CLINICAL STUDY PROTOCOL

AN OPEN-LABEL, MULTICENTER, EXTENSION STUDY OF NKTR-102 IN SUBJECTS PREVIOUSLY ENROLLED IN NKTR-102 STUDIES

Protocol Number: 11-PIR-09

Protocol Version: Amendment 3.0

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Development Phase: 2

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CONFIDENTIALITY STATEMENT

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INVESTIGATOR SIGNATURE PAGE

Nektar Therapeutics

TITLE:	An Open-label, Multicenter, Extension Study of NKTR-102 in Subjects Previously Enrolled in NKTR-102 Studies
PROTOCOL NUMBER:	11-PIR-09
PHASE OF STUDY:	2
PROTOCOL AMENDMENT 3.0 DATE:	14 January 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 § 312.60 through § 312.70, 21 CFR § 11, 50, 54, 56) 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.

1.0 STUDY SYNOPSIS

Name of Sponsor:	Nektar Therapeutics
Name of Finished Product:	NKTR-102 for Injection
Name of Active Ingredient:	NKTR-102 (etirinotecan pegol)
Title of Study:	An Open-label, Multicenter, Extension Study of NKTR-102 in Subjects Previously Enrolled in NKTR-102 Studies
Study Period:	The estimated study duration is approximately 5 years. The duration of treatment in this study is estimated to be approximately 2 years. Subjects may continue to receive repeated cycles of study drug treatment until progression of disease, unacceptable toxicity, death, withdrawal by subject, Investigator decision, lost to follow-up, or study is terminated by the Sponsor.
Phase of Development:	Phase 2
Indication:	Solid tumors
Objectives:	**Primary Objective:** • To provide access to NKTR-102 to subjects who previously received NKTR-102 in a clinical trial and are without signs of disease progression since receiving NKTR-102. **Secondary Objectives:** • To evaluate the safety of continued exposure to NKTR-102. • To observe disease status and survival status in subjects receiving NKTR-102. • To evaluate the efficacy of NKTR-102 in subjects with advanced or metastatic solid tumors.
Endpoints:	• Incidence and duration of toxicities, with severity grading according to National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. • Tumor response per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
Number of Study Sites:	Up to 100 study sites may participate in this study.
Countries:	Multi-national
Number of Subjects (planned):	Up to 150 subjects may be enrolled in this study.
Study Design:	This is a multicenter, open-label, Phase 2 study of NKTR-102 in subjects with solid tumors who received NKTR-102 in a prior Nektar-sponsored clinical study. Following completion of NKTR-102 treatment on a prior NKTR-102 clinical study, subjects will be assessed for eligibility. The Sponsor must assess eligibility criteria prior to enrollment of all subjects. Eligible subjects will continue treatment with NKTR-102 at a dose of 145 mg/m^2 or less in a q21d schedule. Subjects who previously received a dose of NKTR-102 at <145 mg/m^2 will continue at the lower dose in this study. Subjects who underwent dose reduction of NKTR-102 due to observed toxicity prior to participation in the Extension study (Protocol 11-PIR-09) will not be

re-escalated to the previous dose level upon resolution of the toxicity. Dose escalation for NKTR-102 is not permitted.

Disease assessments for tumor response and progression will be performed as per local standard of care until disease progression. Minimal disease evaluation data (best response and date of progression) will be collected within this protocol. Tumor measurements are not required; only an overall assessment of response or progression by the Investigator is required. Subjects may continue to receive repeated cycles of NKTR-102 on this protocol as long as there is evidence of disease control in the judgment of the Investigator or until there is unacceptable toxicity, death, withdrawal of consent by the subject, Investigator decision, subject non-compliance, lost to follow-up, or study is terminated by the Sponsor. After discontinuation of NKTR-102, all subjects, except those who withdraw consent from further study follow-up, are to be followed for disease status (as applicable), subsequent anti-cancer therapy, survival status, and resolution of toxicity attributable to study drug (with contact by phone, through a clinic visit, or through review of medical records approximately every 12 weeks (±4 weeks)).

Concomitant Medications:

Permitted Treatments:

- Palliative and supportive care for disease-related symptoms.
- Standard therapies for concurrent medical conditions, including antiemetic prophylaxis and early interventional antidiarrheal therapy.
- Diarrhea is an expected toxicity of NKTR-102. All subjects must receive optimal antidiarrheal therapy immediately after the FIRST episode of diarrhea or loose stool regardless of severity.
- Premedication with antihistamine and/or corticosteroid is allowed in subsequent cycles following occurrence of a self-limiting allergic/hypersensitivity reaction to a prior infusion of NKTR-102.

Prohibited Treatments:

- Any concurrent chemotherapy (other than NKTR-102), radiotherapy (with the exception of palliative radiation), biological therapy, hormonal agents used for the treatment of cancer, immunotherapy, or other systemic therapy for cancer; megestrol acetate for appetite stimulation may be used.
- Other investigational agents within 28 days prior to Day 1 of Cycle 1 or during the study.
- Investigators must monitor subjects for use of potent cytochrome P450 3A4 (CYP3A4) inducers or inhibitors, as they may induce or inhibit irinotecan or SN38 metabolism. Some of these agents are over-the-counter medications (e.g., St John's Wort); subjects must provide a complete list of all concomitant medications as part of the screening process.

Inclusion Criteria:

Subjects must meet the following criteria to be eligible for enrollment:

1) Subject or subject's legal representative must provide written informed consent
2) Subject is able and willing to comply with the study visit schedule and procedures

3) Subjects must have received prior treatment with NKTR-102 in a Nektar-sponsored study
4) Subjects must be without signs of disease progression since receiving NKTR-102
5) Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at the predose visit of each cycle
6) Women of childbearing potential and men who agree to use adequate contraception during study participation (at least two methods of contraception, one of which includes a barrier method [male condom] by the male partner or abstinence) or a male who has undergone a vasectomy greater than 6 months prior to Cycle 1 Day 1. Appropriate contraception must be used for at least 8 months after the last dose of the study drug on this extension study
7) Subjects must meet requirements with respect to hematopoietic function (hemoglobin $\geq$ 8.0 g/dL or 80 g/L; absolute neutrophil count (ANC) $\geq$ 1.5 X 10^9/L; platelets $\geq$ 75 X 10^9/L).
8) Subjects must be able to receive the first dose of NKTR-102 in the extension study within 8 weeks after receiving their last dose of NKTR-102

Exclusion Criteria:

Subjects who meet any of the following criteria are ineligible for enrollment:

1) Subjects who have received intervening anti-cancer therapy (between their last dose of NKTR-102 and administration of the first dose of NKTR-102 in this extension study)
2) Subjects with 2 dose reductions of NKTR-102 and have a toxicity that requires another dose reduction
3) Female subjects who are pregnant or lactating, who plan to get pregnant, or who have a positive pregnancy test at screening or during participation in this study

Test Product, dose and mode of administration:

NKTR-102 will be administered as an intravenous (IV) infusion over approximately 90 minutes (± 15 minutes) on Day 1 of each 21-day treatment cycle. The dose of NKTR-102 will be 145 mg/m^2 or less. Subjects who received a dose of NKTR-102 at <145 mg/m^2 will continue at the lower dose in this study. Subjects who underwent 2 dose reductions of NKTR-102 due to observed toxicity prior to participation in the Extension study will not be re-escalated to the previous dose level upon resolution of the toxicity. Dose escalation for NKTR-102 is not permitted.

Duration of Treatment:

Subjects will continue to receive study drug treatment until progression of disease, unacceptable toxicity, death, withdrawal by the subject, Principal Investigator decision, lost to follow-up, or study is terminated by the Sponsor.

Reference Therapy, dose and mode of administration, batch number (if applicable):

Not applicable

Disease Evaluation (per Standard of Care):	Tumor assessments will be performed according to local standard of care until disease progression.
Statistical Methods:	The primary objective will be measured by capturing AEs and SAEs using the data capture tools provided for this study. The primary endpoint of this study is to assess the incidence and duration of toxicities, with severity grading according to NCI-CTCAE v. 4.0. The incidence and duration of AEs will be tabulated by MedDRA preferred term, system organ class, severity grading by NCI-CTCAE v. 4.0 criteria and relationship to study drug. The maximum intensity and frequency of AEs will be summarized by treatment (dose level). Tumor response will be summarized by histological tumor type and tabulated using by-subject listings based on disease assessments from this protocol.
NKTR-102 Dose Modification:	NKTR-102 dose modifications are provided in Section **6.7**.
Safety Monitoring:	Clinical examinations including physical examinations and vital signs. Local laboratory assessments including bone marrow, liver, and renal functions will be performed before each cycle of NKTR-102. Other laboratory assessments can be performed at the investigator's discretion.

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BSA	body surface area
C_{max}	maximum concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CPT-11	20-(S)-camptothecin
CRC	colorectal cancer
CRF	Case Report Form
CT	computed tomography
CYP3A4	cytochrome P450 3A4
D5W	dextrose for injection, 5 w/w%
ECG	electrocardiogram
EMEA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
Kg	kilogram
µg	microgram
MBC	metastatic breast cancer
m^2	meters squared
mg	milligram
mL	milliliter
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

Abbreviation or Term	Definition/Explanation
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OTC	over-the-counter
PEG	polyethylene glycol
PK	pharmacokinetic
q14d	once every 14 days
q21d	once every 21 days
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	Serious Adverse Event
SN38	7-ethyl-10-hydroxy-camptothecin
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal elimination phase half-life
TNBC	triple negative breast cancer
TPC	treatment of physician's choice
ULN	upper limit of normal
UGT1A1	uridine diphosphate-glucoronosynl transferase 1A1
US	United States
USP	United States Pharmacopeia
w×3 q4week	weekly for 3 weeks every 4 weeks
WBC	White Blood Cell

2.0 INTRODUCTION

2.1 NKTR-102

NKTR-102 (etirinotecan pegol) is a long acting topoisomerase I inhibitor polymer conjugate that was engineered by attaching irinotecan molecules to a polyethylene glycol (PEG) polymer using a biodegradable linker. Irinotecan is released from NKTR-102 following administration and further metabolized to the active metabolite, 7-ethyl-10-hydroxy-camptothecin (SN38), which causes deoxyribonucleic acid (DNA) damage through the inhibition of topoisomerase 1.

The goal in designing NKTR-102 was to attenuate or eliminate some of the limiting side effects of irinotecan while improving efficacy by modifying the distribution of the agent within the body. The size and structure of NKTR-102 results in a marked alteration of the pharmacokinetic (PK) profile of SN38 derived from NKTR-102 compared with that following irinotecan: the maximum plasma concentration (Cmax) is reduced 5- to 10-fold, and the apparent elimination half-life ($t_{½}$) of SN38 is increased from 2 days to approximately 40 days. This altered profile leads to the prolonged exposure of the tumor to active drug. In addition, the large NKTR-102 molecule does not freely pass out of intact vasculature, possibly accounting for relatively higher concentrations of the compound and the active metabolites in tumor tissues in *in vivo* animal models, where the local vasculature may be relatively more permeable. A single dose of 145 mg/m^2 NKTR-102, the dose used in the Phase 3 metastatic breast cancer (MBC) clinical study (BEACON trial), results in approximately the same plasma exposure (area under the plasma concentration-time curve [AUC]) to SN38 as a 350 mg/m^2 dose of irinotecan, but exposure is protracted, resulting in continuous exposure between dosing cycles and a lower C_{max}. NKTR-102 is therefore being developed as a new chemotherapeutic agent that may improve tolerability and patient outcome.

2.1.1 Description of Nonclinical Studies

Nonclinical experience is summarized in the Investigator's Brochure (IB).

2.1.2 Clinical Experience with NKTR-102

2.1.2.1 Phase 1 Study 06-IN-IR001 (Single-Agent NKTR-102)

The NKTR-102 Phase 1 study, 06-IN-IR001, was open to patients with advanced solid tumors whose tumors had failed prior treatments or those for which no standard treatments were available. The study evaluated three treatment schedules: weekly for 3 weeks every 4 weeks (wx3 q4week), once every 14 days (q14d) and once every 21 days (q21d). In all schedules, NKTR-102 was given as an intravenous (IV) infusion over 90 minutes.

For each schedule, the objectives were:

- To establish the maximum tolerated dose (MTD)/Recommended Phase 2 dose (RP2D),
- To characterize the safety and PK profile in subjects with refractory solid tumors,
- To evaluate subjects for any evidence of anti-tumor activity.

This study has been completed and final data are detailed in the IB.

2.1.2.2 Phase 2 studies

A Phase 2 study (Protocol 08-PIR-05) of NKTR-102 in patients with metastatic breast cancer (MBC) evaluating 2 treatment schedules (145 mg/m^2 q14d and q21d; n = 70 patients with 35 patients per treatment schedule) showed significant antitumor activity. The study showed the following activity in the 2 treatment schedules combined:

- ORR by RECIST version 1.0 in the intent-to-treat population was 29%, with 2 complete responses (3%) and 18 partial responses (26%).
- ORR was maintained in patients with advanced or high-risk disease (ORR equal to 33% in patients who had received prior anthracycline, taxane, capecitabine; ORR in patients with triple negative breast cancer (TNBC) was 33%).
- Median progression free survival (PFS) and overall survival (OS) were 4.7 months and 10.3 months, respectively.

The q21d schedule resulted in less Grade 3 or higher toxicity (68.6% for the q14d and 54.3% for the q21d schedule), fewer serious adverse events (SAEs) (51.4% for q14d schedule and 42.9% for q21d schedule), and slightly fewer patients discontinuing the study drug, but not necessarily exiting the study, due to an adverse event (22.9% for q14d schedule and 20.0% for q21d schedule). Two possible drug-related fatalities (acute renal failure and septic shock) occurred in patients treated with the q14d schedule and none occurred in patients treated with the q21d schedule. There were no observations of Grade 4 diarrhea in the q21d schedule.

Based on these findings, the 145 mg/m^2 q21d regimen was selected for continued investigation in the Phase 3 study in patients with MBC. See the IB for additional information on the Phase 3 study in patients with MBC.

A Phase 2 study (Protocol 08-PIR-04) of NKTR-102 in patients with platinum resistant ovarian cancer (disease progressing within 6 months following last dose of platinum) evaluated 2 treatment schedules (145 mg/m^2 q14d and q21d; n = 71; 36 and 35 patients per treatment

schedule). Preliminary data indicated that NKTR-102 produced a RECIST version 1.0 ORR (confirmed and unconfirmed) of 27% and 22% in the q14d and q21d schedules, respectively. The Gynecologic Cancer InterGroup response (confirmed and unconfirmed) was 47% in q14d and 41% in the q21d schedule (**Vergote et. al., 2010**). In those patients whose disease had progressed following both platinum (within 6 months) and liposomal doxorubicin (n = 33), ORR equaled 21%, median PFS equaled 5.5 months and OS equaled 14.0 months in combined q14d and q21d schedules (**Garcia et. al., 2011**). Common related grade 3/4 toxicities (q14d/q21d schedules) were diarrhea (22%/11%), dehydration (14%/6%), hypokalemia (14%/6%), fatigue (6%/11%), nausea (14%/3%), and neutropenia (8%/9%) (**Vergote et. al., 2010**). Two treatment-related deaths were observed; one patient died due to pre-renal azotemia (q14d schedule) and one patient died due to neutropenic sepsis (q21d schedule). The q21d schedule, overall, had a better toxicity profile, supporting further development using the q21d schedule.

A randomized Phase 2 study (Protocol 08-PIR-03) comparing single-agent NKTR-102 to single-agent irinotecan in 2nd-line KRAS-mutant metastatic colorectal cancer (CRC) patients was completed. The final Clinical Study Report is not yet available.

Combination studies have been completed (Protocol 07-PIR-02 with cetuximab and Protocol 09-PIR-07 with 5-FU/leucovorin). See the IB for additional information on these clinical studies.

2.1.2.3 Clinical Pharmacokinetics of NKTR-102

Clinical PK profiles are consistent with preclinical PK profiles with NKTR-102 infusions demonstrating greater and sustained exposure to SN38 than had been reported for irinotecan infusions. Additionally, proportional increases in the area under the concentration-time curve (AUC) and maximum concentration (C_{max}) were observed for NKTR-102, irinotecan, and SN38.

The apparent elimination $t_{½}$ for SN38 after NKTR-102 administration is approximately 40 days, whereas after irinotecan administration, the SN38 $t_{½}$ has been reported as 29 to 47 hours (**Kehrer et al., 2000**). This greatly increased SN38 $t_{½}$ results in plasma SN38 concentrations that are significantly more sustained between doses than are possible with irinotecan. Cumulative SN38 exposures, as indicated by AUC values, were 0.6 - 4.4 fold higher (mean 1.6, standard deviation 0.8) than those predicted for irinotecan (**Xie et al., 2002**) when administered at equivalent doses and schedules.

Interpatient variability in SN38 clearance and volume of distribution is similar to that reported for SN38 following irinotecan administration.

There has been no obvious correlation of toxicity or SN38 PK parameters with age, race, gender, past or present smoking status, uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) status, or baseline liver or renal function. Further exploratory analyses are ongoing.

2.1.2.4 NKTR-102 Safety Profile

As of May 2015, 871 patients across all NKTR-102 clinical studies (completed and ongoing; single agent and combination therapy) have received at least one dose of NKTR-102. See the current version of the IB for additional safety information.

Observations across all studies (including safety data from ongoing studies) have been generally consistent with regard to the overall safety profile of NKTR-102. Gastrointestinal toxicity, especially diarrhea, is the most common and clinically significant toxicity. Other frequently observed AEs include nausea, vomiting, fatigue, decreased appetite, abdominal pain, constipation, and dehydration.

Diarrhea and dehydration secondary to diarrhea were the most common serious adverse events (SAEs) across all studies evaluating NKTR-102, occurring at frequencies of 9.5% and 4.1%, respectively. Prolonged severe diarrhea with dehydration leading to pre-renal azotemia and subsequent acute renal insufficiency has been fatal in 4 patients (1 patient in each of the Phase 2 studies in metastatic colorectal, ovarian, and breast cancers and 1 patient in the Phase 3 BEACON study). Early onset cholinergic-mediated diarrhea has been observed with NKTR-102. Late-onset, severe diarrhea can occur and may be life-threatening if treatment is delayed. The median time to onset of Grade 3 diarrhea for NKTR-102 in the Phase 3 BEACON study was 43 days (range 3 to 488 days). Early, proactive, and aggressive intervention with anti-diarrheal therapy, IV hydration, and maintenance of electrolyte balance had a significant favorable effect on the clinical course of events, preventing volume depletion and the development of renal failure.

Myelosuppression, especially neutropenia, can occur in patients receiving NKTR-102; however, data from clinical studies evaluating NKTR-102 suggest a lower frequency and severity of neutropenia with NKTR-102 than with irinotecan. NKTR-102 administered at a dose level of 145 mg/m^2 in a q21d schedule in the Phase 3 BEACON study resulted in an overall neutropenia incidence of 21.4%; about one-third of these (7.5%) was ≥ Grade 3 neutropenia. The onset of neutropenia in the concomitant setting of severe diarrhea and dehydration with fever and infection must be carefully monitored and proactively treated as it can potentially lead to neutropenic sepsis, which may be fatal.

Safety results from the Phase 3 BEACON study show a generally manageable safety profile for NKTR-102. Common toxicities (related and unrelated) with a frequency > 20% are listed by grade in **Table 1**.

Table 1: Treatment Emergent Adverse Events with a Frequency > 20%, Study 11-PIR-11 (BEACON, N=425)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Diarrhea	41.6%	14.8%	9.6%	-	-	66.1%
Nausea	36.9%	19.5%	3.5%	-	-	60.0%
Vomiting	26.4%	11.5%	2.8%	-	-	40.7%
Fatigue	14.6%	15.3%	4.5%	-	-	34.4%
Decreased appetite	19.5%	10.1%	1.2%	-	-	30.8%
Constipation	20.0%	6.1%	0.2%	-	-	26.4%
Headache	15.8%	5.4%	1.2%	-	-	22.4%
Asthenia	9.6%	10.1%	1.9%	-	-	21.6%
Abdominal pain	11.5%	8.7%	1.2%			21.4%
Neutropenia	2.1%	11.8%	5.4%	2.1%	-	21.4%

2.1.2.5 Study Drug Discontinuation due to Adverse Events and Physician Decision in Phase 3 BEACON (11-PIR-11) Study

A summary of the most common TEAEs leading to study drug discontinuation (> 1 patient in the NKTR-102 treatment arm) is presented in **Table 2**. There was a higher overall incidence of TEAEs leading to discontinuation in the NKTR-102 treatment arm (11.1%) compared with TPC (6.7%), and there was a higher incidence of diarrhea leading to discontinuation in the NKTR-102 treatment arm (3.1%) compared with the TPC treatment arm (0%). The incidence of neuropathy leading to discontinuation was higher in the TPC treatment arm (2.2%) compared with the NKTR-102 treatment arm (0.2%).

Strict protocol-mandated diarrhea management guidelines were implemented in the BEACON study, including requirements for removal of patients from the study due to diarrhea. Guidelines were created based on the safety experience obtained in the prior phase 2 program where Grade ≥3 diarrhea occurred at a rate of approximately 20% (see IB for details). Dose reductions were required to prevent the possibility of accumulation of active drug upon repeated dosing; occurrence of Grade ≥ 2 diarrhea was controlled by temporary discontinuation of NKTR-102. The BEACON protocol mandated discontinuation after the third occurrence of Grade ≥ 2 diarrhea. Because the incidence of Grade ≥ 3 diarrhea is less than 10% with the implementation of diarrhea management guidelines, and given that the median time to resolution for all Grades

of diarrhea was 1.5 days, any subsequent studies will not require treatment discontinuation after 3 episodes of Grade ≥ 2 diarrhea.

Also of importance, a greater proportion of patients were removed from NKTR-102 (2.8%) for neutropenia compared to TPC (0.2%), despite the lower rate of Grade ≥3 neutropenia with NKTR-102 (9.6%) compared with that of TPC (30.6%). The median time to onset of Grade ≥ 3 neutropenia was 120 days on NKTR-102 compared with 16 days on TPC. The significance of the difference in time to onset is that the clinical decision to discontinue treatment due to neutropenia likely occurs at a much later time point for patients on NKTR-102, when there may be less clinical benefit to continue; this situation is quite different from an appropriate response to the occurrence of early neutropenia (ie, with TPC), where dose delay is more common.

Table 2: Summary of TEAEs Leading to Study Drug Discontinuation by Preferred Term (> 1 Patient in NKTR-102 or TPC Treatment arm) (Safety Population)

Preferred Term[a]	**NKTR-102 (N = 425)**	**TPC (N = 406)**
Total Number of TEAEs Leading to Study Drug Discontinuation [b]	47	27
Number of Patients With at Least One TEAE Leading to Study Drug Discontinuation	47 (11.1%)	27 (6.7%)
Diarrhea	13 (3.1%)	0
Neutropenia[c]	12 (2.8%)	1 (0.2%)
Pleural effusion	2 (0.5%)	2 (0.5%)
Vomiting	2 (0.5%)	0
Neuropathy[d]	1 (0.2%)	9 (2.2%)
Dyspnea	0	2 (0.5%)
Fatigue	0	2 (0.5%)

Abbreviations: TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

a MedDRA v. 14.1

b The total number of TEAEs counts all TEAEs for patients. A patient is counted only once within each summary level. The adverse event that was reported as the primary reason for study drug discontinuation is summarized.

c Neutropenia includes neutropenia, neutrophil count decreased, febrile neutropenia and neutropenic sepsis.

d Neuropathy includes neuropathy peripheral, peripheral sensory neuropathy, paresthesia, neurotoxicity, neuralgia, peripheral motor neuropathy, polyneuropathy.

A higher proportion of patients was withdrawn from treatment due to physician decision in the TPC arm (57/423; 13.5%) compared with the NKTR-102 arm (28/429; 6.5%). Typical reasons for clinical progression included symptoms of underlying disease such as increasing dyspnea, general deterioration, and reduced performance status. In the presence of clinical evidence suggesting progression, benefit/risk assessment may lead to discontinuation of treatments with less tolerable safety profiles (eg, TPC).

The nature, scope, and severity of the safety findings to date with NKTR-102 are clinically manageable and consistent with findings common to treatments for patients with MBC.

2.2 Study Rationale

This study is designed to allow an extension period of NKTR-102 therapy for subjects who previously received NKTR-102 during a clinical study and are without signs of disease progression since receiving NKTR-102.

The estimated study duration is approximately 5 years. The duration of treatment in this study is estimated to be approximately 2 years. Subjects may continue to receive repeated cycles of study drug treatment until progression of disease, unacceptable toxicity, death, withdrawal by subject, Investigator decision, lost to follow-up, or study is terminated by the Sponsor. Since this trial may involve the longest exposure to NKTR-102 to date, it will allow for the collection of safety data, particularly serious adverse events (SAEs) that may appear only after long-term exposure to NKTR-102.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

- To provide access to NKTR-102 to subjects who previously received NKTR-102 in a clinical trial and are without signs of disease progression since receiving NKTR-102.

3.2 Secondary Objectives

- To evaluate the safety of continued exposure to NKTR-102.
- To observe disease status and survival status in subjects receiving NKTR-102.
- To evaluate the efficacy of NKTR-102 in subjects with advanced or metastatic solid tumors.

4.0 STUDY DESIGN

4.1 Study Endpoint

4.1.1 Endpoints

- Incidence and duration of toxicities, with severity grading according to NCI-CTCAE v 4.0.
- Tumor response per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

4.2 Study Design

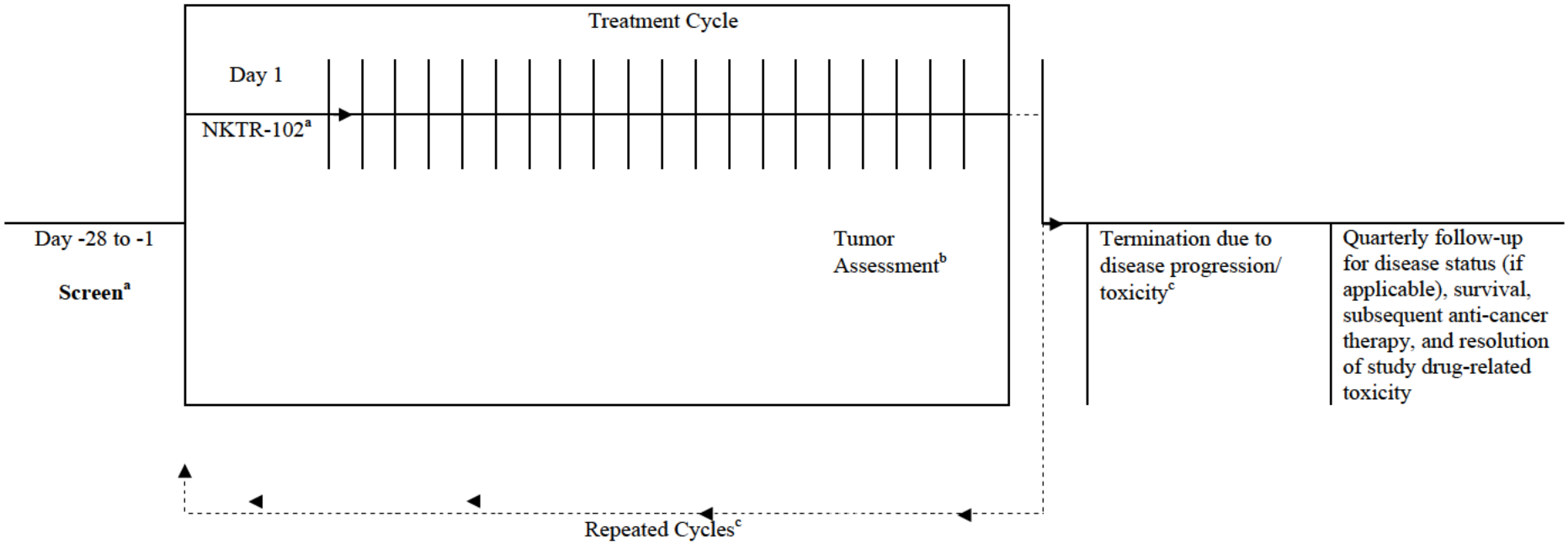
This is a multicenter, open-label, Phase 2 study of NKTR-102 in subjects with solid tumors who received NKTR-102 in a prior Nektar-sponsored clinical study. Following completion of NKTR-102 treatment on a prior NKTR-102 clinical study, subjects will be assessed for eligibility. The Sponsor must assess eligibility criteria prior to enrollment of all subjects.

Eligible subjects will continue treatment with NKTR-102 at a dose of 145 mg/m^2 or less in a q21d schedule as outlined in Section **6.5**. Subjects who previously received a dose of NKTR-102 at <145 mg/m^2 will continue at the lower dose in this study. Subjects who underwent dose reduction of NKTR-102 due to observed toxicity prior to participation in the Extension study (Protocol 11-PIR-09) will not be re-escalated to the previous dose level upon resolution of the toxicity. Dose escalation for NKTR-102 is not permitted.

NKTR-102 will be administered as an IV infusion over approximately 90 minutes (± 15 minutes) on Day 1 of each 21-day treatment cycle. Disease assessments for tumor response and progression will be performed as per local standard of care until disease progression. Minimal disease evaluation data (best response and date of progression) will be collected within this protocol. Tumor measurements are not required; only an overall assessment of response or progression by the Investigator is required. Subjects may continue to receive repeated cycles of NKTR-102 on this protocol as long as there is evidence of disease control in the judgment of the Investigator or until there is unacceptable toxicity, death, withdrawal of consent by the subject, Investigator decision, subject non-compliance, lost to follow-up or study is terminated by the Sponsor. After discontinuation of NKTR-102, all subjects, except those who withdraw consent from further study follow-up, are to be followed for disease status (as applicable), subsequent anti-cancer therapy, survival status, and resolution of toxicity attributable to study drug (with contact by phone, through a clinic visit, or through review of medical records approximately every 12 weeks (± 4 weeks).

A schematic of the study design is presented in **Figure 1**.

Figure 1: Study Schematic



a Pre-treatment safety assessments and NKTR-102 administration will occur on Day 1 of each cycle.

b Tumor assessments will be performed as required by standard of care.

c Treatment cycles will be repeated until disease progression, unacceptable toxicity, death, withdrawal of consent by the subject, Principal Investigator decision, lost to follow-up, or study is terminated by Sponsor (See Section 5.3).

4.2.1 Administrative Structure

Protocol 11-PIR-09 is sponsored by Nektar Therapeutics and will be administered and monitored by Nektar or designee. Monitoring will occur at each site on a periodic basis at Nektar's discretion. Monitors will perform verification of source documentation for study subjects. Site Investigators will provide confirmation to Nektar that the eligibility criteria have been met for each subject. Nektar will then inform the study site that the subject can be offered entry into the Extension study (Protocol 11-PIR-09).

4.3 Blinding

This is an open-label study.

4.4 Method of Assigning Subjects to Treatment Groups

There will be no randomization or subject stratification. Subjects will retain their subject identification number from their original study. Treatment with NKTR-102 will occur as described in Section **6.5**.

4.5 Drug Accountability and Reconciliation

NKTR-102 for Injection will be stored as per instructions provided in the pharmacy manual in a secured site with restricted access.

Study drug accountability will be recorded by the site pharmacist or designee and verified by the Sponsor's designee at the Sponsor's discretion. The pharmacist or designee will:

- Maintain records of product delivery, lot number, inventory, and destruction or return
- Maintain temperature monitoring
- Maintain up-to-date accountability of NKTR-102 for Injection in the drug accountability log
- Document the use of NKTR-102 for Injection by each subject
- Return or destroy unused NKTR-102 for Injection as per Sponsor's instructions

5.0 SELECTION OF STUDY POPULATION

Before any protocol mandated procedure is initiated, each subject or subject's legal representative will sign and date an IRB or IEC-approved informed consent form (ICF).

5.1 Inclusion Criteria

Each subject must meet the following criteria to be eligible for enrollment.

1. Subject or subject's legal representative must provide written informed consent.
2. Subject is able and willing to comply with the study visit schedule and procedures.
3. Subjects must have received prior treatment with NKTR-102 in a Nektar-sponsored study.
4. Subjects must be without signs of disease progression since receiving NKTR-102.
5. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at the predose visit of each cycle.
6. Women of childbearing potential and men who agree to use adequate contraception during study participation (at least two methods of contraception, one of which includes a barrier method [male condom] by the male partner or abstinence) or a male who has undergone a vasectomy greater than 6 months prior to Cycle 1 Day 1. Appropriate contraception must be used for at least 8 months after the last dose of the study drug on this extension study.
7. Subjects must meet requirements with respect to hematopoietic function (hemoglobin $\geq$ 8.0 g/dL or 80 g/L; absolute neutrophil count (ANC) $\geq$ 1.5 X 10^9/L; platelets $\geq$ 75 X 10^9/L).
8. Subjects must be able to receive the first dose of NKTR-102 in the extension study within 8 weeks after receiving their last dose of NKTR-102.

5.2 Exclusion Criteria

Subjects who meet any of the following criteria are ineligible for enrollment.

1. Subjects who have received intervening anti-cancer therapy (between their last dose of NKTR-102 and administration of the first dose of NKTR-102 in this extension study).

2. Subjects with 2 dose reductions of NKTR-102 and have a toxicity that requires another dose reduction.

3. Female subjects who are pregnant or lactating, who plan to get pregnant, or who have a positive pregnancy test at screening or during participation in this study.

5.3 Early Withdrawal/Discontinuation from Study

Subjects may choose to discontinue/withdraw from study drug treatment or the study at any time, for any reason, and without prejudice to further treatment. A subject who withdraws consent from study participation will be asked to state the level of withdrawal:

1. Withdrawal from treatment only; and/or

2. Withdrawal from contact during the post-treatment period (for off-study data, such as subsequent anti-cancer therapy or survival).

In the event of withdrawal of consent, the study staff and/or Investigator must make every effort to ascertain the level of consent withdrawn. An objective of this study is to assess survival status, so site personnel must ascertain if subjects will permit continued follow-up if consent is withdrawn. The type of consent withdrawal must be noted in source documents and CRF.

Subjects may stop NKTR-102 treatment or be withdrawn from the study for any of the following reasons, but will be followed for safety until resolution or permanent sequelae of all toxicities attributable to NKTR-102 (see Section **9.5**):

- Progression of disease
- Adverse Event (unacceptable toxicity)
- Death
- Non-compliance of the subject with protocol-mandated procedures
- Withdrawal of consent by subject
- Physician (Investigator) Decision
- Lost to Follow-Up
- Study is terminated by the Sponsor

5.3.1 Withdrawal Procedures

In the event of a subject's withdrawal from treatment, the Investigator will promptly notify Nektar Therapeutics and will make every effort to complete the End-of-Treatment assessments and ascertain if subjects will permit continued follow-up (i.e., for survival status, subsequent anti-cancer therapy, and disease status). Before a subject is considered "Lost to follow-up", study personnel must attempt to contact the subject at least twice by phone and once by mail with documented receipt. Study personnel may use public records to check for mortality for any subjects considered "Lost to follow-up" or who have withdrawn consent from the study, if permitted by applicable laws or regulations.

6.0 INVESTIGATIONAL PRODUCT(S)/STUDY MEDICATIONS

6.1 Description and Formulation

The drug substance NKTR-102 is a polymeric conjugate prodrug of irinotecan with 3 essential components: a relatively large polymer, a biodegradable linker, and an active agent. In NKTR-102, irinotecan is attached to PEG via a releasable linker that is hydrolyzed in vivo to deliver irinotecan, which is further metabolized to the active metabolite, SN38. **Table 3** provides the nomenclature information for drug substance NKTR-102.

Table 3: Nomenclature

Compound Number/Name:	NKTR-102 (etirinotecan pegol)
Sponsor:	Nektar Therapeutics
Chemical classification:	Topoisomerase 1 Inhibitor

The investigational drug product NKTR-102 for Injection is formulated as a sterile lyophilized powder of NKTR-102 in lactate buffer at pH 3.5, intended for dilution with commercially available 5% Dextrose Injection (w/w%; D5W) or 0.9% Sodium Chloride for Injection before IV infusion. The pH of the formulation is in the range of 3.2 to 4.2, and NKTR-102 for Injection storage condition is 2°C - 8°C, with a shelf-life of 48 months.

Both 5% Dextrose Injection and 0.9% Sodium Chloride for Injection will be locally sourced at each clinical study site.

6.2 Packaging and Labeling

NKTR-102 (drug substance) is light sensitive. The lyophilized drug product NKTR-102 for Injection will be supplied in 25 mL Type 1 amber colored glass vials packaged in cartons of 10 vials per carton. Each vial contains lyophilized NKTR-102 equivalent to 100 mg of irinotecan.

Each vial and carton will be labeled to comply with local regulations.

6.3 Reconstitution and Handling

NKTR-102 for Injection must be reconstituted with D5W or 0.9% Sodium Chloride for Injection to a final concentration range of 0.2 to 1.6 mg/mL. The reconstituted drug may be stored under ambient lighting conditions at room temperature (15 to 30°C) for up to 6 hours prior to start of infusion. Other drugs must not be added to the infusion solution.

NKTR-102 for Injection must be administered as an IV infusion over approximately 90 minutes (± 15 minutes). Premedications are not required to be administered prior to the initial infusion in this study, but may be used for an individual subject, as needed. If a subject has reported symptoms (such as nausea and/or vomiting) in the original study, prophylactic use of anti-emetics may be attempted.

The instructions for reconstitution and administration of NKTR-102 for Injection are described in detail in the Pharmacy Binder.

6.4 Treatment Assignment

This is an open-label trial. There will be no subject randomization or stratification. Subjects will retain the subject identification numbers assigned in the original protocol.

6.5 Dosage and Administration

Body surface area (BSA) will be determined before the start of each cycle, based on baseline height and most recent weight. Body surface area may be calculated based on institutional guidelines. NKTR-102 will be administered as an IV infusion over 90 minutes (± 15 minutes). The recommended dose and schedule of NKTR-102 is 145 mg/m^2 q21d, with BSA capped at 2.4 m^2. Subjects who were previously receiving the 145 mg/m^2 dose will continue to receive this dose in this extension study in a q21d schedule.

Subjects originally enrolled in a clinical study in which a lower-than-recommended dose was administered (e.g., Protocol 12-102-13 in subjects with impaired liver function) or was being administered after a dose reduction will continue to receive that same dose in a q21d schedule in this study. For Protocol 12-102-13 subjects with hepatic dysfunction, as defined in that study, will continue in this extension study (Protocol 11-PIR-09) to receive the originally assigned dose from the 12-102-13 study in a q21d schedule.

Subjects originally enrolled in a clinical study in which a higher-than-recommended dose was being administered (e.g., Protocol 12-102-12 to explore the effects of NKTR-102 on cardiac function) will receive the recommended dose of NKTR-102 of 145 mg/m^2 in a q21d schedule in this extension study (Protocol 11-PIR-09).

Subjects who underwent dose reduction of NKTR-102 due to observed toxicity prior to participation in the Extension study [Protocol 11-PIR-09] will not be re-escalated to the previous dose level upon resolution of the toxicity.

Dose escalation for NKTR-102 is not permitted.

Refer to the Pharmacy Binder for further information.

6.6 Duration of Treatment

The estimated study duration is approximately 5 years. The duration of treatment in this study is estimated to be approximately 2 years. Subjects may continue to receive repeated cycles of study drug treatment until progression of disease, unacceptable toxicity, death, withdrawal by subject, Investigator decision, lost to follow-up, or study is terminated by the Sponsor.

6.7 Dose Modifications and Delays

All adverse events (AEs) will be assessed according to the NCI-CTCAE version 4.0. In the event of multiple toxicities, dose delays and modifications should occur in accordance with the worst toxicity observed.

Specific dose modifications for NKTR-102 will be made for diarrhea, dehydration, hematological, and other non-hematological toxicities. Dose delays may be permitted between cycles.

Prior to initiation of subsequent NKTR-102 cycles, subjects must meet requirements with respect to hematopoietic function (hemoglobin $\geq$ 8.0 g/dL or 80 g/L; ANC $\geq$ 1.5 X 10^9/L; platelets $\geq$ 75 X 10^9/L). Diarrhea must be fully resolved to NCI-CTCAE Grade 0 (a return to normal bowel movement habits) for at least 7 days without supportive antidiarrheal measures prior to retreatment. Any treatment-related non-hematologic toxicities must have resolved to baseline or Grade 1.

If the subject fails to meet the criteria for re-treatment, treatment may be delayed, followed by an additional evaluation to determine feasibility of retreatment. Initiation of subsequent doses may be delayed for a maximum of 28 days to allow recovery from any toxicity to permit retreatment. Subjects whose treatment delays are $\geq$ 14 days but $\leq$ 28 days due to a drug-related toxicity must initiate their next treatment cycle with a dose reduction. Subjects who require > 28 days delay due to unresolved toxicity must be withdrawn from treatment, unless, in the Investigator's opinion, continuing in the study is of benefit for the subject. In this case, the continuation of treatment must be discussed with the Medical Monitor and the reason for continuation must be approved and documented.

Subjects from Protocol 12-102-13 with impaired liver function who are entering the extension study will receive the same dose as that received in the 12-102-13 study. Investigators may choose to reduce the dose of NKTR-102 for either drug-related or non-drug related Grade 3 or higher liver dysfunction only after approval from Nektar Medical Monitor.

Supportive care may be implemented in order to treat diarrhea, nausea, vomiting, anorexia, myelosuppression, and/or other AEs. Dose delays may be implemented to permit recovery if a subject is demonstrating clinical benefit, but with repeated Grade 2 toxicities that would otherwise mandate withdrawal.

Dose reductions may also be implemented for subjects who experience recurrent or specific severe toxicities (see **Table 4**). NKTR-102 doses for an individual subject may be reduced by 25 mg/m^2 based on conditions listed in **Table 4**. Subjects should be discontinued from the study treatment if toxicity would indicate more than 2 dose reductions. Dose re-escalation for NKTR-102 is not permitted.

- For subjects entering this study at a starting dose of 145 mg/m^2: dose reductions to 120 mg/m^2, then to 95 mg/m^2 may occur based on conditions listed in **Table 4**.
- For subjects (i.e., from Protocol 12-102-13) entering this study at a starting dose of 120 mg/m^2: dose reductions to 95 mg/m^2, then to 70 mg/m^2 may occur based on conditions listed in **Table 4**.
- For subjects (i.e., from Protocol 12-102-13) entering this study at a starting dose of 95 mg/m^2: dose reduction to 70 mg/m^2 may occur based on conditions listed in **Table 4**.
- For subjects (i.e., from Protocol 12-102-13) entering this study at a starting dose of 50 mg/m^2: dose reduction should be approved by Medical Monitor.
- **Table 4** provides instructions regarding dose modification.
- DURING A CYCLE: **Table 4**/Column 2 describes the recommended guidelines for management and supportive care during a cycle of therapy.
- INITIATION OF A SUBSEQUENT CYCLE: **Table 4**/Column 3 describes the recommended dose modifications for Day 1 in subsequent cycles of therapy. All dose modifications in a new cycle should be based on the worst toxicity observed in the previous cycle and the dose reduction will be relative to the Day 1 dose of the previous cycle.

Table 4: NKTR-102 Dose Modifications

Toxicity NCI CTCAE Grade	During a Cycle	Dose Modifications for Day 1 of New Cycle
Neutropenia / Febrile Neutropenia		
Grade 1 (ANC <1500/mm^3)		Maintain dose level.
Grade 2 (ANC ≥1000/mm^3, <1500/mm^3)	Consider growth factor support in accordance with local guidelines.	If present on a treatment day, hold therapy until toxicity resolves to ANC≥1500/mm^3. • ↓ 1 dose level after 1st occurrence (provided screening ANC > 2000/mm^3); do not reduce dose for Grade 2 neutropenia if screening ANC was ≥ 1500 and < 2000/mm^3. Consider prophylactic growth factor therapy. • ↓ 1 dose level after 2nd occurrence. Consider prophylactic growth factor therapy. Provided that adequate supportive care has been given to the patient, and the investigator believes it is in the best interest of the patient, retreatment may be attempted for a 3rd episode of Grade 2 ANC.
Grade 3 (ANC ≥500/mm^3, <1000/mm^3)	Consider growth factor support in accordance with local guidelines.	If present on a treatment day, hold therapy until toxicity resolves to ANC ≥ 1500/mm^3. • ↓ 1 dose level after 1st occurrence. Use prophylactic growth factor therapy. • ↓ 1 dose level after 2nd occurrence. Use prophylactic growth factor therapy. Provided that adequate supportive care has been given to the patient, and the investigator believes it is in the best interest of the patient, retreatment may be attempted for a 3rd episode of Grade 3 ANC.
Grade 4 (ANC <500/mm^3)	Consider growth factor support in accordance with local guidelines. Consider use of antibiotic (oral fluoroquinolones) even in the absence of fever or diarrhea.	If present on a treatment day, hold therapy until toxicity resolves to ANC ≥ 1500/mm3. • ↓ 1 dose level after 1st occurrence. Use prophylactic growth factor therapy. • ↓ 1 dose level after 2nd occurrence. Use prophylactic growth factor therapy. Discontinue NKTR-102 after 3rd occurrence.

Toxicity NCI CTCAE Grade	During a Cycle	Dose Modifications for Day 1 of New Cycle
Febrile Neutropenia Grade 3 or 4 (ANC <1000/mm^3 with a single temperature of ≥ 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than one hour	Treat as appropriate (eg, growth factor support; antibiotics); consider hospital admission. Patients should be hospitalized for IV antibiotic therapy if sepsis is suspected.	Retreatment must be delayed until the toxicity is Grade ≤ 1. • ↓ 1 dose level after 1st occurrence. Use prophylactic growth factor therapy. • ↓ 1 dose level after 2nd occurrence. Use prophylactic growth factor therapy. Discontinue NKTR-102 after 3rd occurrence.
Thrombocytopenia		
Grade 1 or 2		Maintain dose level.
Grade 3 (Platelets ≥ 25, <50K)	Consider platelet transfusion if active bleeding. Following platelet transfusion, retreatment must be delayed for 7 days and patient must meet retreatment criteria prior to dosing.	If present on a treatment day, hold therapy until toxicity resolves to platelets ≥ 50K. • ↓ 1 dose level after 1st occurrence. • ↓ 1 dose level after 2nd occurrence. Provided that adequate supportive care has been given to the patient, and the investigator believes it is in the best interest of the patient, retreatment may be attempted for a 3rd episode of Grade 3 thrombocytopenia.
Grade 4 (Platelets < 25K)	Consider platelet transfusion if platelets ≤10K or with active bleeding. Following platelet transfusion, retreatment must be delayed for 7 days and patient must meet retreatment criteria prior to dosing.	If present on a treatment day, hold therapy until toxicity resolves to platelets ≥ 50K. • ↓ 1 dose level after 1st occurrence. • ↓ 1 dose level after 2nd occurrence. Discontinue NKTR-102 after 3rd occurrence.
Anemia		
Grade 1 or 2		**Maintain dose level**
Grade 3 Hgb <8	**Provide** erythropoietin-stimulating agents or transfusion as appropriate.	If present on a treatment day, hold therapy until toxicity resolves to Hgb >8 • ↓ 1 dose level after 1st occurrence. • ↓ 1 dose level after 2nd occurrence. Provided that adequate supportive care has been given to the patient, and the investigator believes it is in the best interest of the patient, retreatment may be attempted for a 3rd episode of Grade 3 anemia

Toxicity NCI CTCAE Grade	During a Cycle	Dose Modifications for Day 1 of New Cycle
Grade 4 Hgb<6.5	Consider erythropoietin-stimulating agents or transfusion as appropriate.	• If present on a treatment day, hold therapy until toxicity resolves to Hgb >8 • ↓ 1 dose level after 1st occurrence. • ↓ 1 dose level after 2nd occurrence. Discontinue NKTR-102 after 3rd occurrence
Diarrhea		
Any Grade	Institute supportive care upon first loose stool. (Unless contraindicated, use loperamide). Monitor bowel function; if diarrhea continues with 1st supportive care agent, consider switching to a 2nd agent or add a 2nd agent (unless contraindicated, use diphenoxylate/atropine). Monitor for dehydration, electrolyte abnormalities; correct if present. Administer antibiotic therapy (oral fluoroquinolones) if the patient develops ileus, fevers, or Grade 3/4 neutropenia. Patients should be hospitalized for IV antibiotic therapy if there is evidence of colitis or ileus even in the absence of neutropenia or fever. If diarrhea is worsening, octreotide may be attempted. Monitor bowel function for continued need for supportive care. Stop supportive care after the patient is 48 hr without diarrhea.	Confirm with the patient that diarrhea is no longer present for ≥ 7 days without having received supportive care prior to retreatment. Treatment may be delayed up to 28 days; after this, contact Medical Monitor.
Grade 1		Maintain dose level; consider prophylactic anti-diarrheal supportive care
Grade 2		• ↓ 1 dose level after 1st occurrence; use prophylactic anti-diarrheal supportive care • ↓ 1 dose level after ≥ 2nd occurrence; use prophylactic anti-diarrheal supportive care Provided that adequate supportive care has been given to the patient, retreatment may be attempted for a 3rd episode of Grade 2 diarrhea (re-instruct the patient on supportive care).

Toxicity NCI CTCAE Grade	During a Cycle	Dose Modifications for Day 1 of New Cycle
Grade 3/4		• ↓ 2 dose levels after 1st occurrence; use prophylactic anti-diarrheal supportive care Provided that adequate supportive care has been given to the patient, retreatment may be attempted for a 2nd episode of Grade 3 diarrhea (re-instruct the patient on supportive care).
Dehydration		
Grade 1: Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	Consider anti-emetic or anti-diarrheal supportive care	Maintain dose level; consider prophylactic anti-diarrheal or anti-emetic supportive care
Grade 2: IV fluids indicated <24 hours	Use anti-emetic and/or anti-diarrheal supportive care	Maintain dose level or ↓ 1 dose level after 1st occurrence; use prophylactic anti-emetic or anti-diarrheal supportive care. • ↓ 1 dose level after ≥ 2nd occurrence; use prophylactic anti-emetic or anti-diarrheal supportive care. Provided that adequate supportive care has been given to the patient, retreatment may be attempted for a 3rd episode of Grade 2 dehydration (re-instruct the patient on supportive care).
Grade 3: IV fluids or hospitalization Indicated; Grade 4: Life-threatening consequences; urgent intervention indicated	Use anti-emetics, anti-diarrheal supportive care, and/or IV fluids as appropriate. Consider hospital admission.	Treatment must be delayed until the toxicity recovered to baseline or Grade < 1. • ↓ 2 dose levels after 1st occurrence; use prophylactic anti-emetic or anti-diarrheal supportive care. Provided that adequate supportive care has been given to the patient, retreatment may be attempted for a 2nd episode of Grade 3 dehydration (re-instruct the patient on supportive care). NKTR-102 must be discontinued for a 2nd episode of Grade 4 dehydration.
Nausea/Vomiting/Abdominal Pain		
Grade 1/2	Consider anti-emetic supportive care.	Maintain dose level; consider prophylactic anti-emetic supportive care.

Toxicity NCI CTCAE Grade	During a Cycle	Dose Modifications for Day 1 of New Cycle
Grade 3	Use anti-emetic supportive care. Consider administration of IV fluids.	Treatment must be delayed until the toxicity recovered to baseline or Grade < 1 • ↓ 1 dose level after 1st occurrence; use prophylactic anti-emetic supportive care • ↓ 1 dose level after 2nd occurrence; use prophylactic anti-emetic supportive care. Provided that adequate supportive care has been given to the patient, retreatment may be attempted for a 3rd episode of Grade 3 nausea/vomiting/abdominal pain
Grade 4	Use anti-emetic supportive care and IV fluids.	Treatment must be delayed until the toxicity recovered to baseline or Grade < 1 2 dose levels after 1st occurrence; use prophylactic anti-emetic supportive care Discontinue NKTR-102 after 2nd occurrence
Other drug-related non-hematologic toxicities (except fatigue/asthenia and alopecia)		
Grade 1/2	Consider supportive care as appropriate	Maintain dose level (for Grade 2 toxicity, the Investigator may use discretion to ↓ 1 dose level after 1st occurrence depending on the nature of the toxicity). If recurrent Grade 2 toxicity Investigator may choose to ↓ 1 dose level; continue supportive care.
Grade 3	Use supportive care as indicated	Treatment must be delayed until the toxicity has resolved or returned to baseline ↓ 1 dose level after 1st occurrence; supportive care as appropriate ↓ 1 dose level after 2nd occurrence Provided that adequate supportive care has been given to the patient, retreatment may be attempted for a 3rd episode of Grade 3 other drug-related non-hematological toxicities (except fatigue, asthenia)
Grade 4	Use supportive care as indicated. Consider hospital admission.	Treatment must be delayed until the toxicity recovered to baseline or Grade < 1 ↓ 2 dose levels after 1st occurrence. Discontinue NKTR-102 after 2nd occurrence

6.8 Antidiarrheal Therapy

Subjects may experience diarrhea following administration of NKTR-102.

To date, *early-onset diarrhea* (occurring during or shortly after infusion of study drug) has rarely been seen with NKTR-102 administration. It is usually transient and only infrequently severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by administration of atropine (0.25 to 1 mg subcutaneous or IV), however, routine prophylactic use of atropine is not recommended.

Late onset diarrhea (occurring more than 24 hours after the infusion) can be life-threatening, because it may be prolonged and may lead to dehydration, hypotension, and renal failure. In the BEACON study, 9.6% of patients reported Grade 3 diarrhea. Among those patients, the median time to onset of Grade 2 or higher diarrhea was 40 days, and the median onset for Grade 3 diarrhea was 43 days. In addition, the median time to resolution of Grade 2 or higher diarrhea was 3.5 days and the median time to resolution of Grade 3 diarrhea was 6 days. There were no incidents of Grade 4 diarrhea.

It should be noted in the patient's medical record whether the subject is currently receiving anti-diarrhea supportive care and the date of the last episode of diarrhea/loose stool.

Diarrhea must be treated promptly with anti-diarrheal therapy; loperamide is recommended. Each subject must be instructed to immediately begin taking anti-diarrheal therapy at the very first episode of poorly formed or loose stools or the earliest onset of bowel movements that are more frequent than normally expected for the subject. Subjects with diarrhea must be carefully monitored, should be given adequate fluid and electrolyte replacement if they become dehydrated, and antibiotic support if they develop ileus, fever, or severe neutropenia.

- Prophylactic antidiarrheal medications must not be used as they can confound the evaluation of recovery to Grade 0 (a return to normal bowel movement habits) and monitoring of diarrhea AEs in subjects receiving NKTR-102.

- Each subject will be instructed to start taking anti-diarrheal therapy (i.e., loperamide) for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the subject.

- One dosage regimen for loperamide used in clinical trials consisted of the following (Note: This dosage regimen exceeds the usual dosage recommendations for loperamide.): ***4 mg at the first onset of diarrhea and then 2 mg every 2 hours until the subject is diarrhea-free for at least 12 hours.*** Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. During the night, the subject may take 4 mg of loperamide every 4 hours.

- The use of drugs with stimulant laxative properties should be avoided because of the potential for exacerbation of diarrhea.

- ***Subjects will be instructed to report the following***: diarrhea for the first time during the infusion of NKTR-102; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; inability to get diarrhea under control within 24 hours; or fever or evidence of infection.

An Institutional Review Board (IRB)-approved subject instruction sheet on the management of diarrhea will be provided to all the subjects.

6.9 Antiemetic Therapy

If a subject experiences nausea and/or vomiting, the subject may be given prophylactic antiemetics treatment prior to the next dose of NKTR-102. The subject must be carefully monitored throughout the study period, and given adequate fluid and electrolyte replacement to prevent dehydration and electrolyte imbalance.

6.10 Use of Growth Factor Support and Transfusions

Upon NKTR-102 administration, subjects may experience neutropenia. Subjects who do not meet retreatment criteria for ANC should return to clinic within 3-7 days for reassessment. If the subject continues not to meet retreatment criteria for ANC, she should return to clinic at weekly intervals for reassessment. Subjects must demonstrate an ANC $\geq$ 1.5 X 10^9/L prior to retreatment with NKTR-102.

Prophylactic use of growth factor support is not permitted, however use of growth factor support in a setting of neutropenia is permitted. Use of growth factor support must follow American Society Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) guidelines or standard of care at the local institution. For example, if a subject required growth factor support during a previous cycle, a subject may be administered prophylactic growth factor support during a subsequent cycle at the investigator's discretion.

Subjects may receive transfusions (platelets or blood products) at the Investigator's discretion.

6.11 Prior and Concomitant Medications

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

All medications (both prescription and over-the-counter [OTC] medications), vitamin and mineral supplements, and/or herbs taken by the subject from Screening through the End-of-Treatment visit will be documented on the concomitant medication eCRF. Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. All concomitant medications administered to study subjects will be recorded in the eCRF.

6.11.1 Permitted Treatments

- Palliative and supportive care for disease-related symptoms.
- Standard therapies for concurrent medical conditions, including antiemetic prophylaxis (see Section **6.9**) and early interventional antidiarrheal therapy (see Section **6.8**).
- Diarrhea is an expected toxicity of NKTR-102. All subjects must receive optimal antidiarrheal therapy immediately after the FIRST episode of diarrhea or loose stool regardless of severity.
- Premedication with antihistamine and/or corticosteroid is allowed in subsequent cycles following occurrence of a self-limiting allergic/hypersensitivity reaction to a prior infusion of NKTR-102.

6.11.2 Prohibited Concomitant Medications

The treatments listed below are prohibited while on study. For treatments prohibited on study, alternative medical intervention should be considered; if a prohibited treatment is required, study drug treatment should be discontinued.

- Any concurrent chemotherapy (other than NKTR-102), radiotherapy (with the exception of palliative radiation), biological therapy, hormonal agents used for the treatment of cancer, immunotherapy, or other systemic therapy for cancer; megestrol acetate for appetite stimulation may be used;
- Other investigational agents within 28 days prior to Day 1 of Cycle 1 or during the study;

- Investigators must monitor subjects for use of potent cytochrome P450 3A4 (CYP3A4) inducers or inhibitors, as they may induce or inhibit irinotecan or SN38 metabolism. Some of these agents are OTC medications (e.g., St John's Wort); subjects must provide a complete list of all concomitant medications as part of the screening process. See **Appendix 2** for a list of agents known to induce and inhibit CYP3A4.

6.11.3 Adequate Forms of Birth Control

Over the course of the study, women of childbearing potential (WCBP) and men must agree to use adequate contraception during study participation (at least two methods of contraception, one of which includes a barrier method [male condom] by the male partner or abstinence) or a male who has undergone a vasectomy greater than 6 months prior to Cycle 1 Day 1. Women of childbearing potential are women who are not 2 years postmenopausal or are not surgically sterile.

Protections against pregnancy should be continued for at least 8 months after the last dose of NKTR-102.

7.0 EVALUATIONS BY VISIT

A summary of study assessments and procedures are shown in the Schedule of Assessments (**Appendix 1**). Laboratory evaluations prior to treatment in this study will be done at local laboratories. Each laboratory must be certified and must be listed on the Statement of Investigator Form FDA 1572.

7.1 Screening

The following procedures will be performed for all potential subjects at a screening visit conducted within 28 days prior to Cycle 1 Day 1. Any procedures, as applicable, that were completed as part of the end-of-study visit for the original protocol may be used and do not need to be repeated if they were performed within 7 days of Cycle 1 Day 1 of this extension study. The maximum delay between treatment with the last dose of NKTR-102 and treatment with NKTR-102 in this study is 8 weeks.

- Informed consent by subject or subject's legal representative
- Medication history (including previous chemotherapy, radiation, treatment with biologics, OTC drugs, herbs and St. John's Wort)
- Demographics including birth date, race/ethnicity, and gender at birth
- Complete physical examination, including height and body weight and vital signs (pulse, temperature, and blood pressure)
- ECOG performance status
- Serum pregnancy test (WCBP only)
- Disease assessment with computed tomography (CT), magnetic resonance imaging (MRI) scanning, or digital photography, unless subject had disease assessment within 8 weeks prior to treatment in the Extension study
- Hematology and serum chemistry: minimally required are hemoglobin, ANC, platelets, and creatinine. Complete blood count (CBC) and other laboratory tests will be obtained at the discretion of the Investigator.
- Assessment of AEs (see Section **9.2** for details on AE collection from the time of the original protocol to the start of the Extension study)

7.2 Treatment Days

For all cycles, safety assessments are required before each treatment cycle. All results must be available before dosing. For all cycles, Day 1 assessments may be performed up to 5 days before Day 1. The following procedures will be performed prior to each dose:

- Symptom-directed physical examination, including body weight
- ECOG performance status
- Vital signs (pulse, temperature, blood pressure)
- Hematology and serum chemistry: minimally required are hemoglobin, ANC, platelets, and creatinine. Complete blood count and other laboratory tests will be obtained at the discretion of the Investigator.
- Body surface area
- Urine pregnancy test (only for WCBP)
- Assessment of concomitant medications
- Assessment of AEs
- Diarrhea must be fully resolved to NCI-CTCAE Grade 0 (a return to normal bowel movement habits) for at least 7 days without supportive antidiarrheal measures prior to treatment. Any treatment-related non-hematologic toxicities must have resolved to baseline or Grade 1
- NKTR-102 for Injection administration

NOTE: Disease assessment (tumor response and progression assessments) should be performed as per local standard of care. Best response and date of progression will be collected in this protocol. Other procedures and evaluations may be performed as clinically indicated and as determined by the investigator.

All safety laboratory evaluations will be performed at a local laboratory. Each laboratory must be certified and must be listed on the Statement of Investigator Form FDA 1572.

7.3 End-of-Treatment Visit

The End-of-Treatment visit is to occur 30 days (± 7 days) after last dose of study drug.

The following procedures will be performed for all subjects at the end of the subject's treatment:

- Complete physical examination, including body weight
- ECOG performance status
- Vital signs (pulse, temperature, blood pressure)
- Urine pregnancy test (only for WCBP)
- Assessment of concomitant medications
- Assessment of AEs

7.4 Quarterly Follow-up

Approximately every 12 weeks (±4 weeks) following the End-of-Treatment visit, subjects will have their medical records reviewed and may be contacted to assess disease status, survival status, receipt of subsequent anti-cancer therapy, and resolution of all toxicity attributable to study drug. Disease status during follow-up will only be assessed if the subject has not demonstrated disease progression since receiving NKTR-102. Quarterly follow-up will continue until death, withdrawal of consent by subject, physician decision, lost to follow-up, or the study is terminated by the Sponsor.

8.0 STUDY OR STUDY SITE TERMINATION

If the Sponsor, Investigator, Medical Monitor, study monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation. Nektar Therapeutics has the right to terminate this study at any time for any reason. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug

A study or study site may also warrant termination under the following conditions:

- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Recording of inaccurate or incomplete data
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate Regulatory Authority
- Insufficient adherence to protocol requirements
- General Good Clinical Practice (GCP) noncompliance as determined by the Sponsor

In the event that the clinical development of the investigational product is discontinued, Nektar Therapeutics shall immediately inform all study Investigators/institutions and Regulatory Authorities. Study termination and follow up will be performed in compliance with the conditions set forth in the ICH sixth efficacy publication (E6) on GCP and local regulatory requirements.

9.0 ASSESSMENT OF SAFETY OR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

In this section, the term study drug refers to NKTR-102 for Injection.

9.1 Adverse Event Definition and Assessment

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not 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 unexpected AE is one of a type not consistent in nature or severity with information in the current IB.

An AE does not include:

- A medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion); an AE is the underlying condition that leads to the procedure
- Pre-existing diseases or conditions present or detected before start of study drug administration and which 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)

9.2 Monitoring Adverse Events

All AEs will be assessed by the Investigator and recorded in the appropriate case report form (CRF), including but not limited to, the date of onset and resolution, seriousness, severity, relationship to study drug, outcome, and action taken with study drug. Adverse events will be reported starting immediately after the subject or subject's legal representative has provided written informed consent through the End-of-Treatment visit (30 ± 7 days from the last dose of study drug in the extension study).

After providing informed consent for the extension study, if the subject is continuing in the original protocol and therefore will not have received the first dose of study drug in the extension study (Protocol 11-PIR-09), any AEs that occur will be collected under the original protocol. For subjects who have ended the original protocol and have provided informed consent for the extension study (Protocol 11-PIR-09), AEs will be collected under the extension study (Protocol 11-PIR-09).

Adverse events that were considered related to study drug in the original protocol and were ongoing when the subject ended the original protocol will be captured as a new AE in the extension study (Protocol 11-PIR-09) marked as continuing. Unrelated AEs that were ongoing at the end of the original protocol may also be captured as new AEs in the extension study (Protocol 11-PIR-09) marked as continuing.

For each AE, the following data elements will be recorded on the CRFs:

- Verbatim description of event
- NCI-CTCAE v. 4.0 grade for AE severity (refer to Section **9.3**)
- Start and stop date of AE
- Relationship/causality attribution to study drug
- Whether or not the administration of study drug was reduced, interrupted, delayed, or permanently discontinued due to the AE
- Whether or not the event was considered as an SAE
- Treatment provided for the AE (pharmacologic or non-pharmacologic)
- Outcome of the AE

9.3 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 event is based on the subject/event outcome or action criteria. All AEs will be assessed for severity using the NCI-CTCAE version 4.0. If a particular AE is not listed in the NCI-CTCAE, the following criteria will be used to assess severity by the Investigator:

  - grade 1 = Mild (asymptomatic or mild symptoms or clinical or diagnostic observations only, intervention not indicated)

- grade 2 = Moderate (minimal, or local or non-invasive intervention indicated or limiting age-appropriate instrumental activities of daily living [ADL])
- grade 3 = Severe (medically significant but not immediately life-threatening or hospitalization or prolongation of hospitalization indicated or disabling, limiting self care ADL)
- grade 4 = Life threatening or disabling (life threatening consequences, urgent intervention indicated)
- grade 5 = Death (related to AE)

Adverse events will be reported using the maximal severity grade experienced for that continuing instance of the AE. Please refer to the CRF Completion Guidelines for detailed reporting instructions.

9.4 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 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 reaction may have been produced by the subject's clinical state or other concomitant therapies or interventions.
- Definitely 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.

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

9.5 Adverse Event Reporting and Follow-up

All AEs will be followed until resolution or until 30 ± 7 days after last dose of study drug administration, whichever is earlier, except related AEs which will be followed until they stabilize or resolve; until the Investigator assesses the event as chronic or stable; start of new cancer therapy; subject lost to follow-up or subject death, whichever is earlier. If an unrelated AE has not completely resolved up to 30 ± 7 days after last dose of study drug, the final outcome of these ongoing AEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

Any new AEs occurring more than 30 ± 7 days after last dose of study drug will be captured only if serious and assessed by the Investigator as related (possibly/definitely related) to study drug (i.e. a related SAE). For specific instructions on identifying and reporting SAEs, see Sections **9.6** and **9.7** below.

This study will use the MedDRA for coding all AEs.

9.6 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, 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 due to the following:
    - A surgery or procedure that was planned before the subject entered the study and which is part of the planned study procedure
    - Nonmedical reasons, in the absence of an AE
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- 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

An unexpected SAE is any SAE in which the nature, frequency or severity is not consistent with that indicated in the IB.

Death is an outcome of an AE, and not an AE in itself. All deaths regardless of causality must be reported. An efficacy failure is not considered an SAE. "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 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.

9.7 Serious Adverse Event Reporting

All SAEs with an onset within **30 days** after the subject's last dose of study drug, whether or not considered related to study drug treatment, will be reported to Nektar Therapeutics Drug Safety or its designee within **24 hours** of when the site becomes aware of the event. In addition, SAEs that are assessed by the Investigator as related to NKTR-102 and occurring **> 30 days** after last dose of study treatment will also be reported to Nektar Therapeutics Drug Safety or its designee within **24 hours** of when the site becomes aware of the event.

[redacted]

The Investigator must complete the SAE Report Form, assess the causality relationship to the study treatment as applicable, and send the completed SAE form by fax to Nektar Therapeutics Drug Safety or designee.

A follow-up report and any additional records (such as hospital records, consultant reports, and autopsy findings) will be faxed to Nektar Therapeutics Drug Safety or designee as soon as these documents become available or promptly upon request.

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

All SAEs will be followed as described in Section **9.8** below.

Pregnancy, although reportable, is not considered an AE/SAE unless a male subject's female partner experienced signs or symptoms of pregnancy complications. 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.

Reporting of SAEs to the IRB/IEC will be done in accordance with the standard operating procedures and policies of the IRB/IEC. Adequate documentation must be provided to Nektar Therapeutics, showing that the IRB/IEC was properly notified. Serious adverse events will be reported by Nektar Therapeutics or designee to the regulatory authorities, per local regulations.

9.8 Serious Adverse Event Follow-up

All SAEs will be followed until the end of study or resolution, unless related to study drug and continuing or reported after the end of the study, in which the related SAE will be followed until any of the following occur (whichever comes first):

- The event resolves.
- The event has stabilized.
- The event returns to baseline, if a baseline value is available.
- It is unlikely that any additional information can be obtained (e.g., subject or health care practitioner refuses to provide additional information; lost to follow-up after demonstration of due diligence with follow-up efforts).
- Further follow-up is not warranted based upon the medical judgment of the investigator.
- Death

All ongoing and new SAEs with a start date within 30 days of last dose of study drug and assessed as "Unrelated" to study drug will be followed until resolution or until 30 ± 7 days after last dose of study drug administration, whichever is earlier.

9.9 Expedited Reporting of SAEs

A SUSAR is a SAE that is considered "unexpected" and assessed as related to the study drug by the Investigator or the Sponsor. All SAEs deemed related to the study drug and not expected based on the most current IB are subject to expedited reporting by the Sponsor to the applicable Regulatory Authorities. Therefore, the investigator or study 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 by the Sponsor to the Regulatory Authorities as soon as possible, but no later than 7 calendar days after Sponsor or Sponsor's designee has first knowledge of the minimum criteria for expedited reporting. Non-fatal or non-life-threatening SUSARs will be reported to the Regulatory Authorities, IRBs/IECs, and Investigators as soon as possible, but no later than 15 calendar days after Sponsor or Sponsor's designee has first knowledge of the SUSAR.

Reporting of SUSARs to all applicable Regulatory Authorities will be done by Nektar Therapeutics Drug Safety or designee as per local country and regional regulations.

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

9.10 Ongoing Safety Monitoring

Subject safety will be assessed throughout the study by a Safety Review Committee consisting of at minimum the Medical Monitor, Sponsor Clinical Lead and Sponsor Pharmacovigilance Lead or designee by review of SAEs.

10.0 EFFICACY EVALUATIONS

Due to the nature of this study, no specific schedule or type of tumor measurements/assessments are dictated within the protocol. These will be conducted as per the local standard of care until disease progression. Data on best response and disease progression (per physician assessment) will be collected according to RECIST criteria version 1.1 (**Eisenhauer et. al., 2009**). Radiographs that document response, stable disease, or progression should be performed according to routine patterns of care and (preferably original) copies should be maintained by the Investigator for review by the Sponsor, if requested.

Approximately every 12 weeks (±4 weeks) following the End-of-Treatment visit, subjects will have their medical records reviewed and may be contacted to assess disease status, survival status, receipt of subsequent anti-cancer therapy, and resolution of all toxicity attributable to study drug. Disease status during follow-up will only be assessed if the subject has not demonstrated disease progression since receiving NKTR-102. Quarterly follow-up will continue until death, withdrawal of consent by subject, physician decision, lost to follow-up, or the study is terminated by the Sponsor.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

Nektar Therapeutics shall implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, 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 Nektar Therapeutics.

11.1 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/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 non-evaluable.

11.2 Monitoring

In accordance with 21 CFR § 312.56, ICH GCP and local regulations, the clinical monitor will periodically inspect all 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, ICH GCP and local regulations: Responsibilities of Sponsors and Investigators, the monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of submitted data; 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 trial. The names and identities of all research subjects will be kept in strict confidence and will not appear in the CRFs or other records provided to or retained by the Sponsor. The IND regulations also require the Investigator to allow authorized representatives of the FDA and European Union Regulatory Authorities 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 prior to initiation of the study.

12.0 STATISTICAL CONSIDERATIONS

12.1 Analysis Populations

Safety Population: The safety population consists of all subjects who receive NKTR-102 for Injection. Unless otherwise stated, all safety analyses will be based on this population.

12.2 Endpoints and Planned Analyses

The primary endpoint of this study is assessment of safety for subjects receiving continued NKTR-102 therapy.

The MedDRA medical dictionary will be used to map the AE/SAE verbatim terms to specific system organ classes and preferred terms. The incidence and duration of AEs will be tabulated by MedDRA preferred term, system organ class, severity and relationship to study drug. The maximum intensity and frequency of AEs will be summarized by treatment (dose level). By-subject listings will be provided. No formal statistical testing is planned for AE or other safety and tolerability data.

Tumor response will be summarized by histological tumor type and tabulated using by-subject listings based on disease assessments from this protocol.

Other data will be tabulated using by-subject listings.

13.0 ETHICS

This study will be conducted according to the provisions of the Declaration of Helsinki (October 2008) and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with the ICH guidelines on GCP (ICH E6), as well as with any and all applicable federal, state and/or local laws and regulations.

13.1 IRB/IEC Approval

Prior to enrollment of subjects into the study, as required by Federal regulations (21 CFR § 56), ICH E6 GCP and local regulations, the protocol and informed consent form will be reviewed and approved by an appropriate IRB or IEC. By signing the Statement of Investigator Form FDA 1572, the Investigator assures that all aspects of the institutional review will be conducted in accordance with current federal regulations. A letter documenting the IRB or IEC approval with the names and titles of the IRB or IEC members must be received by the Sponsor prior to the initiation of the study. Amendments to the protocol will be subject to the same requirements as the original version of the protocol.

The Investigator, the Sponsor or designee will submit a progress report at least once yearly to the IRB or IEC and Regulatory Authorities. The frequency of these reports will depend on local regulations. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB or IEC and to the Sponsor. The results should be reported per the IRB or IEC's local requirements.

The Investigator, the Sponsor or designee is required to notify the IRB or IEC of SAEs, or any other information that may affect the safe use of the study drug during the course of the trial, per the IRB or IEC's local requirements.

13.2 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/subject's legal representative in the language in which the subject/subject's legal representative is fluent. By signing the Statement of Investigator Form FDA 1572, the Investigator ensures that informed consent will be obtained from each subject/legal representative prior to any protocol-specific procedures, and that informed consent will be obtained and documented in accordance with current state and federal regulations. Signed and dated 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 consent form.

14.0 DATA HANDLING AND RECORD KEEPING

14.1 Case Report Forms and Source Documents

14.1.1 Study Records

During the study, the Investigator will maintain adequate records for the study, including medical records, records detailing the progress of the study for each subject, laboratory reports, CRFs, signed informed consent forms, drug disposition records, correspondence with the IRB or IEC and regulatory agencies AE reports, and information regarding subject discontinuation and completion of the study.

14.1.2 Case Report Forms

Case report forms will be used in this study. These forms are used to transmit the information collected in the performance of this study to the Sponsor or Sponsor's designee and Regulatory Authorities. Case Report Forms must be completed in English. The Investigator must review the CRFs for completeness and accuracy and must approve the appropriate CRF as indicated. Furthermore, the Investigator retains full responsibility for the adequacy and accuracy of all data entered on the CRFs.

14.2 Retention of Essential Documents

All records and documents pertaining to the study including, but not limited to, those outlined above (see Section **14.1.1**) will be maintained by the Investigator for a period of at least 2 years after FDA/European Medicines Agency (EMEA) approval of the drug or at least 2 years after withdrawal of the IND under which this study was conducted, whichever is longer. In countries outside the US, as a minimum, records must be kept for the period of time required by the US FDA, and should also comply with the local country regulatory requirements, if longer retention times are required than in the US. In order 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.

14.3 Confidentiality

Attention is drawn to the regulations promulgated by the ICH E6 GCP guidelines, local confidentiality requirements and the FDA under the Freedom of Information Act providing, in part, that information furnished to clinical Investigators and IRBs/IECs will be kept confidential by the FDA/EMEA and local regulatory agencies only if maintained in confidence by the clinical Investigator and IRB/IEC. The Sponsor will comply with the applicable regulations that ensure

the security and privacy of the individually identifiable health information of the study subjects is maintained and the rights of the subjects are protected. By signing this protocol, the Investigator affirms to the Sponsor that the Investigator will maintain, in confidence, information furnished to him/her by the Sponsor and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

15.0 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 trial 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 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.

16.0 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.

2. Garcia AA, Vergote IB, Micha JP et al. The role of NKTR-102 in women with platinum resistant/refractory ovarian cancer and failure on pegylated liposomal doxorubicin (PLD). ASCO Annual Meeting Proceedings. J Clin Oncol. 2011; 29 (suppl; abstr 5047).

3. Kehrer DF, Yamamoto W, Verweij J, de Jonge MJ, de Bruijn P, Sparreboom A. Factors involved in prolongation of the terminal disposition phase of SN-38: clinical and experimental studies. Clin Cancer Res 2000;6: 3451-3458.

4. Vergote IB, Micha JP, Pippitt, Jr CH, et al. Phase II study of NKTR-102 in women with platinum-resistant/refractory ovarian cancer. ASCO Annual Meeting Proceedings. J Clin Oncol. 2010; 28 (suppl; abstr 5013).

5. Xie R, Mathijssen RH, Sparreboom A, et al. Clinical pharmacokinetics of irinotecan and its metabolites in relation with diarrhea. Clin Pharmacol Ther. 2002;72(3):265-75.

17.0 APPENDICES

Appendix 1: Schedule of Assessments

Appendix 2: Cytochrome 3A4 Inhibitors

APPENDIX 1: SCHEDULE OF ASSESSMENTS

Study Procedures	Screening Days -28 to -1	All Cycles[a] Day 1[b]	End of Treatment[c]	Quarterly Follow-up
Informed Consent	X			
Eligibility Criteria	X			
Physical Examination, Vital Signs[d]	X	X	X	
ECOG Performance Status[d]	X	X	X	
Serum Pregnancy Test (for WCBP)	X			
Urine Pregnancy Test (for WCBP)		X	X	
Disease Assessment per standard of care[e]	X	[X]		
CBC[f, g]	X	X		
Serum Chemistry[g]	X	X		
Body Surface Area (BSA)[h]		X		
NKTR-102 Infusion[i]		X		
Concomitant Medications[j]	X	X	X	
Adverse Events	X	X	X	
Survival Follow-up[k]				X

a Cycle length is 21 days.

b Any procedures that were completed as part of the end-of-study visit for the original protocol that match those procedures required during Screening may be used and do not need to be repeated if they were performed within 7 days of Cycle 1 Day 1 of this extension study. For all subsequent cycles, Day 1 assessments may be performed up to 5 days before Day 1. For all cycles, safety assessments are required before each treatment cycle. All results must be available before dosing.

c End-of-treatment visit to occur 30 ± 7 days after last dose of NKTR-102.

d There will be a complete physical exam with height and weight during Screening, symptom-directed physical exams with weight during treatment, and a complete physical exam with weight at the End-of-Treatment. Vital signs include pulse, temperature, and blood pressure. ECOG performance status will be assessed as part of the physical exam.

e Radiological exams or digital photography required during Screening unless subjects had disease assessment within 8 weeks prior to Cycle 1 Day 1 dosing. Disease assessments will occur during the study as per local standard of care (e.g., approximately every 6-12 weeks). CT or MRI scanning is acceptable for radiologic exams.

f If Grade 3 or 4 neutropenia is observed, more frequent CBC with differentials are recommended until Grade 1 or less.

g Minimally required: hemoglobin, ANC, platelets, and creatinine. Other tests obtained according to the Investigator's discretion.

h Body surface area (BSA) will be determined before the start of each cycle, based on baseline height and most recent weight. Body surface area may be calculated based on institutional guidelines.

APPENDIX 1: SCHEDULE OF ASSESSMENTS

Study Procedures	Screening Days -28 to -1	All Cycles[a] Day 1[b]	End of Treatment[c]	Quarterly Follow-up	
					i NKTR-102 dosing administration for Cycle 2+ may occur within ±4 days of the scheduled date.
					j All concomitant medications, including over-the-counter medications, herbal therapies, dietary supplements, and St. John's Wort. k Approximately every 12 weeks (±4 weeks) following the End-of-Treatment visit, subjects will be contacted or have their medical records reviewed to assess disease status, survival status, receipt of subsequent anti-cancer therapy, and resolution of all toxicity attributable to study drug. Disease status during follow-up will only be assessed if the subject has not demonstrated disease progression since receiving NKTR-102. Quarterly follow-up will continue until death, withdrawal of consent by subject, physician decision, lost to follow-up, or the study is terminated by the Sponsor.

APPENDIX 2: CYTOCHROME P450 3A INHIBITORS AND INDUCERS

Strong CYP3A Inhibitors	Boceprevir, clarithromycin, conivaptan, grapefruit juice[a], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil[b], nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole
Moderate CYP3A Inhibitors	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice[a], imatinib, verapamil
Weak CYP3A Inhibitors	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo[c], goldenseal[c], isoniazid, nilotinib, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
Strong CYP3A Inducers	Avasimibe[d], carbamazepine, phenytoin, rifampin, St. John's Wort[e]
Moderate CYP3A Inducers	Bosentan, efavirenz, etravirine, modafinil, nafcillin, phenobarbital

Please note the following: This is not an exhaustive list and is based on Food and Drug Administration (FDA) Guidance for Industry (Draft): Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, February 2012 (FDA Guidance for Industry, 2012) and Scripture C and Figg W, 2006. For the most current information, see the following links: http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm and http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

a The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

b Withdrawn from the United States market because of safety reasons.

c Herbal product.

d Not a marketed drug.

e The effect of St. John's Wort varies widely and is preparation-dependent.