AstraZeneca

Revised Clinical Study Protocol

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An Open-Label 52-week Study to Assess the Long-Term Safety of NKTR-118 in Opioid-Induced Constipation (OIC) in Patients with Non-Cancer-Related Pain

Sponsor:

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
Amendment 1	21 December 2011		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

An Open-Label 52-week Study to Assess the Long-Term Safety of NKTR-118 in Opioid-Induced Constipation (OIC) in Patients with Non-Cancer-Related Pain

National Co-ordinating Investigator (United States only)

International Co-ordinating Investigator

Study center(s) and number of subjects planned

This will be a multi-center study with global participation that may include the following countries: Australia, Belgium, Canada, Croatia, the Czech Republic, France, Germany, Hungary, Israel, Slovakia, Spain, the United Kingdom (UK), and the United States (US). Approximately 1135 patients will be randomized to obtain approximately 125 patients treated with NKTR-118 for 12 months. The number of patients randomized may be adjusted during the study in order to achieve approximately 125 patients with at least 12 months of exposure to NKTR-118. Approximately 130 centers will participate in the study.

Study period		Phase of development
Estimated date of first patient enrolled	1st Quarter [redacted]	III
Estimated date of last patient completed	4th Quarter [redacted]	

Objectives

Primary objective:

The primary objective of this study is to assess the safety and tolerability of NKTR-118 25 mg.

Secondary objectives:

The secondary objectives are to evaluate the long-term safety and tolerability of NKTR-118 25 mg compared with Usual Care using descriptive statistics.

Exploratory objectives:

The exploratory objectives include the collection and storage of deoxyribonucleic acid (DNA) for future exploratory research, and healthcare resource utilization.

Study design

This is a Phase III, 52-week, multi-center, open-label, randomized, parallel group safety and tolerability study of NKTR-118 in the treatment of opioid-induced constipation (OIC) in patients with non-cancer-related pain. Eligible patients will be randomized in a 2:1 ratio to receive either NKTR-118 25 mg daily (QD) or Usual Care treatment for OIC.

Target subject population

Participants may include patients who have completed treatment in the 12-week pivotal study D3820C00005, patients who have completed a 3 month safety extension (Study D3820C00007) of the 12-week pivotal study D3820C00004, or patients not previously treated with NKTR-118 ("new" patients).

New patients must meet the following criteria:

Adult patients who are receiving a stable maintenance opioid regimen (total daily dose of 30 to 1000 mg of oral morphine, or equianalgesic amount[s] of 1 or more other opioid therapies for a minimum of 4 weeks) for non-cancer-related pain and who report a history of <3 spontaneous bowel movements (SBMs)/week and at least 1 OIC associated symptom at screening and have a confirmed diagnosis of OIC will be eligible to be randomized. Confirmed OIC is defined as:

- Documented <3 SBMs/week on average over the 2-week OIC confirmation period. Patients with uneven distribution of SBMs across the 2-week OIC confirmation period (0 SBMs in 1 week with ≥4 SBMs in the other week) will be excluded. In

addition to the SBM frequency criterion, patients must report ≥1 of the following symptoms in at least 25% of the bowel movements (BMs) recorded in the electronic diary (eDiary) during the OIC confirmation period: Bristol Stool Scale (BSS) stool type 1 or 2; moderate, severe or very severe straining, incomplete BM. Patients who have 0 BMs over the 2-week OIC confirmation period will not be randomized.

Investigational product, dosage and mode of administration

NKTR-118 25 mg tablets

Comparator, dosage and mode of administration

The study will include a Usual Care arm. For the Usual Care arm, investigators will be permitted to choose constipation treatment according to their best clinical judgment.

Duration of treatment

The study duration will be 54 to 58 weeks. The study will consist of 52 weeks of open-label treatment followed by a 2 week follow-up period. In addition, new patients will undergo an initial screening period lasting up to 2 weeks, and a 2-week OIC confirmation period, during which the diagnosis of OIC and stability of opioid regimen will be confirmed.

Outcome variable(s):

- **Safety**
  - Incidence, nature, and intensity of adverse events (AEs), treatment-related AEs, serious adverse events (SAEs), AEs leading to discontinuation, and specific safety areas of interest
  - Mean daily prescribed opioid dose
  - Mean bisacodyl dose per week (NKTR-118 group only)
  - Change from baseline in Numeric Rating Scale (NRS) pain score
  - Observed values and change from baseline in composite score of modified Himmelsbach scale
  - Changes in vital signs and physical examination
  - Changes in laboratory assessments (ie, chemistry, hematology, and urinalysis [U/A])
  - Changes in electrocardiograms (ECGs)
- **Health economics**
  - Data on OIC healthcare resource utilization

Statistical methods

This is a general evaluation of long-term safety and tolerability. Therefore, no statistical testing will be conducted. Differences between NKTR-118 25 mg and Usual Care with respect to the evaluation of long-term safety and tolerability will be assessed using descriptive statistics.

The safety analysis set will be used to assess the safety and tolerability. All randomized patients who received at least 1 dose of study drug will be included in the safety analysis set.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol (CSP).

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.2)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
anti-CMV-IgM	Immunoglobulin M antibody to cytomegalovirus
anti-HAV-IgM	Immunoglobulin M antibody to hepatitis A virus
anti-HBc-IgM	Immunoglobulin M antibody to hepatitis B core antigen
anti-HCV	Antibody to hepatitis C virus
AST	Aspartate aminotransferase
AZDD	AstraZeneca Drug Dictionary
B	Blood
BIL	Bilirubin
BM	Bowel movement
BSS	Bristol Stool Scale
BUN	Blood urea nitrogen
Ca	Calcium
CK	Creatine kinase
CNS	Central nervous system
COWS	Clinical Opioid Withdrawal Scale
CPMP	Committee for Proprietary Medicinal Products
CRC	Colorectal cancer
CRF	Case report form
CRO	Contract research organization
CSA	Clinical Study Agreement
CSP	Clinical study protocol
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical study report
CYP3A4	Cytochrome P450 3A4

Abbreviation or special term	Explanation
DBP	Diastolic blood pressure
DEA	Drug Enforcement Administration
dECG	Digital electrocardiogram
DES	(Patient safety) data entry site
DM	Data management
DNA	Deoxyribonucleic acid
EBV VCA IgM + EBNA IgG	Immunoglobulin M antibody to Epstein Barr virus viral capsid antigen + Immunoglobulin G antibody to Epstein Barr virus nuclear antigen
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid
eRT	eResearch Technology
ET	Early termination
FIT	Fecal immunochemical test
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practices
GRand	AstraZeneca's Global Randomization system
H	High
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCV RNA	Hepatitis C virus ribonucleic acid
HDPE	High-density polyethylene
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
I/E	Inclusion/exclusion
INR	International normalized ratio
IP	Investigational product
IPs	Investigational products

Abbreviation or special term	Explanation
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
L	Low
LAR	Laxative Adequate Responder
LIR	Laxative Inadequate Responder
LUR	Laxative Unknown Responder
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NA	North America
NRS	Numeric Rating Scale
OIC	Opioid-induced constipation
PEG	Polyethylene glycol
PGP	P-glycoprotein
PI	Principal Investigator
PR	(PR interval) The time from the onset of the P wave to the onset of the QRS complex on an electrocardiogram.
PRMP	Patient risk management plan
PRN	As occasion requires
PRO	Patient reported outcome
PT	Prothrombin time
QD	Every day
QLAB	Quintiles laboratories
QRS	(QRS interval) The time from the beginning to the end of a QRS complex on an electrocardiogram.
QT	(QT interval) The time from the onset of the QRS complex to the end of the T wave on an electrocardiogram.
QTc	Corrected QT interval
QTcF	Fridericia corrected QT interval
RDW	Red blood cell distribution width
RR	(RR interval)

Abbreviation or special term	Explanation
S	Serum
SAE	Serious adverse event (see definition in Section 6.3.3)
SAP	Statistical Analysis Plan
SBM	Spontaneous bowel movement
SBP	Systolic blood pressure
SDV	Source document verification
SOP	Standard operating procedure
SST	Serum-separating tube
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
U	Urine
U/A	Urinalysis
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

Physiologic effects of opioids on the gastrointestinal (GI) system include decreased gastric motility and gastric emptying, diminished intestinal secretions, and decreased peristalsis in the colon which sometimes may lead to constipation and other abdominal symptoms. Complications of opioid therapy may include fecal impaction, pseudo-obstruction, and hindrance of drug absorption. In the United States (US), patients with a variety of underlying conditions receive in aggregate, a total of approximately 1.2 billion patient days of opioid therapy for pain that is treated for at least 15 days. Estimates of the incidence of constipation within the population of patients taking opioids vary widely (15% to 90%) with differences attributed to varying opioid agents, varying doses, differing underlying diagnoses, and differing criteria used to define constipation.

A well-tolerated and efficacious orally-administered treatment option for constipation due to treatment with opioids remains a major unmet medical need for patients being treated for pain. Current treatment for opioid-induced constipation (OIC) - which includes laxatives, stool softeners, and, if necessary, reflex evacuation via enema - is distinctly sub-optimal, with up to 46% of patients not achieving the desired treatment outcome (Pappagallo 2001). Furthermore, a number of the conventional therapeutic interventions are, quite often, inconvenient at best (eg, enemas, lactulose) and, in some cases impractical. For example, debilitated patients may be unable to self-administer an enema, and a constipated patient with severely inflamed hemorrhoids or neutropenia would not be an ideal candidate for an enema. Fiber supplementation with psyllium requires patients to drink ample quantities of water, which is not always possible. Although generally well-tolerated, side-effects of various treatments for constipation include bloating (lactulose, fiber supplements, and polyethylene glycol [PEG]), cramps, abdominal pain, nausea, diarrhea, dehydration, and electrolyte imbalances.

AstraZeneca is developing NKTR-118, a peripherally acting μ-opioid antagonist, for the treatment of OIC. NKTR-118 is a PEGylated derivative of naloxone; introduction of the PEG moiety reduces the ability of naloxone to enter the central nervous system (CNS). In the periphery, NKTR-118 targets μ-opioid receptors in the enteric nervous system, which mediate OIC. NKTR-118 represents, potentially, the first oral drug in a novel class of therapeutic agents for the specific treatment of OIC. It is hoped that this investigational agent will prove to be practical and convenient, highly effective, and well-tolerated in patients with OIC.

Previous studies have shown that NKTR-118 alleviates symptoms of OIC while preserving the central analgesic effect of opioid therapy. For example, in a Phase II study, in which doses of NKTR-118 5, 25, and 50 mg/day were evaluated against placebo over the course of 4 weeks, NKTR-118 reversed symptoms of OIC as measured by increase in spontaneous bowel movements (SBMs) in patients receiving a wide range of opioid doses for pain. For the 25 mg/day dose group and 50 mg/day dose group, the change from baseline in SBMs per week to the end of Week 1 was 3.6 and 4.4. In the placebo group, the corresponding change

from baseline was 1.9. NKTR-118 was well-tolerated in the Phase II study at 5 and 25 mg/day with the most commonly reported side effects being GI in nature (abdominal pain, diarrhea, and nausea) and most frequent in the 50 mg cohort. No reversal of analgesia or central opioid withdrawal symptoms were seen at any doses tested in the Phase II study.

Based on the above, it is appropriate to proceed with a Phase III long-term 52-week safety study of NKTR-118 in the target population, that is, patients receiving opioid therapy for pain who are experiencing OIC. This study will evaluate the safety and tolerability of NKTR-118 25 mg. The study includes a Usual Care arm to allow for establishing an estimation of the baseline safety event profile in this population. Patients assigned to the Usual Care arm will be treated according to the investigator's clinical judgment. A full description of Usual Care treatment is presented in Section 5.5.2.2. For a detailed description of pre-clinical data, and the results of prior human studies in healthy subjects, please refer to the Investigator's Brochure (IB).

1.2 Research hypothesis

The primary goal of this study is to test the hypothesis that NKTR-118 25 mg is safe and well tolerated in the long-term treatment of OIC.

1.3 Rationale for conducting this study

The goal of this Phase III study is to assess the long-term safety and tolerability of NKTR-118 when administered over 52 weeks in the treatment of OIC in patients taking opioids for their non-cancer-related pain. NKTR-118 is expected to improve the symptoms of OIC by blocking the peripheral effects of opioids without inducing central opioid withdrawal symptoms or interfering with analgesia.

1.4 Benefit/risk and ethical assessment

For a full description of pre-clinical findings regarding NKTR-118 please refer to the IB. Pre-clinical investigations have included a recent dog telemetry study which demonstrated small, transient decreases in blood pressure, left ventricular systolic pressure, cardiac contractility and relaxation indices, as well as increases in heart rate, at blood concentrations about 5 times higher than the maximum dose used in this study (ie, 25 mg). The clinical significance of this finding is uncertain and follow-up preclinical testing is underway in telemetered dogs with lower doses of NKTR-118. While there have been isolated reports of patients with potentially clinically significant blood pressure decreases in trials of NKTR-118, such cases have also been observed with placebo. No clear or consistent cardiovascular safety signal has been observed in human studies to date (see Section 6.3.13.3 for additional guidance).

In Phase I studies in healthy volunteers, in which single doses up to 1000 mg and repeated doses up to 500 mg/day were administered, there were no clinically significant changes in laboratory parameters or electrocardiograms (ECGs). A thorough QT study was recently completed for NKTR-118. Preliminary evaluation of the results indicate that NKTR-118 does not have cardiac ventricular repolarization effects as assessed by Fridericia corrected QT

interval (QTcF). Of the 92 healthy volunteers who received NKTR-118 in Phase I, 2 subjects had a potentially clinically significant decrease in supine blood pressure, as defined by a drop of 20 mmHg or greater in systolic blood pressure (SBP) to a level < 90 mmHg and a concurrent drop of 10 mmHg or greater in diastolic blood pressure (DBP) to a level < 50 mmHg. All of these events occurred at NKTR-118 dose levels of 100 mg, were transient, and resolved spontaneously.

In a Phase I repeated dose study, adverse events (AEs) of dizziness were reported by 4/6 patients at the highest dose of NKTR-118 compared with 2/8 placebo patients. All events of dizziness were transient and resolved spontaneously without the need for any intervention.

In a Phase II study, in which doses of 5, 25, and 50 mg/day were evaluated against placebo, NKTR-118 reversed symptoms of OIC as measured by increases in SBMs/week in patients receiving a wide range of opioid doses for pain. The reversal of OIC was dose-dependent across the dose range of 5 to 50 mg studied. For the 25 mg/day dose group, the change from baseline in SBMs per week to the end of Week 1 was 3.6 and 1.9 for the corresponding placebo group (p=0.002). In the 50 mg/day dose group, the change in SBMs/week was 4.4 and 1.9 for the corresponding placebo group (p=0.0001). For the 5 mg/day dose group, the difference between the active group and the corresponding placebo was not statistically significant, although a numerical trend towards an increase in the number of SBMs/week in the NKTR-118 group was observed (2.6 vs 1.8 in placebo).

NKTR-118 was well-tolerated in the Phase II study at 5 and 25 mg/day with the most commonly reported side effects being GI in nature (abdominal pain, diarrhea, and nausea) and most frequent in the 50 mg cohort. The frequency of any GI AE was 53% in the 25 mg/day dose group and 48% in the corresponding placebo group. In the 50 mg/day dose group, the GI AE frequency was 69% and 27% in the corresponding placebo group. In the 5 mg/day dose group, the frequency was 46% and 34% in the corresponding placebo group. Most of the AEs were rated mild or moderate. During the double-blind phase, a total of 12 patients discontinued the treatment permanently due to AEs (10 patients in the 50 mg dose group, 1 patient in the 25 mg/day dose group, and 1 patient in the 5 mg/day dose group). Most of the discontinuations were due to GI AEs. There was 1 serious adverse event (SAE) of upper abdominal pain in the 50 mg dose cohort, which was considered to be related to the study drug by the investigator. The patient was briefly monitored in a hospital setting due to this event, which resolved spontaneously without medical sequelae. No reversal of analgesia was seen at any dose in Phase II, as measured by changes in the daily opioid dose or by Numerical Rating Scale (NRS) for pain. A significant increase in total Clinical Opioid Withdrawal Scale (COWS) score for the NKTR-118 50 mg group was noted as compared with placebo at Day 1 of the double-blind treatment period. When the GI component of the COWS instrument (eg, diarrhea, abdominal cramps) was removed from calculation of total COWS scores, there was no longer a significant difference, indicating a lack of increase in the components of the scale that reflect CNS withdrawal. Although these data suggest that the risk for reversal of analgesia or precipitation of opioid withdrawal is unlikely, it is recommended that investigators remain vigilant regarding this potential effect of NKTR-118.

As summarized above, participation in this study may carry risks. New risks may be discovered when more patients are exposed to NKTR-118, and when NKTR-118 is delivered over a long-term period of 52 weeks. Previous studies have administered NKTR-118 for up to 4 weeks, and planned Phase III studies will administer NKTR-118 for 12 or 24 weeks (should patients participate in an optional 12 week extension study). Repeated dose toxicity has been investigated after oral administration of NKTR-118 for up to 6 months in rats and 9 months in dogs. These studies suggested no preclinical issues that would cast a doubt on the tolerability of NKTR-118 in this study. Detailed information about chronic exposure in animal studies can be found in the IB. Several steps have been taken to mitigate known and unknown risks. General safety monitoring, including AEs, vital signs, and laboratory assessments combined with exclusion of patients at higher risk for complications from experimental medication and placebo are in place to minimize any risks. ECGs will be recorded and submitted for centralized analysis at screening for new patients, and for all patients at randomization (pre-dose and post-dose/post-initial assessments), and at various time points throughout the study.

Rare cases of GI perforation associated with the use of other peripheral opioid antagonists in OIC have been reported in the post-marketing setting. Such cases of perforation may tend to occur shortly after initiation with drug and appear to be more commonly reported in debilitated patients with multiple co-morbidities, particularly co-morbid conditions that might impair the local or global structural integrity of the GI tract (eg, cancer, peptic ulcer, pseudo-obstruction of the colon, etc.). Therefore, any patient who reports progressive or persistent severe abdominal pain should be evaluated immediately by the site or otherwise referred for urgent medical assessment. Other accompanying symptoms in combination with abdominal pain such as fever, malaise, mental status changes should also mandate urgent medical evaluation. See Section 4.2 and Section 6.3.13.2 for additional guidance.

Patients enrolled in this study may not experience any benefit from being in the study regardless of the treatment arm that they are randomized to. For patients assigned to the NKTR-118 arm, a rescue medication is incorporated in the study design by use of bisacodyl if no SBM has occurred within at least 72 hours since the previous one. Further guidance is provided on the use of bisacodyl and an enema. For patients in the Usual Care group, care of OIC will be managed by the investigator.

The Usual Care arm is included in this study to allow for establishing a baseline rate of AEs in patients receiving usual care for OIC. The AE profile in the Usual Care arm will be compared with the NKTR-118 arm using descriptive statistics. The risks of participating in the Usual Care arm are expected to be low. Patients assigned to receive Usual Care will be subject to the same monitoring procedures during the study as patients in the NKTR-118 treatment group.

In principle, hypersensitivity reactions, including anaphylactic shock, may occur with the administration of any drug. Consequently, NKTR-118 is contraindicated for any patient with a known hypersensitivity to this product or any other peripheral opioid antagonist, such as methylnaltrexone or alvimopan.

There may be benefits to patients as a result of participating in this study. Randomization to either treatment group may provide symptomatic relief from OIC for the duration of the study. The results of the study may ultimately help in the development of NKTR-118 for treatment of OIC, indirectly benefiting all patients suffering from this condition. There is a great medical need to develop a better and pathophysiologically specific oral medication for the treatment of OIC.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to assess the long-term safety and tolerability of NKTR-118 25 mg.

2.2 Secondary objectives

The secondary objectives are to evaluate the long-term safety and tolerability of NKTR-118 25 mg compared with Usual Care using descriptive statistics.

2.3 Exploratory objectives

The exploratory objectives include the collection and storage of deoxyribonucleic acid (DNA) for future exploratory research, and assessment of healthcare resource utilization.

3. STUDY PLAN AND PROCEDURES

This clinical study protocol (CSP) has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a Phase III, 52-week, multi-center, open-label, randomized, parallel group, safety and tolerability study of NKTR-118 in the treatment of OIC in patients with non-cancer-related pain. This will be a study with global participation that may include the following countries: Australia, Belgium, Canada, Croatia, the Czech Republic, France, Germany, Hungary, Israel, Slovakia, Spain, the United Kingdom (UK), and the United States (US). Eligible patients will be randomized in a 2:1 ratio to receive either NKTR-118 25 mg daily (QD) or Usual Care treatment for OIC (see Section 5.5.2.2). Patients entering the study may enroll directly from 12-week pivotal study D3820C00005, directly from the 3-month safety extension (Study D3820C00007) of the 12-week pivotal study D3820C00004, or may be "new patients" who have not previously participated in a NKTR-118 study. Approximately 1135 patients will be randomized, to obtain approximately 125 patients treated with NKTR-118 for 12 months at approximately 130 centers. The number of patients randomized may be adjusted during the study in order to achieve approximately 125 patients with at least 12 months of exposure to NKTR-118. The study will continue until all enrolled patients have completed.

The study duration will be 54 to 58 weeks. New patients will undergo an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period (during which the diagnosis of OIC and stability of opioid regimen will be confirmed), and a 52-week treatment period, followed by a 2 week follow-up period. Patients enrolling from another study (also referred to as 'rollover patients') will do so on the last day of the treatment period of the previous study, at which time they will start the 52-week treatment period, followed by the follow-up visit 2 weeks after the last dose of study drug. Study assessments during the 52-week treatment and follow-up period will be the same for all patients (new patients as well as patients who previously participated in NKTR-118 studies D3820C00005 or D3820C00007).

New Patients

New patients will undergo the same screening and OIC confirmation procedures as patients who participated in the pivotal studies of NKTR-118. They will sign the informed consent form (ICF) at the initial screening visit (Visit S1), within 14 days prior to entering the OIC confirmation period. Screening assessments will include review of inclusion/exclusion (I/E) criteria, collection of demographic information, and assessment of routine safety laboratory parameters (hematology and chemistry), ECG, urine pregnancy test for women of childbearing potential (WOCBP), urinalysis (U/A), urine drug screen, medical history, prior and concomitant medications, daily opioid use, laxative use, physical examination including rectal examination and vital signs, and the Columbia-Suicide Severity Rating Scale (C-SSRS). At the screening visit patients must also adhere to the colorectal cancer (CRC) screening criteria outlined in Appendix E. This includes provision of a stool sample for fecal immunochemical test (FIT) for some patients, and patients at high risk for CRC providing documentation of negative colonoscopy or other appropriate imaging measures performed within 5 years of the screening visit. At screening, patients will receive an electronic diary (eDiary) device and training on how to record information using the device. Patients will be required to record information using the device during a pilot training period, to last a minimum of 5 consecutive days (see Section 3.1.1.1).

In addition, laxative response status will be determined for new patients at the screening visit (Visit S1) based on response to a questionnaire (See Appendix F). On the basis of physician assessment, patients will be grouped into 1 of 3 categories: patients who had inadequate response to laxatives (Laxative Inadequate Responder [LIR]), patients who had adequate response to laxatives (Laxative Adequate Responder [LAR]), and those patients whose laxative responder status could not be confirmed due to lack or infrequent use of laxatives in the 2 weeks before screening (Laxative Unknown Responder [LUR]).

Once new patients have met initial screening requirements (including self-reported active symptoms of OIC at screening [<3 SBMs/week and ≥1 reported symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction in at least 25% of bowel movements (BMs) over the previous 4 weeks]), and have completed at least 5 days of recording using the eDiary device, they will return for Visit S2. At Visit S2, the eDiary recording will be reviewed with the patient and instructions regarding proper recording will be repeated. Patients who experienced difficulty using the device will have the

opportunity to have any questions answered. Daily opioid use, use of other medications, and AEs will also be collected at Visit S2. Confirmation of OIC will be established between Visit S2 and Visit R1 (randomization visit).

During the OIC confirmation period of the study, new patients will be required to stop all laxatives and other bowel regimens, and may use only bisacodyl as rescue medication if a BM has not occurred within at least 72 hours of the last recorded BM. Full details on the bisacodyl rescue regimen (including one time use of an enema if the patient does not have a BM), are provided below. During the OIC confirmation period, patients who fail to have an adequate BM after completing the laxative rescue regimen should be excluded from participation in the study and referred for further medical evaluation. Since the patient is excluded from the study, the investigator should recommend initiation of any therapy deemed most appropriate. Any patient who is obstipated and/or has fecal impaction must not be randomized (see Section 4.2). Bisacodyl for use as a rescue medication will be dispensed at Visit S2.

New patients will return for Visit R1, 2 weeks after Visit S2. At Visit R1, the eDiary will be reviewed with patients. Patients who failed OIC or stable opioid dose confirmation will not be randomized. Patients with confirmed OIC and who have continued on a stable maintenance opioid regimen will be randomized. Patients will be disqualified from randomization if they consumed >4 opioid doses for breakthrough pain per day for more than 3 days during the 2-week OIC confirmation period, or if their maintenance opioid dosing regimen was modified during this same period.

Confirmed OIC is defined as:

- Documented <3 SBMs/week on average over the 2-week OIC confirmation period. Patients with uneven distribution of SBMs across the 2-week OIC confirmation period (0 SBMs in 1 week with ≥4 SBMs in the other week) will be excluded. In addition to the SBM frequency criterion, patients must report ≥1 of the following symptoms in at least 25% of the BMs recorded in the eDiary during the OIC confirmation period: Bristol Stool Scale (BSS) stool type 1 or 2; moderate, severe or very severe straining, incomplete BM. Patients who have 0 BMs over the 2-week OIC confirmation period will not be randomized.

(Note: Patients who have 0 BMs over the 2-week OIC confirmation period should be referred for further medical evaluation.)

New patients will return the e-Diary device at Visit R1.

All Patients

For all patients, randomization will occur at the onset of the 52-week open-label treatment period at Visit R1. Patients will be randomly assigned in a 2:1 ratio to receive either NKTR-118 25 mg QD or to Usual Care treatment for OIC. For patients entering the study

directly from a previous NKTR-118 study, informed consent and randomization will occur at the last visit of the treatment period of the previous study.

During the treatment period, an eDiary will not be employed. However, to facilitate the collection of breakthrough pain opioid use, and any newly prescribed concomitant medication use, patients will be provided with a home diary to record such medication usage between visits.

During the treatment period of the study, patients who receive NKTR-118 will be required to stop all laxatives and other bowel regimens, and may use only bisacodyl as rescue medication if a BM has not occurred within at least 72 hours of the last recorded BM. Patients in the Usual Care treatment group will have their care managed by the investigator. Patients in the Usual Care arm will not be allowed to take any medication for treatment of constipation other than that prescribed by the investigator, without the prior agreement of the investigator.

Bisacodyl for use as a rescue medication will be dispensed to NKTR-118 patients at randomization (Visit R1), and at each visit thereafter until Month 12 (Visit R15).

Unless there is a need for urgent intervention, NKTR-118 patients will not be allowed to take any medication for treatment of constipation, other than bisacodyl, during the course of the study without the prior agreement of the investigator. If after a minimum of 72 hours, a NKTR-118 patient has not experienced a BM, he/she may take bisacodyl rescue therapy (10 to 15 mg dose, ie, 2 to 3 bisacodyl tablets at a time). If the patient remains constipated, bisacodyl rescue therapy may be repeated up to 2 additional times, as necessary, each 10 to 15 mg dose separated by 12 hour intervals. It is recommended that the bisacodyl tablets be taken either at bedtime or before breakfast. If after 3 doses of bisacodyl rescue therapy, the patient still has not experienced a BM, the investigator may prescribe one-time use of an enema. The timing of administration of this therapy should be noted in the home diary. In addition, the site is to record any enema prescription on the enema eCRF. If these secondary interventions fail, the patient should be discontinued from the study and referred for additional medical evaluation. Since the patient is discontinued from the study, the investigator should recommend initiation of any therapy deemed most appropriate.

Throughout the study, investigators will be encouraged to maintain the patient's baseline pain control regimen. If there is a need to control pain, investigators should manage pain per the guidelines provided in the study reference manual with dose adjustments made as needed in accordance with the patient's clinical needs. Concomitant non-opioid analgesics will not be prohibited, but investigators will be encouraged to maintain such drugs at stable doses on-study, if possible.

It is preferred that the investigator manage the patient's opioid medication during the study; however, it is recognized that pain may be managed by a health care provider outside the study. In such cases, communication between the patient's personal physician and the investigator is strongly encouraged. Although it is desirable that patients be maintained on a stable opioid regimen during the study, should changes in the maintenance opioid regimen be necessary they should be reported to the site at the next study visit and recorded on the

maintenance opioid electronic case report form (eCRF). Opioid medication for breakthrough pain should also be reported at the next study visit and recorded on the breakthrough pain medication eCRF.

Patients should bring their new bottle(s) of maintenance or breakthrough pain medication or prescription(s) to each study visit, if any changes have been made.

Unless there is a need for urgent intervention, patients will not be allowed to take any medication for pain control other than their maintenance opioid regimen and approved opioid medication for breakthrough pain during the course of the study without the prior agreement of the investigator (or their personal physician, if pain is managed outside the study, in which case the investigator must be notified of any changes).

Study assessments include:

Electronic Diary (eDiary) Assessments: (collected only for new patients daily starting with pilot training during the screening period and up to the randomization visit [R1])

- Date and time of BMs (recorded at the time of each BM).
- Straining (recorded at the time of each BM)
- Stool consistency (BSS) (recorded at the time of each BM)
- Complete/incomplete evacuation (recorded at the time of each BM)
- Pain level (NRS) recorded each evening.
- Date and time of use of laxative rescue medication (bisacodyl or enema) recorded at the time that medication is taken
- Date and time of use of opioid medication for breakthrough pain recorded at the time that medication is taken as well as the medication and dose administered

Additional Assessments (All Patients):

- Modified Himmelsbach scale to assess centrally mediated opioid withdrawal effects recorded at screening (new patients only), at randomization (initial assessment obtained from last visit of the previous NKTR-118 study for rollover patients, repeat assessment obtained in present study for all patients), and at Week 1, and Months 1, 3, 6, 9, and 12
- NRS for pain will be completed at randomization, Week 1, Week 2, and Months 1, 2, 3, 6, 9, and 12.

- C-SSRS at screening (new patients only), randomization (obtained from last visit of the previous NKTR-118 study for rollover patients), and at each visit thereafter throughout the study, including the follow-up visit
- OIC Healthcare Resource Utilization assessed at selected time points throughout the study
- Recording of concomitant medications (other than laxative medication or opioid medication [maintenance and medication for breakthrough pain]) throughout the study
- Recording of AEs throughout the study, including the follow-up visit
- Recording of daily maintenance opioid regimen throughout the study, including the follow-up visit
- Recording of opioid medication for breakthrough pain throughout the study, including the follow-up visit. Note: Opioid breakthrough pain medication will be recorded on the relevant eCRF at Visit S1 for new patients (to cover medication taken during the previous 60 days). Information obtained at Visit S1 will be entered into the eDiary to facilitate eDiary recording. Between Visits S1 and R1 opioid breakthrough pain medication will be captured only in the eDiary. At all visits from Visit R1 on, opioid breakthrough pain medication will be recorded on the relevant eCRF for all patients.
- Recording of laxative medication throughout the study, including the follow-up visit (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).
- Routine safety laboratories (hematology, chemistry, and total cholesterol) and U/A and clinical assessments at screening (new patients only), randomization (obtained from last visit of the previous NKTR-118 study for rollover patients), and selected time points throughout the study
- ECG at screening (new patients only), randomization (initial ECG obtained from last visit of the previous NKTR-118 study for rollover patients; repeat ECG obtained in current study for all patients), and selected time points throughout the study
- Vital signs and physical examination at screening (new patients only), randomization (initial BP/pulse obtained from last visit of the previous NKTR-118 study for rollover patients, repeat assessment obtained in present study for all patients), and selected time points throughout the study

- Pregnancy test for WOCBP at screening (new patients only), randomization (obtained from last visit of the previous NKTR-118 study for rollover patients), and selected time points throughout the study

3.1.1 Visits S1 and S2 (new patients)

3.1.1.1 Visit S1 (initial screening)

New patients will be asked to bring a prescription or clearly labeled bottle of opioid medication with them to Visit S1 for confirmation of their daily opioid dosing regimen. Patients will also be instructed that should they experience a change in their daily maintenance opioid or breakthrough pain medication dosing regimen during the study, they are to bring a prescription or clearly labeled bottle of opioid medication to their next study visit, for confirmation of the new regimen.

At Visit S1, each patient's laxative response status will be determined based on 4 questions which explore the frequency of laxative use, constipation symptom severity, and laxative side-effects during the previous 2 weeks. The patients will be classified as LIR, LAR, or LUR based on their answers.

The LIR, LAR, LUR algorithm is presented in more detail in Appendix F.

Study personnel and patients will also be trained appropriately regarding proper use of the eDiary recording device. Training procedures will be documented separately from this CSP.

- Patients will receive the eDiary recording device and detailed instructions for its use. The eDiary is to be completed for at least 5 consecutive days of pilot training and will be used to collect daily information regarding BMs, straining, stool consistency, complete/incomplete evacuation, pain level, use of laxative rescue medication, and use of opioid medication for breakthrough pain. However, the pilot period will not be counted towards the 14 day OIC confirmation period, which begins at Visit S2.

The following additional procedures will be performed at Visit S1:

- Signed informed consent prior to any study-related procedures
- Signed genetic informed consent (If necessary, genetic informed consent may be signed at a subsequent visit; genetic informed consent must be obtained before any blood sample for genetic analysis is collected.) Participation in the genetic component of the study is optional.
- Demographics
- Review of inclusion and exclusion criteria including review of CRC screening requirements

- FIT test or verification of previous imaging study, if required
- Review of medical history (including OIC history)
- Complete physical examination (including rectal examination, height, weight, body temperature, respiratory rate)
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs.
- Single 12-lead ECG
- Urine sample will be collected for urine drug screen (urine toxicology), to test for pregnancy (WOCBP), and for U/A.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- C-SSRS to assess suicidal risk, ideation, and behavior
- Modified Himmelsbach scale will be completed.
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs. The daily opioid and breakthrough pain dosing regimens will be confirmed by prescription or clearly labeled bottles of opioid medication. Information from the breakthrough pain medication eCRF will be recorded in the eDiary to allow for daily recording of dosing.
- Use of laxative medication will be asked about and recorded on the appropriate eCRF.
- Use of prior/concomitant medication (not including opioid or laxative medication) will be recorded. Prior medications taken up to 60 days before enrollment will be recorded.
- An appointment for Visit S2 will be made.

Note: Child-Pugh (Appendix G) and Cockcroft Gault classifications will be determined after the screening visit once laboratory results are available. Patients' Child-Pugh and Cockcroft-Gault classifications must be completed before the start of the OIC confirmation period. Likewise, if the FIT test is needed, the results must be evaluated before the start of the OIC confirmation period.

3.1.1.2 Visit S2 (OIC confirmation)

Visit S2 will occur 5 to 14 days after Visit S1, as soon as all initial screening assessments have taken place, results have been reviewed by the investigator, eligibility determined, and a

minimum of 5 days of pilot eDiary recording have been completed. Patients will be asked to bring the eDiary recording device with them to the visit.

At Visit S2, new patients who failed initial screening requirements will return the eDiary, be asked if any AEs have occurred since Visit S1, will be administered the C-SSRS, and will be discontinued from the study. Patients who are discontinued from the study prior to randomization will be considered to be screen failures.

New patients who remain eligible for the current study will begin the 2-week OIC confirmation period. They will have their eDiary recording reviewed and receive repeat instructions regarding proper recording. Patients who experienced difficulty using the device will have the opportunity to have any questions answered. The eDiary is to be completed daily during the OIC confirmation period. Patients will be instructed to notify the study site immediately if the eDiary stops working. In addition, compliance with the eDiary will be assessed by the site remotely at least every 48 hours to confirm that the patient is entering data. The patient will be phoned if any data are missing, and will be considered for discontinuation from the study if greater than 25% of the data are missing (eg, less than 11 days of data are entered).

New patients will be asked to discontinue all laxative and other bowel regimens including herbal products and prune juice (see prohibited medications, Section 5.6) throughout the 2-week OIC confirmation period, and to use only bisacodyl as rescue medication if a BM has not occurred within at least 72 hours since a previous BM. Bisacodyl for use as rescue medication will be dispensed to patients at Visit S2. Patients will be instructed on the guidelines for rescue bisacodyl use. Patients will be asked to return unused bisacodyl at the next visit (Visit R1). Documentation of bisacodyl use will be reviewed with the patient by comparing returned bisacodyl with eDiary records. If a patient does not experience a BM following bisacodyl rescue, the investigator may prescribe one-time use of an enema. The timing of administration of this therapy will be noted. If these secondary interventions fail, the patient should be excluded from the study and referred for additional medical evaluation. Since the patient is excluded from the study, the investigator should recommend initiation of any therapy deemed most appropriate. Any patient who is obstipated and/or has fecal impaction must not be randomized (see Section 4.2).

The following additional procedures will be performed at Visit S2:

For patients who do not continue in the study:

- AEs since Visit S1 will be recorded.
- The eDiary device will be returned.
- C-SSRS to assess suicidal risk, ideation, and behavior.

For patients who continue in the study:

- AEs since Visit S1 will be recorded.
- Use of concomitant medication (other than opioid or laxative medication) since Visit S1 will be recorded.
- Daily maintenance opioid dosing regimen will be asked about and recorded on the appropriate eCRFs.
- Use of laxative medication will be recorded on the appropriate eCRF.
- C-SSRS to assess suicidal risk, ideation, and behavior.
- Bisacodyl will be dispensed.
- An appointment for Visit R1 (randomization) will be made. Patients will be instructed to bring the eDiary recording device, and unused bisacodyl with them to the visit.

3.1.2 Treatment period (all patients: Visits R1 to R15)

Patients randomized to the NKTR-118 treatment group will be asked to bring their bottles of study drug with them to each visit, so that unused study drug tablets can be counted and recorded, and compliance can be determined. Patients randomized to Usual Care will be asked about use of laxatives at each study visit. All patients should be reminded of the importance of adherence to their respective dosing regimens (NKTR-118 or Usual Care).

As was requested of new patients at Visit S1, patients entering the study from a previous NKTR-118 study will be asked to bring a prescription or clearly labeled bottle of opioid medication with them to Visit R1 (randomization) for confirmation of their daily opioid dosing regimen. If a patient forgets to bring their medication prescription/bottle(s) to Visit R1, they will be asked to bring it to Visit R2. All patients will also be reminded that should they experience a change in their daily maintenance or breakthrough pain opioid dosing regimens during the study, they are to bring prescription(s) or clearly labeled bottle(s) of opioid medication to their next study visit, for confirmation of the new regimen(s).

Bisacodyl for use as rescue medication will be dispensed to NKTR-118 patients at each visit. NKTR-118 patients will be asked to return unused bisacodyl at each subsequent visit.

Patients randomized to the NKTR-118 treatment group will be asked to discontinue all laxative and other bowel regimens including herbal products and prune juice (see prohibited medications, Section 5.6) throughout the 52-week treatment period, and to use only bisacodyl as rescue medication if a BM has not occurred within at least 72 hours since a previous BM. If a patient does not experience a BM following bisacodyl rescue (see Section 5.6.2), the investigator may prescribe one-time use of an enema. The timing of administration of this therapy should be noted in the patient diary. In addition, the site is to record any enema

prescription on the enema eCRF. If these secondary interventions fail, the investigator will be free to employ any treatment modality deemed appropriate, and the patient should be referred for additional medical evaluation. In addition the patient should be discontinued from the study.

Patients in the NKTR-118 treatment group will receive their first dose of study drug at the study center at Visit R1. For subsequent visits, patients will self-administer the study drug in the morning (per their usual routine) prior to coming to the study center.

Patients in the Usual Care group will start their Usual Care treatment after meeting with the investigator at Visit R1 to discuss their laxative regimen including dosing guidelines.

Patients who discontinue prematurely from the study after participating in Visit R1 and receiving at least 1 dose of study drug or prescribed Usual Care laxative medication will be asked to return to the study center for an early termination (ET) visit during which unused study drug and assessments normally scheduled for Month 12 (Visit 15) will be obtained. This ET visit should be scheduled as soon as possible after the patient discontinues from the study (see Section 5.8).

During the treatment period, patients will return to the study center at monthly intervals. Visits at Months 4, 5, 7, 8, 10, and 11 will be limited in scope and will consist of the following:

- Daily maintenance and breakthrough pain opioid dosing regimen will be asked about and recorded on the appropriate eCRFs.
- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF)
- Use of concomitant medication (other than opioid or laxative medication) will be asked about and recorded on the concomitant medication eCRF.
- AEs since the previous visit will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Unused study drug will be returned (NKTR-118 patients).
- New 30 day supply of study drug will be dispensed (NKTR-118 patients).
- Unused bisacodyl will be returned (NKTR-118 patients).
- New supply of bisacodyl will be dispensed (NKTR-118 patients).
- An appointment for the next visit will be made.

Procedures for visits at randomization, Week 1, Week 2, and Months 1, 2, 3, 6, 9, and 12 are presented in detail below.

3.1.2.1 Visit R1 (Randomization, Week 0)

New Patients

For new patients, Visit R1 will occur 14 days (-1 day to +3 days) after Visit S2, at the completion of the OIC confirmation period. A minimum of 11 days of eDiary data collection must have been recorded since the start of the OIC confirmation period before the patient can be randomized for the study.

At Visit R1, the eDiary will be reviewed with the patient. Patients who do not meet OIC criteria or who do not meet laxative or stable opioid regimen criteria (ie, consumed >4 additional opioid doses per day for breakthrough pain on more than 3 days during the 2-week OIC confirmation period, or their maintenance opioid dose was modified) will not be randomized. All new patients will return the eDiary device at Visit R1.

Patients who were unable to appropriately use the eDiary device (greater than 25% of the data are missing), will be considered for exclusion from the study.

At Visit R1, the following procedures will be performed:

For new patients who do not continue in the study:

- AEs that occurred since Visit S2 will be recorded.
- The eDiary device will be returned.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Unused bisacodyl will be returned.

For patients who continue in the study, the assessments presented under "All Patients" should be followed. Some assessments scheduled for Visit R1 may already have been obtained at Visit S1 for new patients, and do not need to be repeated (informed consent and genetic informed consent, demographic information, medical history [including OIC history], complete physical examination, determination of LIR/LAR/LUR status, urine drug screen). A urine pregnancy test is required at both visits.

Patients who enter the study from a previous NKTR-118 study

For patients who enter the study from a previous NKTR-118 study (D3820C00005 or D3820C00007), the randomization visit (R1) will correspond with the last visit of the treatment period of the previous study. The majority of assessments scheduled for the last visit of the previous study are also required for the randomization visit of the present study (physical examination, blood pressure/pulse, laboratory assessments, U/A, urine drug screen,

urine pregnancy test, concomitant medications, ECG, NRS for pain, C-SSRS, modified Himmelsbach scale, and AEs) however the order of assessments in the current study should be followed. In addition, some assessments such as demographics, medical history, and laxative tolerance can be obtained from the screening visit of the previous pivotal study that the patient participated in (studies D3820C00004 or D3820C00005).

Patients who are randomized to NKTR-118 will receive a dose of NKTR-118 25 mg at Visit R1. Patients who are randomized to Usual Care will meet with the investigator at Visit R1 and start their Usual Care treatment on the same day according to the investigator's instructions.

All Patients

Visit R1 will be scheduled in the morning. Patients who receive NKTR-118 will be required to remain at the study center for a minimum of 4 hours after receiving the study drug, for observation (see Section 6.3.13.2 regarding abdominal pain), additional ECG and vital sign measurements,and completion of the modified Himmelsbach scale. Patients who receive Usual Care treatment will also be required to remain at the study center for a minimum of 4 hours after completion of initial assessments. During this time they will meet with the investigator to discuss their treatment regimen, and will undergo the same safety observations as patients in the NKTR-118 group.

Pre-dose/Initial Assessments:

- Signed informed consent prior to any study-related procedures (required for patients enrolling from a previous NKTR-118 study; already obtained for new patients)
- Signed genetic informed consent (may already have been obtained for new patients; if necessary, genetic informed consent may be signed at a subsequent visit; genetic informed consent must be obtained before any blood sample for genetic analysis is collected). Participation in the genetic component of the study is optional.
- Demographics (already obtained for new patients; obtained from the previous NKTR-118 pivotal study for rollover patients)
- Medical and surgical history including OIC history (already obtained for new patients; obtained from the previous NKTR-118 studies for rollover patients).
- LIR, LAR, LUR status (already obtained for new patients; obtained from the previous NKTR-118 pivotal study for rollover patients)
- Complete physical examination (including rectal examination) for rollover patients (Note: this will be obtained from last visit of the previous NKTR-118 study, but must also include rectal examination). New patients will have a targeted physical examination (lungs, cardiovascular, abdomen) with weight. Special emphasis should be placed on the pre-randomization abdominal examination so as not to

enroll any patients with an acute abdominal process (see Section 4.2). At the discretion of the investigator, a rectal examination may also be performed for new patients, if necessary to ensure the safety of the patient.

- Pain level question (NRS) (average pain over the previous 7 days) will be completed.

- Sitting blood pressure and pulse must be measured (obtained from last visit of the previous NKTR-118 study for rollover patients). Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours and minutes will be recorded for this measurement.

- 12-lead ECG after resting for 10 minutes, with triplicate ECGs collected over a 5-minute period. (obtained from last visit of the previous NKTR-118 study for rollover patients)

- Urine sample will be collected for urine pregnancy test (WOCBP). The urine pregnancy test result must be negative before the patient may continue with the visit and administration of study drug. Patients enrolling from a previous study will also have U/A and urine drug screen. (Urine pregnancy test, U/A, and urine drug screen will be obtained from last visit of the previous NKTR-118 study)

- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs. For patients who enter the study from a previous NKTR-118 study, the daily opioid and breakthrough pain dosing regimens will be confirmed by prescription or clearly labeled bottles of opioid medication. If a patient forgets to bring their medication prescription/bottle(s) to Visit R1, they will be asked to bring it to Visit R2.

- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).

- Use of concomitant medication (other than laxative or opioid medication) since Visit S2 will be recorded for new patients. Concomitant medications (other than laxative or opioid medication) ongoing at the end of the previous NKTR-118 study will be recorded for rollover patients.

- C-SSRS to assess suicidal risk, ideation, and behavior

- AEs since Visit S2 for new patients will be recorded. For rollover patients, AEs ongoing at the end of the previous NKTR-118 study, as well as resolved AEs meeting medical history criteria, will be recorded as new medical history.

- Modified Himmelsbach scale will be completed by the investigator before the patient receives the dose of study drug (obtained from last visit of the previous NKTR-118 study for rollover patients).

- I/E criteria will be reviewed with the patient.

- Patients who continue to meet I/E criteria (including confirmation of stability of the dose of the opioid) and new patients who also meet OIC criteria will be randomized to a treatment arm using the Interactive Voice Response System (IVRS).

- Unused bisacodyl will be returned (new patients).

- Blood samples will be collected for laboratory assessments (clinical chemistry [including total cholesterol] and hematology) (obtained from last visit of the previous NKTR-118 study for rollover patients).

- Blood sample will be collected for genetic sampling (if genetic informed consent signed). It is preferred that the blood sample for genetic analysis be collected at Visit R1; however, it may be collected at any visit during the study after the patient is randomized.

Dose/Meeting with Investigator:

- For patients randomized to NKTR-118, the first dose of open-label study drug will be administered at the study center and the patient observed for at least 4 hours. The accurate morning dose time in date, hours, and minutes will be recorded. Patients randomized to NKTR-118 will remain at the study center for additional post-dose assessments.

- Patients randomized to Usual Care will meet with the investigator to determine their OIC treatment regimen which will start the same day. Patients randomized to Usual Care will remain at the study center for at least 4 hours and will undergo the same additional assessments as patients in the NKTR-118 group.

Post dose/Additional Assessments:

- Care should be taken to record heart rate and blood pressure, which at this visit should be performed 1 hour post-dose/after initial assessments. (For practical purposes, this can be performed and recorded within a window from 1 hour to 90 minutes post-dose/initial assessments).

  Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours, and minutes will be recorded for this measurement.

  Additionally, if clinically significant decreases in blood pressure are noted at this post-dose/additional vital signs measurement, an additional measurement should be

taken approximately 2 hours later prior to the patient leaving the clinic (please refer to Section 6.3.12.1 for guidelines on management.)

In the event of clinically significant findings compared to the pre-dose/initial measurements (per the judgment of the investigator or delegate) please refer to Sections 5.8 and 6.3.13.3.

- Triplicate 12-lead ECGs will be obtained 2 hours after the dose of study drug (NKTR-118 patients) or 2 hours after initial assessments are completed (Usual Care patients).
- Modified Himmelsbach scale will be completed by the investigator 2 hours after the patient receives the dose of study drug (NKTR-118 patients) or 2 hours after initial assessments are completed (Usual Care patients).
- Study drug will be dispensed and dosing instructions will be provided (NKTR-118 patients only).
- A new supply of bisacodyl will be dispensed (NKTR-118 patients only).
- Patients will be given a home diary to record their use of breakthrough pain opioid medication and other concomitant medications between visits.
- An appointment for Visit R2 (Week 1) will be made. NKTR-118 patients will be instructed to bring study drug and unused bisacodyl with them to the visit.

3.1.2.2 Visit R2 (Week 1)

- Pain level question (NRS) (average pain over the previous 7 days) will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours and minutes will be recorded for this measurement.
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.

- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).
- Use of concomitant medication (other than laxative medication or opioid medication) since the previous visit will be recorded.
- Patients receiving NKTR-118 will bring unused study drug to visit and number of unused study drug tablets will be recorded in order to determine patient compliance. Study drug will be returned to the patient.
- AEs since the previous visit will be recorded.
- Modified Himmelsbach scale will be completed.
- Unused bisacodyl will be returned (NKTR-118 patients).
- New supply of bisacodyl will be dispensed (NKTR-118 patients).
- An appointment for Visit R3 (Month 1) will be made. NKTR-118 patients will be instructed to bring study drug and unused bisacodyl with them to the visit.

3.1.2.3 Visit R3 (Week 2)

Visit R3 will occur at Week 2 ±3 days. At Week 2, the following procedures will be performed:

- Pain level question (NRS) (average pain over the previous 7 days) will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours and minutes will be recorded for this measurement.
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.

- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).
- Use of concomitant medication (other than laxative medication or opioid medication) since the previous visit will be recorded.
- Patients receiving NKTR-118 will bring unused study drug to visit and number of unused study drug tablets will be recorded in order to determine patient compliance. Study drug will be returned to the patient.
- AEs since the previous visit will be recorded.
- Unused bisacodyl will be returned (NKTR-118 patients).
- New supply of bisacodyl will be dispensed (NKTR-118 patients).
- An appointment for Visit R4 (Month 1) will be made. NKTR-118 patients will be instructed to bring study drug and unused bisacodyl with them to the visit.

3.1.2.4 Visit R4 (Month 1)

Visit R4 will occur at Month 1 ±3 days. At Visit R4, the following procedures will be performed:

- Pain level question (NRS) (average pain over the previous 7 days) will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours and minutes will be recorded for this measurement.
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- Serum pregnancy test (WOCBP) will be collected.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.

- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).
- Use of concomitant medication (other than laxative medication or opioid medication) since previous visit will be recorded.
- AEs since the previous visit will be recorded.
- Modified Himmelsbach scale will be completed.
- Unused study drug will be returned (NKTR-118 patients) and the number of unused study drug tablets will be recorded. Patient compliance will be determined (NKTR-118 patients).
- New 30 day supply of study drug will be dispensed (NKTR-118 patients).
- Unused bisacodyl will be returned (NKTR-118 patients).
- New supply of bisacodyl will be dispensed (NKTR-118 patients).
- An appointment for the next visit will be made. NKTR-118 patients will be instructed to bring study drug and unused bisacodyl with them to the visit.

3.1.2.5 Visit R5 (Month 2)

Visit R5 will occur at Month 2 ±3 days. At Visit R5, the following procedures will be performed:

- Pain level question (NRS) (average pain over the previous 7 days) will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Daily maintenance and breakthrough pain opioid dosing regimen will be asked about and recorded on the appropriate eCRFs.
- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).
- Use of concomitant medication (other than opioid or laxative medication) will be asked about and recorded on the concomitant medication eCRF.
- AEs since the previous visit will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior

- Unused study drug will be returned (NKTR-118 patients).
- New 30 day supply of study drug will be dispensed (NKTR-118 patients).
- Unused bisacodyl will be returned (NKTR-118 patients).
- New supply of bisacodyl will be dispensed (NKTR-118 patients).
- An appointment for the next visit will be made. NKTR-118 patients will be instructed to bring study drug and unused bisacodyl with them to the visit.

3.1.2.6 Visit R6 (Month 3)

Visit R6 will occur at Month 3 ±3 days. At Visit R6, the following procedures will be performed:

- Pain level question (NRS) (average pain over the previous 7 days) will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours and minutes will be recorded for this measurement.
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- Serum pregnancy test (WOCBP) will be collected.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).
- Use of concomitant medication (other than laxative medication or opioid medication) since previous visit will be recorded.
- AEs since the previous visit will be recorded.
- Modified Himmelsbach scale will be completed.

- Unused study drug will be returned (NKTR-118 patients) and the number of unused study drug tablets will be recorded. Patient compliance will be determined (NKTR-118 patients).
- New 30 day supply of study drug will be dispensed (NKTR-118 patients).
- Unused bisacodyl will be returned (NKTR-118 patients).
- New supply of bisacodyl will be dispensed (NKTR-118 patients).
- An appointment for the next visit will be made. NKTR-118 patients will be instructed to bring study drug and unused bisacodyl with them to the visit.

3.1.2.7 Visit R9 (Month 6)

Visit R9 will occur at Month 6 ±3 days. At Visit R9, the following procedures will be performed:

- Pain level question (NRS) (average pain over the previous 7 days) will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours and minutes will be recorded for this measurement.
- Complete physical examination (including weight, temperature, respiratory rate)
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry [including total cholesterol] and hematology).
- Serum pregnancy test (WOCBP) will be collected.
- U/A will be collected.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).

- Use of concomitant medication (other than laxative medication or opioid medication) since previous visit will be recorded.
- AEs since the previous visit will be recorded.
- Modified Himmelsbach scale will be completed.
- Unused study drug will be returned (NKTR-118 patients) and the number of unused study drug tablets will be recorded. Patient compliance will be determined (NKTR-118 patients).
- New 30 day supply of study drug will be dispensed (NKTR-118 patients)
- Unused bisacodyl will be returned (NKTR-118 patients).
- New supply of bisacodyl will be dispensed (NKTR-118 patients).
- An appointment for the next visit will be made. NKTR-118 patients will be instructed to bring study drug and unused bisacodyl with them to the visit.

3.1.2.8 Visit R12 (Month 9)

Visit R12 will occur at Month 9 ±3 days. At Visit R12, the following procedures will be performed:

- Pain level question (NRS) (average pain over the previous 7 days) will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours and minutes will be recorded for this measurement.
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- Serum pregnancy test (WOCBP) will be collected.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.

- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).
- Use of concomitant medication (other than laxative medication or opioid medication) since previous visit will be recorded.
- AEs since the previous visit will be recorded.
- Modified Himmelsbach scale will be completed.
- Unused study drug will be returned (NKTR-118 patients) and the number of unused study drug tablets will be recorded. Patient compliance will be determined (NKTR-118 patients).
- New 30 day supply of study drug will be dispensed (NKTR-118 patients).
- Unused bisacodyl will be returned (NKTR-118 patients).
- New supply of bisacodyl will be dispensed (NKTR-118 patients).
- An appointment for the next visit will be made. NKTR-118 patients will be instructed to bring study drug and unused bisacodyl with them to the visit.

3.1.2.9 Visit R15 (Month 12)

Visit R15 will occur at Month 12 ±3 days. At Visit R15, the following procedures will be performed:

- Pain level question (NRS) (average pain over the previous 7 days) will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours and minutes will be recorded for this measurement.
- Complete physical examination (including weight, temperature, respiratory rate)
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry [including total cholesterol] and hematology).
- Urine sample will be collected for U/A, urine drug screen (urine toxicology), and urine pregnancy test (WOCBP).

- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).
- Use of concomitant medication (other than laxative medication or opioid medication) since previous visit will be recorded.
- AEs since the previous visit will be recorded.
- Modified Himmelsbach scale will be completed.
- Unused study drug will be returned (NKTR-118 patients) and the number of unused study drug tablets will be recorded. Patient compliance will be determined (NKTR-118 patients).
- Unused bisacodyl will be returned (NKTR-118 patients).
- An appointment for the next visit will be made.

Following Visit R15, patients may resume any constipation regimen that they and the investigator feel is appropriate.

3.1.3 Final Visit (Visit R16, 2 weeks after Month 12)

Visit R16 will occur 2 weeks after Month 12 and will also have a ±3 day allowable scheduling window. At Visit R16, the following procedures will be performed:

- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours and minutes will be recorded for this measurement.
- Single 12-lead ECG will be collected.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- Serum pregnancy test (WOCBP) will be collected.
- C-SSRS to assess suicidal risk, ideation, and behavior

- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.

- Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).

- Use of concomitant medication (other than laxative medication or opioid medication) since previous visit will be recorded.

- AEs since the previous visit will be recorded.

Table 1 Study Plan

	New Patients		All Patients															
	Screening	OIC Conf	Treatment Period															Final
Week/month	**-W4 to -W2[a]**	**-W2 to W0**	**W0**	**W1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12[c]**	**+2W**
Visits	**S1**	**S2**	**R1[b]**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**	**R11**	**R12**	**R13**	**R14**	**R15**	**R16**
Visit Window (Days)			**+3**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent (& genetic informed consent)[d]	√		√[e]															
Inclusion/Exclusion criteria	√		√															
Randomization			√															
Demographic information	√		√[e]															
Medical and surgical history (including OIC history)	√		√[e]															
CRC risk factor evaluation (including FIT as necessary)	√																	
Complete physical examination (height, weight, temperature, respiratory rate) including rectal examination[f]	√		√[e, f]								√						√	
Sitting blood pressure, pulse[v]	√		√	√	√	√		√			√			√			√	√
LIR, LAR, LUR status[g]	√		√[e]															

Table 1 Study Plan

	New Patients		All Patients															
	Screening	OIC Conf	Treatment Period															Final
Week/month	**-W4 to -W2[a]**	**-W2 to W0**	**W0**	**W1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12[c]**	**+2W**
Visits	**S1**	**S2**	**R1[b]**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**	**R11**	**R12**	**R13**	**R14**	**R15**	**R16**
Visit Window (Days)			**+3**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Pregnancy test for women of childbearing potential[h]	√		√			√		√			√			√			√	√
12-lead electrocardiogram[i]	√		√	√	√	√		√			√			√			√	√
Clinical chemistry and hematology[j]	√		√	√	√	√		√			√			√			√	√
Total Cholesterol			√								√						√	
Genetic sampling[d]			√															
Urinalysis[k]	√		√[e]								√						√	
Urine drug screen[l]	√		√[e]														√	
C-SSRS	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Daily maintenance opioid regimen recorded	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Opioid medication for breakthrough pain recorded	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Laxative medication recorded[w]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Table 1 Study Plan

	New Patients		All Patients															
	Screening	OIC Conf	Treatment Period															Final
Week/month	**-W4 to -W2[a]**	**-W2 to W0**	**W0**	**W1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12[c]**	**+2W**
Visits	**S1**	**S2**	**R1[b]**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**	**R11**	**R12**	**R13**	**R14**	**R15**	**R16**
Visit Window (Days)			**+3**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Modified Himmelsbach Scale[m]	√		√	√		√		√			√			√			√	
Prior/Concomitant medications (other than laxative medication or opioid medication)[n]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pain level (NRS)[o]			√	√	√	√	√	√			√			√			√	
Adverse Events		√[p]	√[p]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
OIC Healthcare Resource Utilization Assessment[o]				√	√	√	√	√			√			√			√	√
Dispense study drug			√			√	√	√	√	√	√	√	√	√	√	√		
Return unused study drug[q]				√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Dispense bisacodyl[r]		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
Return unused bisacodyl[r]			√[s]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
eDiary device dispensed	√																	

Table 1 Study Plan

	New Patients		All Patients															
	Screening	OIC Conf	Treatment Period															Final
Week/month	**-W4 to -W2[a]**	**-W2 to W0**	**W0**	**W1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12[c]**	**+2W**
Visits	**S1**	**S2**	**R1[b]**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**	**R11**	**R12**	**R13**	**R14**	**R15**	**R16**
Visit Window (Days)			**+3**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
eDiary ([daily]: BM, straining, complete/incomplete evacuation, stool consistency (Bristol Stool Scale), pain level [NRS], laxative rescue medication [bisacodyl, enema], opioid medication for breakthrough pain)[t]	√	√																
eDiary review (including proper documentation of bisacodyl and enema use)		√[t]	√[s]															
eDiary device returned		√[u]	√[u]															
Make appointment for next visit	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	

BM bowel movement; CRC colorectal cancer screening; C-SSRS Columbia Suicide Severity Scale; eDiary electronic diary; FIT fecal immunochemical test; LAR laxative adequate response; LIR laxative inadequate response; LUR laxative unknown response; NRS Numeric Rating Scale; OIC opioid-induced constipation

[a] The screening period will last at least 5 days, and up to 14 days.

[b] A minimum of 11 days of eDiary data collection must have occurred since the start of the OIC confirmation period before the patient can be randomized. Day 1 visit requires 4-hour post-dose in-office stay.

[c] Month 12 assessments should be performed at the time of early termination for patients who discontinue early, with the exception that patients who discontinue prior to Visit R1 (randomization) will not be required to have Month 12 assessments.

[d] Genetic informed consent does not need to be obtained at enrollment, but must be obtained before any blood sample for genetic analysis is collected. It is preferred that blood samples for genetic testing be collected at randomization, but blood samples may be collected at W1, W2, M1, M2, M3, M6, M9, M12, or the follow-up visit. Blood samples for genetic analysis are to be obtained for this study even if they were also collected in the previous study.

[e] This information was collected at screening for new patients. Informed consent and genetic informed consent will be collected at Visit R1 for patients who enroll directly from pivotal study D3820C00005 or from the 3-month safety extension (study D3820C00007) of pivotal study D3820C00004. Demographics, medical history, and laxative response status will be obtained from the previous pivotal study that the patient participated in (studies D3820C00004 or D3820C00005).

[f] A complete physical examination including rectal examination is to be performed at all designated visits. At the randomization visit (Visit R1) a complete physical examination is not required for new patients since this was conducted at the screening visit. However, at Visit R1 new patients will have a targeted physical examination (lungs, cardiovascular, abdomen) with weight collected and optional rectal examination at the discretion of the investigator, if necessary to ensure safety.

[g] For new patients, determined based on self reported laxative use over the 2 weeks prior to the screening visit, continued constipation symptoms, and laxative side effects. For patients entering from other NKTR-118 studies, laxative response status will be transcribed from the relevant pivotal efficacy and safety study.

[h] Urine pregnancy tests will be performed at screening (new patients only), randomization (Visit R1), and M12. Any positive urine pregnancy test is to be followed up with a serum pregnancy test. Serum pregnancy tests will be performed at M1, M3, M6, M9, and the follow-up visit.

[i] A single 12-lead ECG will be obtained for new patients at Screening (Visit S1), and for all patients at the follow-up visit. Triplicate ECGs will be performed for all patients at randomization (Visit R1, pre-dose and 2 hours post-dose) and at all other study visits.

[j] Laboratory tests for new patients can be repeated once after consultation with the sponsor if assessment at screening is abnormal and clinically significant as judged by the investigator. Results (including repeat laboratory testing) must be reviewed prior to randomization to ensure patient meets eligibility requirements.

[k] If U/A is positive for blood, protein, or glucose, microscopic testing is to be conducted.

[l] If, in the opinion of the investigator, a patient is undergoing opiate withdrawal or significant exacerbation of pain, the investigator is to conduct a repeat urine drug screen to rule out noncompliance with the opioid regimen as an explanation for withdrawal or pain. In addition, the investigator may perform a urine drug screen anytime during the study, at his/her discretion, to allow appropriate medical management of the patient.

[m] Completed before the first dose for all patients and 2 hours after the first dose for patients randomized to NKTR-118 during Visit R1.

[n] For new patients, prior medications will be collected from 60 days before screening; for patients enrolling from other studies prior medications will be collected from 60 days before randomization.

[o] The NRS will be collected in the eDiary for Visits S1 and S2. Starting with Visit R1 the NRS will be completed in the clinic. The NRS is to be completed at the start of the relevant visits prior to any investigations or discussions about symptoms with study staff. An exception to this is made for Visit R1, since only randomized patients will fill out the questionnaires and interaction with study staff will be necessary to determine whether randomization criteria have been met. As applicable, the OIC Healthcare Resource Utilization Assessment is to be completed after the NRS, and prior to any investigations or discussions about symptoms with study staff.

[p] For new patients who fail initial screening, AEs will be collected at Visit S2. For new patients who fail OIC confirmation, AEs will be collected at Visit R1.

[q] Patients assigned to NKTR-118 will be asked to bring the study drug with them to each visit (to assess compliance); unused study drug will be returned/collected at each visit from M1 through M12.

[r] Starting with Visit R1 bisacodyl will only be dispensed to NKTR-118 patients. Starting with Visit R2, bisacodyl will only be returned by NKTR-118 patients.

[s] New patients only. (All new patients will return unused bisacodyl at randomization, irrespective of which treatment group they are assigned to).

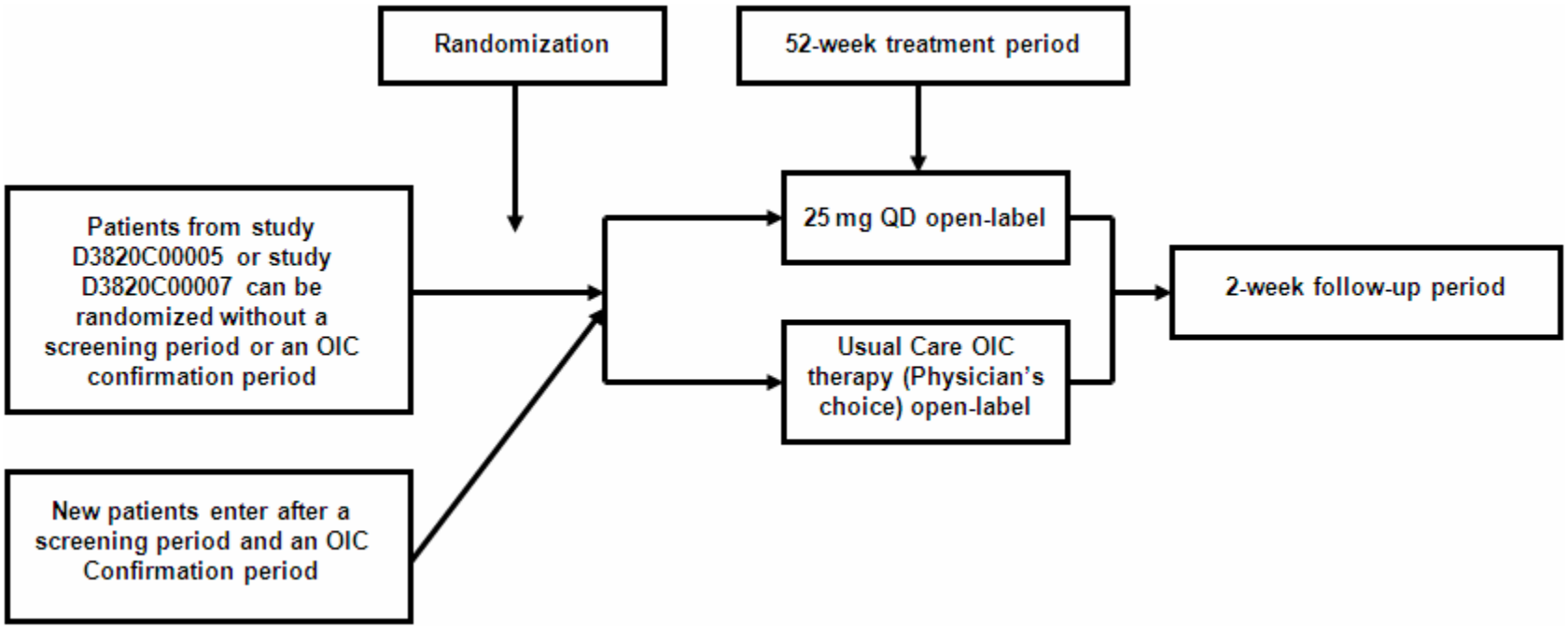
[t] Electronic diary assessments collected by new patients daily during screening and OIC-confirmation. eDiary pilot training will begin at Visit S1.

[u] New patients who do not meet initial screening criteria will return the eDiary device at Visit S2; remaining new patients will return the eDiary device at Visit R1.

[v] Sitting blood pressure and pulse must be measured at each specified visit, with accurate time in date, hours and minutes recorded. Additional details on protocol-mandated methods for collection of vital signs are specified in Section 6.3.12.1. At Visit R1, all patients will have blood pressure and pulse measured pre-dose/as an initial assessment. In addition, patients will have an additional blood pressure and pulse measurement performed 1 hour post-dose/after the initial assessment (for practical purposes, this can be performed within a window from 1 hour to 90 minutes post-dose). If clinically significant decreases in blood pressure are noted at this post-dose measurement, an additional measurement should be taken approximately 2 hours later, prior to the patient leaving the clinic. In the event of clinically significant findings compared to the pre-dose measurement (per the judgment of the investigator or delegate), please refer to Sections 5.8, 6.3.12.1, and 6.3.13.3 for additional guidelines on management.

[w] Laxative medication will be asked about and recorded on the laxative medication eCRF. (For NKTR-118 patients, bisacodyl use will be captured on the bisacodyl drug accountability eCRF).

Figure 1 Study flowchart



3.2 Rationale for study design, doses and control groups

This study is part of the Phase III development program for NKTR-118 in OIC and is one of a program of efficacy/safety studies designed to support registration of this drug for the treatment of OIC.

The primary aims of the study are to establish the safety and tolerability profile of NKTR-118 administered over a 52-week period in patients with confirmed OIC. A Usual Care arm is included to allow estimation of the baseline AE rate in the OIC population receiving usual care for their OIC. Patients randomized to the Usual Care arm will be treated according to the investigator's best clinical judgment. The AE profiles and other safety variables of the Usual Care laxative regimen and NKTR-118 will be compared using descriptive statistics.

The dose of NKTR-118 in the current study (25 mg) was chosen based on Phase II study results that showed a good efficacy and tolerability profile with this dose. Phase II data indicated that doses of 25 mg/day and 50 mg/day were statistically significantly better than placebo in reversing OIC, and that a dose of 5 mg/day showed a numerical (although not statistically significant) trend towards an increase in SBMs/week relative to placebo. NKTR-118 was well-tolerated at the 5 mg/day and 25 mg/day doses; however, a higher incidence of GI-related side effects was seen in the 50 mg/day cohort. The 25 mg dose has been selected as the primary dose to be evaluated for efficacy and safety in the Phase III development program and is the higher of the 2 doses tested in the 2 pivotal Phase III studies. The other dose in the pivotal program is 12.5 mg QD, which is included to explore the minimally efficacious dose range.

As was done in the Phase II study, a wide range of opioids is included in the present study in order to be able to generalize findings to a broad patient population. Patients with pain related to cancer are not included in the present study, since the 2 pivotal Phase III studies will consist of patients who do not have cancer-related pain.

Patients may enter the present study directly from the pivotal study D3820C00005, directly from the 12-week safety extension study (D3820C00007) of the pivotal study D3820C00004, or may be new patients who have not had previous treatment with NKTR-118. New patients are required to undergo the same screening procedures that were required for the pivotal studies in order to ensure a homogeneous study population.

Laxative use is prohibited during the OIC confirmation period (for new patients) and throughout the treatment period for NKTR-118 patients, since these medications could confound the efficacy of NKTR-118. However, patients who do not respond to study treatment with NKTR-118 may take a laxative rescue medication if a BM has not occurred within at least 72 hours. In such cases, bisacodyl has been chosen as a first-line treatment because it is efficacious and suitable for as needed administration. Further guidance is provided on the use of bisacodyl as well as an enema if bisacodyl is ineffective.

Peripheral μ-opioid antagonists are prohibited for use as laxatives in the Usual Care arm because their similarity to NKTR-118 could potentially confound results. In accordance with

the latitude offered to investigators in determining Usual Care treatment, no specific laxative rescue guidelines are provided for the Usual Care arm. To minimize confounding influences, an effort has been made to exclude patients with constipation or diarrhea for reasons other than OIC.

NKTR-118 is expected to improve the symptoms of OIC by blocking the peripheral effects of opioid medication without inducing central opioid withdrawal symptoms or interfering with analgesia. Although there was no indication of opioid withdrawal symptoms or reversal of analgesia in the Phase II study, the current study includes the modified Himmelsbach scale to assess withdrawal symptoms, and the NRS along with ongoing assessment of daily opioid dose to assess pain.

The C-SSRS is included as a safety measure to assess risk for suicidality in this patient population.

Although Phase II data did not show changes in liver enzymes, liver function tests will be monitored after randomization, and specific guidelines for handling possible elevations in liver enzymes are included in the protocol.

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Note: Patients who complete pivotal study D3820C00005 and/or the 12-week short term safety extension study D3820C00007 can enroll directly without confirmation of inclusion criterion #3. All other I/E criteria apply to all patients and must be reviewed at the time of randomization.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

1. Provision of written informed consent prior to any study-specific procedures

2. Men and women who are between the ages of ≥18 and <85 years

3. NEW PATIENTS ONLY: Self-reported active symptoms of OIC at screening (<3 SBMs/week and experiencing ≥1 reported symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction in at least 25% of the BMs over the previous 4 weeks); **and**

   Documented confirmed OIC (<3 SBMs/week on average over the 2-week OIC

confirmation period. Patients with uneven distribution of SBMs across the 2-week OIC confirmation period [0 SBMs in 1 week with ≥4 SBMs in the other week] will be excluded. In addition to the SBM frequency criterion, patients must report ≥1 of the following symptoms in at least 25% of the BMs recorded in the eDiary during the OIC confirmation period: BSS stool type 1 or 2; moderate, severe or very severe straining, incomplete BM). Patients who have 0 BMs over the 2-week OIC confirmation period will not be randomized.

4. NEW PATIENTS ONLY: Receiving a stable maintenance opioid regimen consisting of a total daily dose of 30 mg to 1000 mg of oral morphine, or equianalgesic amount(s) of 1 or more other opioid therapies (see Appendix H) for a minimum of 4 weeks prior to screening for non-cancer-related pain with no anticipated change in opioid dose requirement over the proposed study period as a result of disease progression. The opioid regimen should be confirmed by a prescription or medication bottle. Regimen stability will be confirmed during the 2-week OIC confirmation period. Patients will be disqualified from randomization if they consume >4 additional breakthrough pain medication doses per day for more than 3 days during the 2-week OIC confirmation period, or if their long-acting maintenance opioid dose was modified during this same period. The use of additional doses of opioids for breakthrough pain will be captured in the eDiary during the 2-week OIC confirmation period. Patients who are receiving only short-acting opioids will be allowed in the study if they are receiving doses according to a fixed schedule. Patients who are receiving only a short-acting opioid on an as-needed basis that does not follow a fixed schedule, are not eligible for this study. Intrathecal dosing is permitted as long as the patient is taking another orally dosed opioid that meets the dosing and duration criteria defined above.

   PATIENTS ENROLLING FROM OTHER NKTR-118 STUDIES: Receiving a stable maintenance opioid regimen consisting of a total daily dose of 30 mg to 1000 mg of oral morphine, or equianalgesic amount(s) of 1 or more other opioid therapies (see Appendix H)

5. NEW PATIENTS: Willingness to stop all laxatives and other bowel regimens including prune juice and herbal products throughout the 2-week OIC confirmation period and the 52-week treatment period, and to use only bisacodyl as rescue medication if a BM has not occurred within at least 72 hours of the last recorded BM.

   FOR PATIENTS RANDOMIZED TO RECEIVE NKTR-118: Willingness to stop all laxatives and other bowel regimens including prune juice and herbal products throughout the 52-week treatment period, and to use only bisacodyl as rescue medication if a BM has not occurred within at least 72 hours of the last recorded BM.

FOR PATIENTS RANDOMIZED TO THE USUAL CARE ARM: Willingness to adhere to using approved laxatives throughout the 52-week treatment period.

6. NEW PATIENTS ONLY: Patients must comply with CRC screening criteria as specified in Appendix E.

7. Male patients who are sexually active must use a double-barrier method of contraception (condom with spermicide) from the first dose of investigational product (IP) until 12 weeks after their last dose. Women of childbearing potential must have a negative pregnancy test and confirmed (by the investigator) use of a highly effective form of birth control for 12 weeks before enrollment and until 12 weeks after their last dose. Highly effective forms of birth control are listed in Appendix I. Women of non-childbearing potential can participate in this study without adherence to the pregnancy precautions. Women of non-childbearing potential are defined as women who are either permanently sterilized (hysterectomy or bilateral oophorectomy or bilateral salpingectomy) or are postmenopausal. Any woman who is older than 57 years of age is considered postmenopausal. In addition, women who are older than 50 years of age and amenorrheic with at least 12 months having passed since the last menses (after cessation of all exogenous hormone treatments), are also considered postmenopausal.

8. Be able to understand and comply with the requirements of the study, as judged by the investigator (includes ability to read and write and use the eDiary device)

9. Outpatient status at enrollment and randomization.

In addition, for inclusion in the genetic research, patients must fulfill the inclusion criterion outlined in Appendix D of this CSP.

If a patient declines to participate in the genetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this CSP, so long as they consent.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Is receiving opioid regimen for treatment of pain related to cancer

2. History of cancer within 5 years from the screening visit with the exception of basal cell cancer and squamous cell skin cancer.

3. Medical conditions and treatments associated with diarrhea, intermittent loose stools or constipation, which could confound the interpretation of the results, eg, fecal incontinence or chronic idiopathic constipation. In addition, patients having irritable bowel syndrome (IBS) that has been previously diagnosed by a physician

prior to first initiation of opioid therapy and that meets the following criteria, would be excluded:

- Absence of a structural or biochemical explanation for the abdominal pain symptom
- At least 12 weeks during a period of 12 months, of abdominal discomfort or pain with at least 2 of the following 3 features:
  - Relieved with defecation, and/or
  - Onset associated with a change in frequency of stool, and/or
  - Onset associated with a change in form of stool.

4. Other issues related to the GI tract that could impose risk to the patient (with a special, but not exclusive, emphasis on conditions that might impair the local or global structural integrity of the GI tract) including (but not limited to): inflammatory bowel disease (such as Crohn's disease or ulcerative colitis), intestinal obstruction or pseudo-obstruction, suspected mechanical GI obstruction, or previous history of recurrent bowel obstruction, history of >1 episode of diverticulitis (unless treated with surgery) or clinically important active diverticular disease (as determined by the investigator), history of rectal prolapse, history of GI hemorrhage related to ongoing GI pathology (eg, ulcer), clinically important or severe peptic ulcer disease (per investigator judgment), GI ostomy, intraperitoneal catheter, history of bowel perforation, history of ischemic bowel disease or ischemic colitis, previous small bowel surgery, history of surgical stenosis, known intra-abdominal adhesions, or previous gastric by-pass surgery. In addition, patients having surgery of the colon or abdomen within 60 days of the screening period or expected surgical procedure of the abdomen during the study participation period would be excluded.

5. Acute GI conditions that could impose risk to the patient, eg, acute fecal impaction or complete obstipation, acute surgical abdomen or otherwise suspicious abdominal/rectal examination. In addition, patients who fail to have an adequate BM after completing the laxative rescue regimen (bisacodyl, enema) during the OIC confirmation period should be excluded from participation and referred for further medical evaluation.

6. Any other significant and/or progressive medical condition (eg, neurological, psychiatric, or metabolic) or a clinical symptom that could unduly risk the patient or affect the interpretation of study data (eg, uncontrolled hypothyroidism, inadequately controlled clinical depression, poorly controlled seizure disorder)

7. Any of the following findings and/or conditions:

   - Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 x upper limit of normal (ULN) and/or serum bilirubin >1.2 x ULN (unless elevation is due to Gilbert's syndrome)
   - Diagnosis of liver cirrhosis as defined by Child-Pugh classes of B or C (see Appendix G), or acute liver disease
   - Creatinine clearance <60 mL/min (calculated by the central laboratory using the Cockcroft-Gault formula)
   - Absolute neutrophil count (ANC) <1500 cells/mm^3; platelets <60,000 mm^3; or hemoglobin (Hb) <9 g/dL

8. Signs and symptoms at the time of randomization that the investigator believes may be related to opioid withdrawal

9. Ongoing use of manual maneuvers to induce a BM (eg, digital evacuation or pelvic floor support)

10. Any condition that may have affected the permeability of the blood-brain barrier, eg, multiple sclerosis, recent brain injury, Alzheimer's disease, and uncontrolled epilepsy.

11. Severe background pain (eg, typical average daily pain intensity rating of 8 to 10 on an 11-point NRS) refractory to opioid therapy

12. Patients who are at increased risk for ventricular arrhythmia, including those that have a prior history of serious ventricular arrhythmia, family history of sudden cardiac death, family history of long QT syndrome, have a recent history of myocardial infarction within 6 months before randomization, have overt cardiovascular disease, eg, symptomatic heart failure, have a prolonged repeat QTcF (QTcF >450 ms at screening, confirmed by repeat QTcF on ECG taken within 5 minutes), or are on medications that prolong the QT/QTc interval (see Appendix J)

13. Active substance or alcohol use that in the opinion of the investigator, may compromise patient's ability to comply with the study instructions. Patients with a positive urine drug screen at the screening visit for cocaine, or amphetamine (unless verified by prescription that the patient is receiving amphetamine for treatment of Attention-Deficit Hyperactivity Disorder or other neuropsychiatric condition) will be excluded. Patients receiving methadone will be excluded. The disposition of patients with suspected opiate abuse during the trial will be handled on a case by case basis.

14. Use of prohibited medications as listed in Section 5.6.

15. Pregnancy or lactation

16. Known history of intolerance or hypersensitivity to alvimopan, methylnaltrexone, or other peripherally acting opioid antagonists, or to any other component in the tablets

17. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff, Nektar staff, staff at the study site, and third-party vendors)

18. Previous randomization in the present study or any study with NKTR-118 other than studies D3820C00005 or D3820C00007.

19. NEW PATIENTS ONLY: Is currently participating in or has participated in another clinical study within 30 days prior to screening for this study

20. NEW PATIENTS ONLY: Any receipt of an investigational medication within 30 days of screening

In addition, for inclusion in the genetic research, the exclusion criteria outlined in Appendix D of this CSP apply.

Procedures for discontinuation of incorrectly enrolled patients are described in Section 5.3.

Procedures for discontinuation of patients from the genetic research are described in Appendix D of this CSP.

5. STUDY CONDUCT

5.1 Restrictions during the study

Restrictions regarding laxative use, change in opioid dose, and other restricted medications are provided in Section 5.6.

5.2 Subject enrollment and randomization

New patients will receive an enrollment number and a randomization number. Patients who enter the study from a previous NKTR-118 study will receive a new randomization number for study D3820C00008 but will keep same enrollment number that they had in the previous study. The Principal Investigator (PI) or other qualified designee will:

1. Obtain signed informed consent from the potential patient before any study-specific procedures are performed

2. Assign each potential patient a unique enrollment number, beginning with "E#." The E-code is a 7-digit number made up of the center number and the patient number within that particular center. (NEW PATIENTS ONLY)

3. Determine patient eligibility. Eligibility of new patients will be determined after the screening and OIC confirmation periods, upon completion of the OIC confirmation period (see Sections 4.1 and 4.2). Eligibility of patients who completed pivotal Study D3820C00005 (core) or 12-week safety extension study D3820C00007 will be determined once screening criteria are reviewed.

4. Assign each eligible patient a unique randomization code (patient number), beginning with "#."

If a patient discontinues from participation in the study, then his/her enrollment/randomization code cannot be reused. For patients entering the study from a previous NKTR-118 study, their randomization number from the previous study will also be recorded in the case report form (CRF) for mapping purposes to the patient's previous study.

5.2.1 Procedures for randomization

Randomization codes will be distributed and communicated to study sites by use of an IVRS.

Eligible patients will be randomized to receive NKTR-118 25 mg or Usual Care in a 2:1 ratio. The actual treatment assigned to individual patients will be determined by a randomization scheme that has been loaded into the IVRS database. The randomization scheme will be produced by a computer software program called GRand (AstraZeneca's Global Randomization system). If a patient is discontinued from the study, his/her patient number or enrollment number will not be reused, and the patient will not be allowed to re-enter the study. Randomized patients who discontinue early from the study will not be replaced.

If a randomization number is allocated incorrectly, no attempt should be made to remedy the error once the IP has been dispensed. The patient will continue with the allocated number and IP. AstraZeneca or its representative should be notified as soon as the error is discovered. Subsequent patients will continue using the first unallocated randomization number in the original numbering sequence.

5.3 Procedures for handling subjects incorrectly enrolled

Patients who fail to meet the I/E criteria should not, under any circumstances, be enrolled or randomized. There can be no exceptions to this rule.

In cases where patients who do not meet the selection criteria are randomized in error or are incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the Study Physician and the investigator regarding whether to continue or discontinue the patients from treatment. The Study Physician is to ensure all such decisions are appropriately documented.

5.4 Blinding and procedures for unblinding the study

Since this is an open-label study no procedures for blinding or unblinding are applicable.

5.5 Treatments

5.5.1 Identity of investigational product(s)

NKTR-118 study drug tablets will be round, biconvex, and white film coated. Tablets will be supplied in high-density polyethylene (HDPE) bottles, dispensed every 30 days. Each 30-day supply will consist of 1 bottle of study drug, containing 35 tablets.

5.5.2 Doses and treatment regimens

5.5.2.1 NKTR-118

Patients randomized to the NKTR-118 treatment arm will receive NKTR-118 25 mg daily during the 52-week treatment period of the study (Days 1 to 365). They will be instructed to take 1 tablet daily 1 hour before eating in the morning.

5.5.2.2 Usual Care

Patients randomized to the Usual Care treatment arm will follow a laxative treatment regimen for OIC determined by the investigator according to his/her best clinical judgment. For patients randomized to the Usual Care arm, the investigator is advised to treat the patient's OIC as he or she would usually do, following his/her clinical experience, and using laxative agents that are available for treatment of constipation or OIC in their respective country. The investigator may chose from a broad range of laxatives (see Section 5.6.2). However, peripheral μ-opioid antagonists, such as methylnaltrexone and naloxone containing products, are not allowed. The investigator may choose to re-start the laxative that the patient was taking prior to the start of the study if that agent was effective. The investigator will be free to modify the treatment regimen as he/she sees fit throughout the 52-week duration of the trial. No specific rescue laxative protocol is determined for patients randomized to receive Usual Care.

5.5.3 Additional study drug

Sites will procure bisacodyl 5 mg tablets for use as a laxative rescue medication and will dispense bisacodyl to new patients at Visit S2. In addition, the site will dispense bisacodyl to NKTR-118 patients at randomization, and at all post-randomization study visits including and up to Month 11.

Information regarding rescue laxative and opioid medication for breakthrough pain is provided in Section 5.6.

Patients assigned to the Usual Care arm will procure laxative medications themselves (see Section 5.5.2.2).

5.5.4 Labeling

All clinical trial material will be packaged and labeled by AstraZeneca. The clinical trial material will be clearly marked according to national requirements regarding use for clinical trial investigation only and will also be labeled with the drug name, study reference number, and storage conditions. It is the responsibility of the investigator to ensure that accurate accountability records are maintained throughout the study.

AstraZeneca will provide the IP to the study sites. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language.

5.5.5 Scheduling classification

The control or classification of NKTR-118 as a controlled substance is country dependent. NKTR-118 is currently not controlled in either the UK or in Sweden. The US Drug Enforcement Administration (DEA) has classified NKTR-118 as a Schedule II (C-II) substance based on structural relatedness to noroxymorphone. Preclinical studies of NKTR-118 demonstrated that NKTR-118 has u-opioid antagonistic properties, and abuse liability studies are currently underway to further determine control classification. Additional details regarding safety surveillance activities for NKTR-118 are provided in the Safety Handling Plan.

5.5.6 Storage

All investigational products (IPs) must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions is specified on the IP label and in the IB. All study drug will be stored in original containers until dispensed to the study patients.

The receipt, handling, storage and dispensing of NKTR-118 will be in accordance with applicable country regulatory requirements.

5.6 Concomitant and post-study treatment(s)

5.6.1 Pain medication guidelines

Throughout the study, investigators will be encouraged to maintain a patient's baseline pain control regimen, with dose adjustments made as needed in accordance with the patient's clinical needs. Investigators will retain latitude in making these adjustments as clinically indicated, but it is recommended that the guidelines for the ongoing management of pain in the study reference manual (Chou et al 2009) serve as a framework for dose adjustments on-study. It is anticipated that the majority of the patients in this study will be receiving a long-acting opioid for control of background pain and an immediate-release opioid PRN for breakthrough pain, although some may be receiving only a short-acting opioid on a scheduled basis.

It is recognized that some patients may have their pain managed by personal physicians who are not connected with the study. In such cases, patients will be asked to notify their personal physicians of their participation in the study, and communication between the patient's personal physician and the investigator is strongly encouraged. Although it is desirable that patients be maintained on a stable opioid regimen during the study, should changes in the maintenance opioid regimen be necessary they should be reported to the site at the next study visit and recorded on the maintenance opioid eCRF. Opioid medication for breakthrough pain should also be reported at the next study visit and recorded on the breakthrough pain medication eCRF.

Concomitant non-opioid analgesics will not be prohibited, but investigators will be encouraged to maintain such drugs at stable doses on-study if possible.

Unless there is a need for urgent intervention, patients will not be allowed to take any additional medication for pain control other than their maintenance opioid regimen and approved opioid medication for breakthrough pain without the prior agreement of the investigator (or their personal physician, if pain is managed outside the study, in which case the investigator must be notified of any changes). This includes over-the-counter treatments for pain.

5.6.2 Laxative medication guidelines

During the study, it is advised that the PI be responsible for managing the patient's constipation. New patients may take laxatives during the screening period of the study, but must discontinue use of laxatives at least 24 hours prior to the start of the OIC confirmation period. During the OIC confirmation period, a new patient may take bisacodyl as a laxative rescue medication only if a BM has not occurred within at least 72 hours. If after a minimum of 72 hours, the patient has not experienced a BM, he/she may take bisacodyl rescue therapy (10 to 15 mg dose, ie, 2 to 3 bisacodyl tablets at a time). If the patient remains constipated, bisacodyl rescue therapy may be repeated up to 2 additional times, as necessary, each 10 to 15 mg dose separated by 12 hour intervals. It is recommended that the bisacodyl tablets be taken either at bedtime or before breakfast. If after 3 doses of bisacodyl rescue therapy, the patient still has not experienced a BM, the investigator may prescribe one-time use of an enema. The timing of administration of this therapy will be noted and recorded in the eDiary during the OIC confirmation period. In addition, the site is to record any enema prescription on the enema eCRF. If these secondary interventions fail, the patient should be excluded from the study and referred for additional medical evaluation. Since the patient is excluded from the study, the investigator should recommend initiation of any therapy deemed most appropriate. Any patient who is obstipated and/or has fecal impaction must not be randomized (see Section 4.2).

During the treatment period, guidelines for laxative use differ depending on whether the patient is assigned to the NKTR-118 treatment arm or the Usual Care treatment arm. Laxative use will be tracked during the study by entering information regarding laxative use on the laxative eCRF at each study visit.

Sites will procure and dispense bisacodyl for use as rescue medication at each visit starting with Visit S2 (new patients) or Visit R1 (NKTR-118 patients entering from another study). Bisacodyl will not be dispensed to patients in the Usual Care treatment arm.

NKTR-118 treatment arm

Unless there is a need for urgent intervention, NKTR-118 patients will not be allowed to take any additional medication for treatment of constipation, other than bisacodyl, during the course of the study without the prior agreement of the investigator. This includes over-the-counter treatments for constipation.

NKTR-118 patients will be instructed on the guidelines for rescue bisacodyl use noted above. If these secondary interventions fail, the patient should be discontinued from the study and referred for additional medical evaluation. Since the patient is discontinued from the study, the investigator should recommend initiation of any therapy deemed most appropriate.

NKTR-118 patients will be asked to return unused bisacodyl at each visit during the treatment period. Bisacodyl use will be reviewed with the patient at each visit and recorded on the bisacodyl drug accountability eCRF.

Usual Care treatment arm

Patients in the Usual Care treatment group will have their constipation managed by the investigator according to his/her best clinical judgment (see Section 5.5.2.2). The investigator may chose from a broad range of laxatives (see below). However, peripheral μ-opioid antagonists, such as methylnaltrexone and naloxone containing products, are not allowed (see Section 5.6.3). Patients assigned to Usual Care treatment will not be permitted to take any medication for treatment of constipation other than that prescribed by the PI, without the prior agreement of the PI. No specific rescue laxative protocol is determined for patients randomized to receive Usual Care. Usual care laxative medication will be reviewed with the patient at each visit and recorded on the laxative medication eCRF. This includes bisacodyl if the patient received this medication.

All patients

The following laxative medications are prohibited on-study for patients who receive NKTR-118. These medications do not constitute an exhaustive list of prohibited laxatives. These laxative medications are permitted for patients in the Usual Care arm if prescribed by the investigator as part of their OIC treatment:

- Milk of magnesia or magnesium citrate
- Non-absorbable phosphate
- Cascara

- Senna
- Castor oil/mineral oil
- Epsom salt
- Lactulose
- Polyethylene glycol
- Docusate
- Enemas
- Tegaserod
- Lubiprostone (Amitiza®)
- Drugs blocking fat absorption with an associated laxative effect
- Prucalopride
- Prune juice
- Herbal preparations for constipation
- Bulk laxatives, such as psyllium and methylcellulose
- Any agent that is used in an off-label fashion to treat constipation (eg, colchicine, misoprostol, erythromycin, cholinesterase inhibitors such as donezepil)
- Any experimental constipation therapy

5.6.3 Guidelines for use of other medications

The following opioid antagonists, and mixed agonists/antagonists are prohibited for all patients:

- Pentazocine
- Buprenorphine
- Nalbuphine
- Naloxone and other naloxone containing products, such as oxycodone/naloxone combinations (eg, Targin®)

- Naltrexone and other natrexone containing products such as morphine/naltrexone combinations (eg, Embeda®)
- Methylnaltrexone (Relistor®)
- Alvimopan (Entereg®)

The following strong inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (PGP) are prohibited for all patients;

- Cyclosporine
- Indinavir
- Nelfinavir
- Ritonavir
- Ketoconazole (except for topical use)
- Itraconazole
- Verapamil

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

5.7 Treatment compliance

Each patient is expected to comply with the treatment regimen during the study. The administration of the study drug should be recorded in the appropriate sections of the eCRF. Compliance with NKTR-118 treatment will be assessed by comparing the number of tablets dispensed minus the number of tablets returned versus the number of tablets that should have been taken (1 tablet per day).

5.7.1 Accountability

5.7.1.1 NKTR-118

The study drug provided for this study will be used only as directed in the CSP.

The study personnel will account for all study drugs dispensed to and returned from the patient. This record-keeping consists of a dispensing record that includes the identification of the person to whom the study drug is dispensed, the quantity and the date of dispensing, and the amount of any unused study drug returned to the investigator. This record is in addition to any drug accountability information recorded on the eCRF. Patients must return unused study

drug supplies to the investigator at each visit in which new study drug is dispensed, and at the final visit of the treatment period.

Study site personnel will account for all received study drugs and return all unused study drugs to AstraZeneca or its representative for study drug destruction in accordance with applicable country regulatory requirements. Certificates of delivery and return should be signed.

5.7.1.2 Bisacodyl

The bisacodyl provided by the sites to NKTR-118 patients will be used only as directed in the CSP.

The study personnel will account for all bisacodyl dispensed to and returned from the patient. This record-keeping consists of a dispensing record that includes the identification of the person to whom the bisacodyl is dispensed, the quantity and the date of dispensing, and the amount of any unused bisacodyl returned to the investigator. This record is in addition to any drug accountability information recorded on the eCRF. NKTR-118 patients must return unused bisacodyl to the investigator at each visit in which new bisacodyl is dispensed, and at the final visit of the treatment period.

5.8 Discontinuation from study

Patients are at any time free to discontinue from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator and Visit R15 assessments will be performed. Adverse events will be followed up (see Sections 6.3.4 and 6.3.5); and all study drugs should be returned by the patient.

Discontinued patients will not be replaced.

Patients should be discontinued in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Inadequate pain control after reasonable attempts to control pain have been unsuccessful
- Hepatotoxicity (significantly increased elevations in liver transaminases as defined in Section 6.3.9.2. The protocol for handling patients with elevated liver transaminases including guidelines for discontinuing patients is discussed in Section 6.3.9.2).

- Severe non-compliance to the CSP (including dosing regimen with NKTR-118 or Usual Care, and/or prescribed opioid) as judged by the investigator in consultation with the study physician

- Incorrectly enrolled patients, involving increased safety risk. The investigator should consult with the study physician before discontinuing the patient unless there is a medical urgency.

- Patient is lost to follow-up.

- The patient has a clinically significant or serious AE (eg, new or worsening heart failure) or sustained clinically significant treatment emergent abnormalities in vital signs that would not be consistent with continuation in the study, as determined by the investigator, AstraZeneca, or its representative, or the patient.

- Safety reasons as judged by the investigator.

- Patient becomes pregnant.

- Significantly worsened OIC refractory to medical treatment as judged by the investigator (including failure of the laxative rescue regimen either before or after randomization)

- The patient is unable to comply with the restrictions on the use of concomitant medications as detailed in Section 5.6 (in such cases the investigator should consult with the study physician before discontinuing the patient).

- The patient is unable to tolerate the study drug.

Abdominal pain has been reported as an AE in a previous trial with NKTR-118. The management of severe abdominal pain is discussed in Section 6.3.13.2).

Patients who discontinue prematurely from the study after having been randomized and having received at least 1 dose of study drug or prescribed Usual Care laxative medication will be asked to return to the study center for an ET visit during which assessments normally scheduled for Visit R15 (Month 12) will be obtained. This ET visit should be scheduled as soon as possible after the patient discontinues from the study. Any patient who discontinues and has clinically significant or abnormal results for any safety assessments will have an additional follow-up visit 1 week after discontinuation and at appropriate intervals thereafter, as medically indicated and determined by the investigator. AstraZeneca reserves the right to request follow-up information on any significant events on a case-by-case basis.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The electronic Data Capture (eDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the CSP and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Electronic diary devices will be used for new patients to collect information regarding BMs, straining, stool consistency (BSS), complete/incomplete evacuation, pain level (NRS), use of laxative rescue medication, and use of opioid medication for breakthrough pain (including the name of the opioid medication used, dose, route of administration and dosage form) during the OIC confirmation period. The devices will prompt patients to answer a few repeated questions each day. The data are sent by either wired or wireless means to the eDiary vendor's electronic servers where the data will be stored. Information from the eDiary vendor's server will be uploaded directly into the clinical database. The patients will be asked to bring the devices to Visits S2 and R1 where the devices will be checked for proper function. The eDiaries will also be reviewed with patients at these visits to ensure accuracy.

6.2 Data collection and enrollment

6.2.1 Screening and demographic measurements

The following data will be collected and recorded on the appropriate sections of the eCRF (refer to the Study Plan, Table 1): Some of these measures will have been obtained in the original pivotal studies (D3820C00004 or D3820C00005), or from 12-week double-blind extension study D3820C00007, that the patient participated in as indicated below.

- Signed ICFs will be obtained
- Signed genetic informed consent (may be signed at a subsequent visit)
- Demography (date of birth, sex, and race) for new patients.(obtained from the previous NKTR-118 pivotal study for rollover patients)
- Review of inclusion and exclusion criteria
- Review of medical history (including OIC history) for new patients (obtained from the previous NKTR-118 studies for rollover patients). For rollover patients, any ongoing AEs at the end of the previous NKTR-118 study, as well as resolved AEs in the previous study meeting medical history criteria, should be entered as medical history in this study.

- Complete physical examination (including height and weight) for new patients (obtained from last visit of the previous NKTR-118 study for rollover patients)
- FIT test or verification of previous imaging study, if required for new patients (obtained from previous NKTR-118 pivotal study for other patients).
- Vital signs (sitting blood pressure and pulse, body temperature, respiratory rate) for new patients (initial assessment obtained from last visit of the previous NKTR-118 study for rollover patients). Please refer to Section 6.3.12.1 for proper methodology of vital sign assessment.
- Determination of LIR, LAR, LUR status for new patients (obtained from previous NKTR-118 pivotal study for rollover patients)
- 12-lead ECG for new patients (initial assessment obtained from last visit of the previous NKTR-118 study for rollover patients)
- Laboratory assessments for new patients (obtained from last visit of the previous NKTR-118 study for rollover patients)
- Urine drug screen for new patients (obtained from last visit of the previous NKTR-118 study for rollover patients)
- Urine pregnancy test for new patients (obtained from last visit of the previous NKTR-118 study for rollover patients)
- U/A for new patients (obtained from last visit of the previous NKTR-118 study for rollover patients)
- Genetic sampling (if genetic informed consent signed)
- C-SSRS for new patients (obtained from last visit of the previous NKTR-118 study for rollover patients)
- Prior and current medications for new patients. Concomitant medications (other than laxative or opioid medication) ongoing at the end of the previous NKTR-118 study will be recorded for rollover patients.
- Laxative medication use over the past 60 days recorded for new patients. Laxative medication ongoing at the end of the previous NKTR-118 study will be recorded for rollover patients.
- eDiary device training and distribution for NEW Patients only
- Daily maintenance opioid dosing regimen and opioid medication for breakthrough pain over the past 60 days recorded for new patients. Daily maintenance opioid

dosing regimen and opioid medication for breakthrough pain at the start of the present study will be recorded for rollover patients.

6.2.2 Measurements recorded in eDiary (new patients only)

Patients will be supplied with a handheld eDiary for pilot training and the OIC confirmation period. At Visit S1, new patients will be carefully instructed and trained on how to fill in the eDiary and how to handle the device. Written information will be supplied to each patient. The patients must understand and be willing to use the eDiary and be instructed on how and where to request help if problems occur. If a patient does not fill out the eDiary, there will be a prompt at the end of the day informing the patient that no data has been recorded and to confirm that they have not had any BMs that day. Additional reminder prompts for data consistency will also be included (eg, if a patient records 2 BMs, but fills out the symptom data only once, they will be prompted at the end of the day to fill out the symptom data for the other BM).

The eDiary will be completed each day from the evening of Visit S1 to the morning of Visit R1 (randomization), including days of study visits. The eDiary will include the following daily recordings:

- Date and time of BM (recorded at the time of each BM)
- Stool consistency (BSS) (recorded at the time of each BM)
- Straining (recorded at the time of each BM)
- Complete/incomplete evacuation (recorded at the time of each BM)
- Pain level (NRS) recorded each evening for the average and worst pain level that occurred during the previous 24 hours
- Date and time of use of laxative rescue medication (bisacodyl or enema) recorded at the time the medication is taken
- Date and time of use of opioid medication for breakthrough pain recorded at the time the medication is taken, as well as the medication and dose administered (note: maintenance opioid regimen would be reported separately on the opioid dose eCRF).

6.2.2.1 Bowel movements

All BMs will be recorded as they occur.

6.2.2.2 Stool consistency (Bristol Stool Scale)

Patients will rate stool consistency through completion of the BSS after each BM.

The BSS is a medical aid designed to classify the form of human feces into 7 categories. It was developed by Heaton at the University of Bristol and was first published in the Scandinavian Journal of Gastroenterology in 1997 (Lewis and Heaton 1997).

The form of the stool depends on the time it spends in the colon. The 7 stool types are:

1. Separate hard lumps, like nuts (hard to pass)

2. Sausage-shaped, but lumpy

3. Like sausage, but with cracks on its surface

4. Like a sausage or snake, smooth and soft

5. Soft blobs with clear cut edges (passed easily)

6. Fluffy pieces with ragged edges, a mushy stool

7. Watery, no solid pieces.

Types 1 and 2 indicate constipation, Types 3 and 4 represent "ideal stools," and Types 5 to 7 are tending towards diarrhea or urgency.

6.2.2.3 Straining

The degree of straining with each BM will be recorded at the time of the BM and after the BSS. A single-item straining question, developed and validated through 1:1 interviews with OIC patients will be asked via the electronic diary. The question is provided below:

"How much did you strain during your bowel movement?"

1=Not at all

2=A little bit

3=A moderate amount

4=A great deal

5=An extreme amount.

6.2.2.4 Complete/incomplete evacuation

Patients will record the completeness of evacuation at the time of each BM and after the straining question. A single question on the completeness of evacuation, developed and validated through 1:1 interviews with OIC patients will be asked via the electronic diary. The question is provided below:

"Did you feel like your bowels were completely empty after the bowel movement?"

Patients will provide a yes or a no response to the complete/incomplete evacuation question.

6.2.2.5 Pain level

Patients will rate their pain level at the end of each day, using the NRS (see Section 6.3.7).

6.2.2.6 Use of laxative rescue medication

All bisacodyl and enema laxative rescue medication will be recorded at the time the medication is taken.

6.2.2.7 Use of opioid medication for breakthrough pain

Opioid medication for breakthrough pain will be recorded in the eDiary at the time the medication is taken.

6.2.3 Additional procedures including follow-up procedures

Additional procedures (and follow-up procedures) during the visits after screening are referenced in the Study Plan (Table 1).

6.3 Safety

The PI is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.3.1 Safety variables

Safety variables include:

- Incidence, nature, and intensity of AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, and specific safety areas of interest
- Mean daily opioid dose for Months 1, 3, 6, 9, and 12
- Mean bisacodyl dose per week for Months 1, 3, 6, 9, and 12 (NKTR-118 group only)
- Change from baseline in NRS pain score for Week 1, Week 2, Months 1, 2, 3, 6, 9, and 12.
- Observed values and change from baseline in composite score in modified Himmelsbach scale for the evaluation of centrally mediated opioid withdrawal symptoms for Week 1, Months 1, 3, 6, 9, and 12
- Changes in vital signs and physical examination
- Changes in laboratory assessments (ie, chemistry, hematology, and U/A)
- Changes in ECGs

6.3.2 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration/exacerbation of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.3.3 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent 1 of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix B to the CSP.

6.3.4 Recording of adverse events

Time period for collection of adverse events

All AEs will be collected from the time of signature of informed consent to the follow-up visit (Visit R15), whether or not related to the IP and must be recorded on the eCRF. Unsolicited reports of SAEs will also be collected for 30 days after the last dose of study drug.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca or its representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity or intensity or changes in intensity
- Whether the AE is serious or not
- Investigator causality rating against the study drug (yes or no)
- Action taken with regard to IP
- AE caused patient's discontinuation from study *(*yes or no*)*
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE (including treatment administered and dechallenge/rechallenge information, if applicable).

Intensity is defined as follows:

- Mild (awareness of sign or symptom, but easily tolerated)

- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities).

Other reporting guidance

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.3. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

If a diagnosis of the patient's condition has been made, then the diagnosis should be recorded as the SAE or the AE. In instances of well-recognized symptoms, they can be recorded as the commonly used diagnosis (eg, fever, runny nose, and cough can be recorded as "flu"). However, if a diagnosis of the patient's condition has not been made, or if the individual symptoms are not well recognized, then the individual symptoms should be recorded separately.

Should an overdose occur, it must be reported in accordance with the procedures described in Section 13.2. All overdoses, with or without associated symptoms, should be reported as AEs.

Suicide and attempted suicide, irrespective of the method, but occurring in connection with the use of study drug, should be reported as AEs (serious or nonserious). This event should be identified as suicide or attempted suicide, and the method of the suicide or attempt should be provided. If an attempted suicide meets the criteria for an SAE, the event must be reported according to the guidelines in Section 6.3.5. Suicidal thoughts and preparation for suicide should also be regarded as AEs. All events of suicidality will be monitored via the C-SSRS.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that the IP has interfered with the effectiveness of a contraceptive medication. (To be eligible for this study, WOCBP and at risk of pregnancy must be using a reliable method of contraception; see Inclusion Criterion #7, Section 4.1). Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 13.3.

In the clinical study report (CSR), the terms used by the investigator to record AEs will be mapped to preferred terms using a standard AE dictionary, Medical Dictionary for Regulatory Activities (MedDRA).

Causality collection

The investigator will assess causal relationship between IP and each AE (ie, their relationship to study drug), and answer "yes" or "no" to the question, "*Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product.*"

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as "yes."

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "*Have you had any health problems since the previous visit/you were last asked?,"* or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, and vital signs should therefore only be reported as AEs if they fulfill any of the AE criteria or are the reason for discontinuation of treatment with the IP, or at the discretion of the investigator.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low Hb value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Underlying disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied, which in this study refers to the condition of OIC. Adverse events which are due to disease (ie, OIC) progression, in the opinion of the investigator, should not be reported as an AE, unless they meet SAE criteria (eg, hospitalization, etc., see Section 6.3.3).

Of note, patients in this study must have an opioid-requiring pain condition in order to participate. Any day-to-day type fluctuations in pain control common in this population should not be reported as AEs, unless they meet SAE criteria (eg, hospitalization, etc., see Section 6.3.3).

6.3.5 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other study site personnel must inform appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other study site personnel must inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately, but **no later than the end of the next business day** of when he or she becomes aware of it.

If the eDC system is not available, then the investigator or the other study site personnel reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

Refer to the study-specific Safety Handling Plan for details on SAE reporting using the eDC system.

6.3.6 Daily opioid dose

Opioid doses will be recorded for each patient and the daily opioid dose in morphine equivalents will be calculated. Opioid breakthrough pain medication will be recorded on the relevant eCRF at Visit S1 for new patients (to cover medication taken during the previous 60 days). Information obtained at Visit S1 will be entered into the eDiary to facilitate eDiary recording. Between Visits S1 and R1 opioid breakthrough pain medication will be captured only in the eDiary. At all visits from Visit R1 on, opioid breakthrough pain medication will be recorded on the relevant eCRF for all patients. The daily maintenance opioid dose will be recorded on the relevant eCRF at all visits for all patients. A home diary will be assigned to each patient to facilitate collection of opioid breakthrough pain medication usage.

6.3.7 NRS for pain

Pain intensity is commonly evaluated via single-item measures that require patients to provide a quantifiable categorical and/or numerical rating of their pain. The most evaluated measures of pain intensity include NRS and visual analogue scales; both have been shown to demonstrate excellent psychometric characteristics across a wide range of clinical trial environments. The 11-point NRS has been recommended as the preferred response format for

use in clinical trials (Dworkin et al 2005). The NRS rates pain from 0 (no pain) to 10 (worst pain imaginable). Changes in this scale should generally not be reported as AEs unless standard criteria for AE reporting are otherwise met.

For new patients, during the OIC confirmation period the NRS will be recorded each evening via the eDiary to record the patients' worst pain and average pain during the day. For all randomized patients, patients will be asked to complete the NRS question on paper form at relevant study visits indicating their average pain during the 7 days prior to the visit. Patients are to fill out the questionnaire in a quiet area, without any help from family, friends, or study staff. With the exception of Visit R1, where some interaction with staff will be necessary in order to ensure that randomization criteria have been met, patients are to fill out the NRS prior to any interventions or discussions regarding their OIC with the study staff or the investigator.

6.3.8 Modified Himmelsbach Scale

Patients are rated by examination for symptoms of opioid withdrawal using the modified Himmelsbach scale. The modified Himmelsbach scale will be administered by a clinician at the study site. Patients will be rated with respect to the following symptoms as observed at the time of the assessment: yawning, lacrimation, rhinorrhea, perspiration, tremor, mydriasis, piloerection, and restlessness. The signs will be quantified on a scale of 0 to 3, with 0=none, 1=mild, 2=moderate, 3=severe. (Himmelsbach 1941; Culpepper-Morgan et al 1992, Webster et al 2008). To ensure adequate inter-rater agreement, raters will undergo training on proper scoring using the modified Himmelsbach scale and will receive certification provided by Bracket Global. The modified Himmelsbach scale will be administered at screening, randomization, Week 1, Months 1, 3, 6, 9, and 12. Changes in this scale should generally not be reported as AEs unless standard criteria for AE reporting are otherwise met.

6.3.9 Laboratory safety assessment

Laboratory assessments will be conducted at a central laboratory. Blood and urine samples for determination of clinical chemistry, hematology, and U/A will be taken at the times indicated in the Study Plan (Table 1).

The following clinical laboratory tests (chemistry, hematology, and U/A shown in Table 2) will be performed as specified in the Study Plan.

Table 2 Laboratory assessments

Hematology	Clinical Chemistry	Urinalysis[f]	Stool Analysis
B-Hb	S-Albumin	U-Glucose	FIT Test[g]
B-Hematocrit	S-ALT[a]	U-Blood	
B-Erythrocyte count	S-ALP	U-Protein	
B-Leukocyte count	S-AST[a]	U-Leukocytes	
B-Leukocyte differential count	S-Bicarbonate	U-Pregnancy test (WOCBP)[d]	
B-Neutrophils (Absolute and %)	S-Bilirubin, Direct[b]		
B-Lymphocytes (Absolute and %)	S-Bilirubin, Indirect[b]	**Urine Drug Screen**	
B-Monocytes (Absolute and %)	S-Bilirubin, Total	barbiturates	
B-Eosinophils (Absolute and %)	BUN	benzodiazepines	
B-Basophils (Absolute and %)	S-Ca	cannabinoids	
B-Platelet count	S-Creatinine	cocaine	
B- MCV	S-Chloride	methadone	
B- MCH	S-Glucose	methaqualone	
B- MCHC	S-Potassium	opiates	
B- RDW	S-Sodium	phencyclidine	
	Total cholesterol[c]	propoxyphene	
	TSH	amphetamine	
	S-Pregnancy test[d]	tetrahydrocannabinol	
	Coagulation		
	PT/INR [e]		

ALP alkaline phosphatase, ALT alanine aminotransferase , AST aspartate aminotransferase, B whole blood; BUN blood urea nitrogen, Ca calcium, Hb haemoglobin, INR international normalized ratio, MCH mean corpuscular haemoglobin,MCHC mean corpuscular haemoglobin concentration, MCV mean corpuscular volume, PT prothrombin time, RDW red blood cell distribution width, S serum, TSH Thyroid stimulating hormone, U urine, WOCBP women of childbearing potential.

[a] A separate protocol is outlined regarding additional laboratory tests for elevated liver transaminases (see Section 6.3.9.2).

[b] Direct and Indirect Bilirubin will be assessed only if the Total Bilirubin value is outside the normal reference range.

[c] Total cholesterol will be assessed at randomization, Month 6, and Month 12.

[d] Serum pregnancy tests will be performed at Months 1, 3, 6, 9, and the follow-up visit; urine pregnancy tests will be performed at screening (new patients), randomization, and Month 12). Any positive urine pregnancy test is to be followed up with a serum pregnancy test.

[e] PT/INR is assessed only at screening for new patients in order to calculate Child-Pugh classification. Screening values from studies D3820C00004 or D3820C00005 will be used for patients who participated in these pivotal studies. INR is also to be assessed during the study if patients meet criteria for significant elevation in liver transaminases (See Section 6.3.9.2)

[f] If urinalysis is positive for blood, protein, or glucose, microscopic testing is to be conducted.

[g] New patients at average risk for CRC who are ≥50 years old (and who have not had a colonoscopy, barium enema, flexible sigmoidoscopy or virtual colonoscopy) will be asked to take a FIT test as indicated in Appendix E. Patients who enroll from studies D3820C00005 or D3820C00007 will not be required to have additional FIT testing

Serum chemistry and hematology tests will be performed for new patients at Visit S1 (screening), and for all patients at randomization, Week 1, Week 2, Months 1, 3, 6, 9, 12, and at follow-up. Total cholesterol will be assessed at randomization, Month 6, and Month 12.

Urine drug screening tests will be performed for new patients at Visit S1 (screening) and for all patients at randomization, Month 12, and anytime during the study, at the discretion of the investigator, to allow appropriate medical management of the patient. Urinalysis will be performed for new patients at Visit S1 (screening) and for all patients at randomization, Month 6, and Month 12. Urine pregnancy tests (for all WOCBP) will be performed for new patients at Visit S1 (screening) and for all patients at randomization, and Month 12. Any positive urine pregnancy test is to be followed up with a serum pregnancy test. Serum pregnancy tests for WOCBP will be performed at Months 1, 3, 6, 9, and the follow-up visit.

For blood volume, see Section 7.1.

6.3.9.1 Urine drug screen

As noted above, urine drug screening tests will be performed on all new patients at screening (Visit S1) and for all patients at randomization, Month 12, and anytime during the study, at the discretion of the investigator, to allow appropriate medical management of the patient. For patients enrolling from studies D3820C00005 or D3820C00007, initial urine drug screen information will be obtained from the last visit in these studies. In addition, if, in the opinion of the investigator, a patient is undergoing opiate withdrawal or significant exacerbation of pain, the investigator is to conduct a urine drug screen to rule out non-compliance with the opioid regimen as an explanation for withdrawal or pain. Based on the results of the urine drug screen, clinical picture, and severity of the potential opiate withdrawal symptoms, the investigator will decide if the patient should be discontinued from the study. If the patient tests positive for other illicit drugs, it is up to the investigator to decide after consulting with the study physician, whether these drugs may compromise the patient's ability to comply with study instructions, and whether the patient should be continued in the study.

6.3.9.2 Handling of subjects with elevated liver transaminases

The investigator will be alerted from the central laboratory regarding patients developing ALT or AST >3x ULN during the study, ie, all values above >3x ULN with no upper limit will be alerted. How to handle these patients is described in detail in this section.

All patients with ALT or AST >3x ULN, regardless of whether they stop or continue the intake of study drug, must be closely monitored with repeated laboratory liver tests every third day or more frequently if judged necessary by the investigator until the liver tests begin to improve. Thereafter, liver tests will be performed at an interval decided to be appropriate by the investigator. All patients must be followed until the liver tests have returned to baseline or until a firm explanation (diagnosis) for the elevated liver transaminases has been established.

The specific laboratory tests to be used for confirmation and monitoring include ALT, AST, alkaline phosphatase (ALP), bilirubin (BIL), conjugated BIL, INR, albumin, creatine kinase (CK), Hb, white blood cells (WBC), neutrophils, eosinophils, basophils, lymphocytes, monocytes, sodium, potassium, and creatinine.

Subjects who can continue the intake of study drug

- Patients with ALT or AST >3x ULN but ≤8x ULN and no clinical signs or symptoms indicating liver dysfunction can, at the discretion of the investigator, continue the intake of study drug with close monitoring.

The patients must be brought back to the study center for an unscheduled visit without any delay, but not later than 72 hours after the test results have been received, for specific evaluation of the underlying cause for the ALT or AST elevation and confirmatory laboratory testing.

A medical history focused on risk factors for liver injury (alcohol consumption, exposure to toxic agents, infections, medications and drug use including herbal remedies, etc) should be obtained, evaluation of recent symptoms (AEs), and physical examination should be done and all relevant information should be captured in appropriate eCRF modules.

Confirmatory laboratory testing should be done and more frequent monitoring of liver tests should be initiated.

Subjects who stop intake of study drug

Patients with the following findings should immediately be contacted and instructed to stop intake of study drug:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN AND (total bilirubin >2x ULN or INR >1.5). For further instructions on actions to be taken for patients meeting Hy's law criteria, see Appendix K.
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Patients must be brought back to the study center for an unscheduled visit without any delay, the next day if possible, but no later than within 72 hours after the test results have been received, for specific evaluation of the underlying cause of the ALT or AST elevation and confirmatory laboratory testing.

A medical history focused on risk factors for liver injury (alcohol consumption, exposure to toxic agents, infections, medications and drug use including herbal remedies, etc) should be obtained, evaluation of recent symptoms (AEs), and physical examination should be done and all relevant information should be captured in appropriate eCRF modules.

Confirmatory laboratory testing should be done and more frequent monitoring of liver tests should be initiated.

In addition, the following blood samples for differential diagnosis purposes should be taken in all patients who stop intake of study drug:

- Alcohol misuse: Carbohydrate deficient transferrin, S-ethanol
- Viral hepatitis: Immunoglobulin M antibody to hepatitis A virus (anti-HAV-IgM), Hepatitis B surface antigen (HBsAg), immunoglobulin M antibody to hepatitis B core antigen (anti-HBc-IgM), antibody to hepatits C virus (anti-HCV), hepatitis C virus ribonucleic acid (HCV RNA), immunoglobulin M antibody to Epstein Barr virus viral capsid antigen + immunoglobulin G antibody to Epstein Barr virus nuclear antigen (EBV VCA IgM + EBNA IgG, immunoglobulin M antibody to cytomegalovirus (anti-CMV-IgM).
- Autoimmune hepatitis: anti-nuclear antibody, anti-mitochondrial antibody, smooth muscle antibody, immunoglobulin G, immunoglobulin M, immunoglobulin A
- Hereditary disorders: S-Iron and total iron-binding capacity, S-Ferritin, ceruloplasmin, alpha 1-antitrypsin

Imaging techniques and additional examinations can be done if there is a clinical indication as judged by the investigator (eg, ultrasound, computed tomography, liver biopsy). The results of all testing should be entered in the appropriate eCRF modules. It is important that every effort is made to find an explanation for the elevated liver enzymes.

6.3.10 Physical examination

A complete physical examination (general appearance, skin, neck, [including thyroid], eyes, ears, nose, throat, chest, lungs, heart, abdomen, back, lymph nodes, extremities, and basic nervous system evaluation) including rectal examination, will be performed for new patients at screening, for patients entering from another study at randomization, and for all patients at Month 6 and Month 12. In addition, at randomization, new patients will have a targeted physical examination (lungs, cardiovascular, abdomen) with weight and optional rectal examination at the discretion of the investigator, if necessary to ensure safety (see Section 3.1.2.1).

For new patients, significant findings that are present prior to the start of study drug (Visit R1) must be included in the Medical History/Current Medical Conditions eCRF page. For patients enrolling from studies D3820C00005 or D3820C00007, significant findings that meet the definition of an AE must be recorded on the AE eCRF. In addition, for all patients, any significant findings made after the start of study drug (Visit R1) that meet the definition of an AE must be recorded on the AE eCRF.

6.3.10.1 CRC Risk Factor Evaluation

New patients must comply with the CRC screening criteria as specified in Appendix E. Patients enrolling from studies D3820C00005 or D3820C00007 will already have complied with these criteria. These criteria are modified from American College of Gastroenterology

Guidelines for Colorectal Cancer (CRC) Screening (Rex et al 2000, Rex et al 2009) and are intended to make a reasonable and practical good faith effort to rule out underlying colorectal malignancy as a potential contributor to constipation symptoms and to avoid enrolling patients with underlying malignancy into prolonged clinical trials. Patients are classified into high and average CRC risk groups based on their family history. Further division is made based on age, race, and previous diagnostic evaluation for CRC. A FIT test is required for those new patients who are ≥50 years of age and at average risk for CRC, unless they provide verification of negative colonoscopy, flexible sigmoidoscopy, barium enema study, or virtual colonoscopy. For more details, please refer to Appendix E.

6.3.11 ECG

6.3.11.1 Resting 12-lead ECG

Digital ECGs (dECG) for all patients at all centers will be conducted at the center using a machine provided by the central ECG laboratory and will be transmitted to the central ECG laboratory. The ECG machine will also print off 2 copies of the ECG by default, 1 copy that can be provided to the central ECG laboratory for digitization and analysis if necessary. Digital ECGs will be performed for new patients at screening, and for all patients at randomization, and all study visits after randomization. Digital ECGs will be obtained after the patient has been resting in a supine position for at least 10 minutes. A single 12-lead ECG will be obtained for new patients at Screening (Visit S1) and for all patients at the follow-up visit. Triplicate ECGs will be performed for all patients at the randomization visit (Visit R1, pre-dose/as an initial assessment and 2 hours post-dose/after initial assessments have been completed), and at all other study visits during which ECGs are collected (Week 1, Week 2, Months 1, 3, 6, 9, and 12). After the patient has been supine for at least 10 minutes, 3 standard 12-lead dECG recordings will be performed within a 5-minute period while the patient remains supine.

All dECGs will be documented by recording date, time, heart rate, QRS duration, PR interval, RR interval, QT, and QTcF. QTcF intervals will be calculated using the Fridericia formula (Puddu et al 1988).

If indicated, additional ECG assessments can be made at the discretion of the investigator. These assessments should be entered as an unscheduled assessment on the appropriate eCRF.

The investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF, if the investigator considers it clinically significant. Abnormal values shall not be recorded as AEs unless deemed clinically significant.

Quality assurance of the ECG waveform and patient demographics will be conducted by a central EGC laboratory operator. Digital ECGs will be processed through a computer interpretation program and then reviewed, first by an ECG analyst and then by a board-certified cardiologist. Electrocardiogram reports will be provided to the study sites (preferably by email although fax is possible) once the analysis is complete.

It is the investigator's judgment whether the findings/results on the central ECG laboratory report are clinically relevant or not and whether the findings will result in the discontinuation of the patient from the study based on the I/E or discontinuation criteria.

6.3.12 Vital signs

6.3.12.1 Pulse and blood pressure

Blood pressure (sitting) and pulse/heart rate (sitting) must be measured for new patients at screening and for all patients at randomization, Week 1, Week 2, Months 1, 3, 6, 9, 12, and the follow-up visit. The following measures should be employed consistently for every measurement:

- All measurements must be made in the sitting position.
- The patient must be sitting still at least 5 minutes before measurement.
- An appropriately sized cuff should be used.
- The arm should be at rest without movement, preferably in a supported position.
- The arm should be kept at approximately heart level.
- At least 2 measurements should be taken
  - If the 2 measurements are generally consistent with each other (within 10 mmHg for either SBP or DBP) the last reading should be recorded in the eCRF
  - If the 2 measurements differ (ie, are not within 10 mmHg for either SBP or DBP) neither result should be recorded in the eCRF. Instead the process must be repeated.
  - This process may be repeated up to 2 more times; if at the end of the third measurement the 2 measurements still differ, then the average of the 2 measurements should be recorded in the eCRF

Note: at Visit 3 (randomization) care should be taken to record heart rate and blood pressure, which at this visit should be performed pre-dose/as an initial assessment and 1 hour post-dose/after the initial assessment (for practical purposes, this can be performed and recorded within a window from 1 hour to 90 minutes post-dose). If clinically significant BP decreases (in the judgment of the investigator or delegate) are noted at the 1-hour post-dose measurement, the BP should be repeated approximately 2 hours later before the patient leaves the clinic to ensure that the BP is within normal limits for that patient (in the judgment of the investigator or delegate). If the BP value is still significantly low by the time of potential discharge, the investigator should consider discontinuing the patient from the study (see

Sections 5.8 and 6.3.13.3), although it is recommended that the investigator consult with the Study Physician prior to discontinuing the patient.

For management of markedly abnormal heart rates or blood pressures, please refer to Sections 5.8 and 6.3.13.3.

6.3.12.2 Body temperature, respiratory rate, and weight

Body temperature, respiratory rate, and weight will be measured for new patients at screening and for all patients at randomization, Month 6, and Month 12.

6.3.13 Other safety assessments

6.3.13.1 C-SSRS

The C-SSRS is a unique, simple, and short method of assessing both behavior and ideation that tracks all suicidal events, and provides a summary of suicidality (Posner et al 2007). It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.

The C-SSRS will be administered at all study visits by a trained rater. The trained rater will record the clinical observation on the scale, which will be used as the source document. If at all possible, the same individual should perform the assessment at each visit to reduce scoring variability. In the event the primary rater is not available, a designated back-up rater who meets the same qualifications may perform the C-SSRS.

If a patient indicates having a rating of type 4 or 5 suicidal ideation on the C-SSRS suicidal ideation scale at any time since the previous visit when the C-SSRS was administered or indicates having had any suicidal behavior since the previous visit, the patient should be referred to a mental health professional immediately. If the C-SSRS is administered by a rater other than the PI, it is recommended that the PI confirms suicidal ideation before making a referral to mental health services, however this should not delay the referral.

6.3.13.2 Persistent or progressive severe abdominal pain

Rare cases of GI perforation associated with the use of other peripheral opioid antagonists in OIC have been reported in a post-marketing setting. Such cases of perforation have been reported to occur shortly after initiation with drug and appear to be more commonly reported in debilitated patients with multiple co-morbidities, particularly co-morbid conditions that might impair the local or global structural integrity of the GI tract (eg, cancer, peptic ulcer, pseudo-obstruction of the colon, etc.; see Section 1.4 and Section 4.2).

While abdominal pain has been reported in association with NKTR-118 use in a Phase II OIC trial, any at-risk patient who reports progressive or persistent severe abdominal pain should be evaluated immediately by the site or otherwise referred for urgent medical assessment. Other associated symptoms with abdominal pain such as fever, malaise, and or mental status changes should also mandate urgent medical evaluation.

In addition, it should be emphasized that a thorough screening abdominal/rectal examination is an important element in identifying pre-treatment findings that might identify a patient who is at high risk for perforation. The investigator should maintain a low threshold for considering abdominal x-rays, further abdominal/rectal examination, or other diagnostic aids based on clinical assessment and patient history.

6.3.13.3 Blood pressure and heart rate measurements

Pre-clinical investigations have included a recent dog telemetry study which demonstrated small, transient decreases in blood pressure, left ventricular systolic pressure, cardiac contractility and relaxation indices, as well as increases in heart rate, at blood concentrations about 5 times higher than the maximum dose used in this study (ie, 25 mg). The clinical significance of this finding is uncertain and follow-up preclinical testing is underway in telemetered dogs with lower doses of NKTR-118. While there have been isolated reports of patients with potentially clinically significant blood pressure decreases in trials of NKTR-118, such cases have also been observed with placebo. No clear or consistent cardiovascular signal has been observed in human studies to date.

Therefore, care should be taken in the measurement of heart rate and blood pressure at all visits; for specific instructions on methods for measurement, please refer to Section 6.3.12.1. For specific instructions regarding the potential need for discontinuation based on sustained clinically significant vital sign abnormalities, please refer to Section 5.8. It should be noted that vital sign abnormalities should generally be reported as AEs only if they fulfill AE criteria proper or are the reason for discontinuation of treatment with the IP (see Section 6.3.4).

In general, the investigator should maintain a low threshold for considering additional diagnostic tests (eg, ECGs, echocardiogram, additional orthostatic measurements, chest x-rays, etc.) as appropriate, based on clinical assessment and patient history.

6.3.14 Safety specific areas of interest

Specific safety topics of interest for this trial include, but are not limited to, the following:

- Opioid withdrawal
- Abuse liability
- Bowel perforation type events (eg, ischemic colitis) (See Section 6.3.13.2)
- Cardiovascular type events (including, but not limited to, abnormalities in blood pressure and heart rate)

The topics listed above, as well as other topics which may be subsequently determined by AstraZeneca, will be subject to enhanced surveillance activities. Furthermore, an adjudication committee will independently assess certain of these areas of interest (ie, bowel perforation type events, cardiovascular type events, etc.). Additionally, the topics above will be analyzed for presentation in the CSR in accordance with the Statistical Analysis Plan (SAP).

Additionally, routine safety monitoring and patient risk management processes as outlined in AstraZeneca clinical trial standard operating procedures (SOPs) and in the Patient Risk Management Plan (PRMP) will be carried out to protect patients in clinical studies with NKTR-118.

6.4 Patient reported outcomes (PROs)

The following PRO is utilized in this study:

6.4.1 NRS

See Section 6.3.7.

6.4.2 Administration of PRO questionnaire

The NRS (for pain) will be self-administered at the study center. All patients will be instructed to answer the questions on their own, without help from others (family, friends, or study staff). In addition, for visits after randomization (Visit R1), the questionnaire is to be filled out at the start of the relevant visits, prior to any investigations or discussions about patients' symptoms with the study staff. An exception to this is made for the randomization visit, since only randomized patients will fill out the questionnaire and interaction with study staff will be necessary to determine whether randomization criteria have been met.

6.5 Efficacy (Not applicable)

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics

See Appendix D for details on pharmacogenetic sampling.

6.8.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from all patients post-randomization, even if collected in another NKTR-118 study. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may discontinue due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit R1 (randomization), it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1.

6.9 Health economics

6.9.1 OIC Healthcare Resource Utilization Form

Opioid-induced constipation related healthcare resource utilization data will be collected at Week 1, Week 2, Months 1, 2, 3, 6, 9, 12, and at the follow-up visit through patient interviews. If a patient is taken off the study as a result of a resource utilization (eg, an ER visit for manual disimpaction), the data should be recorded in the OIC healthcare resource utilization form prior to discontinuation. A health care resource utilization form will be used to collect information on whether the patient had any contact or visited with a health care provider (physician or other health care practitioner, urgent care center or hospital emergency room, or inpatient hospital) for the management of their OIC, including the details of the type and number of visits, as well as the reason for the visit (such as the use of enemas, manual disimpaction, and treatment of anal fissures). As applicable, the interview will be conducted after the patient completes filling out the PRO questionnaire (NRS), and prior to any other interventions or discussions regarding the patient's OIC with the study staff or the investigator.

The PI must report medication use reported on the OIC Healthcare Resource Utilization Form (eg, enemas) on the laxative medication eCRF. The OIC Healthcare Resource Utilization Form should not be used to report AEs but they should be reported on the AE eCRF.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 3 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry[a]	8.5 SST	10	85
	Hematology	4 EDTA	10	40
	Bicarbonate	3.5 SST	10	35
	Coagulation (PT/INR)	4.5 Sodium Citrate	1	4.5
Pharmacogenetics		10 EDTA	1	10
Total		30.5	32	174.5

EDTA Ethylenediaminetetraacetic acid, SST serum-separating tube

[a] Additional samples may be collected for patients who have elevated liver transaminases (see Section 6.3.9.2), who require repeat laboratory testing at screening, or who require a serum pregnancy test.

Urine samples will be taken from each patient for the purpose of drug screening and U/A. Urine samples from WOCBP will be used to test for pregnancy at selected visits.

7.2 Handling, storage and destruction of biological samples

The samples will be used up, disposed of after analyses, or retained for further use as described here.

The laboratory will provide detailed instructions of all laboratory procedures, handling, and shipment of laboratory samples before the study start. The samples should be properly taken, handled, labeled, and shipped in accordance with the instructions provided by the laboratory. Samples should be shipped to the laboratory by courier unless otherwise agreed.

The analyte stability limits defined by the laboratory will be applied to all analyses performed on behalf of AstraZeneca. The laboratory will not analyze samples that fall outside these stability limits. Analytical data found to have been derived from a sample that fell outside these stability limits would not be reported. The standards of procedures followed by the laboratory may be amended in accordance with their SOPs. The laboratory will inform AstraZeneca or its representative of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples – not applicable

7.2.2 Pharmacogenetic samples

Refer to Appendix D for collection and storage of pharmacogenetic samples.

7.3 Labeling and shipment of biohazard samples

The PI ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C "IATA 6.2 Guidance Document".

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their life cycle.

The PI at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca or its representative keeps oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

The PI:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca or its representative.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented, and the signed document returned to the study site.
- Ensures that the patient and AstraZeneca or its representatives are informed about the sample disposal.

AstraZeneca or its representatives ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Institutional Review Board (IRB) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The investigator should submit the written approval to AstraZeneca or its representative before enrollment of any patient into the study.

The IRB should approve all advertising used to recruit patients for the study.

AstraZeneca or its representative should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca or its representative will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca or its representative will provide Regulatory Authorities, IRBs, and PIs with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

Each PI is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca or its representative will provide this information to the PI so that he/she can meet these reporting requirements.

8.4 Informed consent

The PI(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated ICF before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the investigator's Study File.
- Ensure a copy of the signed and dated ICF is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an IRB.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the PI and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised CSP).

The amendment is to be approved by each IRB and if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to the IRB, see Section 8.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's IRB are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca or its representative and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative or its representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures, the eDiary recording device, and other system(s) utilized.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative or its representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)

- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative or its representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

9.3.1 Source data

Refer to the CSA for location of the source data.

9.4 Study agreements

The PI at each center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of the CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

Prior to a patient's enrollment in the study and any study-related procedures are undertaken, the following should be fulfilled:

- Signed CSA between AstraZeneca and the PI/study center
- Signed CSP and other agreements between AstraZeneca and the PI/study center
- Written approval of the study by the IRB
- Signed and dated Financial Disclosure forms.

9.4.1 Archiving of study documents

The investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as "the last visit of the last patient undergoing the study." The end of study definition is for the entire study.

The study is expected to start in 1st Quarter [redacted] and to end by 4th Quarter [redacted].

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with NKTR-118.

10. DATA MANAGEMENT BY ASTRAZENECA

10.1 Electronic case report form

The eCRF and the protocol are both confidential. The eCRF will be created by the contract research organization (CRO) and programmed into the eDC system. All study sites will need internet access to access the eCRFs and will only have access to data for patients at their own study sites. Data management (DM) and other co-ordinator teams will have access to data at all study sites.

All eCRFs are to be completed by an authorized member of the investigational staff and reviewed and signed by the investigator. All entries, corrections, and alterations are to be made by the responsible investigator or an authorized member of the investigational staff. All eCRFs are to be completed in a manner that ensures accurate interpretation of data.

It is each investigator's responsibility to ensure that all discontinued orders or changes in the study or other medications entered on the patient's eCRF correspond to the entries on the patient's medical records.

The eCRFs for any patient leaving the study should be completed at the time medication is terminated for whatever reason.

The eCRFs must accurately reflect data contained in patient's records (eg, source documents).

10.2 Data flow

After data are entered into the eCRF by study site, autoqueries that are generated by the eDC system should be addressed by study site. Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

Data entered in the eDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the PI has signed the eCRF electronically as per eCRF instructions, then the patient's data will be locked.

The data collected through third party sources will be obtained and reconciled against study data.

The data will be validated as defined in the DM Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

At the monitoring visit, the Study Monitor must perform the Source Document Verification (SDV) of the required fields on completed forms and if there are no open queries, freeze the form. Data management will run manual consistency checks outside of the eDC system and will raise manual queries for study sites to address; if the form is frozen, DM will unfreeze to allow study sites to amend data. The same process is to be followed by any other groups creating manual queries in the eDC system (eg, for SAE reconciliation). Once all data are entered, SDV complete on required fields, manual queries and electronic data reconciliation complete, and all queries closed, then the casebook can be signed. Once the casebook is signed, DM will then lock the casebook so that no amendments can be made.

10.3 Database lock

When all data have been coded, validated, signed, and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Once all patient casebooks are locked, the final data transfer can be sent to statistics. A database lock checklist will also be completed by DM and the programmer to confirm all applicable quality control checks were performed.

10.4 Coding

All AEs and medical/surgical histories recorded in the eCRF will be coded using MedDRA. All medications will be classified according to the AstraZeneca Drug Dictionary (AZDD). All coding will be performed by the CRO. The coding will occur outside of the eDC system and will be merged with the clinical datasets sent to statistics.

10.5 Investigator site file

At the beginning of the study, an investigator's study file will be established at the study center. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95) and as required by the applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

10.6 SAE reconciliation

The CRO will perform SAE reconciliation between the CRO Clinical Study database and the AstraZeneca Clinical Patient Safety database.

10.7 ECG data

ECG data will be processed by a central laboratory and the results will be sent electronically to AstraZeneca or its representative.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

11.1.1 Adverse events

A treatment-emergent adverse event (TEAE) is defined as any AE that started on or after the first dose of study drug up to the last dose of study drug. An AE already present at the time of the first dose of study drug that worsens in intensity following exposure to study drug or an AE with an unknown/not reported onset date will also be considered as treatment-emergent. Adverse events occurring after the last dose of study drug will also be summarized, which among other purposes, may assess any potential withdrawal-type effects.

Time to onset of an AE (in days) will be calculated as:

AE start date – Date of the first dose of study drug + 1.

Duration of an AE (in days) will be calculated as:

AE resolution date – AE start date + 1.

11.1.2 NRS for pain

The 11-point NRS for pain ranging from 0 (no pain) to 10 (worst imaginable pain) will be reported based on the average pain experienced during the 7 days before the study visit. Change from baseline in average NRS values will be calculated for Weeks 1 and 2, Months 1, 2, 3, 6, 9, and 12 as the post-baseline value minus the baseline value. Negative changes from baseline indicate improvement.

For all patients, the NRS (7-Day recall) collected at Visit R1 will serve as the NRS baseline value.

11.1.3 Daily opioid dose

Opioid doses will be recorded for each patient, including both the maintenance dose and dosing for breakthrough pain. However, the daily opioid dose in morphine equivalents (mg/day) will be calculated using only the maintenance dosing information. The mean daily opioid dose (mg/day) for an interval will be calculated as the sum of daily opioid doses

(mg/day) for the interval divided by the number of days within the interval in which the data were collected. The mean daily opioid dose will be calculated for the following time intervals: randomization in this study to Month 1, Months 1 to 3, Months 3 to 6, Months 6 to 9, and Months 9 to 12. For rollover patients, the mean daily opioid dose will also be calculated for the following time intervals: randomization in the previous NKTR-118 study (D3820C00005 or D3820C00007) to Months 1, 3, 6, 9, and 12.

11.1.4 Mean Bisacodyl dose per week

The mean bisacodyl dose per week (mg) will be calculated as

> (sum of bisacodyl doses (mg) during the period of interest/number of days in the period of interest) x 7.

The mean bisacodyl dose per week (mg) will be assessed for the following time intervals (NKTR-118 group only): randomization to Month 1, Months 1 to 3, Months 3 to 6, Months 6 to 9, and Months 9 to 12.

11.1.5 Modified Himmelsbach Scale

The scores for each of 8 signs are summed to give a composite score ranging from 0 to 24 for each visit, where higher values indicate greater severity of symptoms. If more than 25% of the 8 signs are missing at a visit, the composite score will be set to missing. The composite score will be summarized at Week 1, Months 1, 3, 6, 9, and 12. Changes from baseline to Week 1, Months 1, 3, 6, 9, and 12 in the modified Himmelsbach scale will be calculated as the post-baseline value minus the baseline value. Negative changes from baseline indicate improvement.

For the new patients, baseline modified Himmelsbach values will be defined as the latest non-missing value collected prior to the first dose of study drug in this study (screening, Visit S1 or Week 0, Visit R1). For patients entering the study from a previous NKTR-118 study (D3820C00005 or D3820C00007), the primary baseline modified Himmelsbach values will be defined as the latest non-missing value collected prior to the first dose of study drug in the previous pivotal study (D3820C00004 or D3820C00005) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline modified Himmelsbach will be defined as the data collected at the final visit from the previous study.

11.1.6 Laboratory safety assessments

Changes from baseline to each visit for all patients who have a baseline laboratory test and the corresponding post-baseline laboratory test (Week 1, Week 2, Months 1, 3, 6, 9, 12, and 2 week follow-up) will be calculated as the post-baseline test value minus the baseline test value.

For the new patients, baseline laboratory values will be defined as the latest non-missing value collected prior to the first dose of study drug in this study (screening, Visit S1 or Week 0, Visit R1). For patients entering the study from a previous NKTR-118 study (D3820C00005 or D3820C00007), the primary baseline laboratory values will be defined as the latest

non-missing value collected prior to the first dose of study drug in the previous pivotal study (D3820C00004 or D3820C00005) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline laboratory values will be defined as the data collected at the final visit from the previous study.

Laboratory test results will also be compared with the laboratory reference ranges, and values that are outside the applicable reference range will be flagged as high (H) or low (L). In addition, markedly abnormal values or changes from baseline will be identified.

11.1.7 Physical examination

Observed results and change from baseline to Months 6 and 12 for physical examination will be reported.

For the new patients, baseline physical examination results will be defined as the latest non-missing value collected prior to the first dose of study drug in this study (screening, Visit S1 or Week 0, Visit R1). For patients entering the study from a previous NKTR-118 study (D3820C00005 or D3820C00007), the primary baseline physical examination results will be defined as the latest non-missing value collected prior to the first dose of study drug in the previous pivotal study (D3820C00004 or D3820C00005) (screening, Visit 1 or Week 0, Visit 3), and supportive physical examination results will be defined as the data collected at the final visit from the previous study.

11.1.8 Weight

Change from baseline to Week 12 for weight will be calculated as the visit assessment minus the baseline value. Markedly abnormal values or changes from baseline will be identified.

For the new patients, baseline weight will be defined as the latest non-missing value collected prior to the first dose of study drug in this study (screening, Visit S1 or Week 0, Visit R1). For patients entering the study from a previous NKTR-118 study (D3820C00005 or D3820C00007), the primary baseline weight will be defined as the latest non-missing value collected prior to the first dose of study drug in the previous pivotal study (D3820C00004 or D3820C00005) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline weight values will be defined as the data collected at the final visit from the previous study.

11.1.9 Body temperature and respiratory rate

Change from baseline to Months 6 and 12 for body temperature and respiratory rate will be calculated as the post-baseline test value minus the baseline test value. Markedly abnormal values or changes from baseline will be identified.

For the new patients, baseline temperature and respiratory rates will be defined as the latest non-missing value collected prior to the first dose of study drug in this study (screening, Visit S1 or Week 0, Visit R1). For patients entering the study from a previous NKTR-118 study (D3820C00005 or D3820C00007), the primary baseline temperature and respiratory rates will be defined as the latest non-missing value collected prior to the first dose of study drug in the previous pivotal study (D3820C00004 or D3820C00005) (screening, Visit 1 or

Week 0, Visit 3), and supportive baseline temperature and respiratory rates will be defined as the data collected at the final visit from the previous study.

11.1.10 ECG

Changes from baseline to each post-baseline visit (Week 0 [2 hours post-dose], Week 1, Week 2, Months 1, 3, 6, 9, 12, and 2 week follow-up) for ECG interval data and rate data will be derived as the post-baseline value minus the baseline value for the same assessment. Markedly abnormal values or changes from baseline will be identified.

For the new patients, baseline ECG values will be defined as the latest non-missing value collected prior to the first dose of study drug in this study (screening, Visit S1 or Week 0, Visit R1 [pre-dose]). For patients entering the study from a previous NKTR-118 study (D3820C00005 or D3820C00007), the primary baseline ECG values will be defined as the latest non-missing value collected prior to the first dose of study drug in the previous pivotal study (D3820C00004 or D3820C00005) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline ECG values will be defined as the data collected at the final visit from the previous study.

11.1.11 Vital signs

Changes from baseline in vital signs (sitting blood pressure and pulse) at each post-baseline visit (Week 0 [1 hour post-dose], Week 1, Week 2, Months 1, 3, 6, 9, 12, and 2 week follow-up) will be derived as the post-baseline value minus the baseline value for the same assessment. Markedly abnormal values or changes from baseline will be identified.

For the new patients, baseline vital sign values will be defined as the latest non-missing value collected prior to the first dose of study drug in this study (screening, Visit S1 or Week 0, Visit R1 [pre-dose]). For patients entering the study from a previous NKTR-118 study (D3820C00005 or D3820C00007), the primary baseline vital sign values will be defined as the latest non-missing value collected prior to the first dose of study drug in the previous pivotal study (D3820C00004 or D3820C00005) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline vital sign values will be defined as the data collected at the final visit from the previous study.

11.1.12 C-SSRS

Occurrence of suicidal behavior after baseline up to the final assessment (Visit R16) will be defined as having answered “yes” to at least 1 of the 4 suicidal behavior sub-categories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post-baseline evaluation.

Occurrence of suicidal ideation after baseline up to the final assessment (Visit R16) will be defined as having answered “yes” to at least 1 of the 5 suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without

specific plan], and active suicidal ideation with specific plan and intent) at any post-baseline evaluation.

For the new patients, baseline C-SSRS will be defined as the latest non-missing value collected prior to the first dose of study drug in this study (screening, Visit S1 or Week 0, Visit R1). For patients entering the study from a previous NKTR-118 study (D3820C00005 or D3820C00007), the primary baseline C-SSRS will be defined as the latest non-missing value collected prior to the first dose of study drug in the previous pivotal study (D3820C00004 or D3820C00005) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline vital sign values will be defined as the data collected at the final visit from the previous study.

11.2 Calculation or derivation of patient reported outcome variables

11.2.1 NRS for pain

See Section 11.1.2.

11.3 Calculation or derivation of health economic variables

11.3.1 Healthcare resource utilization

Healthcare resource utilization will be assessed as the number of healthcare visits per patient year for the management of their OIC, which will be calculated as follows:

(total number of visits/number of days on study drug) x 365.25

The healthcare resource utilization will be summarized by type of OIC healthcare utilization category (healthcare practitioner, urgent care, ER).

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Safety analysis set

All randomized patients who received at least 1 dose of study drug (25 mg NKTR-118 or Usual Care) will be included in the safety analysis set. The safety analysis set will be used to assess safety and tolerability variables.

12.2 Methods of statistical analyses

A comprehensive SAP will be finalized before database lock.

This is a general evaluation of long-term safety and evaluation. Therefore, no statistical testing will be conducted. Differences between NKTR-118 25 mg and Usual Care with

respect to the evaluation of long-term safety and tolerability will be assessed using descriptive statistics.

The evaluation of safety in this study may be influenced by the fact that certain patients will be newly randomized to NKTR-118 (or no treatment [ie, Placebo/Usual Care], whereas other patients may have already been randomized to one of these two groups in their previous NKTR-118 pivotal study). For the purposes data presentation, patients will be summarized based on randomized treatment group in this study.

For new patients, baseline will be defined as the latest non-missing value collected prior to the first dose of study drug in this study (screening, Visit S1 or Week 0, Visit R1). For patients entering the study from a previous NKTR-118 study (D3820C00005 or D3820C00007), the primary baseline will be defined as the latest non-missing value collected prior to the first dose of study drug in the previous pivotal study (D3820C00004 or D3820C00005) (screening, Visit 1 or Week 0, Visit 3), and a supportive baseline will be defined as the data collected at the final visit from the previous study. Where appropriate, to assess the potential impact of the previous treatment, the change from baseline in safety parameters for the rollover patients will be summarized using both the primary (ie prior to first dose of study drug in the pivotal study) and supportive (final visit of previous study) baseline values.

The baseline data (including demographics, response to laxatives, medical history) for patients entering the study from a previous study will be pulled from the corresponding prior study databases and integrated with the data from this study in the analysis datasets. Additional medical history obtained during the previous studies (including adverse events ongoing at the end of the previous study) will also be reported.

Where appropriate, AEs and other relevant safety measurements will be summarized for each treatment group by whether the patient is new or a rollover, as well as by the combination of treatment in the previous study and current study treatment.

All major safety variables will also be presented by means of an outlier analysis. For labs, ECGs, and vital signs, these outlier criteria will be provided by the safety physician(s) and included in the SAP. For analyses such as modified Himmelsbach and NRS, generally accepted outlier criteria are not available but will be determined as appropriate before the time of database lock.

12.2.1 Safety analyses

Adverse events will be coded using the MedDRA dictionary. Three sets of AE summaries will be generated: (1) all AEs recorded in the clinical database, (2) all TEAEs (as defined in Section 11.1.1), and (3) AEs occurring after the last dose of study drug.

Number of events and proportions will be tabulated by preferred term and system organ class. An event that occurred 1 or more times on the date of or subsequent to first dose of study drug will contribute 1 observation to the numerator of the proportion. The denominator of the proportion will comprise all patients in the Safety analysis set. Adverse events will also be

summarized by intensity and separately, by causality (as determined by the investigator). Should a patient experience the same preferred term/system organ class within multiple intensity or causality categories, the patient's worst occurrence (most severe/most related) will be retained in the tabulations. Serious AEs and commonly occurring AEs will be summarized in a generally similar manner. Adverse events of special interest may be further summarized and analysis of AEs occurring within specific time periods (e.g. after 3 months, after 6 months, etc.) may be considered.

Adverse events, SAEs, AEs leading to death, and AEs leading to study discontinuation will be tabulated for each treatment group. Descriptive statistics for time to onset and duration of select AEs may be summarized by treatment group. Adverse events that could potentially be indicative of centrally mediated opioid withdrawal, abuse potential, and bowel perforation will be identified prior to database lock and will also be summarized by each treatment group.

The mean daily opioid dose will be summarized for the following intervals: randomization to Month 1, Months 1 to 3, Months 3 to 6, Months 6 to 9, and Months 9 to 12. The mean bisacodyl dose per week will be summarized only for the NKTR-118 treatment group using descriptive statistics for the following intervals: randomization to Month 1, Months 1 to 3, Months 3 to 6, Months 6 to 9, and Months 9 to 12. The observed composite modified Himmelsbach score and change from baseline will be summarized by treatment group at Week 1, Months 1, 3, 6, 9, and 12 using descriptive statistics. The observed score and change from baseline in the NRS pain scores (average in the 7 days prior to the study visit) will be summarized by treatment group for Weeks 1 and 2, Months 1, 2, 3, 6, 9, and 12.

All laboratory test results, vital signs (sitting blood pressure and pulse), ECG results, body temperature, respiratory rate, and weight will be summarized for each treatment group using descriptive statistics at each visit for observed values and change from baseline.

The overall incidence, as well as shifts from baseline to each post-baseline visit, of potentially clinically significant laboratory test results, vital signs, ECG results, body temperature, respiratory rate, and weight will be summarized by treatment group. For visits where triplicate ECGs are obtained, the mean value of the 3 measurements will be used in the analysis.

Physical examination results (normal/abnormal by body system) will be summarized for each visit by treatment group. Changes from baseline in the physical examination results will be assessed using shift tables.

The proportion of patients with suicidal behavior and suicidal ideation throughout the study based on the C-SSRS will be presented for each treatment group. The proportion of patients within each of the 4 suicidal behavior categories and within each of the 5 suicidal ideation sub-categories will also be presented for each treatment group. Descriptive statistics on the total number of attempts, total number of interrupted attempts, and total number of aborted attempts will be summarized for each treatment group.

Total exposure to NKTR-118 25mg will be summarized combining the data from the current study with the exposure data from the previous NKTR-118 pivotal studies (D3820C00004 and D3820C00005).

Safety parameters may also be summarized by age group, gender, race, region, response to laxatives (LIR, non-LIR), and previous treatment with NKTR-118 (yes, no), as appropriate.

12.2.2 Health Economics

The percentage of patients with at least 1 healthcare visit will be summarized for each OIC healthcare utilization category (healthcare practitioner, urgent care center, ER) by treatment group. The total number of visits and number of healthcare visits per patient year will be summarized by treatment group using descriptive statistics for each OIC healthcare utilization category. In addition, the number of procedures (eg enemas, manual disimpactions, treatment of anal fissures, treatment of bowel necrosis, and other) will also be summarized by treatment group using descriptive statistics.

12.2.3 Interim analyses

No interim analysis is planned.

12.3 Determination of sample size

No formal sample size calculation was performed for this long-term safety study. The sample size determination is based on the regulatory exposure requirement (ICH E1 (1994)) that at least 300 patients need to complete 6-months of treatment with NKTR-118 25 mg and of those at least 100 patients need to complete 12-months of treatment with NKTR-118 25 mg. The number of patients randomized may increase or decrease in order to meet these exposure requirements.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The PI is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.5.**

In the case of a medical emergency the investigator should contact the following personnel below:

Name	Role in the study	Address & telephone number
Dr. [redacted]	North America (NA) Study Physician – Responsible for protocol implementation in US & Canada	[redacted] [redacted] [redacted]560 Tel: [redacted] Fax: [redacted] 24 hour urgent medical contact: Tel: [redacted]
Dr. [redacted]	Europe Study Physician – Responsible for protocol implementation in Europe	[redacted] [redacted] [redacted] [redacted] Tel: [redacted] Fax: [redacted] 24 hour urgent medical contact: Tel: [redacted]
Dr. [redacted]	Australia Study Physician - Responsible for protocol implementation in Australia	[redacted] [redacted] [redacted] Tel: [redacted] Fax: [redacted] 24 hour urgent medical contact: Tel: [redacted]
Quintiles Lifecycle Safety	SAE reporting (US)	Tel: [redacted] Fax: [redacted]
Quintiles Lifecycle Safety	SAE reporting (other countries)	Please refer to study-specific Safety Handling Plan
Other contact information		
Quintiles Laboratories (QLAB)	Central laboratory	[redacted] [redacted] [redacted] [redacted] [redacted] Tel: [redacted]

Name	Role in the study	Address & telephone number
eRT (ECG laboratory)	Central ECG laboratory	[redacted] Tel: [redacted]
Fisher Clinical Services	Packaging and distribution; Study drug return and destruction	[redacted] Tel: [redacted]
Perceptive Informatics	Patient randomization and trial supply management	[redacted] Tel: [redacted]
PHT Corporation	eDiary	[redacted] Tel (toll free): [redacted] Tel: [redacted] Fax: [redacted]
Bracket Global	Scale user agreements and acquisitions; Rater training; and translations	[redacted] Tel: [redacted]

13.2 Overdose

For the NKTR-118 program, overdose is defined as a dose ingested (or taken via any other route), confirmed by the patient (if possible), in excess of the total daily dose specified for the patient in their treatment group of the protocol. All reports of overdose (with or without associated AEs) are to be collected.

No cases of overdose have been previously reported with NKTR-118. No specific antidote for overdose with NKTR-118 has been identified to date.

If a patient on opioid therapy receives an overdose with NKTR-118, the patient should be monitored closely for evidence of opioid withdrawal symptoms and reversal of central analgesic effect. In cases of known or suspected overdose, symptomatic treatment as well as monitoring of vital functions should be performed. In cases of severe intoxication, intensive care procedures are recommended. Close medical supervision and monitoring should be continued until the patient recovers.

For recording purposes:

- If an overdose is reported during the course of a study, the patient is evaluated by the investigator/site staff to determine whether an SAE, non-serious AE, or no symptoms have been experienced after the overdose has been taken.

- If the patient experiences an overdose with an associated SAE, the investigator/site staff will capture details of the SAE and associated information on OVERDOSE, AELOG, and SAE modules in the eCRF.

- If the patient experiences an overdose with an associated non-serious AE, the investigator/site staff will capture details of the non-serious AE and associated information on OVERDOSE and AELOG modules in the eCRF.

- If the patient experiences an overdose with no symptoms, the investigator/site staff will capture details of the overdose and associated information on OVERDOSE module only in the eCRF.

- The OVERDOSE module (found in Module Package Library) is the preferred way of collecting overdose information. If the OVERDOSE module cannot be used, for example, if a CRO is managing the study and is unable to use the module, the Clinical Study Overdose template, may be used. This form is also used if the overdose occurred in a person not enrolled in the study, eg, accidental ingestion by a relative of the patient.

For reporting purposes:

- If an overdose occurs in the course of an AstraZeneca study, the investigators/site staff inform appropriate AstraZeneca representatives immediately, but no later than the end of the next business day of when he or she becomes aware of it.

- The designated AstraZeneca representative or its representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety Data Entry Site (DES).

- The following timelines will apply on reports of overdose:

  - Fatal/life-threatening SAEs are sent to DES within 1 calendar day of initial notification of the overdose.

- Other SAEs are sent to DES within 4 calendar days of initial notification of the overdose.

- Overdoses with no symptoms or with associated non-serious AEs are sent to DES within 5 calendar days of initial notification of the overdose.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca or its representative on the pregnancy form. The outcomes of any conception occurring from the date of the first dose until 12 weeks after the date of last dose must be followed up and documented.

13.3.1 Maternal exposure

Requirements for contraception in WOCBP are specified in Inclusion Criterion #7 (see Section 4.1).

If a patient becomes pregnant during the course of the study, IP should be discontinued immediately.

In clinical studies, when a study participant becomes pregnant, the PREGREP module is used to report the pregnancy, and the PREGOUT module is used to record the outcome.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects, spontaneous miscarriages or ectopic pregnancy should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives **within 1 day,** ie, immediately, but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.3.5 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure

Male patients must refrain from fathering a child or donating sperm during the study and 12 weeks following the last dose, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated. Male patients who are sexually active must use a barrier (condom with spermicide) method of contraception from the first dose of IP until 12 weeks after their last dose.

Pregnancy of the patients' partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented. In addition, whenever possible, efforts should be made to complete the PREGREP and PREGOUT modules (see Section 13.3.1).

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives **within 1 day** ie, immediately, but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.3.5 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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Clinical Study Protocol Appendix B

Drug Substance	NKTR-118
Study Code	D3820C00008
Edition Number	1.0
Date	[redacted]

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	NKTR-118
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	NKTR-118
Study Code	D3820C00008
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix D
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the NKTR-118 clinical development programme to explore how genetic variations may affect the clinical parameters associated with NKTR-118. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest genes or gene categories as candidates for influencing not only response to NKTR-118 and/or agents used in combination or as comparators but also susceptibility to Opioid-Induced Constipation (OIC) for which NKTR-118 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to Opioid-Induced Constipation (OIC).

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) and/or susceptibility to Opioid-Induced Constipation (OIC) and/or agents used in combination and/or as comparators.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All patients enrolled in countries/centres who approve this genetic research will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, patients must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant

- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

3.1.4 Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at the randomization visit (post-randomization). Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at the randomization visit, it may be taken at any subsequent visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored up to a maximum of 25years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrollment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results

with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

Genetic informed consent must be obtained prior to collection of the genetic sample.

4.2 Subject data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7. LIST OF REFERENCES

Not applicable.

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Clinical Study Protocol Appendix E	
Drug Substance	NKTR-118
Study Code	D3820C00008
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Date	[redacted]

Appendix E
Guidelines for Required Colorectal Cancer Screening

1. GUIDELINES FOR REQUIRED COLORECTAL CANCER SCREENING

Patients must comply with the colorectal cancer (CRC) screening criteria as specified below. These criteria are modified from American College of Gastroenterology Guidelines for Colorectal Cancer Screening (Rex et al., 2000, Rex et al. 2009) and are intended to make a reasonable and practical good faith effort to rule out underlying colorectal malignancy as a potential contributor to constipation symptoms and to avoid enrolling patients with underlying malignancy into prolonged clinical trials.

Patients are classified as having a **high risk** for CRC if they have at least a single first degree relative previously diagnosed with CRC or advanced adenoma (adenoma >1 cm in size, or high grade dysplasia or villous elements) before age 60 or at least 2 first degree relatives with CRC or advanced adenoma (diagnosed at any age). All other patients are considered to have **average risk** for CRC. First degree relative is defined as a sibling, child or parent, either living or deceased.

Any patient with **average risk (i.e. no family history) for CRC**, regardless of their age, who has had a colonoscopy within 10 years, or a barium enema, flexible sigmoidoscopy, or virtual colonoscopy within 5 years of study start that was normal does not require additional testing.

Patients with **average risk for CRC who are <50 years old** can participate without additional testing. The respective age cut-off for African-American subjects is <45 years of age.

Patients with **average risk for CRC who are ≥50 years old** (and who have not had a colonoscopy within 10 years, or barium enema, flexible sigmoidoscopy or virtual colonoscopy within 5 years from the study start) will be asked to provide a stool sample for a fecal immunochemical test (FIT). If FIT is negative, the patient may participate in the study. If FIT is positive, the patient must have an appropriate evaluation for colorectal cancer with colonoscopy or other appropriate imaging modality (Rex et al.,2000; Rex et al., 2009) and provide documentation for negative results before he/she can be re-screened for the study. The respective age cut-off for required FIT in African-American subjects is ≥45 years of age.

Patients with **high risk for CRC** must have had colonoscopy **or** (double contrast barium enema **AND** flexible sigmoidoscopy), or virtual colonoscopy at least within 5 years from the screening visit or they are not eligible to participate in the study.

2. LIST OF REFERENCES

Rex et al 2000
Rex DK, Johnson DA, Lieberman DA, Burt RW, Sonnenberg A. Colorectal cancer prevention 2000: screening recommendations of the American College of Gastroenterology. Am J Gastroenterol 2000;95(4):868-77.

Rex et al 2009
Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American College of Gastroenterology guidelines for colorectal cancer screening 2008. Am J Gastroenterol 2009;104:739-50.

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Clinical Study Protocol Appendix F	
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Appendix F
Guidelines for Determination of Laxative Response Status

1. GUIDELINES FOR DETERMINATION OF LAXATIVE RESPONSE STATUS

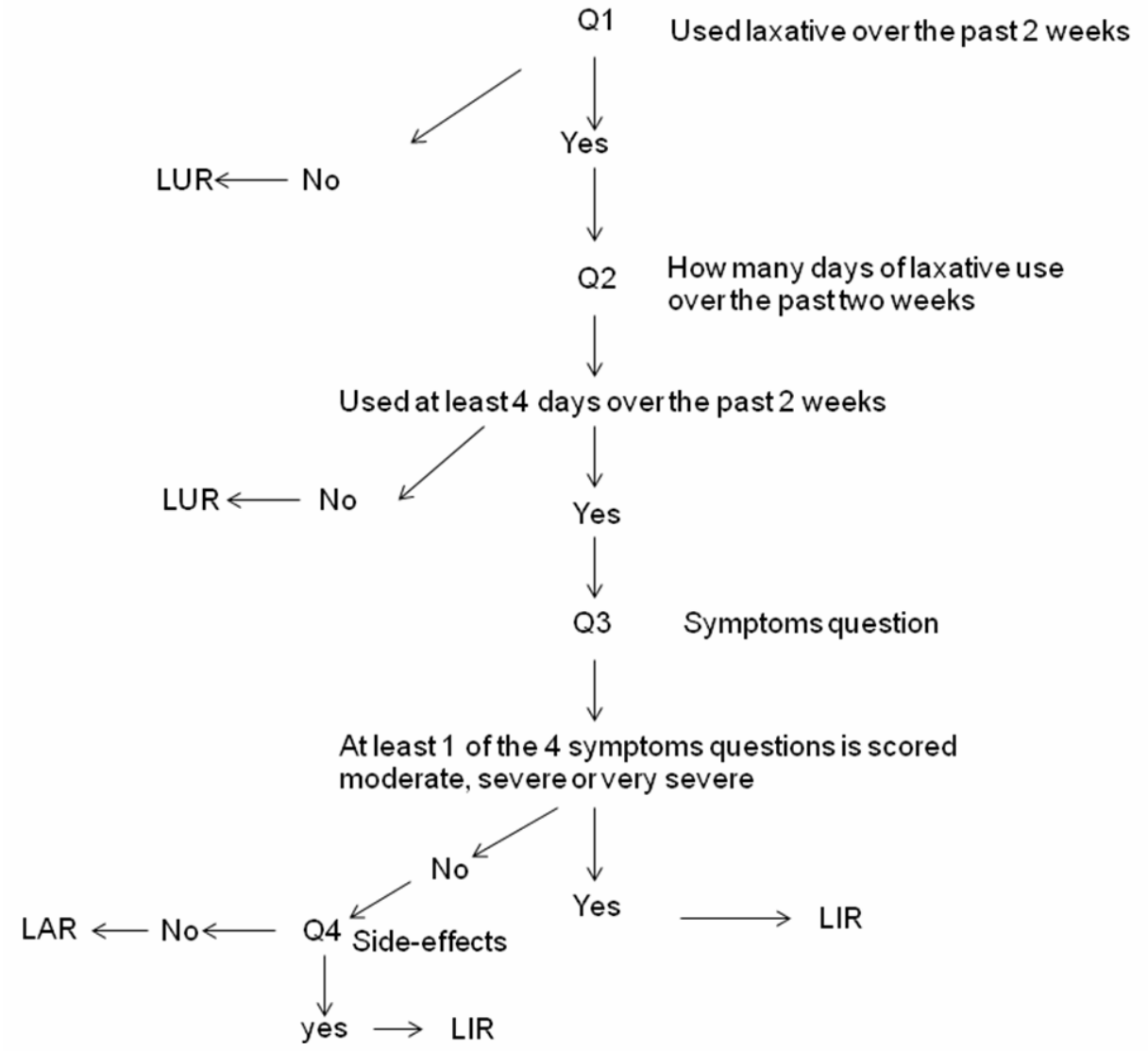
At the Screening visit, each patient's laxative response status will be determined based on 4 questions which explore the frequency of laxative use, constipation symptom severity, and laxative side-effects during the previous 2 weeks. The patients will be classified as LIR, LAR, or LUR based on their answers. Patients who report having used laxatives over the previous 2 weeks will be asked about the frequency of laxative use (total days used) and constipation symptom severity.

- If the patient reports having used laxative(s) on a minimum of 4 days with continued moderate, severe, or very severe stool symptoms in response to at least 1 of the symptom questions, he/she will be classified as LIR. In addition, patients who report side-effects from laxatives will be classified as LIR.

- If the patient reports having used laxative(s) on a minimum of 4 days and reports absent or minimal constipation symptoms (as defined above) over the previous 2 weeks and no associated side-effects from laxatives, he/she will be classified as LAR.

- If the patient reports no use of laxatives over the previous 2 weeks, or reports infrequent use, as defined by less than 4 daily laxative uses over the previous 2 weeks, he/she will be classified as LUR.

Figure 1 Determination of Laxative Response Status



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Clinical Study Protocol Appendix G	
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Appendix G
Child-Pugh Classification

1. CRITERIA FOR CHILD-PUGH CLASSIFICATION

Table 1 Criteria for Child-Pugh Classification

	Points Scored for Observed Findings		
	1	**2**	**3**
Encephalopathy grade*	none	1 or 2	3 or 4
Ascites	absent	slight	moderate
Serum bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, sec prolonged	<4	4 to 6	>6

*Grade 0: normal consciousness, personality, neurological examination
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity
Grade 4: unrousable coma, no personality/behavior, decerebrate

Mild=5 or 6 points; Moderate=7 to 9 points; Severe =10 to 15 points

2. LIST OF REFERENCES

U.S. Department of Health and Human Services, Food and Drug Administration, 2003
U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling. May 2003:14.

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Clinical Study Protocol Appendix H	
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Appendix H
Morphine Equivalents Conversion Chart

1. MORPHINE EQUIVALENTS CONVERSION CHART

Table 1 Dose Equivalents for Opioid Analgesics

Oral Dose (mg)	Analgesic	Parenteral Dose (mg)	Oral Morphine Equivalents (mg)
15	Morphine	5	15
100	Codeine	60	15
-	Fentanyl[a]	0.1 (intravenous)	15
10	Hydrocodone	-	15
4	Hydromorphone	1.5	15
2	Levorphanol	1	15
150	Meperidine	50	15
5	Methadone	5	15
10	Oxycodone	-	15
5	Oxymorphone	1	15
100	Propoxyphene	-	15
60	Tapentadol	-	15
67.5	Tramadol	-	15

Note: All doses listed in the above chart will be regarded as equianalgesic. For example, 10 mg of oral hydrocodone corresponds to 15 mg of oral morphine equivalents. And one mg of parenteral oxymorphone is considered to be equivalent to 15 mg of oral morphine.

[a] For the 72 hr fentanyl patch (25 µg/hr), the equianalgesic daily dose of oral morphine will be considered to be 15 mg every 4 hh OR 45 mg BID of MS-Contin (i.e., 90 mg/day of morphine). For transmucosal fentanyl (i.e., the fentanyl "lollipop"), an 800 µg dose will be regarded as equivalent to 30 mg of oral morphine.

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Clinical Study Protocol Appendix I	
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Appendix I
Highly Effective Forms of Birth Control

1. HIGHLY EFFECTIVE FORMS OF BIRTH CONTROL

1. Total sexual abstinence (for the total duration of the trial including the followup period)
2. Vasectomized sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
3. Tubal occlusion
4. Intra-uterine Device (provided that coils are copper-banded)
5. Levonorgestrel Intrauterine System (e.g. Mirena)
6. Medroxyprogesterone injections (Depo-Provera)
7. Etonogestrel implants (Implanon, Norplan)
8. Normal and low dose combined oral pills
9. Norelgestromin / ethinylestradiol transdermal system
10. Intravaginal device (e.g., ethinylestradiol and etonogestrel)
11. Cerazette (desogestrel)

In addition to the use of a highly effective form of birth control, WOCBP are instructed to use a barrier method of contraception during sexual intercourse (female or male condom).

The following methods are considered **NOT** to be highly effective and are therefore not acceptable contraceptive methods in NKTR-118 trials

1. Triphasic combined oral contraceptives
2. All progesterone only pills, except Cerazette
3. All barrier methods, if intended to be used alone
4. Non-copper containing IUDs
5. Fertility awareness methods
6. Coitus interruptus

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Clinical Study Protocol Appendix J	
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Appendix J
Drugs that prolong QT/QTc interval

1. DRUGS THAT PROLONG QT/QTC INTERVAL

This list should not be considered comprehensive therefore investigators need to use their judgment when reviewing the medication list from individual patients and restrict patients who must stay on drugs that may increase the QT interval.

Table 1 Drugs that Prolong QT/QTc Interval

Concomitant Medication	Class
Disopyramide	Antiarrhythmic 1A
Procainamide	Antiarrhythmic 1A
Quinidine	Antiarrhythmic 1A
Mexiletine	Antiarrhythmic 1B
Propafenone	Antiarrhythmic 1C
Flecainide	Antiarrhythmic 1C
Amiodarone	Antiarrhythmic III
Dofetilide	Antiarrhythmic III
Ibutilide	Antiarrhythmic III
Sotalol	β blocking agent III
Bepridil	Ca channel blocker IV
Metoclopramide	Prokinetic
Dolasetron	Anti-emetic
Granisetron	Anti-emetic
Ondansetron	Anti-emetic
Droperidol	Anti-emetic
Levomethadyl	Opioid agonist
Methadone	Opioid agonist
Chlorpromazine	Antipsychotic
Haloperidol	Antipsychotic
Pimozide	Antipsychotic
Thioridazine	Antipsychotic
Risperidone	Antipsychotic
Ziprasidone	Antipsychotic
Amitriptyline	Antidepressant
Nortriptyline	Antidepressant
Protriptyline	Antidepressant
Desipramine	Antidepressant

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Clinical Study Protocol Appendix K	
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Appendix K

Actions required in cases of combined increase of Aminotransferase and Total Bilirubin - Hy's Law

1. ACTIONS REQUIRED IN CASES OF AST OR ALT ≥ 3X ULN OR TBL ≥ 2X ULN

The Investigator is responsible for, without delay, determining whether the subject meets potential Hy's law (PHL) criteria; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe.

1.1 Identification

In cases of AST or ALT ≥ 3x ULN or TBL ≥ 2x ULN, please follow the instructions below.

For studies using central laboratories:

- When a subject has an AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit, the central laboratory will immediately send an alert to the Investigator (also sent to the AstraZeneca representative)

- If the Quintiles study team or AZ representative are made aware that a local laboratory sample meeting PHL criteria was collected outside of the central laboratory, eg local hospital, the Quintiles study team will:

  - Request the investigative site to conduct a repeat test with the central laboratory

  - Instruct the Investigator to complete the appropriate laboratory CRF modules with the original laboratory test result.

For studies using local laboratories and for laboratory samples collected outside scheduled study visits, eg, at a local hospital the Investigator reviews each laboratory report to identify and notify the Quintiles study team and/or AZ representative when a subject has an increase in AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit.

1.2 Follow-up

1.2.1 Potential Hy's Law Criteria not met

If the Investigator determines that the subject **has not** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- The Investigator informs the Quintiles study team and/or AZ representative that the subject has not met PHL criteria
- The Investigator performs follow-up on subsequent laboratory results according to the guidance provided in the CSP.

1.2.2 Potential Hy's Law Criteria met

If the Investigator determines that the subject **has** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- The Investigator immediately contacts the appropriate Quintiles representative who will then inform the AZ study team
- The Quintiles Study Physician contacts the Investigator, and the AZ representative if appropriate, to provide guidance, discuss and agree with the Investigator an approach for the study subject's follow-up and the continuous review of data
- The Investigator will follow the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated, by conducting repeated testing and observations. To investigate the etiology of the event and establish if another explanation/ alternative cause other than Drug Induced Liver Injury (DILI) caused by the Investigational Product (IP) is possible, the Investigator will also perform diagnostic investigations as discussed with the Quintiles Study Physician
- The Investigator will complete the Liver CRF Modules. The Investigator and the Quintiles Study Physician are in continuous contact for update on follow-up status and approach. They will agree on the appropriate time for review of the compiled information
- If at any time during follow-up the Investigator (in consultation with the Quintiles Study Physician) determines that the PHL case meets serious criteria, it is reported as an SAE using standard reporting procedures and referred for immediate review and assessment.

1.3 Review and Assessment

The Quintiles Study Physician is responsible for arranging a review to reach agreement on whether there is an alternative explanation for the elevations in liver biochemistry other than

DILI caused by the IP, which should take place as soon as possible and not later than 3 weeks after the biochemistry data for the PHL case was made available to the Investigator.

If there is an agreed alternative explanation for the AST or ALT **and TBL** elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE. If the alternative explanation is **not** an AE, the Investigator will record the alternative explanation on the appropriate CRF.

If the alternative explanation is an AE or an SAE it should be recorded on the AE and SAE CRF accordingly and handled according to AZ standard processes.

If it is agreed that there is **no** other explanation that would explain the AST or ALT and TBL elevations:

- The Investigator reports the HL case (reported term 'Hy's Law') as an SAE according to AZ standard processes.
- The 'Medically Important' serious criterion is used if no other serious criteria apply
- As there is no apparent explanation for the HL case other than DILI to the IP, the case is assigned a causality assessment of related.

If, despite Investigator attempts to conduct follow-up according to agreed approach and CSP guidance, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for a HL case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made.

2. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf