2.0 SYNOPSIS

Name of Sponsor: Nektar Therapeutics	**Individual Study Table Referring to Part of the Dossier:** Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: NKTR-118		
Name of Active Ingredient: PEG-Naloxol		

Title of Study:

A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Evaluate the Efficacy, Safety and Tolerability of NKTR-118 in Patients with Opioid-Induced Constipation (OIC)

Investigator(s):

A list of investigators is available in Appendix 16.1.4.

Study Center(s):

A total of 54 clinical sites in 4 countries screened or randomized at least 1 patient in this study: 38 in the United States, 7 in Germany, 5 in Romania, and 4 in Canada.

Publication (reference):

None.

Study Period (Years): 04 Jan 2008 – 24 Mar 2009 **Phase of Development:** 2

Objectives:

Primary Objective:

- To evaluate the efficacy of PEG-naloxol (NKTR-118) at various dose levels, with efficacy defined as the change from baseline in the number of spontaneous bowel movements (SBMs) per week.

Secondary Objectives:

- The main secondary objective was to evaluate the safety and tolerability of NKTR-118, thereby enabling the identification of an effective dose that preserves opioid-conferred analgesia.
- Delineate the dose-response for NKTR-118 across a range of underlying opioid doses, with response defined as the change in SBMs per week from baseline.
- Characterize the pharmacokinetics (PK) of NKTR-118 in patients.

Methodology:

This was a multicenter, international, randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study of the efficacy, safety, and tolerability of NKTR-118 in patients with documented OIC. The diagnosis of OIC was confirmed during a 2-week screening period (see eligibility criteria in Section 9.3). Only those patients with confirmed OIC were randomized. Screening assessments included routine safety laboratories (hematology and chemistry), electrocardiogram (ECG), pregnancy test for women, urinalysis (U/A), prothrombin time (PT)/partial thromboplastin time (PTT), toxicology panel, medical history, and physical examination (PE). Patients with confirmed OIC were randomized and entered a 1-week on-study, single-blind placebo run-in period, followed by 4 weeks of randomized double blind treatment with NKTR-118 or placebo. Patients were randomized within each cohort in a 1:1 ratio (active:placebo). Randomization was stratified based on total daily opioid dose at baseline. The patient's daily maintenance opioid dose was converted to the equivalent dose in mg for orally administered morphine, expressed as morphine equivalent units (MEU) (low stratum 30 to 100 MEU; high > 100 to 1000 MEU). Patients returned to the study center approximately 2 weeks following their last dose of study

treatment for a follow-up visit.

This study planned to enroll up to 4 sequential dose cohorts comprising approximately 240 patients. Approximately 16 patients per cohort were planned for inclusion in the PK substudy. Enrollment of the next successive cohort began only after an independent Dose Evaluation Safety Committee (DESC) had evaluated the aggregate safety data from the current cohort, including a review of all individual occurrences of clinically significant pain progression (CSPP), occurrences of possible opioid withdrawal, change in Numeric Rating Scale (NRS) pain score for the cohort, any change in mean daily opioid use for individual patients and overall, and specific adverse events (AEs) of special interest at each cohort level. A copy of the DESC charter can be found in Appendix 16.1.3.

The doses of NKTR-118 for Cohorts 1, 2, 3, and 4, respectively, were originally scheduled to be 5 mg, 25 mg, 50 mg, and 100 mg once daily (QD); however, upon review of safety data from the 50 mg cohort, the DESC recommended against a fourth dose cohort at 100 mg, but that consideration could be given to a fourth cohort that would be dosed at an intermediary dose such as 37.5 mg. The DESC further indicated that the safety and tolerability profile of the 50 mg QD dose supported completion of enrollment and study participation for this dose cohort. In Amendment 6.0, the dose of the fourth cohort was changed to 38 mg QD.

After a preliminary analysis was performed on the first 3 cohorts, the Sponsor made the decision to end the study after completion of the third cohort. Amendment 6.0 was never enacted except for the revisions to the statistical section which formed the basis for the final statistical analysis plan (SAP). Amendment 6.0 was finalized prior to unblinding of the efficacy results. The final SAP reflecting changes made to the statistical section of Amendment 6.0 was written and approved by an external independent consulting statistician who remained blinded to any study results until after the final SAP was approved.

A PK substudy was conducted in conjunction with the main study, in which approximately 16 patients were to be included per cohort, with the intent that approximately 8 patients receiving NKTR-118 would be included in this substudy.

Number of Patients (Planned and Analyzed):

Planned: This study planned to enroll approximately a total of 240 patients into 4 sequential dose cohorts. However, enrollment was stopped after 3 cohorts. Each patient received placebo or NKTR-118 at doses of 5 mg QD (Cohort 1), 25 mg QD (Cohort 2), or 50 mg QD (Cohort 3).

Analyzed: There were a total of 207 randomized patients who received at least 1 dose of placebo run-in medication in this study. There were 5, 12, and 5 patients with evaluable PK data in the 5, 25, and 50 mg dose groups, respectively, within the PK analysis population.

Diagnosis and Main Criteria for Inclusion:

This study enrolled male and female patients ≥ 18 years of age on a stable opioid dose of 30 mg/day to 1000 mg/day who had documented OIC with ≤ 5 SBMs over the 2-week OIC screening period, which corresponded to < 3 SBMs/week.

Test Product, Dose and Mode of Administration, Batch Number:

NKTR-118 is a PEGylated derivative of naloxone.

NKTR-118 was provided in a 125 mL clear glass bottle that contained 4.167 g, which was stored frozen at -25°C to -15°C. A pharmacist or other delegated person at each site prepared the patient doses by taking a bottle of NKTR-118 and diluting it with 100 mL of sterile water to create a 4% solution that was then drawn up by the pharmacist or other delegated person into oral syringes (either 1 mL or 3 mL) for dosing. These syringes were stored refrigerated at 2°C to 8°C. This was done on a weekly basis, providing each patient with an 8-day supply. Once a patient was randomized, the pharmacist was supplied with study medication for the full treatment period, including measuring column, oral syringes, and directions. A certificate of analysis, including lot number, was maintained in the site's regulatory binder.

The batch numbers used in this study were: NKTR-118 Solution Lot C08C004, API Lot #149011; and NKTR-118 Solution Lot C08J040, API Lot #149014.

Duration of Treatment:

There was a 1-week placebo run-in period in each cohort, during which all patients received a single morning dose of placebo. After the placebo run-in period, patients received either placebo or NKTR-118,

depending on randomization, for 4 weeks. Patients attended a follow-up visit 2 weeks after stopping double-blind study treatment.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo consisted of sterile water mixed with a bittering agent to replicate the bitterness of the NKTR-118 active drug. This placebo formula was used for all patients during the 1-week placebo run-in period directly preceding the 4-week randomized treatment period. Patients randomized to placebo received blinded study medication of equal volume to the active medication in their cohort. The placebo packaging batch numbers used in this study were: B080058, B080244, and B090290. Placebo contained no active drug.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

The primary efficacy variable was the change from baseline in SBMs/week at Visit 6 (end of double-blind study treatment period Week 1) and defined as SBMs/week during the first week of double-blind study treatment period (between Visit 4 and Visit 6) minus baseline SBMs/week. Baseline was defined as the average SBMs/week during the 2-week OIC screening period.

Secondary Efficacy Endpoints:

Secondary efficacy endpoints included the following:

- Change from baseline in SBMs/week during double-blind study treatment period Weeks 2, 3, and 4 and defined as number of SBMs during the second, third, and fourth week of double-blind study period, respectively, minus baseline SBMs/week.
- Change from baseline in SBMs/week across the 28-day double-blind period.
- Time from first dose of the study treatment in the double-blind period to first laxation.
- Dose-response relationship with response defined as change from baseline in the number of SBMs/week.
- Clinical laboratory evaluation of FSH, LH, testosterone, prolactin, and estradiol.
- Patient Assessment of Constipation Symptom-Questionnaire (PAC-SYM) at Visit 4 (Day 1 of double-blind treatment period prior to first dose of the study treatment), Visit 7 (Day 1 of Week 4 of double-blind study treatment period), Visit 9 (end of double-blind study treatment period).
- Patient Assessment of Constipation Quality of Life-Questionnaire (PAC-QOL) at Visit 4 (Day 1 of double-blind treatment period prior to first dose of the study treatment), Visit 7 (Day 1 of Week 4 of double-blind study treatment period), Visit 9 (end of double-blind study treatment period).
- Short Form Health Survey (SF-36) at Visit 4 (Day 1 of double-blind treatment period prior to first dose of the study treatment), Visit 7 (Day 1 of Week 4 of double-blind study treatment period), Visit 9 (end of double-blind study treatment period).

Pharmacokinetics:

The endpoints for the PK analyses included standard noncompartmental PK parameters derived from plasma concentration data.

Safety:

Secondary safety endpoints included the following:

- Opioid withdrawal symptoms as measured by the Clinical Opiate Withdrawal Scale (COWS) scheduled 3 times during the trial
    1. At the beginning of the placebo run-in period–Visit 3 (Week 1, Day 1 of placebo run-in period)
    2. Two hours after the initial dose of double-blind study treatment period on Visit 4 (Week 1, Day 1 of double-blind study treatment period) if the patient did not experience any evidence of withdrawal or at the onset of any symptom complex felt to be consistent with opioid withdrawal, and
    3. Three days after the initial dose of double-blind study treatment period (Week 1, Day 4 of double-blind study treatment period)
- Daily opioid requirement and mean and maximal daily NRS score

- Daily bisacodyl rescue medication
- Adverse events, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), study discontinuation due to AEs
- Adverse events of special interest: CSPP, moderate-to-severe opiate withdrawal (MSOW) confirmed by COWS score of ≥ 13; MSOW without a COWS score
- Clinical laboratory evaluation:
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Pregnancy test results
  - Electrocardiograms, vital signs (sitting and standing systolic and diastolic blood pressure, temperature, pulse, and respiration), and physical examination (PE)

Statistical Methods:

Analysis of the primary endpoint was conducted based on the modified intent-to-treat (MITT) population. The primary endpoint was summarized by cohort and treatment group. The Wilcoxon rank sum test was used to compare the treatment groups (NKTR-118 vs placebo) within each cohort. The Wilcoxon signed rank test was used for the within group comparisons.

An exact Wilcoxon rank sum test was performed as a supplementary analysis for the primary endpoint to confirm that the normal approximation provides results sufficiently close to those of the exact test to give confidence in using the normal approximation for the Wilcoxon rank sum tests of all secondary endpoints. The reported *P* values for Wilcoxon rank sum test and exact Wilcoxon rank sum test were sufficiently close throughout the efficacy endpoints analyses. Therefore the *P* values based on Wilcoxon rank sum test were reported in this clinical study report.

Consistent with the protocol, an exact stratified Wilcoxon rank sum test (with a stratification factor of baseline opioid dose) was performed as a supplementary analysis for the primary endpoint.

EFFICACY RESULTS:

The majority of patients in the MITT population were female (62.2%) and Caucasian (86.5%). The mean patient age was 49.7 years, with a range of 21 to 80 years. Height and weight were comparable across all groups. A total of 194 patients received at least 1 dose of double-blind study medication.

Primary Efficacy Endpoint Result: The primary endpoint for this study was change from baseline in SBMs/week to the end of the first week of double-blind study drug administration.

For Cohort 1 (5 mg), the mean change in SBMs/week from baseline to the end of Week 1 was 2.6 for NKTR-118 patients and 1.8 for placebo patients. The primary endpoint for the 5 mg group was not statistically significant. For Cohort 2 (25 mg), the mean change in SBMs/week from baseline to the end of Week 1 was 3.6 for NKTR-118 patients and 1.9 for placebo patients. The primary endpoint for the 25 mg group was statistically significant ($P = 0.0020$). For Cohort 3 (50 mg), the mean change in SBMs/week from baseline to the end of Week 1 was 4.4 for NKTR-118 patients and 1.9 for placebo patients. The primary endpoint for the 50 mg group was highly statistically significant ($P = 0.0001$).

In addition to the primary efficacy analysis, the change in weekly SBM frequency was also studied. For the MITT population, baselines SBMs were comparable between NKTR-118 and placebo patients across all cohorts. During double-blind treatment, NKTR-118 patients had more SBMs than placebo patients at all postdose timepoints. The mean number of SBMs/week across the 28-day double-blind period increased with each successive dosing cohort, from 4.2 SBMs/week for 5 mg patients to 4.6 SBMs/week for 25 mg patients to 6.2 SBMs/week for 50 mg patients.

Secondary Efficacy Endpoints Included:

1) Change from Baseline in SBMs/Week During Weeks 2, 3, and 4

For Cohort 1 (5 mg), the mean change in SBMs/week from baseline during Weeks 2, 3, and 4 were slightly higher for NKTR-118 patients compared to placebo patients (2.1 vs 1.7, 2.3 vs 1.5, and 2.1 vs 1.7, respectively). This secondary endpoint for the 5 mg group was not statistically significant.

For Cohort 2 (25 mg), the mean change in SBMs/week from baseline during Week 2 was 2.8 for NKTR-118 patients and 2.5 for placebo patients. This secondary endpoint for the 25 mg group was not statistically significant. However, for Cohort 2 (25 mg), the mean change in SBMs/week from baseline during Weeks 3 and 4 were 3.1 vs 1.4 and 3.5 vs 1.0 for the NKTR-118 patients compared to the placebo patients, respectively. Both of these secondary endpoints for the 25 mg group were statistically significant (P = 0.0092 and P = 0.0002, respectively).

For Cohort 3 (50 mg), the mean change in SBMs/week from baseline during Weeks 2, 3, and 4 were 4.3, 5.2, and 3.9 for NKTR-118 patients and 1.0, 1.1, and 0.7 for placebo patients, respectively. These secondary endpoints for the 50 mg group were highly statistically significant (P = <0.0001, P = <0.0001, and P = 0.0002, respectively).

2) Change from Baseline in SBMs/Week Across the 28-day Double-Blind Period

For Cohort 1 (5 mg), the mean change in SBMs/week from baseline across the 28-day double blind period was 2.3 for NKTR-118 patients and 1.7 for placebo patients. This secondary endpoint for the 5 mg group was not statistically significant.

For Cohort 2 (25 mg), the mean change in SBMs/week from baseline across the 28-day double blind period was 3.2 for NKTR-118 patients and 1.7 for placebo patients. This secondary endpoint for the 25 mg group was statistically significant (P = 0.0022).

For Cohort 3 (50 mg), the mean change in SBMs/week from baseline across the 28-day double blind period was 4.6 for NKTR-118 patients and 1.2 for placebo patients. This secondary endpoint for the 50 mg group was highly statistically significant (P = <0.0001).

3) Time to First Laxation

The time to first laxation was not statistically significantly different between NKTR-118 (5 mg) and placebo groups, with respective median time to first laxation of 6.2 vs 28.2 hours. The time to first laxation was statistically significantly shorter in the NKTR-118 (25 mg) and (50 mg) cohorts compared to placebo with respective P = 0.0012 and P = 0.0016. The median time to first laxation for NKTR-118 (25 mg) vs placebo was 6.6 vs 48.6 hours and was 2.9 vs 44.9 hours for NKTR-118 (50 mg) vs placebo.

4) Laboratory Evaluation of FSH, LH, Testosterone, Prolactin, and Estradiol

There were no meaningful changes in the levels of the 5 reproductive hormones evaluated in this study in patients treated with placebo or NKTR-118 across the 3 cohorts.

5) Health Outcomes Assessments: PAC-SYM, PAC-QOL, and SF-36.

The majority of mean PAC-SYM scores at all postdose timepoints for abdominal symptoms, rectal symptoms, stool symptoms, and the total mean scores were < 2 at most double-blind timepoints, indicating mild gastrointestinal (GI) symptoms for placebo and NKTR-118 patients.

NKTR-118 patients in all 3 cohorts reported greater satisfaction compared with placebo patients as measured by the PAC-QOL.

NKTR-118, 25 mg patients experienced statistically significant SF-36 scale scores that were higher than placebo for physical functioning, mental health, social functioning, and vitality at various (but not all) postdose timepoints.

Post hoc analysis showed that the proportion of responders (ie, patients who showed an increase of ≥ 2 SBMs/week from baseline) across the 28-day double-blind period was significantly higher in the NKTR-118 group vs placebo group in both the 25 mg (75% vs 26%) and 50 mg cohorts (92% vs 29%; P = 0.0003 and P = 0.0001, respectively). However, the difference between the NKTR-118 and placebo groups in the 5 mg cohort was not statistically significant.

PHARMACOKINETICS RESULTS:

NKTR-118 was rapidly absorbed independent of dose and duration of dosing. Systemic exposure to NKTR-118 was dose proportional, and the elimination rate was independent of dose. Pharmacokinetic steady-state was achieved rapidly with no appreciable accumulation occurring after QD dosing. There were no differences in PK characteristics between males and females.

Glucuronidation of NKTR-118 is a minor metabolic pathway. No metabolite exceeded 10% in abundance relative to parent NKTR-118 in plasma or urine and no metabolite accumulated after 28 days of dosing. Further, no indication of induction or inhibition of any metabolic pathway was observed during the 28-day

dosing period.

The observed lack of accumulation after QD dosing is consistent with the trend in predose concentration values, dose proportional PK, and apparent terminal elimination half life (t½) values typically less than the dosing interval observed in this study. The following table shows the mean NKTR-118 PK parameters in the evaluable PK population.

Mean (CV%) NKTR-118 PK Parameters: Evaluable PK Population

Day	Dose (mg)	N	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (hr*ng/mL)	$T_{1/2}$ (hr)
1	5	5	1.7 (84.7)	9.1 (52.2)	34.01 (48.8)	NC
	25	12	1.5 (61.1)	70.6 (42.3)	327.7 (47.7)	NC
	50	5	1.5 (91.3)	123.7 (36.3)	426.8 (22.1)	NC
28	5	4	1.5 (81.7)	8.0 (49.2)	39.0 (23.1)	17.4 (8.3)
	25	9	1.4 (43.9)	81.1 (45.7)	334.8 (51.4)	14.1 (4.9)
	50	4	1.6 (101.7)	100.0 (41.9)	403.6 (36.7)	20.3 (10.3)

N: number of patients with evaluable PK data.
CV%: Coefficient of variation, expressed as percent of mean value.
NC: not calculated for Day 1.

All of these findings are consistent with those previously reported following administration of NKTR-118 in healthy subjects. Overall, NKTR-118 possesses predictable PK characteristics and does not require complex dosing regimens or dosing adjustments to achieve efficacy in patients with OIC.

SAFETY RESULTS:

In both Cohort 1 (5 mg) and Cohort 2 (25 mg), approximately 75% of patients experienced ≥ 1 TEAE during the double-blind study period with minimal difference noted between the 2 treatment arms, placebo and NKTR-118. However in Cohort 3 (50 mg), the TEAE data revealed a shift towards the NKTR-118 arm with 85% of patients experiencing TEAEs as compared to 56% in the placebo arm. Most TEAEs occurring in patients treated with NKTR-118 were reported to be either Grade 1 or 2 in severity. Sixteen patients in Cohort 1 (5 mg), 16 patients in Cohort 2 (25 mg) and 23 patients in Cohort 3 (50 mg) experienced at least 1 TEAE that was assessed as being causally related to the study drug. The majority of study drug (NKTR-118) related TEAEs reported within all 3 cohorts were in the System Organ Class (SOC) of GI disorders with diarrhea, abdominal pain, and nausea accounting for the most frequent TEAEs.

Five of 194 patients (2.5%) who entered the double-blind study period, 1 in each treatment arm across all cohorts except the placebo arm of Cohort 2 (25 mg), experienced a total of 7 SAEs. Of these 7 SAEs, 4 were experienced by patients in the NKTR-118 arm and 3 were reported in the placebo group. Of the 4 SAEs experienced by NKTR-118 patients, 1 SAE reported in Cohort 3 (50 mg) was assessed as being related to the study drug NKTR-118. This study drug-related treatment-emergent SAE of abdominal cramping was experienced by the patient shortly after administration of the first dose of the study drug. A detailed account of this SAE is provided in Section 14.3.3. One patient randomized to the placebo arm of Cohort 3 (50 mg) experienced an SAE during the placebo run-in study period.

The most frequent study drug-related Grade 3/4 TEAE reported across all 3 dose cohorts was abdominal pain. Less than 15% of patients in the NKTR-118 group who entered the double-blind study period experienced Grade 3 TEAEs. A total of 4 patients experienced Grade 4 TEAEs during the study, 2 in the NKTR-118 arm of Cohort 1 (5 mg) and Cohort 2 (25 mg), respectively and 2 in the placebo arm of Cohort 1 (5 mg). Patient 43003, randomized to NKTR-118 arm in Cohort 2 (25 mg), experienced an AE of pulmonary embolism that had a fatal outcome. However, this event was assessed by the investigator as being unrelated to the study medication.

In addition to TEAEs and SAEs, an independent DESC also reviewed specific AEs of interest that were identified within the protocol; namely events that qualified for CSPP, MSOW with a documented COWS score of ≥ 13 and also without a documented COWS score of ≥ 13, and all treatment-related AEs that led to study drug discontinuation and early termination from the study. The DESC reviewed per patient safety data on an ongoing basis and aggregate safety data for each cohort after 40 patients within a cohort had completed the first week of double-blind study treatment. Following DESC review, if no safety concerns were identified, the DESC provided written recommendation to proceed with dose escalation to the next

successive cohort with a higher dose level. The DESC did not identify any safety concerns at the end of Cohort 1 (5 mg) and at the end of Cohort 2 (25 mg) thereby allowing evaluation of 25 mg QD dose level in Cohort 2 (25 mg) and 50 mg QD dose level in Cohort 3.

However, following review of 8 AEs of special interest and the aggregate safety data from patients in Cohort 3 (50 mg), the DESC recommended against dose escalation to a fourth dose cohort at 100 mg, as GI intolerability would likely lead to a significant number of patients terminating from treatment early. The DESC recommended that consideration could be given to a fourth cohort that would be dosed at an intermediary dose such as 37.5 mg. The DESC further indicated that the safety and tolerability profile of the 50 mg QD dose supported completion of enrollment and study participation for this dose cohort. In Amendment 6.0, the dose of the fourth cohort was changed to 38 mg QD.

The Sponsor made the decision to perform a preliminary analysis of the primary endpoint to determine if further dose cohorts were required to define the appropriate Phase 3 dose. As a result of this analysis, the 25 mg QD dose was identified as a safe and tolerable dose appropriate for Phase 3 testing and, the decision was made to end the study after completion of the third cohort. Amendment 6.0 was never enacted except for the revisions to the statistical section which formed the basis for the final SAP. Amendment 6.0 was finalized prior to unblinding of the efficacy results.

Mean daily opioid levels remained relatively steady from baseline throughout double-blind treatment for all cohorts. There were no statistically significant changes from baseline in the mean daily opioid levels between the NKTR-118 arm and placebo arm in Cohort 2 (25 mg) and Cohort 3 (50 mg); however statistically significant differences were seen between the NKTR-118 arm and placebo arm in Cohort 1 (5 mg).

Opioid withdrawal was measured by a change in the total COWS score between the NKTR-118 and placebo groups. There was no statistically significant difference in the total COWS score between NKTR-118 vs placebo in the double-blind treatment period in Cohort 1 (5 mg) and Cohort 2 (25 mg). However, in Cohort 3 (50 mg), a statistically significant difference in total COWS score was noted between the NKTR-118 and placebo groups, but only at Day 1 of the double-blind treatment period. A post hoc analysis demonstrated that this increase in Day 1 total COWS score for the NKTR-118, 50 mg dose group was primarily due to increases in the GI component scores for the patients experiencing an increase in COWS score from baseline, consistent with the finding that patients in the 50 mg dose group receiving NKTR-118 experienced more GI side effects than those receiving placebo. When the GI component of the COWS instrument was removed from calculation of total COWS scores for both the NKTR-118 and placebo groups in the 50 mg cohort, there was no longer any significant difference in COWS score between the NKTR-118 and placebo groups indicating a lack of increase in the components of the scale that reflect CNS withdrawal.

Mean pain on average over the last 24 hours and worst mean pain in the last 24 hours as measured by NRS remained relatively consistent from baseline through postdose timepoints for all 3 cohorts.

Mean bisacodyl rescue medication use was numerically lower for the NKTR-118 arms of Cohort 2 (25 mg) and Cohort 3 (50 mg) vs placebo at all postdose timepoints; however, a statistical comparison was not done.

No differences in mean clinical laboratory parameters were noted between NKTR-118 and placebo, and no meaningful trends in change from baseline values over time were detected. Similarly, no trends in shifts from normal clinical laboratory values at baseline to abnormal values postdose were noted among NKTR-118 patients. Vital signs, PE results, and ECG findings were largely normal, and no trends were detected.

The NKTR-118 dose cohorts of 5 mg and 25 mg were generally well tolerated; however, GI AEs occurred more frequently in the 50 mg QD cohort.