NEKTAR

**Nektar Therapeutics**

**Statistical Analysis Plan**

# 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

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| Protocol Number: | 14-181-08 |
| Protocol Version: | Amendment 2.0 22 Jan 2016 |
| Statistical Analysis Plan Version: | 1 |
| Date: | October 03, 2017 |

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# ABBREVIATIONS

| Abbreviation or Term | Definition |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ALP | alkaline phosphatase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| ATC | anatomical, therapeutic, or chemical |
| BID | twice daily |
| BMI | body mass index |
| BP | blood pressure |
| mBPI-SF | Modified Brief Pain Inventory-Short Form |
| CI | confidence interval |
| CLBP | chronic low back pain |
| COWS | Clinical Opiate Withdrawal Scale |
| CRO | clinical research organization |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CYP3A | cytochrome P 450 enzyme isoform 3A |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eC-SSRS | electronic Columbia-Suicide Severity Rating Scale |
| ET | early termination |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GSP | Good Statistical Practice |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IXRS | Interactive Voice and Web Response System |
| MADDERS™ | Misuse, Abuse, and Divergent Drug Event Reporting System |
| MedDRA | Medical Dictionary for Regulatory Activities |

| Abbreviation or Term | Definition |
|---|---|
| MMRM | mixed model repeated measures |
| NSAID | non-steroidal anti-inflammatory drug |
| NRS | Numeric Rating Scale |
| PHQ-8 | Personal Health Questionnaire Depression Scale |
| PK | pharmacokinetic |
| QTcF | corrected QT interval, Fridericia's correction |
| RR | respiratory rate |
| SAP | statistical analysis plan |
| SOC | system organ class |
| SOWS | Subjective Opiate Withdrawal Scale |
| TBL | total bilirubin |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| US | United States |
| WHO | World Health Organization |

# 1.0 ADMINISTRATIVE STRUCTURE

This study is being conducted under the sponsorship ofNektar Therapeutics. Statistical analyses will be performed by the Biometrics Department at Nektar Therapeutics and a contract research organization (CRO). Pharmacokinetic (PK) concentrations will be analyzed by Nektar India. Central clinical laboratories and central electrocardiograms (ECGs) are used for processing of laboratory safety specimens and ECG data. The Interactive Voice and Web Response System (IXRS) provider will manage the study drug distribution and inventory management.

# 2.0 INTRODUCTION

This document is a description of the planned statistical analyses of the data captured according to Nektar Therapeutics Protocol14-l8l-08, "A Phase 3 Multicenter, Open-Label, 52-Week Study to Evaluate the Long-Term Safety and Tolerability ofNKTR-181 in Subjects with Moderate to Severe Chronic Low Back Pain or Chronic Noncancer Pain".

This Phase 3 study will be conducted in accordance with the protocol, Good Clinical Practice (GCP), Good Statistical Practice (GSP), and all applicable regulatory requirements.

Analyses of pharmacokinetics will be addressed in a separate analysis plan.

# 3.0 STUDY OBJECTIVES

## 3.1 Primary Objective

The primary objective of the study is 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 Objectives

The secondary objective is to evaluate the effectiveness ofNKTR-181 as measured by the modified Brief Pain Inventory-Short Form (mBPI-SF).

# 4.0 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 ofNKTR-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 of protocol), and during a complete 12-hour dosing interval in a substudy of approximately 100 subjects at selected sites.

The three study periods are described in further detail in Study Protocol 14-181-08, Sections 6.1 to 6.3. A schematic of the study design is presented in Section 1.1, and the Schedule of Assessments is presented in Section 1.2 of the protocol.

## 4.1 Method of Randomization

Randomization is not applicable to this study.

# 5.0 STUDY ENDPOINTS

Key Safety Endpoint:

- 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 Endpoints:

- • The mBPI-SF assessed at clinic visits.

# 6.0 ASSESSMENTS

## 6.1 Efficacy Assessments

### 6.1.1 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.

## 6.2 Safety Assessments

Safety assessments include adverse events and serious adverse events, clinical laboratory tests, vital signs, twelve-lead ECGs, relevant and significant medication history (including history of substance or opioid abuse, medical/surgical history, and concurrent illnesses), pregnancy tests, drug and alcohol screening, Columbia-Suicide Severity Rating Scale (C-SSRS) suicidality assessment, Clinical Opiate Withdrawal Scale (COWS; **Wesson, 2003**), Subjective Opiate Withdrawal Scale (SOWS; **Handelsman, 1987**), and Misuse, Abuse, and Divergent Drug Event Reporting System (MADDERS™).

# 7.0 STATISTICAL CONSIDERATIONS

Statistical analysis of this study will be the responsibility of Nektar Therapeutics or its designee using the SAS® software version 9.4 or greater. Other analyses than those stated in the statistical analysis plan might be performed to gain information needed for the planning and analyses of future studies.

## 7.1 General Considerations

Generally, if not specified, continuous data will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum, maximum). Categorical data will be summarized by the number and percentage of subjects. All assessments, if necessary, will be summarized by Denovo naive, Denovo opioid experienced, Rollover by treatment received in feeder study. All statistical tests, as deemed necessary, will be 2-sided with a significance level of 5%.

## 7.2 Study Day

- The day of the titration start (Visit 3 date) will be called Titration Day 1. Visit 10 is the end of titration, the dose at visit 10 is defined as stable dose. The day of the stable dose (Visit 10 date) wil1 be called Day I . Study day will be calculated from the Day 1.
- Baseline is defined as the last non-missing observation prior to or on Titration Day 1. Change from baseline variables will be calculated as the post-baseline value minus baseline value.

## 7.3 Analysis Sets

Denovo opioid experienced subjects are defined as de novo subjects who are 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

Denovo naive patients are defined as de novo subjects who are not opioid experienced subjects.

**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 population.

**Completers Analysis Set:** All subjects in the Safety Analysis Set who complete 52-week exposure to NKTR-181.

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

## 7.4 Definition of Visit Window

Deviations are to be expected between subjects in the actual number of study days from Day 1 to when planned visits are carried out. To handle this for tables, figures, listings, and analyses where data are to be grouped by visit, visit numbers will be defined according to **Table 1**.

The following windows will apply only for summaries for value and change value by visit and summaries for abnormalities. If multiple assessments were performed within the visit window, the following will be applied:

- If there are multiple records in the same visit window, the measurement closest to the scheduled visit day will be used.
- If two visits are equidistant from the scheduled day, the later will be assigned to the visit.
- In the summaries for abnormalities, the worst case will be summarized for that visit regardless of how close to the scheduled visit it is.

## Table 1: Windowed Visits for Summary

| Visit | Scheduled Study Day | Windowed Visits for Labs | Windowed Visits for Vital Signs | Windowed Visits for ECG | Windowed Visits for CSSRS | Windowed Visits for mBPI | Windowed Visits for COWS |
|---|---|---|---|---|---|---|---|
| Baseline | First dose | <=first dose date | <=first dose date | <=first dose date | <=first dose date | <=first dose date | <=first dose date |
| The Titration visits | | go with the actual visit | go with the actual visit | NA | NA | go with the actual visit | NA |
| Visit 10 - Stable Dose | 1 | Day 1 | Day 1 | Day 1 | Day 1 | Day 1 | NA |
| Visit 11 | 30 | Day2 to 45 | NA | NA | NA | Day2 to 45 | NA |
| Visit 12 | 60 | Day46 to 75 | NA | NA | NA | Day46to 75 | NA |
| Visit 13 | 90 | Day76 to 105 | Day2 to 105 | Day2 to 105 | Day2 to 105 | Day76 to 105 | NA |
| Visit 14 | 120 | NA | NA | NA | NA | Day106 to 135 | NA |
| Visit 15 | 150 | NA | NA | NA | NA | Day136 to 165 | NA |
| Visit 16 | 180 | NA | NA | NA | NA | Day165 to 195 | NA |
| Visit 17 | 210 | Day106 to 225 | Day106 to 225 | Day106 to 225 | Day106 to 225 | Day196 to 225 | NA |
| Visit 18 | 240 | NA | NA | NA | NA | Day226 to 255 | NA |
| Visit 19 | 270 | NA | NA | NA | NA | Day256 to 285 | NA |
| Visit 20 | 300 | Day226 to one day before visit 21 | Day226 to one day before visit 21 | Day226 to one day before visit 21 | Day226 to one day before visit 21 | Day286 to one day before visit 21 | NA |
| Visit 21 | 357 from Titration Day 1 | go with the actual visit | NA | NA | go with the actual visit | go with the actual visit | go with the actual visit |
| Visit 22 | 364 from Titration Day 1 | go with the actual visit | go with the actual visit | go with the actual visit | go with the actual visit | go with the actual visit | go with the actual visit |
| 3-day Safety Follow-up | 3 days after ET visit | 3 to 6 days after ET visit | 3 to 6 days after ET visit | NA | NA | NA | 3 to 6 days after ET visit |
| 14-day Safety Follow-up | 14 days after ET visit | >=7 days after ET visit | NA | NA | NA | NA | >=7 days after ET visit |

Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; NA, not applicable.

# 8.0 STATISTICAL ANALYSES

## 8.1 Subject Disposition

Frequency counts and percentages will be tabulated for all subjects who complete or early discontinue from the study drug. Reasons for early discontinuation from study drug will be summarized by the highest titrated dose level.

## 8.2 Protocol Deviations

Subjects with major protocol deviations and violations will be listed and summarized by the highest dose level which a subject was titrated to and for each study site and for overall subjects. Major protocol deviations or violations may include but not limited to the followings:

Subjects who entered the study even though they did not satisfy the entry criteria;

1. Subjects who developed withdrawal criteria during the study but were not withdrawn from study medication;
2. Subjects who received prohibited medication.

Subjects with one or more protocol deviations or violations in the same category/type will be counted once for that category.

Protocol deviations and violations will be will be captured by searching relevant data fields reported in the clinical database using computer algorithms and site monitoring by clinical research associates. All deviations and violations will be reviewed by medical monitors. Final determination of major deviations and violations will be reviewed by the study team at regular intervals throughout the trial (including the clinical study manager, the Medical Monitor, and the statistician).

Subjects who have protocol deviation/violation will also be presented in a data listing.

## 8.3 Demographic and Baseline Disease Characteristics

Demographic and baseline characteristics including age (years) sex, race, ethnicity, smoking history, height (cm), weight (kg), body mass index (BMI; $kg/m^2$), and time since diagnosis of chronic noncancer pain will be summarized descriptively by highest titration dose level.

General medical history including past or present clinically significant medical conditions collected at screening will be summarized and presented in a data listing. Medical history of noncancer pain onset will be summarized.

Age will be calculated as follows:

$$\text{Age} = \frac{\text{Date of informed consent - Date of birth}}{365.25}$$ rounded down to the integer value in years.

BMI will be calculated as follows:

BMI = (weight in kilograms)/ (height in meters)$^2$

Time to noncancer pain onset will be calculated as follows:

$$\frac{\text{Date of informed consent - Date of onset noncancer pain}}{365.25}$$ rounded off to one decimal place in year.

Partial dates for date of onset in the calculation will be imputed. If year and month in the initial diagnosis are presented and day is missing, the first day of the month will be imputed. If year is presented but month/day is missing, missing day and month will be imputed as January 1. No imputation will be done if the year is missing.

## 8.4 Prior and Concomitant Medication

Prior and concomitant medications are recorded on the electronic case report form (eCRF) and coded to anatomical, therapeutic, or chemical code and preferred drug name using the World Health Organization (WHO) Dictionary (Version WHODRUG2014MAR01 WHO Drug Dictionary Enhanced [DDE]).

Prior medications are defined as medications taken before or on the date of first dose of NKTR-181 in 14-181-08 (Visit 3), including medications continued during treatment.

Concomitant medications are defined as medications taken on or after the date of first dose of NKTR-181 in 14-181-08 (Visit 3) including medications initiated prior to the date of first dose and continued during treatment, and medications initiated on or after the date of first dose.

Prior and concomitant medications will be tabulated separately for the Safety Population by WHO DDE ATC level 2 classifications, preferred term. The number and percent of subjects taking medication will be calculated. If the ATC level 2 classification is missing, the next non-missing level of classification will be used (level 1). If a subject reports the same ATC level 2 classification multiple times, the ATC level 2 classification will be incremented by one. As with ATC level 2 classification, if a subject reported multiple medications within the same preferred

term, the preferred term increments by one. Percentages will be calculated using the total number of subjects in the corresponding dose level in the Safety Population.

Prior and concomitant medications will be presented in a data listing.

## 8.5 Study Drug Exposure and Drug Compliance

Duration of exposure to study drug, cumulative dose of the study drug, and compliance of the study drug will be summarized for NKTR-181 on the Safety Analysis Set for the overall study period based on the Safety Analysis Set. The exposure duration of the study drug will be also summarized by time interval (e.g., ≥ 1 month, ≥ 2 months, ..., ≥ 12 months, and > 13 months).

The exposure duration (days) will be calculated as the number of days exposed to study drug: date of last dose - the date of first dose + 1.

The cumulative dose (mg) will be calculated as the sum of the number of tablets taken times the dosage per tablets at each dosage level. A subject's compliance of the study drug will be calculated according to the following:

$$\text{Compliance} = \frac{\text{number of tablets taken}}{\text{number of tablets planned}} \times 100$$

Compliance will be calculated based on the drug administration recorded in the CRFs. The number of tablets taken will be calculated as the total number of tablets dispensed minus the total number of tablets returned. If the number of returned tablets is missing due to any reason, it will be assumed that the subject took all dispensed tablets during that period. For those subjects who are lost to follow-up, it will be assumed that they took the number of dispensed tablets up until the last day of contact.

The number of tablets planned will be calculated as the prescribed number of tablets per day multiplied by the number of days potentially exposed to the study drug:

$$n \times (\text{the date of last dose} - \text{the date of first dose} + 1)$$

where n is related to the dose level. n is 2 for 100mg and 200mg, n is 4 for 300mg and 400mg, and n is 6 for 500mg and 600mg. The number of tablets planned will be adjusted for the first dose and the last dose time of the study drug.

## 8.6 Efficacy Endpoint

The mBPI-SF will be assessed at each visit during the study. The mean of the 4 intensity items (3-6) will be calculated and used as a measure of pain severity. The mean of the 7 interference items (9A-9G) will be calculated and used as a measure of Pain interference. Change from baseline to each month (visit) will be calculated for the Pain severity, Pain interference, and each individual score, if applicable.

If there are missing items when the pain severity score and pain interference score are calculated, the mean of the completed items in one dimension (dimensions include pain severity and pain interference) will be imputed to substitute the missing item, provided that more than 50% of the items in one dimension are completed (**Halling, 1999**).

The change from baseline and value for mBPI-SF dimentions and individual scores at each visit will be summarized descriptively over time.

In addition, an exploratory analysis will be performed on mBPI. The change from baseline to the end of the long term safety study will be analyzed. Baseline will be considered as last non-missing assessment on or prior to the first dose in this long term safety study (visit 3). The change from baseline will be analyzed using Mixed Model Repeated Measure (MMRM) analysis. The model will include change from baseline as dependent variable, baseline score as a covariate, subject's status (De Novo or Rollover with NKTR-181 or Rollover with Placebo), time, subject's status and time interaction as fixed effects. Point estimates on the Least Squared means over time will be calculated with corresponding 95% confidence intervals different dose levels. These analysis will be applied to both pain intensity and interference based on mBPI. The pain intensity means and LSmeans over time will be present graphically.

### 8.6.1 Responder Rates Based on mBPI Pain Intensity

Pain intensity score reduction based on the mBPI Pain Intensity subscale for each visit will be used to classify responder where:

Pain intensity score reduction = (mBPI Pain Intensity change from visit 3/visit 3 mBPI Pain Intensity)*100.

Three responder rates will be calculated at each time point, where responders are defined as subjects with:

- Pain intensity score reduced by 30% from visit 3 mBPI Pain Intensity,
- Pain intensity score reduced by 50% from visit 3 mBPI Pain Intensity,

- Pain intensity score reduced according to multiple cut-offs of 10% increments from the visit 3 mBPI Pain Intensity.

Responder rate = (no. of responders / total no. of subjects)*100, where total no. of subjects is the number of all the subjects in the analysis set. Subjects, who discontinue prior to the time point or have a missing pain score at that time point, will be counted as non-responders.

The number and percentage of responders in each dose level for pain intensity score reduction according to multiple cut-offs of 10% increments from baseline will be presented.

### 8.6.2 Time to Dose Level increase after the Titration Period

Time to dose level increase after the titration period will be calculated for all subjects. Dose level increase is defined as the first dose level increased from the stable dose to a stable higher dose level. The stable higher dose is defined as an increased dose taken by the subject for at least 2 weeks. The first time when the subject reached the stable higher dose is defined as the date of the dose level increase. The time to dose level increase is calculated as follows:

Date of dose level increase – the stable dose date+ 1.

The visit 10 date in the long term safety will be used as the stable dose date. The time to discontinuation will be estimated using the Kaplan-Meier method. If a subject completed the treatment per the protocol without dose increase (increase to a stable level) will be censored at the date of last dose of treatment.

### 8.6.3 Time to Discontinuation

Time to treatment discontinuation due to any reason will be calculated for all subjects. The time to discontinuation is calculated as follows:

Date of last dose – date of first dose + 1.

The first dose date is the first titration dose in the long term safety study. The time to discontinuation will be estimated using the Kaplan-Meier method. If a subject completed the treatment per the protocol, the subject will be censored at the date of last dose of treatment. Time to treatment discontinuation due to AE, lack of efficacy, and time to treatment discontinuation due to any reason will be summarized separately.

### 8.6.4 Rescue Medication

A subject's rescue medication use will be calculated based on drug accountability recorded in CRF. The mean number of occasions rescue medication per day will be presented by dose level

using descriptive statistics. The mean number of occasions rescue medication per day will be derived for each visit, if appropriate, as well as overall. The frequency of subjects using any rescue medication in terms of mean number of occasions rescue medication per day will be summarized by dose level by visit as well as overall.

The mean number of occasions rescue medication per day will be calculated as follows:

(sum of number of occasions of rescue medication) /
(exposure duration of study drug in days).

The number of rescue medication taken based on drug administration will be calculated as the total number of tablets dispensed minus the total number of tablets returned. If the number of returned tablets is missing, it will be assumed that the subject took the dispensed all tablets during that visit. For those subjects who are lost to follow-up, it will be assumed that they took the number of prescribed tablets up until the last day of contact.

## 8.7 Safety Endpoints

Safety analysis will be performed on the Safety Analysis Set.

### 8.7.1 Adverse events

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after the first administration of study drug (Visit 3) but on or prior to the end of study. Adverse events will be mapped to system organ class (SOC) and preferred term using MedDRA, version 17.1 or later.

The number and percent of subjects who had TEAEs, serious TEAEs, AEs with death outcome, AEs that led to study drug withdrawal, and AE of interest will be summarized. AE of interest is AEs which may indicate potential abuse. The list of abuse related AE of interest is in **Appendix 2** to **Appendix 4**. For withdrawal symptoms (Error! Reference source not found.), only the preferred terms occurred after last dose of treatment will be considered as withdrawal. Adverse events will also be summarized by SOC and preferred term and presented by maximum reported intensity and by Investigator's causality assessment. Corresponding data listings will be presented as well.

An AE that was present at treatment initiation, but resolved and then reappeared while the subject was on treatment, is a TEAE (regardless of the intensity of the AE when the treatment was initiated). If the start date of an AE is incomplete and cannot be categorized as occurring before or after the first dose, then the AE will be considered as TEAE. If the start time of AE is provided then the AE start date and time will be used to classify the AE as TEAE or not. If the

start time is not provided and the AE occurs on the same day of first study drug administration then the AE will be classified as TEAE.

The duration of AEs will be calculated, partial dates for AE start, will be imputed as follows: If AE start date is missing, the missing day will be imputed as the first day of the month if the month of AE occurrence is after the month of first dose date. If the month of AE occurrence is the same month as first dose then the missing day will be imputed as the same day as the first dose date. If the month of AE occurrence is not the same as the month of first dose date then the missing day will be imputed as the first day of the month. If AE start month is missing and AE start year is the same as the year of the first dose, the missing month will be imputed as the month of the first dose date. If AE start year is not the same as the first dose year, the missing month and day of AE occurrence will be imputed as January 1 of the year. If AE start year is missing, no imputation will be done. If there is insufficient data for AE start date to make this comparison, the AE will be considered as treatment-emergent.

Partial dates for AE stop date will be imputed as follows: if the day and month are both missing, the missing date will be imputed as the treatment termination date or 14 days after last dose of study drug whichever is later. If only the day is missing but month and year are present, the missing day will be imputed as the last day of the month. No imputation will be done if the year is missing. For unresolved/resolving/unknown AEs with a completely missing stop date, there will be no imputation.

### 8.7.2 Clinical and Subjective Opiate Withdrawal Scales

The COWS consists of 11 items to provide a description of the symptoms of withdrawal that can be directly observed by a physician interviewer: increased resting pulse rate, gastrointestinal upset, sweating, tremor, restlessness, yawning, pupil size, anxiety or irritability, arthralgias, piloerection of skin, and runny nose or tearing.

The total score of the COWS is the sum of the responses to the 11 items, which can range from 0 to 48, with higher scores indicating greater withdrawal severity. If there are missing items when the total score is calculated, the total score will be set to missing. Total score between 5 and 12 inclusive indicates mild withdrawal; between 13 and 24 inclusive indicates moderate withdrawal; between 25 and 36 inclusive indicates moderately severe withdrawal; and total score greater than 36 indicates severe withdrawal.

The SOWS is a self-rating scale which has been shown to be a reliable and valid measure of the opiate withdrawal syndrome. It contains 16 symptoms whose intensity the subject rates on a 5-point scale of 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely. The total

score is a sum of item ratings, and ranges from 0 to 64. If there are missing items when the total score is calculated, the total score will be set to missing.

The total score for COWS and SOWS will be calculated at all scheduled assessment time points.

The COWS and SOWS total scores will be summarized descriptively. The total score of COWS will be summarized categorically by dose level.

### 8.7.3 C-SSRS

The C-SSRS is a 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. The C-SSRS will be administered 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 C-SSRS will be administered the "Since Last Visit" version of the scale at all the other required visits according to the scheduled assessments. 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.

Suicidal Ideation Score: The maximum suicidal ideation category (1-5 on the CSSRS) present at the assessment. Assign a score of 0 if no ideation is present. Suicidal ideation is a "yes" answer at any time during treatment to any one of the five suicidal ideation questions on the C-SSRS.

Suicidal behavior: A "yes" answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.

Suicidal ideation or behavior: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

The score at each assessment for each patient will be used for determining treatment emergence.

Treatment-emergent suicidal ideation: An increase in the maximum suicidal ideation score during treatment from baseline (excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale).

Treatment-emergent serious suicidal ideation: An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment from not having serious suicidal ideation (scores of 0-3) at baseline (excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale).

Emergence of serious suicidal ideation: An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment from no suicidal ideation (scores of 0) at baseline (excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale).

An improvement in suicidal ideation at a time point is considered as a decrease in suicidal ideation score at the time point of interest (e.g., the last measurement during treatment) from the baseline measurement.

Emergence of suicidal behavior compared to all prior history: The occurrence of suicidal behavior (Categories 6-10) during treatment from not having suicidal behavior (Categories 6-10) prior to treatment.

Number of subjects with Suicidal Ideation and Suicidal Behavior during treatment will be summarized in a table. Number of subjects with suicide-related Treatment-Emergent events and shift-table of changes in C-SSRS Categories from baseline during Treatment will be summarized as well.

### 8.7.4 MADDERS™

Abuse-related events, also called misuse- and abuse-related events, consists of a related group of phenomena that include actual abuse (i.e., use intended to produce a euphoric effect), misuse (use outside of prescribing instructions to produce a therapeutic effect), suicide-related events, therapeutic error, overdose, diversion, addiction, withdrawal, tampering, and diversion (**Smith, 2013**). Until recently, these terms were used inconsistently, and consensus definitions of these terms for the purpose of clinical trials were not available, making it impossible to reliably quantify the rate of these events in studies.

Investigators are trained to identify any potentially abuse-related event, and at the time of identifying the event complete a Supplemental Adverse Event Form. In addition, a Supplemental Drug Accountability Form is completed for any subjects who have drug accountability discrepancies identified at any visit. Each time either of these events is completed, a Classification Form is completed by the investigator indicating the investigator's classification of the event in question. Finally, all subjects complete an interview-based assessment at the final visit of the study to identify any undetected abuse-related events that may have occurred during the study. Any events that have led to the completion of a Classification Form are provided to an Adjudication Committee for review and final classification.

Incidence of aberrant drug behavior according to MADDERS™ assessment will be summarized. Incidence per person-month will be summarized if applicable.

### 8.7.5 Clinical Laboratory Evaluations

All clinical laboratory results and change from baseline values will be summarized descriptively by treatment arm. Change from baseline via -categorical variable indicating whether the individual values are inside or outside the lab normal ranges will be tabulated using shift tables.

In addition to change from baseline summaries, hepatic function results (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin [TBL]) will be summarized by treatment arm for an elevation of ALT or AST >1 to ≤ 3 X ULN; > 3 to ≤ 5 X ULN, and > 5 to ≤ 8 X ULN.

Individual results that are outside of normal range will be flagged in data listings.

### 8.7.6 Vital Signs and ECGs

The following variables will be derived for systolic and diastolic supine blood pressure and supine pulse rate and/or ECG parameters:

- Change from baseline.
- Treatment-emergent change from baseline, see **Appendix 1** (treatment-emergent decrease/increase).
- Categorical variable indicates whether the individual values are inside or outside the predefined clinical relevant ranges.
- Overall interpretation of ECGs as normal or abnormal will be recorded at the visits as specified in the assessment schedule.

Descriptive statistics will be presented for scheduled visits on observed data. In addition to the descriptive statistics, treatment-emergent abnormal value and shifts from baseline to post-baseline result will be presented. All the summaries mentioned above will be performed by the dose level in which subjects were titrated.

Data listings with flagging for values outside normal ranges will be presented.

## 8.8 Pharmacokinetics and Pharmacodynamics

Pharmacokinetics/pharmacodynamics will be analyzed on PK Analysis Set. The Nektar Therapeutics Pharmacology group will estimate PK parameters and analyze PK/PD data. Detailed descriptions of PK analysis will be included in a PK analysis plan developed separately.

## 8.9 Handling of Multiplicity

No corrections for multiplicity will be made.

## 8.10 Handling Missing Values

No other missing data imputation will be performed unless otherwise stated in this document.

# 9.0 CHANGES OF ANALYSIS FROM PROTOCOL

Not applicable.

## 10.0 REFERENCES

1. 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.
2. Halling J., Langstrom G., Wiklund I. Handling missing data in Quality of Life questionnaires: experiences from clinical trials. 6th Annual Conference of the International Society for Quality of Life Research, Barcelona, Spain, Nov 3-6, 1999.
3. 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.
4. 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.
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*Reference for Vital Sign and ECG Ranges*

## Extended Reference Ranges for Vital Signs Used in the Statistical Analyses

| Variable Type | Variable | SI Unit | Outside lower limit if | Outside upper limit if | Treatment emergent decrease if | Treatment emergent increase if |
|---|---|---|---|---|---|---|
| SBU | SBP supine/standing | mmHg | <90 | >160 | <-30 | >30 |
| DBU | DBP supine/standing | mmHg | <50 | >100 | <-15 | >15 |
| PLU | Pulse rate supine | beats/min | <40 | >100 | <-20 | >20 |
| SBD | Standing-supine change in SBP | mmHg | <-25 at least once at 2 or 5 min | NA | NA | NA |
| DBD | Standing-supine change in DBP | mmHg | <-15 at least once at 2 or 5 min | NA | NA | NA |

Abbreviation: NA, not applicable

## Reference Ranges for ECG Variables

| Interval | Unit | Outside lower limit if | Outside upper limit if | Treatment emergent decrease if | Treatment emergent increase if |
|---|---|---|---|---|---|
| RR | ms | <400 and <500 | >1333 and >2000 | NA | NA |
| PR interval | ms | <100 | >240 | NA | >40 and >60 |
| QRS | ms | <70 | >120 | NA | >15 and >30 |
| QTc | ms | <300 | >450, >480 and >500 | NA | >30 and >60 |

Abbreviation: NA, not applicable

***Abuse related adverse events of interest (MedDRA 18.0)***

| System Organ Class | Higher Level GT | Higher Level Term | Preferred term |
|---|---|---|---|
| Nervous system disorders | | | Dizziness |
| Psychiatric disorders | Mood disorders and disturbances NEC | Emotional and mood disturbances NEC | Euphoric Mood |
| | | | Mood altered |
| | | | Elevated mood |
| | | Affect alterations | Inappropriate affect |
| General disorders and administration site conditions | General system disorders NEC | Feelings and sensations NEC | Feeling drunk |
| | | | Feeling abnormal |
| | | | Feeling of relaxation |
| Nervous system disorder | Neurological disorders NEC | Disturbances in consciousness NEC | Sedation |
| General disorders and administration site conditions | General system disorders NEC | Asthenic conditions | Sluggishness |
| Nervous system disorder | Neurological disorders NEC | Disturbances in consciousness NEC | Somnolence |

### *Abuse potential adverse event terms of interest characterized as psychotomimetic in nature*

| System Organ Class | Higher Level GT | Higher Level Term | Preferred term |
|---|---|---|---|
| Psychiatric disorders | Psychiatric and behavioural symptoms NECPsychiatric disorders | Abnormal behaviour NEC | Abnormal behaviour |
| Nervous system disorders | Sleep disturbances (incl subtypes) | Abnormal sleep-related events | Abnormal dreams |
| Psychiatric disorders | Schizophrenia and other psychotic disorders | Psychotic disorder NEC | Acute psychosis |
| | Mood disorders and disturbances NEC | Emotional and mood disturbances NEC | Anger |
| | Anxiety disorders and symptoms | Anxiety symptoms | Agitation |
| | Deliria (incl confusion) | Confusion and disorientation | Confusional state |
| | Communication disorders and disturbances | Communications disorders | Communication disorder |
| | Deliria (incl confusion) | Deliria | Delirium |
| | Disturbances in thinking and perception | Delusional symptoms | Delusion |
| | Schizophrenia and other psychotic disorders | Delusional disorders | Delusional disorder, unspecified type |
| | Dissociative disorders | Dissociative states | Depersonalisation |
| | Disturbances in thinking and perception | Perception disturbances | Derealisation |
| | Deliria (incl confusion) | Confusion and disorientation | Disorientation |
| | Dissociative disorders | Dissociative states | Dissociation |
| | | | Dissociative disorder |
| | Cognitive and attention disorders and disturbances | Cognitive and attention disorders and disturbances NEC | Disturbance in attention |
| Nervous system disorders | Dissociative disorders | Dissociative states | Dysarthria |
| Psychiatric disorders | Mood disorders and disturbances NEC | Emotional and mood disturbances NEC | Emotional disorder |
| Psychiatric disorders | Anxiety disorders and symptoms | Fear symptoms and phobic disorders (incl social phobia) | Fear |
| | | Perception disturbances | Flashback |

| System Organ Class | Higher Level GT | Higher Level Term | Preferred term |
|---|---|---|---|
| | Disturbances in thinking and perception | Thinking disturbances | Flight of ideas |
| | | Perception disturbances | Hallucination |
| | | | Hallucination, auditory |
| | | | Hallucinations, mixed |
| | | | Hallucination, olfactory |
| | | | Hallucination, synaesthetic |
| | | | Hallucination, tactile |
| | | | Hallucination, visual |
| | Personality disorders and disturbances in behaviour | Behaviour and socialisation disturbances | Hostility |
| Nervous system disorders | Neurological disorders NEC | Paraesthesias and dysaesthesias | Hypoaesthesia |
| Psychiatric disorders | Disturbances in thinking and perception | Perception disturbances | Illusion |
| | Personality disorders and disturbances in behaviour | Behaviour and socialisation disturbances | Indifference |
| | Mood disorders and disturbances NEC | Emotional and mood disturbances NEC | Irritability |
| | Dementia and amnestic conditions | Amnestic symptoms | Memory impairment |
| | Cognitive and attention disorders and disturbances | Cognitive and attention disorders and disturbances NEC | Mental impairment |
| | Mood disorders and disturbances NEC | Fluctuating mood symptoms | Mood swings |
| Musculoskeletal and connective tissue disorders | Muscle disorders | Muscle tone abnormalities | Muscle rigidity |
| Psychiatric disorders | Sleep disorders and disturbances | Parasomnias | Nightmare |
| Nervous system disorders | Neurological disorders NEC | Paraesthesias and dysaesthesias | Paraesthesia |
| Psychiatric disorders | Personality disorders and disturbances in behaviour | Behaviour and socialisation disturbances | Paranoia |

| System Organ Class | Higher Level GT | Higher Level Term | Preferred term |
|---|---|---|---|
| | Schizophrenia and other psychotic disorders | Psychotic disorder NEC | Psychotic disorder |
| Nervous system disorders | Neurological disorders NEC | Sensory abnormalities NEC | Sensory disturbance |
| Psychiatric disorders | Disturbances in thinking and perception | Delusional symptoms | Somatic delusion |
| | | Perception disturbances | Somatic hallucination |
| | Psychiatric and behavioural symptoms NEC | Abnormal behaviour NEC | Staring |
| | Sleep disorders and disturbances | Dyssomnias | Stupor |
| | Disturbances in thinking and perception | Thinking disturbances | Thinking abnormal |
| | | | Thought blocking |
| | Schizophrenia and other psychotic disorders | Brief psychotic disorder | Transient psychosis |

### *Drug Withdrawal- Related Adverse Events Occurring Following Drug Discontinuation (Preferred Terms; MedDRA 18.0)*

| System Organ Class | Preferred term |
|---|---|
| Cardiac disorders | Syncope |
| Gastrointestinal disorders | Vomiting |
| | Diarrhoea |
| | Nausea |
| General disorders and administration site conditions | Hyperhidrosis |
| | Pain |
| Musculoskeletal and connective tissue disorders | Chills |
| Nervous system disorders | Headache |
| | Agitation |
| | Dyssomnia |
| | Insomnia |
| | Poor quality sleep |
| | Syncope |
| | Terminal insomnia (lower level term of interest: early morning awakening) |
| | Tremor |
| Psychiatric disorders | Agitation |
| | Anhedonia |
| | Anxiety |
| | Dysphoria |
| | Dyssomnia |
| | Dysthymic disorder |
| | Feeling of despair |
| | Insomnia |
| | Morose |
| | Negative thoughts |
| | Nervousness |

| System Organ Class | Preferred term |
|---|---|
| | Obsessive thoughts |
| | Terminal insomnia (lower level term of interest: early morning awakening) |
| | Depressed mood |
| | Depression |
| | Poor quality sleep |
| Skin and subcutaneous tissue disorders | Hyperhidrosis |
| Vascular disorders | Syncope |

**Nektar Therapeutics**

# PHARMACOKINETIC ANALYSIS PLAN

## 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**

[redacted] [redacted]

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**Protocol Version** Amendment 2.0 15 Jan 2016

**Version:** 1.0 Final

**Date:** 17 October 2017

# SIGNATURE PAGE

# LIST OF ABBREVIATIONS

| | |
|---|---|
| °C | Degrees Centigrade |
| $AUC_{(0\text{-}last)}$ | Area under the plasma drug concentration-time curve (from time=0 hr to the last measurable concentration) |
| $AUC_{(0\text{-}inf)}$ | Area under the plasma drug concentration-time curve (from time=0 hr to infinity) |
| BLQ | Below the limit of quantification |
| $C_{max}$ | Maximum observed plasma drug concentration |
| cm | Centimeter |
| g | Gram |
| hr | Hour |
| kg | Kilogram |
| L | Liter |
| mg | Milligram |
| mL | Milliliter |
| N | Sample Size, Number of Subjects |
| PK | Pharmacokinetic/Pharmacokinetics |
| SD | Standard Deviation |
| T | Time |
| $T_{max}$ | Time at which $C_{max}$ is observed |
| $t_{1/2}$ | Terminal half-life |

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# 1.0 INTRODUCTION

NKTR-181 is a new molecular entity (NME) opioid analgesic designed with the intent of preserving opioid analgesic effectiveness, while reducing the rate and extent of entry of the molecule into the CNS, and thereby reducing CNS-related side effects.

The intent of this document is to provide guidance for the PK analysis of data captured according to protocol number 14-181-08, "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 Non-cancer Pain". This PK analysis plan (PKAP) describes the planned analysis of the PK data and the description of the tables, listings, and figures (TLFs) to be presented in the Clinical Study Report (CSR). A separate statistical analysis plan provides the description of the planned statistical analyses to support the primary and secondary objectives of the study.

This PKAP extends and supersedes the descriptions of PK analyses provided in the protocol; any substantially different analysis will be identified in the CSR. Should additional analyses beyond those described in the PKAP be required, they may be performed and will be identified in the appropriate section of the CSR. Deviations from this PKAP, both substantial and non-substantial, will be documented in the CSR.

# 2.0 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of NKTR-181 in subjects with moderate to severe chronic low back pain or chronic non-cancer pain.

## 2.2 Secondary Objectives

The secondary objective of the study is to evaluate the effectiveness of NKTR-181 as measured by the modified Brief Pain Inventory-Short Form (mBPI-SF).

## 2.3 Objective of the Pharmacokinetic Analysis

To characterize the pharmacokinetics of NKTR-181 and its metabolites oxycodol and oxycodone in subjects enrolled in the PK sub-study using noncompartmental analysis.

To evaluate NKTR-181 pharmacokinetics using sparse samples collected in subjects enrolled in the study.

# 3.0 STUDY DESIGN

## 3.1 General Description

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. Study may include newly enrolled subjects (approximately 250 De Novo Subjects) and subjects who have recently completed Study 14-181-07 (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

The three study periods are described in further detail in Study Protocol 14-181-08, Sections 6.1 to 6.3. A schematic of the study design is presented in Section 1.1, and the Schedule of Assessments is presented in Section 1.2 of the protocol.

## 3.2 Pharmacokinetic Assessment

This study will investigate the PK of NKTR-181 in patients with chronic low back pain or chronic non-cancer pain. Sparse blood samples for PK analysis will be collected from all subjects at follows: Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 17, 20, 21, 22, Unscheduled visits, end of treatment, and Early Termination visits.

In addition, a subset of approximately 100 subjects will be participating in the PK sub-study. The PK sub-study commences after a stable dose has been identified. This may occur as early as the second visit following the start of the Treatment phase. 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. PK samples will be obtained 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours postdoc.

# 4.0 PHARMACOKINETIC ENDPOINTS

## 4.1 Pharmacokinetic Endpoints for the PK Sub-study

The endpoints for PK analyses include non-compartmental PK parameters derived from plasma NKTR-181, oxycoldol, and oxycodone concentration data.

Where possible, the following plasma PK parameters will be calculated for all three analytes:

$C_{max:}$ Maximum observed plasma concentration expressed in units of ng/mL.

$T_{max:}$ Time that $C_{max}$ was observed expressed in units of hr.

$AUC_{(0\text{-}last)}$: Area under the plasma concentration-time curve from time =0 to the time of the last measureable concentration. $AUC_{(0\text{-}last)}$ will be expressed in units of ng.hr/mL.

$AUC_{(0\text{-}12)}$: Area under the plasma concentration-time curve from time =0 to the time of the last time-point (12 hour post morning dose). $AUC_{(0\text{-}12)}$ will be expressed in units of ng.hr/mL.

Dose normalized $C_{max:}$ Dose normalized maximum observed plasma concentration expressed in units of ng/mL/mg.

Dose normalized $AUC_{(0\text{-}last)}$: Dose normalized area under the plasma concentration-time curve expressed in units of ng.hr/mL/mg.

Metabolite to parent ratio for $AUC_{(0\text{-}last)}$ ($M/P_{AUC(0\text{-}last)}$) calculated as:

$$(AUC_{(0\text{-}last)metab} * MW_{parent}) / (AUC_{(0\text{-}last)parent} * MW_{metab})$$

Metabolite to parent ratio for $C_{max}$ ($M/P_{Cmax}$) calculated as:

$$(C_{max\ metab} * MW_{parent}) / (C_{max\ parent} * MW_{metab})$$

Molecular Weight (MW) Table:

| Analyte | Molecular Weight (g/mol) |
|---|---|
| NKTR-181 (parent) | 595.72 |
| Oxycodol (metabolite) | 317.38 |
| Oxycodone (metabolite) | 315.36 |

## 4.2 Pharmacokinetic Evaluation based on Sparse Sampling Data

NKTR-181 concentration-time data at each dose level and study visit during Treatment period will be pooled from all subjects and described by descriptive statistics to evaluate trends in drug concentrations with dose and study visits. No formal statistical tests will be conducted. Furthermore, visual inspection of drug concentrations at each dose level and study visit will be performed. Only patients on a stable dose level will be included in the graphical analysis.

# 5.0 PK ANALYSIS POPULATION

## 5.1 PK Sub-Study Population

The PK sub-study population included all subjects in the PK subgroup who received NKTR-181 and had relatively complete individual analyte concentration-time profiles that allow computation of meaningful PK parameter values. Subjects with pre-dose BLQ levels in the PK sub-study population will be excluded from the descriptive summary tables. The number and % of subjects with pre-dose BLQ samples will be tabulated by dose level and overall.

## 5.2 Sparse Sampling PK Population

Subjects who received at least one dose of NKTR-181 and had at least one plasma sample will be included in the sparse sampling PK population. The PK analysis data set will include all plasma samples from all subjects with the following exceptions: Subjects with only pre-first dose NKTR-181 concentration available for the entire duration of the study and post-dose samples with BLQ concentrations.

# 6.0 PHARMACOKINETIC DATA EVALUATION

## 6.1 Bioanalysis of Plasma Samples

Concentrations of NKTR-181, oxycoldol, and oxycodone in plasma samples will be assayed using validated methods. NKTR-181 levels will be analyzed for both spare samples and PK subgroup samples. Oxycodol and oxycodone levels will be analyzed for the PK subgroup samples only.

For the purpose of the PK analysis, plasma concentration values reported as below the limit of quantification (BLQ) will be treated as zero for pre-dose samples. Plasma concentrations values reported as BLQ at all other times will be considered as missing. Concentration values in any sample matrix reported as NR (not received) or NA (not analyzed) will be treated as missing values.

Unreliable results, such as those arising from procedural errors during conduct of the study or analytical errors will not be used.

## 6.2 Calculation of Plasma Drug Pharmacokinetic Parameters

All parameter values listed in Section **4.0** will be determined by non-compartmental analysis. PK parameter calculations will be based on the actual sampling times. Calculation of AUC will be performed using linear trapezoidal rule.

## 6.3 Presentation of Individual and Mean Plasma Drug Concentrations and PK Paramters

### 6.3.1 Listings and Tables

Listings for blood collection dates and times will be generated by subject, and treatment. Sampling time deviations will be computed as differences between scheduled (nominal) and actual sampling times and expressed in minutes and as a percentage of the nominal time.

Plasma analyte concentrations at each nominal PK sampling time will be tabulated by treatment using descriptive statistics, including the number of observations (n), n listed as BLQ, arithmetic mean, geometric mean, standard deviation, standard error of the mean (SEM), CV%, median, minimum and maximum. Missing and BLQ concentration values will be treated using the criteria provided in Section **6.1**. Missing concentration values will not be included in the descriptive statistics.

For the PK sub-study, plasma PK parameters will be listed by subjects and summarized by dose level using descriptive statistics, including, n, geometric mean, mean, standard deviation, CV%, median, minimum and maximum.

For sparse PK sampling, number of subjects and samples at each dose level and study visit will be tabulated and summarized using descriptive statistics, including, n, median, and range.

### 6.3.2 Plots

The following plots will be generated for the PK sub-study population:

Plots of individual plasma NKTR-181, oxycoldol, and oxycodone concentration versus actual time on linear and semi-log scales for each subject by treatment.

Overlay plots of mean (± SEM) plasma NKTR-181, oxycoldol, and oxycodone concentrations in each treatment versus nominal time on linear and semi-log scales.

Overlay plots of mean (± SEM) concentration versus nominal time for all treatments by analyte on linear and semi-log scales

Spaghetti plots of individual plasma concentration versus nominal time for all subjects by treatment by analyte on linear and semi-log scales

The following plots will be generated for the sparse PK population:

Plots of plasma NKTR-181 concentrations by dose and study visit for subjects who enter the Stable dose Treatment Period.

## 6.4 Reporting Conventions

Rounding for the reporting of PK parameters will be **3** significant figures except $C_{max}$ and AUC for NKTR-181 oxycodol, and oxycodone which will be rounded to **4** significant figures. The same convention will be followed for descriptive statistics, except for n, which will be rounded to the whole value. Descriptive statistics will not be performed if n<3 and summary tables will only include median, minimum, and maximum. . Percentages presented in tables will be rounded to one decimal place. If "%" is part of the column heading, do not repeat the "%" sign in the body of the table.

## 7.0 REFERENCES

1. Clinical Study Protocol Number 14-181-08.