Nektar Therapeutics

CLINICAL STUDY PROTOCOL

A PHASE 3 MULTICENTER, OPEN-LABEL, 52-WEEK STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF NKTR-181 IN SUBJECTS WITH MODERATE TO SEVERE CHRONIC LOW BACK PAIN OR CHRONIC NONCANCER PAIN

Protocol Number: 14-181-08

Protocol Version Amendment 2.0

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Supersedes: Protocol amendment 1.0 dated 22 May 2015
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IND Number: 109,963

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INVESTIGATOR SIGNATURE PAGE

Nektar Therapeutics

TITLE:	A Phase 3 Multicenter, Open-Label, 52-Week Study to Evaluate the Long-Term Safety and Tolerability of NKTR-181 in Subjects with Moderate to Severe Chronic Low Back Pain or Chronic Noncancer Pain
PROTOCOL NUMBER:	14-181-08
PHASE OF STUDY:	3
PROTOCOL AMENDMENT DATE:	15 Jan 2016
STUDY SPONSOR:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

PRINCIPAL INVESTIGATOR COMMITMENT:

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that I understand my responsibilities pursuant to Federal Regulations (21 CFR § 312) and ICH E6 Good Clinical Practice guidelines, as well as with any and all applicable federal, state and/or local laws and regulations, and agree to conduct the study in accordance with the protocol referenced herein.

PROTOCOL APPROVAL PAGE

A Phase 3 Multicenter, Open-Label, 52-Week Study to Evaluate the Long-Term Safety and Tolerability of NKTR-181 in Subjects with Moderate to Severe Chronic Low Back Pain or Chronic Noncancer Pain

SPONSOR: **Nektar Therapeutics**
455 Mission Bay Boulevard South
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LIST OF STUDY CONTACTS

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ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BP	blood pressure
mBPI-SF	Modified Brief Pain Inventory-Short Form
CFR	Code of Federal Regulations
CNS	central nervous system
COWS	Clinical Opiate Withdrawal Scale
COX-2	cyclooxygenase-2
C-SSRS	Columbia-Suicide Severity Rating Scale
%CV	percent coefficient of variation
CYP3A	cytochrome P450 enzyme isoform 3A
DCI	data collection instruments
ECG	Electrocardiogram
eCOA	electronic clinical outcome assessments
eCRF	electronic case report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EOS	end of study
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

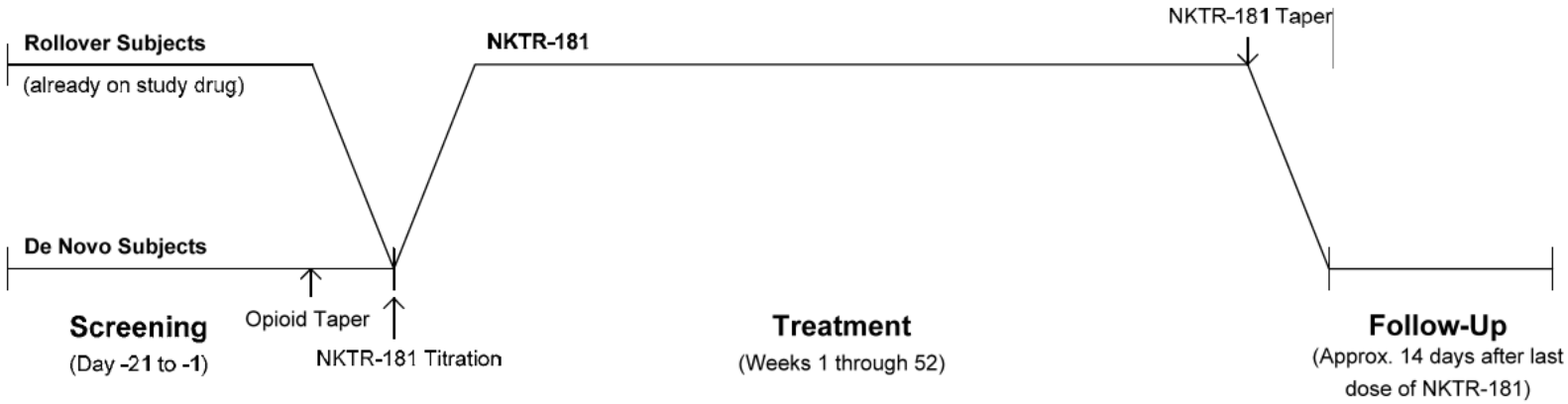
Abbreviation or Term	Definition
IND	Investigational New Drug
IRB	Institutional Review Board
IXRS	Interactive Voice and Web Response System
MAD	multiple ascending dose
MADDERS™	Misuse, Abuse, and Divergent Drug Event Reporting System
MedDRA	Medical Dictionary for Regulatory Activities
MSE	morphine sulfate equivalent
NME	new molecular entity
NSAID	non-steroidal anti-inflammatory drug
PAMORA	peripherally acting mu-opioid receptor antagonist
PD	Pharmacodynamic
PHQ-8	Personal Health Questionnaire Depression Scale
PK	Pharmacokinetic
q12h	every 12 hours
QTcF	corrected QT interval (Fredericia)
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
SOWS	Subjective Opiate Withdrawal Scale
SUSAR	suspected unexpected serious adverse reactions
T	temperature
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

1.0 STUDY SYNOPSIS

Name of Sponsor:	Nektar Therapeutics
Name of Finished Product:	NKTR-181 tablets
Name of Active Ingredient:	NKTR-181
Title of Study:	A Phase 3 Multicenter, Open-Label, 52-Week Study to Evaluate the Long-Term Safety and Tolerability of NKTR-181 in Subjects with Moderate to Severe Chronic Low Back Pain or Chronic Noncancer Pain
Duration of Study:	Approximately 57 weeks for each subject
Phase of Development:	3
Objectives:	Primary: • To evaluate the long-term safety and tolerability of NKTR-181 in subjects with moderate to severe chronic low back pain or chronic noncancer pain. Secondary: • To evaluate the efficacy of NKTR-181 as measured by the modified Brief Pain Inventory-Short Form (mBPI-SF).
Study Population	Opioid non-tolerant adults 18-75 years of age, inclusive, with moderate to severe chronic low back painor chronic noncancer pain.
Number of Subjects (planned):	Approximately 600 subjects are expected to be enrolled. This number may increase or decrease to meet the International Conference on Harmonisation (ICH) regulatory exposure requirements for NKTR-181 of at least 300 subjects who complete 26 weeks of NKTR-181 treatment and at least 100 subjects who complete 52 weeks of NKTR-181 treatment. The subjects will comprise those qualifying to rollover from completing Study 14-181-07 and Study 14-181-12 as well as newly enrolled ("De Novo") subjects qualifying for this study. Approximately 250 De Novo Subjects will be enrolled in the trial.
Number of Study Sites:	Approximately 100
Countries:	USA
Key Inclusion Criteria:	1. Clinical diagnosis of moderate to severe chronic low back pain for > 3 months before signing the informed consent form (ICF). 2. Newly enrolled subjects ("De Novo Subjects") who are treating their chronic low back pain with no less than 10 mg but no more than 60 mg of morphine sulfate equivalents/day for at least the 7 days prior to signing the ICF.. 3. Subjects who have completed Study 14-181-07 or Study 14-181-12 and meet entry criteria are eligible ("Rollover Subjects").
Study Design:	Open-label, multicenter, safety and tolerability study of NKTR-181 in the treatment of moderate to severe chronic low back pain or chronic noncancer pain. The study will be divided into the following 3 periods: • **Screening**: Up to 21 days • **Treatment**: Up to 52 weeks (inclusive of a 1-week taper) • **Follow-up**: Approximately 14 days after last dose of study drug

Test Product, Dose and Mode of Administration:	Name: NKTR-181 tablet(s) Dose, Route, and Frequency: NKTR-181 100-mg and 200-mg tablets will be administered orally twice daily (BID) as doses of 100 mg, 200 mg, 300 mg, 400 mg, 500 mg and 600 mg BID. Each dose will consist of tablets as follows: 100-mg dose = 1 x 100-mg tablet 200-mg dose = 1 x 200-mg tablet 300-mg dose = 1 x 200-mg tablet + 1 x 100-mg tablet 400-mg dose = 2 x 200-mg tablets 500–mg dose = 2 x 200-mg tablet + 1x 100-mg tablet 600-mg dose = 3 x 200 mg tablet Subjects should take NKTR-181 BID at approximately 8 AM and 8 PM.
Safety:	Key Safety Endpoints: Safety and tolerability will be evaluated based on the following: • Incidence, type, seriousness, and severity of adverse events (AEs) reported • Clinical laboratory evaluations • Electrocardiograms (ECGs) • Vital signs (respiratory rate, pulse, heart rate, blood pressure, and temperature) • Drug withdrawal as measured by the Clinical Opiate Withdrawal Scale (COWS) and the Subjective Opiate Withdrawal Scale (SOWS) • Incidence of aberrant drug behavior according to MADDERS™ assessment • Suicidality assessment (Columbia-Suicide Severity Rating Scale [C-SSRS])
Efficacy:	Efficacy Endpoint: • Efficacy will be evaluated based on the mBPI-SF administered at clinic visits.
Pharmacokinetics:	Plasma concentrations of NKTR-181 and selected metabolites will be tabulated by time and subject and assessed for relationship to dose during the treatment phase. These data will be pooled with those from other studies during population PK analyses and investigation of exposure-response relationships for efficacy and safety.
Statistical Methods:	Summaries for the assessment of long-term safety will be presented by De Novo and Rollover Subjects separately and for all subjects combined. The frequency and percentage of subjects experiencing treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to withdrawal from the study drug will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, preferred term, severity, and relationship to the study drug. Laboratory test results, vital signs, ECGs, SOWS, COWS, and change from baseline will be summarized using descriptive statistics. The relationship between duration of exposure and the frequency and severity of AEs will be examined. Time-to-event endpoints will be estimated using the Kaplan-Meier method. Change over time from baseline in each question and metric of the mBPI-SF will be summarized using descriptive statistics.

1.1 Study Schematic



1.2 Schedule of Assessments

Assessment Period	**Screening** Up to 21 days		**Treatment*** 52 weeks							**Follow-Up** 14 days		**Unscheduled Visit**
Visit	**1**	**2[1]**	**3**	**4, 5, 6, 7, 8, 9** (Flexible)	**10, 13, 17, & 20**	**11 &12**	**14-16 & 18-19**	**21/ET[2]**	**22/EOT**	**23**	**24/EOS**	
Dayse	≤ 21 days prior to Visit 3		1	Every 4-10 Days after previous visit	Every 30 (- 3)	Every 30 (- 3)	Every 30 (- 3)	D357 (+ 3)	D364 (+ 3)	72 hours	14 (± 2)	
Written informed consent	X											
Inclusion/exclusion criteria	X	X	X									
Demographics[3]	X											
PHQ-8[4]	X											
Medical history[5]	X											
Alcohol breath test[6]	X											
Physical examination[7]	X											
Vital signs[8]	X		X	X	X				X	X		X
12-lead electrocardiogram[9]	X				X				X			X
Clinical laboratory tests[10]	X		X	X	X	X		X	X	X	X	X
Pregnancy test[11]	X		X		X				X			X
Urine drug screen[12]	X		X	X	X							
eC-SSRS[13]	X		X		X			X	X			
Taper opioid analgesics[14]		X										
Dose titration assessment				X								
mBPI-SF[15]			X	X	X	X	X		X			X
COWS		X[16]	X[16]					X	X	X	X	X
SOWS[17]		X						X	X	X	X	
PK blood sample collection			X[18]	X[19]	X	X		X	X			X
Discontinue current analgesics			X									
Dispense/review/collect/instruct study drug			X	X	X	X	X	X[20]	X[21]			X
Opioid side effect training			X									
Abuse & diversion assessment				X	X	X	X		X			X
Concomitant medications[22]			⟷									X
Adverse events[22]			⟷									X

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index, COWS, Clinical Opiate Withdrawal Scale; eC-SSRS, electronic Columbia–Suicide Severity Rating Scale; ECG, electrocardiogram, EOS, end of study; EOT, end of treatment; ET, early termination; mBPI-SF, modified Brief Pain Index-Short Form; MSE, morphine sulfate equivalent; NRS numerical rating scale;, PHQ-8, Personal Health Questionnaire Depression Scale PK, pharmacokinetic; SOWS, Subjective Opiate Withdrawal Scale; TBL, total bilirubin.

* If at any time a subject does not tolerate study drug between protocol-mandated visits in the Treatment Period, per Investigator discretion, an unscheduled visit should occur.

FOOTNOTES:

1. There is no Visit 2 for Rollover Subjects.
2. If a subject was dosed with study drug and discontinues from the study before completing all of the scheduled assessments, then assessments for Visit 21/ET and all safety follow-up procedures should be completed for this subject.
3. Demographics include birth date, race/ethnicity, smoking status, height, weight, BMI, and sex at birth. For Rollover Subjects, all demographic information (except weight and BMI) will be carried forward from Study 14-181-07 or Study 14-181-12.
4. The Personal Health Questionnaire Depression Scale (PHQ-8) is a self-administered (i.e., the subject completes the scale) version of the Primary Care Evaluation of Mental Disorders for mood.. Subjects who score 10 or greater are not eligible to participate in this study.
5. Medical history includes medication history, history of substance or opioid abuse, medical/surgical history and concurrent illnesses and will be collected for all subjects and noted as to whether the condition is active. All relevant medical history will be collected and carried forward for Rollover Subjects. Ongoing adverse events that occurred in Study 14-181-07 and Study 14-181-12 will continue to be followed for Rollover Subjects.
6. Subjects who have a positive alcohol breath test will not be eligible for participation in this study.
7. Physical examination, including all major organ systems (general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric) will be performed for all De Novo Subjects. Physical examinations will not be conducted on Rollover Subjects.
8. Vital signs (respiratory rate, blood pressure, pulse, and temperature) will be measured after subjects have been resting for at least 5 minutes.
9. Subjects must be resting quietly in the supine position for > 5 minutes prior to collection of 12-lead ECG. During the treatment period, if an ECG is obtained and reveals that the subject's QTcF interval is > 500 msec or has an increase of ≥ 60 msec compared to baseline QTcF and confirmed with a second ECG within 30 minutes, treatment with study medication should be interrupted. In the event this occurs, the investigator should contact the Medical Monitor as soon as possible to discuss if the subject can continue on treatment or if the subject should stop study medication. Subjects who are discontinued will be required to complete the ET Visit and all safety follow-up procedures.
10. Clinical laboratory tests will include hematology, chemistry, and urinalysis at Visits 1, 10, 13, 17, 20, 21, and 22. Clinical laboratory tests will include only ALT, AST, ALP, and TBL at all other visits indicated. Clinical laboratory tests will be collected at Visits 23 and 24 only if results from previous visits were abnormal and clinically significant. Conjugated bilirubin is required only at Visit 1.
11. Pregnancy tests are required only for females of childbearing potential. Serum pregnancy test is required at Visit 1 (sent to central laboratory). Urine pregnancy test is required for subsequent visits. A negative pregnancy test result must be obtained before the administration of the study drug.

12. Urine dipstick drug test to screen for amphetamines, cannabinoids, cocaine, and opioids. Urine drug screen at visits 1 and 3 is done for De Novo subjects only. Urine drug screen at visit 4 is done for Rollover subjects only. No urine drug sceen will be conducted at visits 5, 6,7,8 and 9. Rollover Subjects will have urine collected for testing at central lab rather than being tested onsite. Opioids will not be tested for Rollover Subjects at Visits 1 and 3. De Novo Subjects on non-opioid analgesics at the time of Visit 1 must have a negative urine drug screen at Visit 1 and Visit 3. De Novo subjects on opioid analgesics at the time of Visit 1 must have a negative urine drug screen for all drugs except opioids. Dipstick urine drug screen tests will be provided by the sponsor.
13. The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is a subject self-report rating scale (i.e., the subject completes the scale) to lifetime and study-defined suicidal ideation and to assess suicidal ideation and behaviors since the time of the last visit. Subjects who answered YES to Question 4 or Question 5 within the past 12 months of the Baseline/Screening version of the eC-SSRS (Visit 1) are not eligible to participate in this study
14. De Novo subjects taking opioid analgesics will begin to taper their opioids over the next 7-14 days. Subjects must be on ≤ 30 morphine sulfate equivalents (MSE)/day for at least 3 days before proceeding to Visit 3.
15. The modified Brief Pain Inventory-Short Form (mBPI-SF) is a subject self-report rating (i.e., the subject completes the rating inventory) of pain and the impact of that pain on daily function.
16. De Novo Subject undergoing opioid taper will have COWS administered at Visit 2. All subjects will be administered COWS at Visit 3. COWS score must be ≤ 12 to enter the Treatment Period.
17. De Novo Subjects taking opioid analgesics at Visit 2 will complete a SOWS assessment daily while tapering their opioids over the next 7-14 days. All subjects will complete the SOWS on the two days prior to Visit 21 and daily between Visits 21 and 22. Subjects will then complete the SOWS twice daily for three days following the last dose of study drug (i.e., following Visit 22), then daily for the remainder for the study (i.e., through Visit 24).
18. A PK sample will be collected on all subjects at Visit 3. PK sample at Visit 3 must be collected prior to the subject taking the first dose of study medication for De Novo Subjects.
19. For subjects participating in the PK substudy, the dosing period PK collection may be completed when a stable dose has been identified. This may occur as early as the second visit following the start of a dose level. Subjects will be reminded to *not* take their AM dose on the planned dosing period PK collection visit. A predose sample will be obtained and the subject will take their AM dose in the clinic. PK samples will be obtained 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose.
20. Dispense taper study drug only for subjects completing study. Taper study drugs are not dispensed at Early Termination.
21. Study drug is not dispensed at Visit 22/EOT. Final study drug and rescue medication reconciliation conducted at Visit 22/EOT.
22. Collection of concomitant medications and adverse events will start after the signing of the ICF through study completion.

2.0 INTRODUCTION

2.1 Background

The Centers for Disease Control and Prevention estimates that over 100 million people in the United States (US) currently live with chronic pain, negatively impacting their quality of life and ability to function. Opioid analgesics are effective agents for the relief of moderate to severe pain; however, their clinical utility is limited by central nervous system (CNS)-related adverse effects, such as sedation, cognitive impairment, and respiratory depression. In addition, the issues of abuse and overdose-related death are significant public health problems. Although abuse-deterrent opioid formulations are currently available, the mechanisms built into these drugs can be subverted. An opioid analgesic with clinically meaningful analgesia, reduced CNS side effects, and reduced potential for abuse when taken orally may fill an important unmet medical need.

2.2 NKTR-181

NKTR-181 is a new molecular entity (NME) opioid analgesic that has been engineered using Nektar's advanced polymer conjugation technology platform. NKTR-181 is not a prodrug or a reformulation of a marketed opioid. The unique physiochemical properties of NKTR-181 impart its reduced rate of entry into the CNS and reduced opioid-related CNS adverse effects, including measures of abuse liability.

According to the Controlled Substances Act, NKTR-181 is currently designated as a Schedule II drug.

Please refer to the NKTR-181 Investigator's Brochure for detailed preclinical and clinical study data.

2.3 Study and Dose Rationale

This study is designed to provide adequate safety data in subjects with chronic low back pain or chronic noncancer pain in order to fulfill ICH requirements for new chemical entities. The dose range to be utilized is 100-mg NKTR-181 twice daily (BID) to 600-mg NKTR-181 BID. This dose range has been established based upon safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) data from three Phase 1 studies and the findings of a completed Phase 2 study in opioid-naïve subjects with moderate to severe chronic pain due to osteoarthritis of the knee. Phase 1 multiple ascending dose (MAD) studies established a dose that was not tolerated in opioid-naïve, healthy subjects (500-mg NKTR-181 every 12 hours [q12h]) and demonstrated 400-mg NKTR-181 q12h to be a safe and well-tolerated dose. In both studies, pupillometry

demonstrated robust CNS mu-opioid agonist effects consistent with known, approved extended-release/long-acting (ER/LA) opioids.

Evidence supporting the minimum dose of 100-mg NKTR-181 BID comes from the Phase 1 clinical program and a completed Phase 2, enriched-enrollment, randomized withdrawal design study in approximately 200 subjects with moderate to severe chronic pain due to osteoarthritis of the knee. In this Phase 2 study, 49% of subjects were randomized at 100-mg NKTR-181 BID and an average 40% reduction in average daily pain scores was demonstrated during the open-label titration period, consistent with known, approved opioid analgesics.

Recently, over 330 opioid-naïve subjects gradually titrated to a dose of 400mg q12h in the ongoing Phase 3 study (14-181-07) have shown a good safety and tolerability profile. In addition, the current long term safety study (14-181-08) and the second efficacy study (14-181-12) both allow inclusion of opioid-experienced subjects who are expected to tolerate higher doses of NKTR-181. Thus, titration to a maximum dose of 600mg q12h will be allowed in a measured step-wise approach starting at the lowest dose available so as to ensure tolerability while managing chronic pain.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

- To evaluate the long-term safety and tolerability of NKTR-181 in subjects with moderate to severe chronic low back pain or chronic noncancer pain.

3.2 Secondary Objective

- To evaluate the effectiveness of NKTR-181 as measured by the modified Brief Pain Inventory-Short Form (mBPI-SF).

4.0 STUDY DESIGN

4.1 Summary of Study Design

This is a multicenter, Phase 3, open-label safety and tolerability study in which approximately 600 subjects will receive open-label NKTR-181 for up to 12 months (52 weeks) from approximately 100 sites. Subjects may include newly enrolled subjects (approximately 250 De Novo Subjects) and subjects who have recently completed Study 14-181-07 or Study 14-181-12 (Rollover Subjects).

The study comprises 3 periods:

- **Screening:** Up to 21 days; Visits 1-2
- **Treatment:** 52 weeks; Visits 3-22
- **Safety Follow-Up:** Approximately 14 days after the last dose of study drug; Visits 23-24

This study will also investigate the PK of NKTR-181 in patients with chronic low back pain or chronic noncancer pain. Blood samples for PK analyses will be collected from all subjects according the Schedule of Assessments (Section **1.2**), and during a complete 12-hour dosing interval in a substudy of approximately 100 subjects at selected sites.

A schematic of the study design is presented in Section **1.1**, and the Schedule of Assessments is presented in Section **1.2**.

5.0 SELECTION OF STUDY POPULATION

5.1 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. Willing and able to provide written informed consent.

2. Willing and able to understand and comply with all study procedures, including swallowing oral medications.

3. Females or males, age 18 to 75 years of age at time of signing the informed consent form (ICF) (either for this study, Study 14-181-07, or Study 14-181-12), inclusive.

4. Body mass index (BMI) of 18-45 kg/m^2, inclusive.

5. In good general health as determined by medical history and physical examination; clinical laboratory tests and vital signs are not indicative of ongoing medical illness.

6. Women must be either surgically sterile (by means of hysterectomy or bilateral oophorectomy) or be post-menopausal (defined as spontaneous cessation of menses for at least 1 year. Women of childbearing potential must commit to use 2 highly effective forms of contraception such as a barrier contraception (e.g., 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 and continued until 2 weeks following the last dose of study drug.

   Males with female partners of child-bearing potential must agree to use a barrier contraception (e.g., 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 and continued until 2 weeks following the last dose of study drug. This criterion may be waived for male subjects who have had a vasectomy > 6 months before signing the ICF.

5.1.1 Rollover Subjects

Rollover Subjects must also meet the following criteria in order to be eligible for the study:

1. Must fully complete through the End of Treatment Visit of Study 14-181-07 or Study 14-181-12 prior to receiving study drug.

2. Have no break in treatment with study drug.

5.1.2 De Novo Subjects

De Novo Subjects must also meet the following criteria in order to be eligible for the study:

1. Are not eligible for Study 14-181-07 or Study 14-181-12.
2. Have a clinical diagnosis of moderate to severe chronic low back pain for > 3 months.
3. Be non-tolerant to opioid analgesics (i.e., currently taking no less than 10 mg but no more than 60 mg of morphine sulfate equivalents [MSE]/day for at least the 7 days prior to signing the ICF).
4. Negative urine drug screen (except opioids) and/or alcohol breathalyzer test during screening.
5. Not currently participating or have previously participated in another drug or biologic study within 30 days before signing the ICF.
6. Approximately 250 De Novo subjects will be enrolled.

5.2 Exclusion Criteria for ALL Subjects

Subjects who meet any of the following criteria will not be permitted entry into the study:

1. Females who are pregnant or breastfeeding.
2. Known history of hypersensitivity, intolerance, or allergy to opioids or acetaminophen.
3. Any history within the past year or current evidence of substance, alcohol, or opioid abuse.
4. Have not received any prior treatment for chronic pain.
5. Untreated moderate to severe sleep apnea.
6. Have chronic migraines as the primary pain condition.
7. Any history of seizures (with the exception of pediatric febrile seizures).
8. Diagnosed as having current cancer-related pain or having been diagnosed with or treated for cancer (excluding superficial basal cell carcinoma) within the past 5 years.

9. Currently have any pending application(s) for any disability/worker's compensation related to their pain.

10. Score of 10 or greater on the Personal Health Questionnaire Depression Scale (PHQ-8; **Kroenke, 2009**) at Visit 1.

11. 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 (eC-SSRS) at Visit 1.

12. Score of > 12 on the Clinical Opiate Withdrawal Scale (COWS) at Visit 3.

13. Clinically significant abnormalities in vital signs or clinical laboratory results (including hematology, chemistry, or urinalysis; total bilirubin [TBL] > 1.5 X upper limit of normal [ULN]; alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 2.0 X ULN; or creatinine clearance (calculated by Cockcroft-Gault) (< 60 mL/min.)

14. Have undergone surgical procedures within the 4 weeks prior to ICF or plans to have surgical procedure on source of pain during the time of participation in the study.

15. QTcF interval > 450 msec for males and > 470 msec for females, or any clinically significant abnormality on a 12-lead ECG per central read.

16. 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 (e.g., basal cell carcinoma).

17. 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

18. Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the subject from adhering to the protocol.

5.3 Removal of Subjects from Study Therapy or Assessment

Subjects may choose to discontinue the study at any time, for any reason, and without prejudice to further treatment.

Subjects may stop participating in or be withdrawn from the study for any of the following reasons but are to be followed for safety until resolution or for 14 days after the subject's last study visit, whichever comes first (see Section **10.1.5**):

- Lack of efficacy
- Occurrence of an unacceptable AE
- Opioid withdrawal
- Noncompliance of the subject with protocol-mandated procedures
- Continued participation is no longer in the subject's best interest in the opinion of the Investigator
- The subject is lost to follow-up. Before a subject is considered "lost to follow-up," study personnel must contact the subject at least twice by phone and once by mail with documented receipt(s)
- Death
- The study is terminated by the sponsor

During the treatment period, if an ECG is obtained and reveals that the subject's QTcF interval is > 500 msec or has an increase of ≥ 60 msec compared to baseline QTcF and confirmed with a second ECG within 30 minutes, treatment with study medication should be interrupted. In the event this occurs, the investigator should contact the Medical Monitor as soon as possible to discuss if the subject can continue on treatment or if the subject should stop study medication.

In the event of a subject's withdrawal, the Investigator will promptly notify the sponsor and make every effort to complete the ET assessments specified in the Schedule of Assessments (Section **1.2**).

6.0 TREATMENT PLAN

6.1 Screening Period (Visits 1-2)

Subjects will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations. Subjects will be eligible to enter the Screening Period in 2 ways:

- If they are currently enrolled in and expected to complete Study 14-181-07 or Study 14-181-12 through the End of Treatment Visit.; these subjects (either on NKTR-181 or placebo) may be eligible to enroll in this study as a **Rollover Subject**

- If they have a clinical diagnosis of moderate to severe chronic low back pain for > 3 months,and are non-tolerant to opioid analgesics (i.e., currently taking no less than 10 mg but no more than 60 mg MSE/day for at least the 7 days prior to signing the ICF); such subjects may be eligible to enroll in this study as a **De Novo Subject**

6.1.1 Rollover Subjects

Rollover Subjects should have no break in treatment with study drug. Visit 1 (Screening) will take place concurrently with a scheduled, on treatment clinic visit, during Study 14-181-07 and Study 14-181-12.

The End of Treatment Visit in Study 14-181-07 and Study 14-181-12, where the subject has completed tapering to the 100-mg NKTR-181 BID starting dose for this study, will be the first visit of the Treatment Period (Visit 3). There is no Visit 2 for Rollover Subjects.

6.1.2 De Novo Subjects

As of this protocol amendment, de-novo subjects with chronic low back pain and taking opioid containing medications are eligible to enroll. At Visit 2, De Novo Subjects will have their eligibility re-confirmed and concomitant medication and AEs will be assessed. **At Visit 2, De Novo Subjects who remain eligible will begin to taper current opioid analgesics.** De Novo Subjects who have been taking opioid-containing medications prior to study start (currently taking no less than 10 mg but no more than 60 mg MSE/day for at least the 7 days prior to signing the ICF) will decrease their opioid dose to no more than 30 mg MSE/day over the 7-14 days following Visit 2**. De Novo Subjects must be taking no more than 30 mg MSE/day for the 3 days prior to entry into the Treatment Period, in order to reduce the potential for opioid withdrawal when transitioning onto NKTR-181.** Subjects who experience breakthrough pain will be allowed rescue medication, as outlined in Section **6.4**

De Novo Subjects will record the Subjective Opiate Withdrawal Scale (SOWS) score daily and COWS at each clinic visit. Subjects experiencing opioid withdrawal will be treated appropriately according to the Investigator's clinical practice.

6.2 Treatment Period (Visits 3-20)

At Visit 3, subjects will be evaluated for entry into the Treatment Period. The Investigator or qualified sub-Investigator will complete the COWS (**Wesson, 2003**). The subject must score ≤ 12 to continue in the Treatment Period. Subjects who score greater than 12 will complete their Screening Period and end study participation and will be treated appropriately for withdrawal according to the investigators clinical practice. A Rollover Subject's last COWS assessment during Study 14-181-07 or Study 14-181-12 will satisfy this requirement. De Novo Subjects will discontinue all current analgesics including their prior opioid medication.

All subjects will begin dosing with 100-mg NKTR-181 BID with dose escalation in stepwise increments of 100-mg (e.g., from 200-mg BID to 300-mg BID) up to a maximum dose of 600-mg BID. All dose escalations will occur prior to visit 10. The dose of NKTR-181 will not exceed 600 mg BID in this study. Subjects will be instructed to take study drug BID, preferably at 8 AM and 8 PM. Subjects will also receive training on the recognition and management of constipation and other opioid related side effects. Side effects should be managed according to standard of care practices.

If a subject cannot tolerate 100-mg NKTR-181 BID, the subject will be discontinued from the study; these subjects will be required to complete the Early Termination (ET) visit (Visit 21/ET) and safety follow-up requirements. Refer to the Schedule of Assessments (Section **1.2**) for complete information regarding all assessments to be completed at the ET Visit and safety follow-up requirements.

Within 4-10 days after receiving the first dose of NKTR-181, subjects will return to the clinic at which time the Investigator will assess for tolerability and effectiveness. **Tolerability** and **effectiveness** will be assessed based on Investigator (or qualified sub-Investigator) clinical judgment. The Investigator (or qualified sub-Investigator) will determine whether the subject should remain at the current dose or titrate to the next dose level.

Subjects will return to the clinic for assessments of tolerability and effectiveness every 4 to10 days for up to 6 more times over a 5-week period until a stable dose is achieved. A **stable** dose is a dose that is effective and tolerated on two sequential visits (i.e., after at least 8 days of continuous treatment). Subjects who continue to tolerate study drug but do not have adequate relief of pain, based on the Investigator's clinical judgment, will continue dose escalations of 100-mg BID increments until the maximum dose of 600-mg NKTR-181 BID is reached.

Subjects who do not achieve adequate pain control at 600-mg NKTR-181 BID will be classified as non-responders and will be discontinued from further participation in the study. Non-responders will be required to complete the ET Visit (Visit 21/ET) and safety follow-up requirements.

Subjects will begin a monthly clinic visit schedule after a tolerable, effective and stable dose is achieved. **Doses of NKTR-181 may be adjusted upwards (up to a maximum dose of 600-mg NKTR-181 BID) or downwards as needed during the Treatment Period, based on the Investigator's (or qualified sub-Investigator's) assessment of effectiveness and tolerability.**

If at any time a subject cannot tolerate study drug between protocol-mandated visits, per Investigator discretion, an unscheduled visit should occur. For subjects with tolerability issues, the dose of NKTR-181 may be adjusted downwards, as necessary, based on the Investigator's clinical judgment in a stepwise 100-mg changes (e.g., 300-mg BID may be lowered to 200-mg BID). Dose adjustments may occur at unscheduled visits, however, an unscheduled visit will not replace a regularly scheduled visit, and the subject should be seen at all regularly scheduled visits.

Throughout the Treatment Period, subjects who experience breakthrough pain will be allowed rescue medication, as outlined in Section **6.4**. Note: If subject is off of study drug for 3 days or more, sponsor **must** be consulted prior to restarting study drug.

Subjects will report their pain experience at each visit using the mBPI-SF. At quarterly intervals, subjects will be assessed for vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory testing.

Following 51 weeks of NKTR-181 treatment, subjects will begin a 1-week taper from study drug. The NKTR-181 dose will be decreased over the 1-week period until all subjects are receiving 100-mg BID for at least 2 days. Subjects will return to the site for their End of Treatment visit (Visit 22/EOT). Following completion of Visit 22/EOT **or** completion of an ET Visit at any time after receiving study drug, subjects will proceed to the Safety Follow-Up Period.

The COWS and SOWS will be administered according to the Schedule of Assessments (Section **1.2**) to monitor for opioid withdrawal. Subjects experiencing opioid withdrawal will be treated appropriately according to the Investigator's clinical practice.

6.2.1 Pharmacokinetic Substudy

Blood samples for PK analysis will be collected from all subjects as described in the Schedule of Assessments (Section **1.2**). In addition, serial blood samples will be collected predose through

12 hours postdose in a subset of approximately 100 subjects at sites participating in the PK substudy.

At sites that agree to participate in the sub-study for PK analysis, all subjects will complete the dosing period PK collection when a stable dose has been identified. This visit may occur as early as the second visit following the start of a dose level. During the visit, subjects will complete all regular study procedures according to the Schedule of Assessments (Section **1.2**).

The PK collection visit will be scheduled to start in the morning, prior to the subject taking their morning dose of NKTR-181. Subjects should be reminded in advance of the visit to hold their morning dose of study drug and to bring their study drug supply to the clinic with them. Subjects will take their morning dose of NKTR-181 in the clinic after a predose PK sample is drawn.

To facilitate sample collection, a peripheral saline lock may be inserted for this visit. Refer to Section **8.1** for sample collection instructions.

6.3 Safety Follow-Up Period (Visits 23-24)

To capture evidence of withdrawal following discontinuation of study drug, all subjects (including ET subjects) will record SOWS measurements and be administered COWS assessments as described in the Schedule of Assessments (Section **1.2**).

During the Safety Follow-Up Period, clinical laboratory samples will be collected only if a prior laboratory result was considered abnormal and clinically significant.

6.4 Rescue Medication

Nektar will provide over-the-counter analgesics, including aspirin, acetaminophen, ibuprofen, and naproxen, for subjects who experience breakthrough pain. The subject, in consultation with the Investigator, will be allowed to choose which rescue medication(s) they will use. Subjects may use their selected rescue medications up to the maximum daily dose indicated on the label, at any time during the study.

6.5 Monitoring of Hepatic Transaminases

Hepatic function testing (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin [TBL]) will be performed according to the Schedule of Assessments (Section **1.2**). In the event that an elevation of ALT or AST > 3 X ULN is observed in an individual study subject, the subject should be contacted immediately and the procedures in **Table 1** should be followed. The Medical Monitor or

designee may be contacted for further discussion as needed. If a subject's study drug is interrupted for 3 days or more due to elevated hepatic transaminase levels, sponsor **must** be consulted prior to restarting study drug.

Table 1: Recommended Procedures for Subjects with Elevated Aminotransferase Test Results

Magnitude of Elevation in ALT or AST	Recommendation
> 3 to ≤ 8 X ULN	The subject should be seen for an unscheduled visit as soon as possible. At the unscheduled visit, the subject will be examined for clinical signs and/or symptoms of hepatic dysfunction [fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)]. Repeat hepatic function tests should be performed. Review the subject's current list of concomitant medications to assess for confounding medications that could cause elevations in AST and/or ALT. The subject should return every 48 to 72 hours for examination and repeat hepatic function testing until all test values are ≤ 2.0 X ULN or return to baseline.
> 3 X ULN and hyperbilirubinemia (> 1.5 X ULN)	Study medication should be permanently discontinued.
> 3 X ULN with ongoing, unresolved symptoms such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia (> 5%)	Study medication should be permanently discontinued.
> 5 X ULN for ≥ 2 weeks	Study medication should be permanently discontinued.
> 8 X ULN	Study medication should be permanently discontinued.

6.6 Prior and Concomitant Medications

Commencing with signing the ICF, all medications (both prescription and over-the-counter), vitamin and/or mineral supplements, and/or herbs the subjects take through the End of Study (EOS) (or ET) will be documented on the concomitant medication electronic case report forms (eCRFs). Documentation will include start and stop date, dose and route of administration, dosing frequency, and indication.

6.6.1 Prohibited and Restricted Medications

Subjects must not take any medication for chronic pain during the study (through the end of the Treatment Period) that was not provided by the sponsor (including rescue medication) and should be reminded of such at each study visit. Use of moderate to strong cytochrome P450 3A4 (CYP3A4) inhibitors and inducers is prohibited throughout the study.

Subjects who have been taking opioid-containing medications prior to study start (no less than 10 mg MSE/day and no more than 60 mg MSE/day) will be eligible to participate. However, the opioid must be tapered to no more than 30 mg MSE/day for at least 3 days prior to Visit 3, then completely discontinued prior to starting NKTR-181. Concomitant use of opioids with NKTR-181 is prohibited. Use of these medications will be documented on the concomitant medication eCRFs and will include start and stop date, dose and route of administration, dosing frequency, and indication.

6.6.2 Permitted Medications

Subjects may use the following medications while participating in this study:

- Medications for stable diseases (e.g., metformin for diabetes. Note that NKTR-181 may increase the exposure of metformin; serum glucose levels should be monitored closely)
- Hypnotics or barbiturates if stable for at least 21 days prior to screening
- Adjuvant analgesics (e.g., antiepileptics, muscle relaxants for muscle spasms, triptans for migraine [no opioid treatment for migraine will be allowed])
- Aspirin (≤ 325 mg) for cardiovascular prophylaxis
- Antiemetics for nausea and vomiting
- Psyllium husks, stool softeners, laxatives, enemas, and peripherally acting mu-opioid receptor antagonists (PAMORAs; e.g., MOVANTIK™) for opioid-induced constipation
- Medications to treat AEs or exacerbation of existing medical conditions
- Hormonal birth control
- Injected, topical, optical, or inhaled/nasal corticosteroids

Allowed rescue medication is described in Section **6.4**

6.7 Assigning Subject Numbers

Each subject will be assigned a unique subject number at Visit 1 of the Screening Period after signing the ICF. This unique subject number will be used on all subjects' study information. Subject numbers assigned to those subjects who fail the Screening Period or who withdraw from the Treatment Period will not be reassigned. Rollover Subjects will retain their subject ID from Study 14-181-07 or Study 14-181-12. For De Novo Subject, the first 4 digits will be the unique

site number (XXXX) followed by another 4-digit subject ID (YYYY), which together will be the unique subject number (e.g., XXXX-YYYY). The second set of 4 digits (YYYY) will be sequential within sites, starting with 8001 (indicating that the subject is a De Novo Subject).

7.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

7.1 Description and Formulation

7.1.1 Study Drug Description

NKTR-181 (referred to as the study drug) will be administered orally in tablet form. Study drug tablets are white-coated and are available in dosing strengths of 100 mg and 200 mg.

NKTR-181 dosage strengths to be evaluated are 100 mg, 200 mg, 300 mg, and 400 mg BID. Each dose of study drug will consist of matching tablets as follows:

- 100-mg dose = 1 × 100-mg NKTR-181 tablet
- 200-mg dose = 1 × 200-mg NKTR-181 tablet
- 300-mg dose = 1 x 200-mg NKTR-181 tablet + 1 x 100-mg NKTR-181 tablet
- 400-mg dose = 2 × 200-mg NKTR-181 tablets
- 500-mg dose = 2 × 200-mg tablets + 1 × 100-mg NKTR-181 tablet
- 600-mg dose = 3 × 200-mg NKTR-181 tablets

7.1.2 Rescue Medication

For subjects who are experiencing breakthrough pain, the sponsor will provide aspirin, acetaminophen, ibuprofen, and naproxen for use as rescue medication. Aspirin will be provided in 325-mg tablets for oral use. Acetaminophen will be provided in 500-mg tablets for oral use. Ibuprofen will be provided in 200-mg tablets for oral use. Naproxen will be provided in 220-mg tablets for oral use, as directed on label.

7.2 Study Drug Packaging and Labeling

NKTR-181 tablets are packaged in cold-sealed blister packs that are inserted into wallets and contained in a metalized pouch with a desiccant. Sufficient drug to provide up to 10 days of dosing will be packaged in a wallet. Pouches and wallets are minimally labeled to be compliant with US Food and Drug Administration (FDA).

7.3 Study Drug Storage

Study drug must be stored at controlled room temperature in a secure area. NKTR-181 is designated a Schedule II drug and must be handled, stored, and accounted for in accordance with all federal, state, and local regulations for a Schedule II drug.

7.4 Accountability and Reconciliation

The Investigator is responsible for ensuring accountability of all study medications supplied and appropriate storage and allocation of these supplies.

The Investigator is responsible for ensuring that all study drugs and rescue medications received at the site are inventoried and accountability performed and that dispensed study drug is recorded in both the eCRF and the study drug accountability logs. The Investigator or designee will verify study drug accountability with subjects during site visits. Any discrepancies should be investigated. The Investigator will not supply study drug or rescue medication to any person except those who are subjects in this study and will not dispense study drug or rescue medication from any site other than those listed on Form FDA 1572. Study medication and rescue medication may not be relabeled or reassigned for use by other subjects.

All unused or damaged study drug or rescue medication will be returned and unit counts will be performed whenever medication is returned. The site must account for all medication received. The site will retain and store all study drug and rescue medication until inventoried by the study monitor. All returned, unused, and damaged study drug and rescue medication will be returned to the sponsor or designee for destruction.

8.0 PHARMACOKINETIC MEASUREMENTS

This study will investigate the PK of NKTR-181 in patients with chronic low back pain or chronic noncancer pain.

8.1 Pharmacokinetic Blood Sample Collection

Blood samples for PK analysis will be collected from all subjects according to the Schedule of Assessments (Section **1.2**). Each participating site will be provided instructions for specimen collection, processing, storage, packaging, and shipment. **The first PK blood sample must be collected from all subjects prior to receiving the first dose of study drug (Visit 3)**.

In a PK substudy of approximately 100 subjects at selected sites, serial blood samples will also be collected during a complete 12-hour dosing interval as shown in **Table 2**.

Table 2: Pharmacokinetic Sample Collection Times in the PK Substudy

Time (hours)	Event[a]	Sample Name	Actual Time (*example)*
Predose	*Cryovial Preparation*		Approximately 15 - 30 min
Predose	*Sample collection*	Predose	Within 15 mins prior to dosing
0:00	**NKTR-181 dosing**		9:00 AM
0:30	*Sample collection*	0.5 hour postdose	9:30 AM
1:00	*Sample collection*	1.0 hour postdose	10:00 AM
2:00	*Sample collection*	2.0 hours postdose	11:00 AM
3:00	*Sample collection*	3.0 hours postdose	12:00 PM
4:00	*Sample collection*	4.0 hours postdose	1:00 PM
5:00	*Sample collection*	5.0 hours postdose	2:00 PM
6:00	*Sample collection*	6.0 hours postdose	3:00 PM
8:00	*Sample collection*	8.0 hours postdose	5:00 PM
12:00	*Sample collection*	12.0 hours postdose	9:00 PM

[a] Cryovials for PK sample collection must be prepared in advance of the first sample collection time on the day of collection and must undergo processing steps following sample collection according to the instructions provided in the Laboratory Manual.

8.2 Pharmacokinetic Analysis of Samples

Plasma concentrations of NKTR-181 and selected metabolites will be tabulated by time and subject and inspected for relationship to dose during the treatment phase. These data will be pooled with those from other studies during Population PK analyses and investigation of exposure-response relationships for efficacy and safety that will be specified in a population PK Analysis Plan.

9.0 EFFICACY ASSESSMENTS

9.1 Modified Brief Pain Inventory-Short Form (mBPI-SF)

The mBPI-SF (**Mendoza, 2006**) was developed to provide information on pain intensity and the degree to which pain interferes with patient functioning. Using a 0 to 10 numerical rating scale (NRS), subjects rate 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. With 0 being "no interference" and 10 being "interferes completely," the mBPI-SF asks for ratings of the degree to which pain interferes with mood, walking and other physical activity, work, social activity, relations with others, and sleep.

10.0 ASSESSMENT OF SAFETY

10.1 Adverse Events and Serious Adverse Events

10.1.1 Adverse Events Definition and Assessment

An AE is defined as any untoward medical occurrence in a subject who is administered a medicinal product and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, regardless of whether or not it is considered related to the medicinal product. An AE can also arise from any use of the drug and from any route of administration, formulation, or dose. This definition includes intercurrent illnesses or injuries, and exacerbation of preexisting conditions as well as events attributed to protocol-mandated procedures. Clinical laboratory abnormalities will only be reported as AEs if they are deemed clinically significant by the Investigator and/or are associated with signs and symptoms, require treatment, or require follow-up.

An AE does not include the following:

- A medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion); an AE is the underlying condition that leads to the procedure.
- Preexisting diseases or conditions present or detected before the start of study drug administration that do not worsen or increase in severity or frequency after the administration of study drug.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery for a condition that has not worsened on study, social and/or convenience admissions to grant families a respite in caring for a subject).
- Adverse events that start in Study 14-181-07 and Study 14-181-12 and are ongoing during this study will continue to be followed for Rollover Subjects.

10.1.2 Monitoring Adverse Events

All AEs will be assessed by the Investigator and recorded on the eCRF, including but not limited to the following: the event term, the date of onset and resolution, seriousness, severity, relationship to study drug, outcome, treatment of the event, and action taken with the study drug. Adverse events will be reported starting immediately after the subject has provided written informed consent through the EOS Visit (Visit 24/EOS).

Any AE attributed to a protocol-mandated procedure occurring after the subject has provided informed consent but prior to the first dose of study drug should be recorded on the eCRF as an AE.

Adverse events that are not attributed to protocol-mandated procedures occurring after signing of the informed consent but before the first dose of study drug will be reported as medical history.

Example 1:

Thrombophlebitis associated with a blood draw for assessments required prior to dosing per protocol is an event that is related to protocol-mandated procedures. In this scenario, the event of "thrombophlebitis" will be captured as an AE on the eCRF page, and it will be documented as being "unrelated" to study drug as applicable.

Example 2:

An ankle sprain following an unexpected fall from a flight of stairs while at home, after the subject has provided informed consent, but before the first dose of study drug, is clearly unrelated to any protocol-mandated procedures and would therefore be captured as medical history in the medical history section of the eCRF.

10.1.3 Grading of Adverse Events

The severity of an event and the seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of an event is based on the subject/event outcome (Section **10.1.6**). All AEs will be assessed for severity by the Investigator using the following criteria:

- Mild: The event results in mild or transient discomfort, not requiring or needing only minimal intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache);
- Moderate: The event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication); and
- Severe: The event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention.

10.1.4 Causality Relationship of Adverse Events

The relationship of each AE to the study drug will be evaluated by the Investigator using the following definitions:

- Not related: The AE is clearly not related to the study drug(s). The AE can be explained to be likely related to other factors such as concomitant medications or the subject's clinical state;
- Unlikely related: The AE is doubtfully related to the study drug(s). The current knowledge or information about the AE indicates that a relationship to the study drug is unlikely;
- Possibly related: The AE may be related to the study drug(s). A plausible temporal sequence exists between the time of administration of the study drug and the development of the AE, and it follows a known response pattern to the study drug. The AE is unlikely explained by the known characteristics of the subject's clinical state or other concomitant therapies or interventions administered to the subject; and
- Related: The AE is clearly related to the study drug(s). A plausible temporal sequence exists between the time of administration of the study drug and the development of the AE, and it follows a known response pattern to the study drug. The AE cannot be reasonably explained by the known characteristics of the subject's clinical state or other concomitant therapies or interventions administered to the subject. Additionally, the occurrence of this AE can be confirmed with a positive re-challenge test or supporting laboratory data.

The causality criteria of "related" and "possibly related" will be considered related to the study drug as applicable for regulatory reporting requirements.

10.1.5 Adverse Event Reporting and Follow-up

All ongoing AEs must be followed until resolution or for 14 days after the subject's last study visit, whichever comes first. If the AE has not completely resolved by the Visit 24/EOS, the final outcome of these ongoing AEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

For specific instructions on identifying, reporting, and following serious adverse events (SAEs), see Sections **10.1.7** and **10.1.8**.

10.1.6 Serious Adverse Event Definition

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening, i.e., in the opinion of the Investigator or sponsor, the AE places the subject at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death;
- Requires inpatient hospitalization or prolongation of an existing hospitalization that occurs during the course of a subject's participation in a clinical study, except for those that occur due to any of the following:
    - A surgery or procedure that was planned or anticipated before the subject entered the study and that is part of the planned study procedure; or
    - Nonmedical reasons, in the absence of an AE;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect; or
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed above.

Death is an outcome of an AE, and not an AE in itself. All fatal events regardless of causality must be reported. "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity. "Inpatient hospitalization" means that the subject has been admitted to a hospital for medical reasons for any length of time. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

10.1.7 Serious Adverse Event Reporting

All SAEs regardless of causality attribution occurring during the conduct of the study should be reported to Nektar Therapeutics Drug Safety or its designee within **24 hours** of when the site becomes aware of the event.

SAEs assessed by the Investigator as related to study drug and occurring after a subject's final study visit but within 14 days after the subject's last dose of study drug will also be reported to Nektar Therapeutics Drug Safety or its designee within **24 hours** of when the site becomes aware of the event.

Follow-up reports and any additional records (such as hospital records, consultant reports, and autopsy findings) should be emailed or faxed to Nektar Therapeutics Drug Safety or designee within **24 hours** of when the site becomes aware of the additional information. All SAEs and subsequent follow-up information must be reported to Nektar Therapeutics Drug Safety or its designee via:

- [redacted]
- [redacted]
- [redacted]

The Investigator must complete the SAE form, assess the causality relationship to the study drug, as applicable, and send the completed SAE form via email or fax to Nektar Therapeutics Drug Safety or designee.

Any medication or other therapeutic measures used to treat the event will be recorded.

All SAEs will be followed as described in Section **10.1.8**.

Reporting of SAEs to the Institutional Review Board (IRB) will be done in accordance with the standard operating procedures (SOPs) and policies of the IRB. Adequate documentation must be provided to the sponsor, showing that the IRB was properly notified. Serious AEs will be reported by the sponsor or designee to the regulatory authorities, per local regulations.

10.1.8 Serious Adverse Event Follow-up

All SAEs will be followed until resolution, stabilization of condition, return to baseline, or until follow-up is no longer possible.

Any SAE occurring after the end of the study for a subject but within 14 days of the subject's last dose of study drug will be captured only if assessed by the Investigator as related to study drug.

10.1.9 Expedited Reporting of Serious Adverse Events

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is considered "unexpected" and is assessed by the Investigator or the sponsor as related to the study drug. All SAEs deemed related to the study drug and not expected based on the most current NKTR-181 Investigator's Brochure are subject to expedited reporting to the applicable regulatory authorities by the sponsor. Therefore, the Investigator or site personnel must report all SAEs to Nektar Therapeutics Drug Safety or its designee within **24 hours** of first becoming aware of the event.

Fatal or life-threatening SUSARs will be reported to the regulatory authorities by the sponsor as soon as possible but no later than 7 calendar days after the sponsor or its designee has first knowledge of the minimum criteria for expedited reporting, with a full written report within 8 calendar days later. Nonfatal or nonlife-threatening SUSARs will be reported to the regulatory authorities, IRBs, and Investigators as soon as possible but no later than 15 calendar days after the sponsor or its designee has first knowledge of the SUSAR.

Reporting of SUSARs to all applicable regulatory authorities will be made by Nektar Therapeutics Drug Safety or its designee as per local country and regional regulations.

Notification of SUSARs to the central IRBs will be made by Nektar Therapeutics Clinical Operations or its designee in accordance with the SOPs and policies of the IRBs. Reporting to local IRBs will be made by the applicable study site personnel per their institutional guidelines. Adequate documentation must be provided to Nektar Therapeutics Clinical Operations or its designee showing that the local IRB was properly notified.

Reporting of SUSARs to all participating clinical Investigators will be done by Nektar Therapeutics Clinical Operations or its designee per local regulations.

10.2 Special Reporting Situations

10.2.1 Misuse or Abuse

Potentially aberrant drug behavior will be identified, assessed, and quantified using the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS^{TM}) with every study drug reconciliation and at the EOT Visit or ET Visit. The MADDERS™ consists of a set of forms completed by Investigators or qualified sub-Investigators when potentially abuse-related events are identified and upon the completion of each subject in the study (**Smith, 2013**).

10.2.2 Pregnancy

Pregnancy tests will be conducted according to the Schedule of Assessments (Section **1.2**). The sponsor must be notified within **24 hours** of the initial report and any follow-up reports of a male subject's female partner or a female subject becoming pregnant during the course of the study and for 2 months after the last dose of the study drug. Pregnancy, although reportable, is not considered an AE/SAE unless a female subject or male subject's female partner experiences signs or symptoms of pregnancy complications; however, the contact information for pregnancy reporting is the same as for SAE reporting and listed in Section **10.1.7**. Females who become pregnant will be followed every trimester until the outcome of the pregnancy is known. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring.

10.3 Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Assessments (Section **1.2**). Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided instructions for specimen collection, processing, storage, packaging and shipment. Results of laboratory tests will be provided to the site.

Clinical laboratory test data will be reviewed by the Investigator or qualified sub-Investigator. Additional clinical laboratory tests may be ordered at the Investigator's or qualified sub-Investigator's discretion. All additional testing will be performed by the designated central laboratory.

The Investigator or qualified sub-Investigator will review all lab results for clinical significance. Any laboratory result deemed clinically significant will be recorded as an AE as described in Section **10.1**.

Clinical laboratory tests that will be conducted for this study are listed in **Table 3**.

Table 3: Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
• Hemoglobin • Hematocrit • Red blood cells • White blood cells • Platelet count • Neutrophils (absolute) • Lymphocytes (absolute) • Monocytes (absolute) • Eosinophils (absolute) • Basophils (absolute) • Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration	• AST • ALT • ALP • Gamma-glutamyl transferase (GGT) • Albumin • Creatinine • Glucose • Total protein • TBL • Conjugated bilirubin • Sodium • Potassium • Chloride • CO_2 content or bicarbonate • Blood urea nitrogen	• Specific gravity • pH • Glucose • Protein • Bilirubin • Ketones • Leukocytes • Blood For positive protein, white blood cell or blood, a microscopic examination will include the following: • Red blood cells • White blood cells • Epithelial cells • Bacteria • Crystals • Casts

Abbreviations: AST; alanine aminotransferase; ALT, aspartate aminotransferase; ALP, alkaline phosphatase; CO2, carbon dioxide; TBL, total bilirubin.

10.4 Vital Signs

Vital sign measurement will be recorded according to the Schedule of Assessments (Section **1.2**). Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure (BP), and temperature. Pulse and BP measurements will be taken after the subject has been resting for at least 5 minutes.

10.5 Twelve-Lead Electrocardiograms

Twelve-lead electrocardiograms (ECGs) will be performed on a calibrated 12-lead machine according to the Schedule of Assessments (Section **1.2**). Subjects must be resting quietly in the supine position for at least 5 minutes before the 12-lead ECG. Interpretation of 12-lead ECGs and interval duration measurements will be performed by a designated ECG laboratory. Interpretation of ECGs and interval duration measurements will be provided to the site.

The Investigator or qualified sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance. During the treatment period, if an ECG is obtained and reveals that the subject's QTcF interval is > 500 msec or has an increase of ≥ 60 msec compared to baseline QTcF and confirmed with a second ECG within 30 minutes, treatment with study medication should be interrupted. In the event this occurs, the investigator should contact the Medical Monitor as soon as possible to discuss if the subject can continue on treatment or if the subject should stop study medication. Subjects who are discontinued will be required to complete the ET Visit and all safety follow-up procedures. Any ECG interpretation deemed to be clinically significant will be reported as an AE as described in Section **10.1**.

10.6 Medical History

Relevant and significant medication history, including history of substance or opioid abuse, medical/surgical history, and concurrent illnesses will be collected for all subjects and noted as to whether the condition is active. All relevant medical history will be collected and carried forward for Rollover Subjects.. Ongoing adverse events that occurred in Study 14-181-07 and Study 14-181-12 will continue to be followed for Rollover Subjects.

10.7 Pregnancy Tests

Serum pregnancy tests will be performed on women of childbearing potential at Visit 1 via the designated central laboratory. Women of childbearing potential must have a negative pregnancy test at Visit 1 in order to continue in the study. Urine pregnancy tests will be performed at the site on women of childbearing potential according to the Schedule of Assessments (Section **1.2**). Urine pregnancy tests will be provided by the sponsor. A negative pregnancy test result must be obtained before the administration of the study drug.

A pregnancy test does not need to be performed on women who are postmenopausal for at least 1 year or surgically sterile for at least 3 months before signing the ICF (Section **10.2.2**).

If a female subject or a male subject's female partner becomes pregnant, administration of the study drug must be discontinued immediately, and the sponsor notified within 24 hours of the initial report of the pregnancy.

10.8 Drug and Alcohol Screening

Subjects will undergo an alcohol breath test at the first visit during the Screening Period (Visit 1). Subjects who have a positive alcohol breath test will not be eligible for participation in this study. Disposable, individual use alcohol breathalyzers will be provided by the sponsor.

Urine samples will be collected for drug screening at Visits 1 and 3 and according to the Schedule of Assessments (Section **1.2**). Samples will be screened for amphetamines, cannabinoids, cocaine, and opioids. Urine drug screen at visits 1 and 3 is done for De Novo subjects only. Urine drug screen at visit 4 is done for Rollover subjects only. No urine drug screen will be conducted at visits 5, 6, 7, 8 and 9. Rollover Subjects will have urine collected for testing at central lab rather than being tested onsite. **Opioids will not be tested for Rollover Subjects at Visits 1 and 3.** De Novo subject on non-opioid analgesics at the time of Visit 1 must have a negative urine drug screen at Visit 1 and Visit 3. De Novo subjects on opioid analgesics at the time of Visit 1 must have a negative urine drug screen for all drugs except opioids. Dipstick urine drug screen tests will be provided by the sponsor.

10.9 Suicidality Assessment

The C-SSRS is a validated suicidality assessment instrument administered to prospectively assess the severity and frequency of suicidal ideation and behaviors. The C-SSRS identifies the full range of suicidal ideation and behavior and monitors change from visit to visit (**Posner, 2011**). For this study, the electronic version (validated eC-SSRS) will be used. The eC-SSRS is a fully structured, patient self-report clinical interview designed and developed for computer administration (**Mundt, 2010**; **Mundt, 2013**). The eC-SSRS will administer the "Baseline/Screening" version of the scale at Visit 1. It assesses suicidal ideation and behavior over the lifetime and over the past 12 months. The eC-SSRS will administer the "Since Last Visit" version of the scale at all the other required visits according to the Schedule of Assessments (Section **1.2**). The "Since Last Visit" version asks about any suicidal thought or behaviors the subject may have had since the last time the scale was administered.

10.10 Opioid Withdrawal

10.10.1 Clinical Opiate Withdrawal Scale (COWS)

Opiate withdrawal will be assessed using the COWS (**Wesson, 2003**). The scale consists of 11 evaluations of physical components of withdrawal and is based on clinician observations and questions.

The COWS will be administered by the Investigator or qualified sub-Investigator at Visit 3 prior to any other study assessments. The COWS must be ≤ 12 in order for the subject to continue participation in the study. Subjects who score greater than 12 will complete their Screening Period, end study participation, and be treated appropriately for withdrawal according to the Investigator's clinical practice. A COWS assessment will be administered by the Investigator or qualified sub-Investigator at Visits 3, 21, and 22/EOT (or ET Visit), and during the Safety Follow-Up Period at Visits 23 and 24/EOS. Subjects experiencing opioid withdrawal will be treated appropriately according to the Investigator's clinical practice.

10.10.2 Subjective Opiate Withdrawal Scale (SOWS)

Opiate withdrawal will be further assessed using the SOWS (**Handelsman, 1987**). The SOWS is a self-administered scale for grading opiate withdrawal symptoms. It contains 16 symptoms that the subject rates for intensity on a scale of 0 (not at all) to 4 (extremely). The SOWS will be completed by the subject according to the Schedule of Assessments (Section **1.2**). The SOWS may be completed in the clinic or at home depending on the requirements of the Schedule of Assessments.

Subjects will complete the SOWS at Visit 2 (De Novo Subjects only), 21, and 22/EOT (or ET Visit) in the clinic. Subjects will complete the SOWS daily between Visits 21 and 22/EOT. Subjects will complete the SOWS BID for 3 days following the last dose of study drug (from Visit 22/EOT or Early Termination) and then once daily throughout the remainder of the Safety Follow-Up Period (i.e., through Visit 24). Subjects experiencing opioid withdrawal will be treated appropriately according to the Investigator's clinical practice.

11.0 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

11.1 General Considerations

Statistical analyses of this study will be the responsibility of Nektar or its designee. Data collected from eCRFs, Interactive Voice and Web Response System (IXRS), or clinical laboratory evaluations will be listed by subject identification.

Generally, if not specified, continuous data will be summarized by descriptive statistics, including sample size, mean, standard deviation, median, and range. Categorical data will be summarized by the number and percentage of subjects. Data analysis will be performed using SAS® version 9.2 or greater.

Summaries for the assessment of long-term safety will be presented by De Novo Subjects and Rollover Subjects separately and for all subjects combined.

All analyses will be conducted on the Safety Analysis Set as defined in Section **11.3**.

Additional exploratory analyses of the data may be conducted as deemed appropriate. A detailed Statistical Analysis Plan (SAP) describing the statistical methodologies will be developed by the sponsor or its designee.

11.2 Determination of Sample Size

Approximately 600 subjects are expected to be enrolled (dosed). This number may increase or decrease to meet the International Conference on Harmonisation (ICH) regulatory exposure requirements for NKTR-181.

No formal sample size calculation will be performed for this long-term safety study. The sample size determination is based on the regulatory exposure requirement (ICH E1 A [1995]) that at least 300 subjects must complete 6 months (26 weeks) of NKTR-181 treatment and at least 100 subjects must complete 12 months (52 weeks) of NKTR-181 treatment.

11.3 Analysis Sets

Safety Analysis Set: The Safety Analysis Set includes all subjects who received at least 1 dose of study drug. Analyses of safety will be summarized for this analysis set.

Pharmacokinetic (PK) Analysis Set: The PK Analysis Set consists of all subjects who received at least 1 dose of NKTR-181 and have at least 1 PK data available.

11.4 Subject Disposition

Frequency counts and percentages of all subjects who are enrolled, receive study drug, and complete the study or discontinue early will be presented. Reasons for discontinuing the study will be summarized.

11.5 Demographic and Baseline Disease Characteristics

Demographic and baseline characteristics will be summarized descriptively for overall subjects.

11.6 Prior and Concomitant Medications

Prior and concomitant medications will be reported at each visit and coded to Anatomical, Therapeutic, or Chemical (ATC) level and preferred drug name according to the World Health Organization Drug Dictionary. Prior and concomitant medications will be summarized by treatment group, ATC classification, and preferred drug name.

11.7 Study Drug Exposure

The duration of study drug exposure will be summarized descriptively.

11.8 Rescue Medication

Rescue medication use over time will be summarized descriptively.

11.9 Safety Analyses

Safety assessments are important endpoints of this study. All safety analyses will be based on the Safety Analysis Set and will be presented by subject group (De Novo Subjects or Rollover Subjects) and for all subjects combined. Safety data such as AE reports, clinical laboratory test results, vital signs, and ECGs will be descriptively summarized. Suicidality assessments (C-SSRS) will also be tabulated.

11.9.1 Time to Discontinuation

The time to discontinuation from study drug due to AEs and time to discontinuation due to any reason will be summarized using Kaplan-Meier estimates.

11.9.2 Incidence of Aberrant Drug Behavior as Measured Using MADDERS™

The incidence of aberrant drug behavior as measured using MADDERS™ will be presented in a data listing.

11.9.3 Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.1 or later. The incidence of treatment emergent adverse events (TEAEs) will be presented by severity and relationship to study drug as perceived by the Investigator.

Adverse events, serious adverse events (SAEs), AEs by intensity, AEs by causality, AEs leading to death, and AEs leading to study discontinuation will be tabulated by System Organ Class and Preferred Term.

The event rate (per 100 patient years) of TEAEs by preferred term will be calculated and summarized descriptively. The relationship between drug exposure and the frequency and severity of AEs will be examined.

11.9.4 Clinical Laboratory Results

All clinical laboratory results and change from baseline will be summarized descriptively. Individual results that are outside of normal range will be summarized by shift tables and flagged in data listings. Observed values and change from baseline will be summarized over time.

11.9.5 Twelve-Lead Electrocardiogram Measurements

Electrocardiogram measurements will be tabulated and summarized. Observed values and changes from baseline in ECG parameters will be summarized descriptively. The proportions of subjects with potentially clinically significant values at post-baseline will be tabulated.

11.9.6 Vital Signs

Vital signs will be tabulated and summarized. Observed values and changes from baseline in vital signs will be summarized descriptively. The changes from baseline to each visit and to endpoint will be summarized. The proportions of subjects with potentially clinically significant values post-baseline will be tabulated.

11.9.7 Clinical and Subjective Opiate Withdrawal Scales

Individual item and total score from the COWS and the SOWS will be summarized over time.

11.10 Efficacy Analyses

11.10.1 Modified Brief Pain Inventory–Short Form

The mBPI-SF will be assessed at each visit during the study. The change from baseline and value at each visit will be summarized descriptively over time.

11.10.2 Time to Stabilization of Pain Scores During the Study

The time to stabilization of pain scores since the first dose during the study will be estimated using the Kaplan-Meier method.

11.11 Missing Data

Missing data will not be imputed. Final statistical considerations and methodology for handling missing data will be detailed in a separate document (SAP).

11.12 Pharmacokinetics

Individual subject PK concentration-time data, as well as summary statistics for each treatment (e.g., mean, median, standard deviation and/or standard error, and percent coefficient of variation [% CV]), will be tabulated. In addition, summaries for each treatment by sex will also be provided. Results from this study will be pooled with those from other Phase 3 studies for population PK analyses and to allow exploration of possible exposure-response relationships for efficacy and safety.

12.0 STUDY OR STUDY SITE TERMINATION

The sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor will implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

All protocol deviations and the reasons for such deviations are to be documented in the source documents and reported to the sponsor.

13.1 Changes to the Protocol

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/independent ethics committee (IEC), except when necessary to eliminate immediate hazards to the subject. Any deviation may result in the subject having to be withdrawn from the study and rendering that subject nonevaluable.

13.2 Monitoring

In accordance with Code of Federal Regulations 21 CFR 312.56, ICH GCP and local regulations, the clinical monitor will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR 312 Subpart D (Responsibilities of Sponsors and Investigators), ICH GCP, and local regulations, the monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs; ensure that all protocol requirements, applicable FDA, ICH GCP, and local regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects in this study. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the sponsor. The Investigational New Drug Application (IND) regulations also require the Investigator to allow authorized representatives of the sponsor, IRB/IEC, and FDA to inspect and make copies of the same records. The names and identities of the subjects need not be divulged to the sponsor; however, the records must nevertheless be inspected. This can be accomplished by blacking out the subject's name and replacing the name with the subject's study identification number. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the Investigator must inform the sponsor of these restrictions before initiation of the study.

13.3 Direct Access to Source Data/Documents for Audits and Inspections

Members of the sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA or other regulatory agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the Investigator should notify the sponsor immediately. The Investigator will ensure that the auditors have access to the clinical supplies, study site facilities, laboratory and that all data (including original source documentation) and all study files are available, if requested.

14.0 ETHICS

This study will be conducted to be consistent with the principles that have their origin in the Declaration of Helsinki and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with the ICH GCP guidelines (ICH E6), as well as with any and all applicable federal, state and/or local laws and regulations.

14.1 Institutional Review Board/Independent Ethics Committee Approval

Before enrollment of subjects into the study, as required by federal regulations (21 CFR § 56), ICH GCP and local regulations, the current protocol and ICF will be reviewed and approved by an appropriate IRB or IEC. A letter documenting the IRB or IEC approval must be received by the sponsor before the initiation of the study at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator will submit a progress report at least once yearly to the IRB or IEC. However, the frequency of these reports will depend on IRB or IEC requirements. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB or IEC per the IRB or IEC requirements, and in compliance with FDA regulations and ICH GCPs.

The Investigator, the sponsor, or designee shall promptly notify the IRB or IEC of any SAEs, or any other information that may affect the safe use of the study drug during the course of the study, per the IRB or IEC local requirements, and in compliance with FDA regulations and ICH GCPs.

14.2 Written Informed Consent

Written informed consent must be obtained from each subject or subject's legal representative before entering the study. Subjects/legal representatives will be informed of the nature of the study, and the ICF must be presented to each subject/legal representative in the language in which the subject/legal representative is fluent.

Informed consent will be obtained and documented by each subject or subject's legal representative prior to any protocol-specific procedures. Signed ICFs will be retained by the Investigator with the study records. Each subject/legal representative will be given a copy of the signed and dated ICF.

15.0 DATA HANDLING AND RECORD KEEPING

15.1 Data Collection Instruments and Source Documents

15.1.1 Study Records

During the study, the Investigator will maintain adequate records for the study, including a record of potential subjects screened and medical records, and records detailing the progress of the study for each enrolled subject, laboratory reports, eCRFs, signed ICFs, drug accountability records, correspondence with the IRB or IEC and regulatory agencies' AE reports, and information regarding subject discontinuation and completion of the study.

15.1.2 Data Collection Instruments (DCIs)

Data collection instruments (DCIs) (e.g., eCRFs, eCOA, paper forms) will be used in this study. These instruments are used to transmit the information collected during the performance of this study to the sponsor or sponsor's designee and regulatory authorities. The Investigator must review the DCIs for completeness and accuracy and must approve all data, including any changes made. Furthermore, the Investigator retains full responsibility for the appropriateness and accuracy of all data collected in the DCIs.

15.2 Retention of Essential Documents

All records and documents pertaining to the study including, but not limited to, those outlined above (see Section **15.1.1**) will be maintained by the Investigator for a period of at least 2 years after FDA approval of the drug or at least 2 years after withdrawal of the IND under which this study was conducted, whichever is longer. To avoid any possible errors, the Investigator will contact the sponsor before transferring or destroying any study records. The Investigator will also promptly notify the sponsor in the event of accidental loss or destruction of any study records.

16.0 PUBLICATION POLICY

All data are the property of the sponsor. However, it is intended that the results of the study will be published and/or presented at scientific meetings. Any formal presentation or publication of data from this study will be considered as a joint publication by the Investigator(s) and appropriate sponsor personnel. Authorship will be determined by mutual agreement.

The sponsor must receive copies of any intended communication in advance of submission for publication (at least 14 days for an abstract or oral presentation and 30 days for a journal submission). The sponsor will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged, and provide any relevant supplementary information.

The Investigator may be required to sign the clinical study report if it is to be used in a registration submission to the health authorities of some countries.

17.0 REFERENCES

1. Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.

2. Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse 1987;13(3):293-308.

3. Kroenke K, Strine TW, Spitzer RL, et al. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009;114(1-3):163-173.

4. Mendoza T, Mayne T, Rublee D, et al. Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis. Eur J Pain. 2006;10(4):353-361.

5. Mundt JC, Greist JH, Gelenberg AJ, et al. Feasibility and validation of a computer-automated Columbia-Suicide Severity Rating Scale using interactive voice response technology. J Psychiatr Res. 2010;44(16):1224-1228.

6. Mundt JC, Greist JH, Jefferson JW, et al. Prediction of suicidal behavior in clinical research by lifetime suicidal ideation and behavior ascertained by the electronic Columbia-Suicide Severity Rating Scale. J Clin Psychiatry. 2013;74(9):887-893.

7. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-1277.

8. Smith SM, Dart RC, Katz NP, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain. 2013;154(11):2287-2296.

9. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 2003; 35(2):253-259.

18.0 APPENDICES

Not applicable.