance was > 60 mL/min;
6. Had clinical diagnosis of OA in one or both knees (consistent with the American College of Rheumatology Functional Class I to III OA of the knee as documented by medical records) for a minimum of 6 months prior to signing the consent form. When documented attempts to obtain records were unsuccessful, the Principal Investigator, or qualified sub-investigator, was to have completed the clinical diagnostic criteria worksheet as described in the Study Manual. Attempts to obtain medical records supporting the diagnosis of OA continued while the patient was participating in the study.
7. Had been on a stable regimen of non-opioid pain medication for the management of moderate to severe chronic pain due to OA of the knee for at least 30 days prior to signing the consent form:
    - A stable dosing regimen was defined as using the same non-opioid OA pain medication(s) daily on at least 5 days per week during the 30 days prior to signing the consent form. If the patient alternated medications (eg, 2 or 3 different medications), the medications were considered to be stable if taken in the same order at the same dose for the 30 days prior to signing the consent form, and this regimen was continued throughout the study.
    - Medications for OA pain of the knee that were taken PRN were not considered "stable" for purposes of this study. In cases where a patient was on both a stable

medication and a PRN medication for OA of the knee, the patient refrained from taking any PRN medication for at least 30 days prior to signing the consent form in order for their regimen to be considered stable and to establish a true baseline pain score. However, if multiple medications for OA pain of the knee were alternated (eg, 2 or 3 different medications) in the same order at the same dose for the 30 days prior to signing the consent form, and this regimen was continued throughout the study, it was considered stable, as described above. Patients must not have taken any PRN medication for OA pain of the knee during the trial and were reminded of such at each study visit.

8. Not experiencing adequate pain relief with their current dosing regimen. At the screening visit, the patient self-reported their average daily OA knee pain for the 7 days (assuming normal activity level) prior to signing the consent form as ≥ 4 on a 0-10 NRS. The patient's self-reported pain was ascertained in a non-leading manner and qualification criteria were not disclosed to the patient.
9. Women of childbearing potential agreed to use highly effective methods of birth control (defined as those, alone or in combination, that result in a low failure rate [ie, less than 1% per year] when used consistently and correctly, such as surgical sterilization, an intrauterine device, or 2 barrier methods [eg, condom or cervical barrier, such as the diaphragm]). Protections against pregnancy were continued for at least 2 months after the last dose of study drug. Male patients agreed to use double barrier contraception during the time of participation in this trial and for at least 2 months after the last dose of study drug. This criterion was waived for male patients who had a vasectomy > 6 months prior to signing the consent form.
10. Patients with a Hospital Anxiety Depression Scale score of > 10 on either the anxiety or depression scales had to receive Medical Monitor approval prior to inclusion in the Baseline Period.

Exclusion Criteria:

1. Females who were pregnant or lactating;
2. Had a known history of hypersensitivity, intolerance, or allergy to opioids;
3. Diagnosed as having rheumatoid arthritis, gout, pseudo-gout, Paget's disease, fibromyalgia, migraine headaches, or any chronic pain symptom or treatment for that symptom that in the Investigator's opinion would have interfered with the assessment of pain and other symptoms of OA;
4. Had any medical condition that would have precluded study participation in the opinion of the Investigator, including psychiatric diagnoses;
5. Had clinically significant abnormalities of vital signs or clinical laboratory results (including hematology, chemistry, and urinalysis);
6. Had clinically significant electrocardiographic abnormalities including QTc ≥ 450 msec;

7. Currently taking opioid-containing medications for any condition, had taken opioid-containing medications for pain related to OA within 6 months prior to signing the consent form, or had taken opioid-containing medications for more than 7 days for the treatment of conditions not related to OA (eg, tooth extraction, minor surgery, or cough) within 6 months prior to signing the consent form;
8. Had received systemic corticosteroids within 30 days prior to signing the consent form (use of topical corticosteroids to treat localized dermatological conditions permitted);
9. Had received intra-articular visco-supplementation in any joint within 90 days prior to signing the consent form or had received 2 or more intra-articular injections (steroid or visco-supplementation) within 1 year prior to signing the consent form;
10. Was known or suspected to be currently abusing alcohol or drugs, or had a history (within 5 years prior to signing the consent form) of active drug or alcohol abuse;
11. Had a positive urine drug screen and/or alcohol breath test during Screening Period testing;
12. Had positive serology for the surface antigen of hepatitis B (HBsAg) or hepatitis C (anti-HCV) during Screening Period testing;
13. Known to be human immunodeficiency virus positive;
14. Donated blood or plasma within 30 days prior to signing the consent form;
15. Participated in another drug or biologic study within 30 days prior to signing the consent form through study completion;
16. Had initiated therapy with selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors for depression or other approved indications within 3 months prior to signing the consent form (patients on a stable dose for greater than 3 months for the treatment of approved indications prior to signing the consent form were included);
17. Underwent surgical procedure on the target joint within the 5 years prior to signing the consent form or planned to have surgery on the target joint during the time of participation in the study;
18. Any other reason that, in the opinion of the Investigator or Medical Monitor, would have rendered the patient unsuitable for participation in the study.

Study Results

A total of 295 patients received at least 1 dose of study drug during the open-label Titration Period, and 213 patients (107 in the NKTR-181 group and 106 in the placebo group) were subsequently randomized into the double-blind treatment phase. Of the 213 randomized patients, 193 (90.6%) completed the study.

Overall, the demographic and baseline characteristics were comparable between the NKTR-181 and placebo groups and consistent with the patient population.

The primary efficacy endpoint in this study was not met as the study did not demonstrate that NKTR-181 resulted in a significant difference versus placebo in reduction in pain intensity. The treatment group difference for the LS mean (SE) change in pain intensity due to OA of the knee from randomization to the end of treatment was -0.04 (0.218).

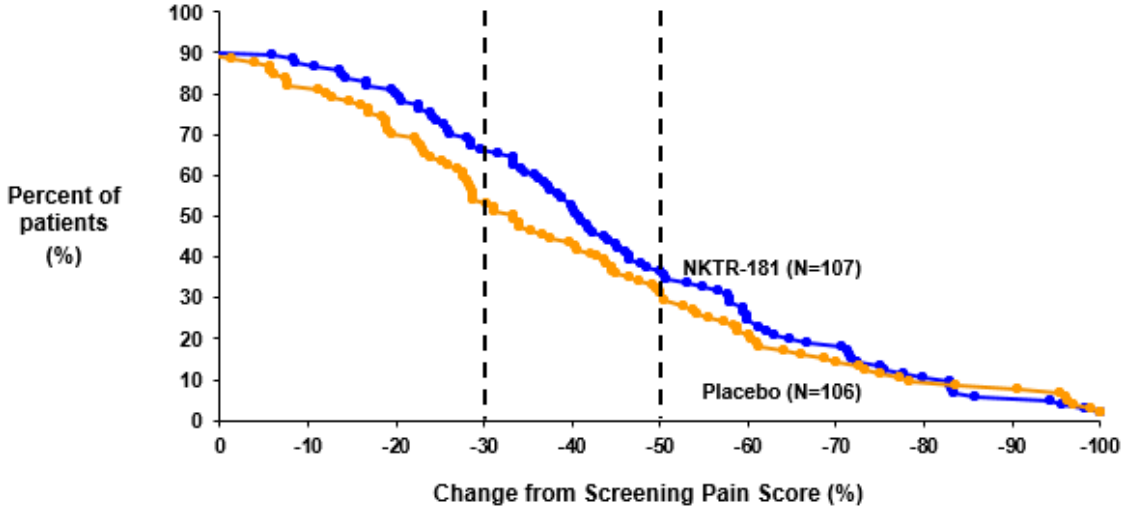
A post-hoc review of factors that might have contributed to the lack of statistically significant difference between groups suggested that certain aspects of the study design likely contributed:

- Study 04 was an add-on study in which the patients did not discontinue their current analgesic therapies. Rather, NKTR-181 was added to their baseline analgesic medication regimen. Since approximately 91% of the patients were taking NSAIDs, it may have been easier for patients in the placebo group to maintain their pain reduction during the double-blind Treatment Period. A post-hoc analysis showed that among patients who were not taking concomitant NSAIDs during the double-blind Treatment Period (n = 25; including 15 in the NKTR-181 group and 10 in the placebo group), the difference between groups in pain score was -0.74, which is similar in magnitude to the difference between groups observed in the pivotal Phase 3 study (-0.55).
- A lower level of pain at screening and/or less stringent pain reduction requirements to qualify for randomization, as well as the short duration of the double-blind Treatment Period (3 vs 12 weeks) may have contributed to the difficulty in detecting a difference between the treatment groups. Most patients titrated to either the 100 mg (48.8%) or the 200 mg (27.2%) q12h dose of NKTR-181, with only 23.9% of patients titrating to 300 or 400 mg q12h dose. A post-hoc analysis showed that patients who were titrated to the higher NKTR-181 doses (ie, 300 and 400 mg) achieved better results relative to placebo (-0.48), than did patients who were titrated to the lower NKTR-181 doses (ie, 100 and 200 mg; -0.01).

It was observed that, during the open-label Titration Period, the pain scores among patients who subsequently were randomized to NKTR-181 treatment dropped from 6.83 at screening to 3.99 at randomization (ie, the end of the open-label titration phase). A 41% reduction from the Screening Pain Score is consistent with the analgesic effect seen in the Phase 3 study in CLBP, and with the effect seen in clinical studies with other opioids.

Other efficacy findings also showed numerical evidence of effect. Based on a review of the cumulative distribution of percentage reduction in NRS score at the end of treatment, separation between NKTR-181 and placebo was evident at multiple pain reduction thresholds (Figure A-2). The proportions of patients in the NKTR-181 and placebo groups who achieved a $\geq$ 30% reduction in the NRS were 65.1% and 53.8%, respectively (p = 0.0747), and those who achieved a $\geq$ 50% reduction from the Screening Pain Score represented 35.9% and 31.1% of the NKTR-181 and placebo groups, respectively (p = 0.4999).

Figure A-2. Cumulative Distribution of Percent Reduction from Screening Pain Score at 3 Weeks in Study 04



Additionally, a greater proportion of patients in the NKTR-181 group (54.3%) relative to the placebo group (37.5%) rated their global assessment of pain relief measured by the Patient Global Assessment at the end of the study as very much/much improved ($p = 0.0152$).

The results of Study 04 provided important insights on potential limitations in study design that helped to inform the protocol and study design of the Phase 3 study (Study 07).

APPENDIX 4: TITRATION PROCEDURE FOR STUDY 07

During the open-label Titration Period, all patients began dosing with NKTR-181 100 mg q12h and continued on this dose for 1 week. After 1 week, patients were assessed for tolerability. Patients who did not tolerate the 100 mg dose were discontinued from the study. Patients who tolerated the 100 mg NKTR-181 dose had their dose increased to 200 mg. If patients had tolerability issues at the 200 mg dose, their dose was reduced to 100 mg. All patients were then assessed for randomization criteria every week and dispositioned, as follows:

- Patients who tolerated their current dose of NKTR-181 but did not meet randomization criteria (described in Section 6.2.4) titrated upward at increments of 100 mg once per week until randomization criteria were met, the dose was not tolerated, or the maximum dose of 400 mg NKTR-181 q12h was reached (by no later than Week 6 of Titration Period).
- Patients who tolerated their current dose of NKTR-181 and met randomization criteria continued their current dose of NKTR-181 for 1 additional week (ie, a total of 14 days) to ensure that they continued to tolerate and respond to a stable dose of NKTR-181. Patients who continued to meet randomization criteria in the subsequent week were randomized.
- Patients who could not tolerate a given dose of NKTR-181 or could not meet the randomization criteria by the end of the 7-week Titration Period were discontinued from the study.

APPENDIX 5: STUDY 07 ENROLLMENT CRITERIA

Inclusion Criteria

1. Willing and able to provide written informed consent.
2. Willing and able to understand the study procedures, complete the pain evaluation scales and questionnaires presented, and comply with all study procedures, including swallowing oral medications.
3. Females or males 18 to 75 years of age at time of signing the consent form, inclusive.
4. Clinical diagnosis of moderate to severe, chronic (≥ 6 months at time of signing the consent form), non-neuropathic low back pain, consistent with Quebec Task Force Classification for Spinal Disorders Grade I-II.
5. Patients who had not experienced adequate pain relief or failed treatment with non-opioid analgesics (eg, NSAIDs, cyclooxygenase-2 inhibitors) and for whom opioid analgesia was necessary. Patients was taking no more than 10 mg MSE/day of short-acting opioids for the 14 days prior to signing the consent form.
6. BMI of 18-39 kg/m^2, inclusive.
7. In good general health as determined by medical history and physical examination; clinical laboratory tests and vital signs were not indicative of ongoing medical illness.
8. Women must have been either surgically sterile (by means of hysterectomy or bilateral oophorectomy) or post-menopausal (defined as spontaneous cessation of menses for at least 1 year). Women of childbearing potential must have committed to use 2 highly effective forms of contraception such as a barrier contraception (eg, condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) through the duration of the study in addition to either an intrauterine device or hormonal contraception, continuing until 2 weeks following the last dose of study drug.
9. Males with female partners of child-bearing potential must have agreed to use a barrier contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) throughout the duration of the study until 2 weeks following the last dose of study drug in addition to their female partner using either an intrauterine device or hormonal contraception, continuing until 2 weeks following the last dose of study drug. This criterion may have been waived for male patients who had a vasectomy > 6 months before signing the consent form.

Exclusion Criteria:

1. Females who were pregnant or breastfeeding.
2. Known history of hypersensitivity, intolerance, or allergy to opioids, acetaminophen, and/or hydrocodone.

3. Any history within the past year or current evidence of substance, alcohol, or opioid abuse.
4. Taking extended-release/long-acting opioids within 6 months of signing the consent form.
5. Had not received any prior treatment for CLBP.
6. Untreated moderate to severe sleep apnea.
7. Underwent surgical procedure on the low back within 12 months before signing the consent form or planned to have surgical procedure on low back during the time of participation in the study.
8. Had facet nerve root blocks or radiofrequency ablation procedures within 3 months of screening.
9. Had started physical therapy or chiropractic therapy within 4 weeks of screening or during the study.
10. Any history of seizures (with the exception of pediatric febrile seizures).
11. Had compression of a spinal nerve root with neurological radicular signs.
12. Had spinal fracture, tumor, abscess, or other pathology in the low back/abdominal region confirmed by historical record or imaging studies.
13. Currently had any pending application(s) for any disability/worker's compensation related to their pain.
14. Score of 10 or greater on the Personal Health Questionnaire Depression Scale at Visit 1.
15. Answered YES to Question 4 or Question 5 within the past 12 months of the Baseline/Screening version of the electronic Columbia-Suicide Severity Rating Scale at Visit 1.
16. Score of > 12 on the COWS at the start of the open-label Titration Period (Visit 3).
17. Clinically-significant abnormalities in vital signs or clinical laboratory results including hematology, chemistry, or urinalysis; total bilirubin > 1.5 X ULN; ALT and AST > 2.0 X ULN; or creatinine clearance < 60 mL/min (calculated by Cockcroft-Gault).
18. QTcF > 450 msec for males and > 470 msec for females, or any clinically significant abnormality on a 12-lead ECG per central read.
19. Received systemic or epidural corticosteroids within 3 months before signing the consent form or received intra-articular corticosteroids (non-target location) within 30 days before signing the consent form. Use of topical or inhaled/nasal corticosteroids was permitted.
20. Positive urine drug screen and/or alcohol breathalyzer test during screening.
21. Currently participating or have previously participated in another drug or biologic study within 30 days before signing the consent form and through study completion.

22. Use of neuroleptics within 3 months prior to signing the consent form.
23. Any chronic pain symptom (of equal or greater severity) or treatment for that symptom that, in the Investigator's opinion, would confound pain assessments and other symptoms of chronic low back pain.
24. Any history of malignancy likely to result in significant disability or likely to require significant medical or surgical intervention within the next 3 months. This does not include minor surgical procedures for localized cancer (eg, basal cell carcinoma).
25. History of unstable or deteriorating cardiac disease within the previous 12 months of screening including but not limited to the following:
    - Unstable angina pectoris or myocardial infarction
    - Congestive heart failure requiring hospitalization
    - Uncontrolled clinically significant arrhythmias
26. Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol.

APPENDIX 6: STATISTICAL METHODS AND SENSITIVITY ANALYSIS RESULTS IN STUDY 07

Handling of Missing Data

If the Daily Pain Score was missing for more than 3 days within the same week, the Weekly Pain Score for that week was considered missing. For the prespecified analysis of the primary endpoint, missing data were categorized into 4 groups and handled as follows:

- **Discontinuation due to AE:** If a patient discontinued treatment because of an AE, MI was applied to impute the missing pain scores from a truncated normal distribution (range from 0 to 10) with mean and standard deviation calculated using the Screening Pain Score of all randomized patients in the ITT population.
- **Discontinuation due to opioid withdrawal symptom:** If a patient discontinued treatment because of an opioid withdrawal symptom, MI was applied to impute the missing pain scores using a truncated normal distribution (range from 0 to 10) with mean and standard deviation calculated from the Randomization Baseline Pain Score in the treatment group to which the patient belongs.
- **Discontinuation due to lack of efficacy:** If discontinuation was due to lack of efficacy, the missing pain scores were imputed using last mean carried forward (LMCF) method (SAS macro written by James Roger, available at www.missingdata.org.uk). The LMCF method is implemented using a Bayesian model. The model includes a patient's individual covariate offset ($\sum_s X_{iks}\beta_s$) that is not related to the treatment and time and the intercept of treatment and time (A_{jk}).

$$E[Y_{ik}] = A_{jk} + \sum_s X_{iks}\beta_s$$

Here i indicates the ith patient, j the jth treatment (NKTR-181 vs placebo), k the kth week, and s the sth covariate. The imputation process involves 2 steps: a parameter estimation step and an imputation step. For all patients who have the last available pain score observed at Week p, the Weekly Pain Scores are split into 2 parts: the observed values prior to withdrawal, and the unobserved values which need to impute (after Week p). This leads to a mean consisting of 2 parts μ1 and μ2 and a variance-covariance matrix with 4 components Σ11, Σ12, Σ21, and Σ22. In the Bayesian model, the means use flat improper priors and the covariance matrix uses approximate inverse-Wishart priors with degrees of freedom equal to the dimension of the matrix. The parameter estimation step draws parameter estimates from their posterior distribution (draw 10 times to create 10 sets of imputations). At the imputation step, the last mean at Week p, $E_p[Y_{ik}] = A_{jp} + \sum_s X_{iks}\beta_s$, is used to impute all the missing pain scores after Week p.

This entire process is repeated for all the weeks with missing values due to lack of efficacy. Covariates used in the imputation model include age, Screening Pain Score, Randomization Baseline Pain Score, and gender.

- **Discontinuation due to other reasons or data missing for any other reason:** If a patient discontinued for a reason other than those listed above, or results were not available for any other reason, MI was conducted using the Markov Chain Monte Carlo (MCMC) method implemented in PROC MI in SAS 9.4. The MI with MCMC method assumes non-monotone missing. The imputation model includes Weekly Pain Scores (at Week 2, 4, 6, 8, 10, and 12) along with age, Screening Pain Score, Randomization Baseline Pain Score, and gender. The imputation is conducted separately for the NKTR-181 group and the placebo group.

Ten imputations were produced. The prespecified ANCOVA model was applied after each imputation and the results were combined using standard MI techniques.

Table A-4 shows the number of patients with missing Week 12 measurements categorized into the 4 reasons described above.

Table A-4. Summary of Missing Week 12 Weekly Pain Score in Study 07

Reason for Missing Week 12 Value	Patients, n	
	NKTR-181	Placebo
Discontinuation due to AE	26	8
Discontinuation for opioid withdrawal symptom	1	1
Discontinuation due to lack of efficacy	4	7
Other (eg, lost to follow-up)	23	36
Total	54	52

Prespecified Sensitivity Analyses

- **Sensitivity analysis #1**: This sensitivity analysis differed from the primary analysis with respect to the imputation method for missing values due to "other" reasons. This sensitivity analysis imputed these missing values applying the same imputation method used for missing values due to adverse events, as described above for the primary analysis.
- **Sensitivity analysis #2**: This sensitivity analysis assumed data were missing at random. A mixed-effect model with repeated measures (MMRM) was applied directly to the incomplete data without explicitly imputing the missing data first. The model set Weekly Pain Score change (at Week 2, 4, 6, 8, 10, and 12) from Randomization Baseline as the dependent variable. There were 4 fixed effects in the model: Randomization Baseline

Pain Score, treatment group, study week, and the interaction of treatment group and study week.

- **Sensitivity analysis #3**: This sensitivity analysis used each patient's own Screening Pain Score to impute missing values due to adverse event, Randomization Baseline Pain Score to impute missing values due to opioid withdrawal symptom, and last observed Weekly Pain Score to impute missing values due to lack of efficacy. Single imputation, rather than MI, was used for missing values due to these 3 reasons. However, for missing values due to other reasons, the same MCMC method used in the primary analysis was applied.

- **Sensitivity analysis #4**: This sensitivity analysis added investigational site as a covariate to the ANCOVA model used in the primary analysis.

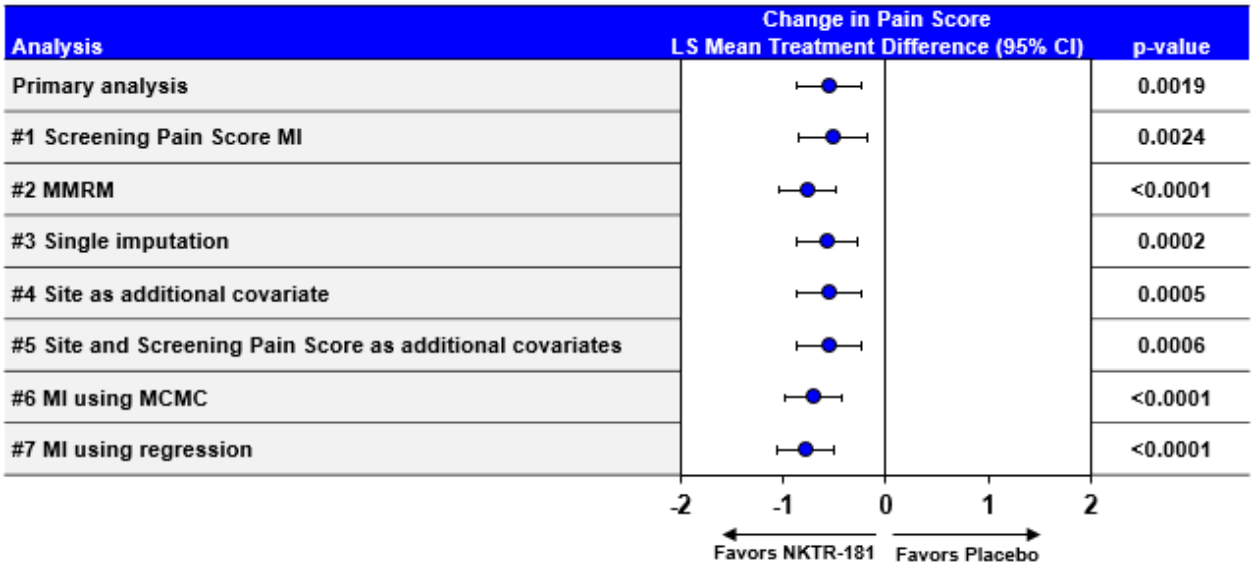
- **Sensitivity analysis #5**: This sensitivity analysis added investigational site and Screening Pain Score as covariates in the ANCOVA model used in the primary analysis.

Ad-Hoc Sensitivity Analyses

- **Sensitivity analysis #6**: This sensitivity analysis imputed all missing values, regardless of reasons for discontinuation, using MI (10 times) applying the MCMC method implemented in PROC MI in SAS 9.4, assuming non-monotone missing. The imputation model included treatment group, gender, age, Screening Pain Score, Randomization Baseline Pain Score, and Weekly Pain Scores from Week 1 to Week 12. Categorical variables are used as classification variables.

- **Sensitivity analysis #7**: This sensitivity analysis imputed all missing values regardless of reason for discontinuation using MI (10 times) through the regression method implemented in PROC MI in SAS 9.4. Variables were arranged to form a monotone missing pattern. A regression model was fitted for the first variable with the least missing values, including all preceding variables without missing values as covariates. A new regression model was then fitted using the completed data for that variable in addition to all the variables without missing values to impute the missing values for the next variable. The process continued sequentially for each variable with missing values until the last variable was imputed. The Week 12 pain score was imputed last using the following covariates: treatment group, gender, age, Screening Pain Score, Randomization Baseline Pain Score, and Weekly Pain Scores from Week 1 to Week 12.

Figure A-3. Sensitivity Analysis Results for Study 07



LS = least squares; MCMC = Markov Chain Monte Carlo; MI = multiple imputation;
MMRM = mixed-effect model with repeated measures

- **Tipping point analysis**: In addition to the sensitivity analyses that vary the details of the MI, a "tipping-point" analysis (Yan et al. 2009) was conducted to assess the "shift" in Week 12 pain score needed for treatment effect to become not statistically significant. The analysis was based on Sensitivity Analysis #7. According to this analysis, a 2.75- or 2.25-point increase in Weekly Pain Score at Week 12 for each missing value in the NKTR-181 treatment group and no increase for missing values in the placebo group was required in order for the estimated difference to change from significant to non-significant at the 0.05 or 0.01 significance level. A shift of either of this magnitude is unlikely, which implies that the conclusion of a significant treatment effect is unlikely changed by missing values.

APPENDIX 7: SAFETY DATA FOR STUDY 04 AND STUDY 07 (POOLED)

Table A-5. Overview of Adverse Events Reported in Study 04 and Study 07 (Pooled)

	Patients, n (%)		
	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,484	NKTR-181 N = 416	Placebo N = 407
Patients reporting ≥ 1:			
AE	935 (63.0%)	210 (50.5%)	180 (44.2%)
Severe AE	37 (2.5%)	8 (1.9%)	5 (1.2%)
AE leading to study drug discontinuation	194 (13.1%)	34 (8.2%)	12 (2.9%)
SAE	11 (0.7%)	5 (1.2%)	6 (1.5%)
Death	1 (<0.1%)	0	0

Table A-6. Adverse Events Reported ≥ 3% of Patients in Study 04 and Study 07 (Pooled)

	Patients, n (%)		
	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,484	NKTR-181 N = 416	Placebo N = 407
Patients reporting ≥ 1 AE	935 (63.0%)	210 (50.5%)	180 (44.2%)
Constipation	483 (32.5%)	36 (8.7%)	12 (2.9%)
Nausea	204 (13.7%)	39 (9.4%)	22 (5.4%)
Somnolence	127 (8.6%)	9 (2.2%)	2 (0.5%)
Headache	94 (6.3%)	11 (2.6%)	16 (3.9%)
Dry mouth	79 (5.3%)	9 (2.2%)	1 (0.2%)
Vomiting	77 (5.2%)	17 (4.1%)	7 (1.7%)
Fatigue	70 (4.7%)	5 (1.2%)	1 (0.2%)
Dizziness	59 (4.0%)	11 (2.6%)	1 (0.2%)
Pruritus	57 (3.8%)	3 (0.7%)	0
Diarrhoea	39 (2.6%)	9 (2.2%)	22 (5.4%)
Drug Withdrawal Syndrome	32 (2.2%)	14 (3.4%)	12 (2.9%)

Table A-7. Adverse Events that Led to Withdrawal of Study Drug in ≥ 5 Patients in Study 04 and Study 07 (Pooled)

	Patients, n (%)		
	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,484	NKTR-181 N = 416	Placebo N = 407
Patients reporting ≥ 1 AE	194 (13.1%)	34 (8.2%)	12 (2.9%)
Nausea	47 (3.2%)	3 (0.7%)	1 (0.2%)
Constipation	46 (3.1%)	8 (1.9%)	0
Somnolence	26 (1.8%)	3 (0.7%)	1 (0.2%)
Vomiting	24 (1.6%)	3 (0.7%)	0
Dizziness	21 (1.4%)	1 (0.2%)	0
Fatigue	13 (0.9%)	3 (0.7%)	0
Headache	12 (0.8%)	0	2 (0.5%)
Pruritus	7 (0.5%)	1 (0.2%)	0
Diarrhoea	6 (0.4%)	0	2 (0.5%)
Migraine	6 (0.4%)	0	0
Hyperhidrosis	5 (0.3%)	1 (0.2%)	0
Dry mouth	5 (0.3%)	0	0
Aspartate aminotransferase increased	5 (0.3%)	0	0

Table A-8. Serious Adverse Events in Study 04 and Study 07 (Pooled)

	Patients, n (%)		
	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,484	NKTR-181 N = 416	Placebo N = 407
Patients reporting ≥ 1 SAE, n (%)	11 (0.7%)	5 (1.2%)	6 (1.5%)
Atrial fibrillation	2 (0.1%)	0	0
Angioedema	1 (<0.1%)	0	0
Blindness transient	1 (<0.1%)	0	0
Cellulitis	1 (<0.1%)	0	0
Cerebrovascular accident	1 (<0.1%)	0	0
Coronary artery stenosis	1 (<0.1%)	0	0
Gastrointestinal infection	1 (<0.1%)	0	0
Herpes virus infection	1 (<0.1%)	0	0
Infective exacerbation of chronic obstructive airways disease	1 (<0.1%)	0	0
Large intestine perforation	1 (<0.1%)	0	0
Pneumonia	1 (<0.1%)	0	0
Pulmonary embolism	1 (<0.1%)	0	0
Chest pain	0	1 (0.2%)	0
Diverticulitis	0	1 (0.2%)	0
Hypertension	0	1 (0.2%)	0
Renal failure	0	1 (0.2%)	0
Rib fracture	0	1 (0.2%)	0
Bacterial infection	0	0	1 (0.2%)
Bladder cancer	0	0	1 (0.2%)
Diverticulum intestinal	0	0	1 (0.2%)
Dysarthria	0	0	1 (0.2%)
Gastroenteritis	0	0	1 (0.2%)
Malignant hypertension	0	0	1 (0.2%)
Skin abrasion	0	0	1 (0.2%)

APPENDIX 8: ADDITIONAL SAFETY TABLES

Table A-9. ECG Changes from Baseline at End of Titration/Treatment in Study 04 and Study 07 (Pooled)

Change from Baseline, Mean (SD)	Open-Label Titration	Double-Blind Treatment	
	NKTR-181 N = 1,484	**NKTR-181 N = 416**	**Placebo N = 407**
ECG mean heart rate (beats/min)	n = 1,374 2.0 (9.77)	n = 389 1.0 (9.25)	n = 377 1.7 (9.52)
PR interval, single beat (msec)	n = 1,373 1.4 (12.90)	n = 389 -1.5 (11.92)	n = 379 -3.3 (12.92)
QRS duration, single beat (msec)	n = 1,381 0.8 (6.90)	n = 391 -0.6 (7.02)	n = 381 -0.8 (7.26)
QT interval, single beat (msec)	n = 1,380 -5.1 (22.37)	n = 391 -2.1 (21.55)	n = 381 -3.4 (22.77)
QTcF interval, single beat (msec)	n = 1,380 -1.4 (15.34)	n = 391 0.0 (15.75)	n = 381 -0.6 (15.12)
RR interval, aggregate (msec)	n = 1,381 -25.6 (125.98)	n = 391 -14.5 (117.29)	n = 381 -19.4 (124.44)

ECG = electrocardiogram; QTcF = Corrected QT interval, Fridericia's correction; SD = standard deviation

Table A-10. CNS-Mediated Adverse Events in Study 07 and Study 08

	Patients, n (%)			
	Study 07			Study 08
	Open-Label Titration	Double-Blind Treatment		
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301	NKTR-181 N = 638
Patients with ≥ 1 CNS-mediated AE	469 (39.4)	81 (26.2)	53 (17.6)	238 (37.3)
Nausea	176 (14.8)	32 (10.4)	18 (6.0)	76 (11.9)
Somnolence	107 (9.0)	8 (2.6)	1 (0.3)	31 (4.9)
Vomiting	67 (5.6)	15 (4.9)	5 (1.7)	35 (5.5)
Dry mouth	66 (5.6)	7 (2.3)	1 (0.3)	18 (2.8)
Fatigue	61 (5.1)	4 (1.3)	1 (0.3)	13 (2.0)
Pruritus	52 (4.4)	2 (0.6)	0	21 (3.3)
Dizziness	47 (4.0)	7 (2.3)	1 (0.3)	19 (3.0)
Drug withdrawal syndrome	32 (2.7)	14 (4.5)	12 (4.0)	38 (6.0)
Sedation	20 (1.7)	0	1 (0.3)	4 (0.6)
Insomnia	19 (1.6)	4 (1.3)	5 (1.7)	17 (2.7)
Hyperhidrosis	15 (1.3)	0	1 (0.3)	2 (0.3)
Decreased appetite	13 (1.1)	4 (1.3)	1 (0.3)	8 (1.3)
Hot flush	12 (1.0)	3 (1.0)	3 (1.0)	8 (1.3)
Feeling abnormal	12 (1.0)	0	0	3 (0.5)
Pruritus generalised	12 (1.0)	0	0	5 (0.8)
Irritability	10 (0.8)	2 (0.6)	1 (0.3)	9 (1.4)
Anxiety	9 (0.8)	1 (0.3)	4 (1.3)	12 (1.9)
Euphoric mood	8 (0.7)	0	1 (0.3)	2 (0.3)
Lethargy	7 (0.6)	0	0	6 (0.9)
Vision blurred	6 (0.5)	1 (0.3)	0	2 (0.3)
Sleep disorder	5 (0.4)	0	0	2 (0.3)
Restlessness	4 (0.3)	0	3 (1.0)	2 (0.3)
Disturbance in attention	4 (0.3)	0	0	2 (0.3)

	Patients, n (%)			
	Study 07			Study 08
	Open-Label Titration	Double-Blind Treatment		
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301	NKTR-181 N = 638
Erectile dysfunction	3 (0.3)	0	0	2 (0.3)
Memory impairment	3 (0.3)	0	0	2 (0.3)
Night sweats	2 (0.2)	1 (0.3)	0	2 (0.3)
Urinary retention	2 (0.2)	1 (0.3)	0	0
Vertigo	2 (0.2)	0	1 (0.3)	4 (0.6)
Asthenia	2 (0.2)	0	1 (0.3)	3 (0.5)
Feeling jittery	2 (0.2)	0	0	2 (0.3)
Affect lability	2 (0.2)	0	0	1 (0.2)
Cold sweat	2 (0.2)	0	0	1 (0.2)
Cognitive disorder	2 (0.2)	0	0	0
Urinary hesitation	2 (0.2)	0	0	0
Depression	1 (< 0.1)	4 (1.3)	2 (0.7)	12 (1.9)
Agitation	1 (< 0.1)	1 (0.3)	0	0
Presyncope	1 (< 0.1)	1 (0.3)	0	1 (0.2)
Libido decreased	1 (< 0.1)	0	1 (0.3)	4 (0.6)
Poor quality sleep	1 (< 0.1)	0	1 (0.3)	0
Confusional state	1 (< 0.1)	0	0	1 (0.2)
Mental status changes	1 (< 0.1)	0	0	1 (0.2)
Nightmare	1 (< 0.1)	0	0	1 (0.2)
Accidental overdose	1 (< 0.1)	0	0	0
Autonomic nervous system imbalance	1 (< 0.1)	0	0	0
Delusion	1 (< 0.1)	0	0	0
Disorientation	1 (< 0.1)	0	0	0
Dyssomnia	1 (< 0.1)	0	0	0
Elevated mood	1 (< 0.1)	0	0	0

	Patients, n (%)			
	Study 07			Study 08
	Open-Label Titration	Double-Blind Treatment		
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301	NKTR-181 N = 638
Libido increased	1 (< 0.1)	0	0	0
Piloerection	1 (< 0.1)	0	0	0
Yawning	1 (< 0.1)	0	0	0
Syncope	0	2 (0.6)	0	1 (0.2)
Mood swings	0	1 (0.3)	0	0
Panic attack	0	0	1 (0.3)	1 (0.2)
Dysarthria	0	0	1 (0.3)	0
Nervousness	0	0	1 (0.3)	0
Sleep apnoea syndrome	0	0	0	3 (0.5)
Drug intolerance	0	0	0	2 (0.3)
Mood altered	0	0	0	2 (0.3)
Aggression	0	0	0	1 (0.2)
Amenorrhoea	0	0	0	1 (0.2)
Amnesia	0	0	0	1 (0.2)
Androgen deficiency	0	0	0	1 (0.2)
Apathy	0	0	0	1 (0.2)
Ataxia	0	0	0	1 (0.2)
Carbon dioxide increased	0	0	0	1 (0.2)
Convulsion	0	0	0	1 (0.2)
Diplopia	0	0	0	1 (0.2)
Dizziness postural	0	0	0	1 (0.2)
Drug abuse	0	0	0	1 (0.2)
Drug dependence	0	0	0	1 (0.2)
Drug withdrawal headache	0	0	0	1 (0.2)
Feeling drunk	0	0	0	1 (0.2)

	Patients, n (%)			
	Study 07			Study 08
	Open-Label Titration	Double-Blind Treatment		
	NKTR-181 N = 1,189	NKTR-181 N = 309	Placebo N = 301	NKTR-181 N = 638
Hypopnoea	0	0	0	1 (0.2)
Loss of consciousness	0	0	0	1 (0.2)
Mental impairment	0	0	0	1 (0.2)

APPENDIX 9: NARRATIVES

SAE, Death Preferred Term(s): Cerebrovascular accident

A 66-year-old male with low back pain experienced cerebrovascular accident and died while enrolled in Study 07. On 07-Apr-2016, he initiated treatment with NKTR-181 at 100 mg q12h. The most recent dose of NKTR-181 prior to the onset of the event was not reported. Medical history included low back pain, hypertension, hypercholesterolemia, chronic pain, and depression. Allergies were reported as unknown. Concomitant medications included hydrochlorothiazide, atenolol, simvastatin, and ibuprofen.

On (b) (6), unknown number of days after the last dose of NKTR-181 prior to the event, the patient experienced cerebrovascular accident. According to his roommate, the patient was in chronic pain all the time. The roommate stated the patient had slurred speech and was not "acting right." The patient was in asystole when the Fire Department arrived. The Fire Department performed cardiopulmonary resuscitation, and administered a total of 3 rounds of epinephrine, 2 mg of naloxone, 100 mg of sodium bicarbonate, flumazenil, and orotracheal intubation. The patient remained in asystole during transport and his pupils were fixed and dilated. The patient had a return of spontaneous circulation at the hospital but lost pulses again. Resuscitation efforts were unsuccessful, and the patient expired.

On (b) (6), the patient died, with cause of death listed on the death certificate as hypertension, hyperlipidemia, and morbid obesity.

The Investigator considered the cerebrovascular accident as severe and unlikely related to NKTR-181. The Sponsor agrees with the Investigator's causality assessment.

Non-serious AE, Preferred Term(s): Accidental Overdose

A 21-year-old white female had a case classified as "accidental overdose" in Study 07. Her past medical history included CLBP, scoliosis, muscle spasms, depression, anxiety, deep vein thrombosis, anemia and allergies (cat). Concomitant medications included ibuprofen, methocarbamol, sertraline, and cetirizine. Although she had a reported ongoing history of anemia, at screening she had a hemoglobin of 14.1 g/dL and a hematocrit of 44%. Other chemistry and hematology values at screening were within normal limits. Her vital signs at screening (18-May-2016) were a blood pressure of 116/70 mmHg, heart rate 84 beats/min and temperature of 36.9°C.

She was to start titration of NKTR-181 at 100 mg q12h on 01-Jun-2016. Vital signs on 01-June-2016 showed a blood pressure of 120/64 mmHg, heart rate 84 beats/min and temperature 37.1°C. She was instructed to take 1 tablet from each of 2 study medication cards (NKTR-181 100 mg and placebo) q12h. However, beginning on 01-Jun-2016, she took 2 tablets q12h from the same card, using the cards in succession. Thus, she either received double the dose for 5 days and 3 days of placebo or vice versa instead of the intended 100 mg q12h. Upon discovery on 09-Jun-2016, the site reported the accidental misuse as an overdose as the dose she

received was higher than intended for that period although within the protocol defined range of study doses. On 09-Jun-2016, blood pressure was 120/62 mmHg, heart rate was 88 beats/min, and temperature was 37° C. The "overdose" was considered mild, non-serious, unrelated to study drug, and was considered resolved on 09-Jun-2016. No action was taken. No other signs or symptoms associated with the overdose were reported. The patient was not titrated to higher NKTR-181 doses and did not enter the randomized portion of the study. She received her end of study visit on 16-Jun-2016.

A MADDERS evaluation was triggered for prespecified AEs associated with drug abuse or abuse potential, as well as for any drug accountability discrepancy such as missing pills. The MADDERS Adjudication Committee assessed the event with a primary classification of "therapeutic error" and a supplemental classification of "overdose." This case is consistent with a medication error and not a clinical AE of overdose.

APPENDIX 10: CLINICAL OPIATE WITHDRAWAL SCALE (COWS) ASSESSMENT

APPENDIX 1
Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

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APPENDIX 11: SUBJECTIVE OPIATE WITHDRAWAL SCALE (SOWS) ASSESSMENT

Assessment of Withdrawal from Opioids

The Subjective Opiate Withdrawal Scale (SOWS)

Date ..... Time .....

		PLEASE SCORE EACH OF THE 16 ITEMS BELOW ACCORDING TO HOW YOU FEEL NOW (CIRCLE ONE NUMBER)				
	SYMPTOM	NOT AT ALL	A LITTLE	MODERATELY	QUITE A BIT	EXTREMELY
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Range 0-64. Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987)
Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse*, 13, 293-308.