AstraZeneca

Revised Clinical Study Protocol

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A Randomized, Double-Blind, Placebo-Controlled 12-Week Extension Study to Assess the Safety and Tolerability of NKTR-118 in Patients with Non-Cancer-Related Pain and Opioid-Induced Constipation (OIC)

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Quintiles Global Project Manager [redacted]

Date

[redacted]

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	[redacted]		

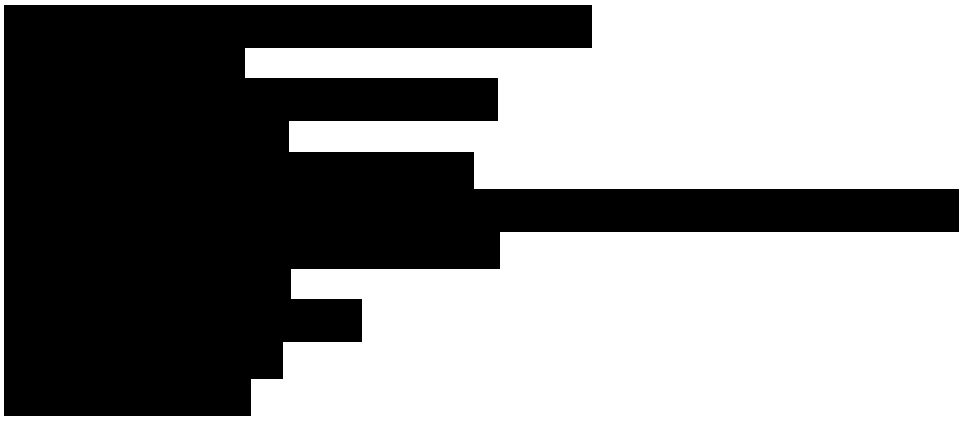
Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Randomized, Double-Blind, Placebo-Controlled 12-Week Extension Study to Assess the Safety and Tolerability of NKTR-118 in Patients with Non-Cancer-Related Pain and Opioid-Induced Constipation (OIC)

National Co-ordinating Investigator



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). Up to 630 randomized patients could potentially participate in this study. Approximately 120 centers will participate in the study.

Study period		Phase of development
Estimated date of first patient enrolled	[redacted]	III
Estimated date of last patient completed	[redacted]	

Objectives

Primary objective:

- To compare NKTR-118 12.5 and 25 mg with placebo regarding long-term safety and tolerability in the treatment of opioid-induced constipation (OIC) using descriptive statistics.

Secondary objectives:

- To assess the impact of NKTR-118 12.5 and 25 mg on symptoms of constipation and quality of life.

Exploratory objectives:

- To assess patient health status index and healthcare resource utilization.

Study design

This is a 12-week extension of the Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group 12 week study D3820C00004 to evaluate the safety and tolerability of NKTR-118 12.5 and 25 mg and placebo in the treatment of OIC in patients with non-cancer-related pain. Patients will continue on their randomized dose from the D3820C00004 study. Patients who successfully complete the 12-week extension study may be eligible to participate in a 52-week long-term safety extension study.

Target subject population

Patients who successfully completed the D3820C00004 study will be eligible to participate.

Investigational product, dosage and mode of administration

NKTR-118 12.5 and 25 mg tablets.

Comparator, dosage and mode of administration

Matching placebo tablets.

Duration of treatment

The study duration will be up to 14 weeks, consisting of a 12-week treatment period, and a follow-up visit 2 weeks after the last dose of study drug.

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
  - Change from baseline in mean daily prescribed opioid dose
  - Mean bisacodyl dose per week
  - Change from baseline in Numeric Rating Scale (NRS) pain score
  - Observed 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)
- **Efficacy**

  Additional secondary efficacy variables:
  - Change from baseline in Patient Assessment of Constipation Symptoms (PAC-SYM)
  - Change from baseline in Patient Assessment of Constipation Quality of Life (PAC-QOL)
- **Health economics**
  - Data on the Euroqol 5 Dimension (EQ-5D) questionnaire for Weeks 4 and 12.
  - Data on OIC healthcare resource utilization

Statistical methods

This is a general evaluation of safety and tolerability. Therefore, no statistical testing will be conducted. Differences between NKTR-118 12.5 and 25 mg and placebo with respect to the evaluation of long-term safety, tolerability, and efficacy 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.

The efficacy analyses will be based on a modified Intent-to-Treat (ITT) analysis set that will include all randomized patients who received at least 1 dose of study drug and have at least 1 post-baseline efficacy measurement (PAC-SYM or PAC-QOL).

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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
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
DBP	Diastolic blood pressure

Abbreviation or special term	Explanation
DEA	Drug Enforcement Administration
dECG	Digital electrocardiogram
DES	(Patient safety) data entry site
DM	Data management
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
EDTA	Ethylenediaminetetraacetic acid
ePRO	Electronic patient reported outcome
EQ-5D	Euroqol 5 Dimension Instrument
ER	Emergency room
eRT	eResearch Technology
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practices
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
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational product
IPs	Investigational products
IRB	Institutional Review Board

Abbreviation or special term	Explanation
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
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
NA	North America
NRS	Numeric Rating Scale
OIC	Opioid-induced constipation
PAC-QOL	Patient Assessment of Constipation Quality of Life
PAC-SYM	Patient Assessment of Constipation Symptoms
PD	Pharmacodynamic
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
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 studying the long term effect 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 12.5 and 25 mg when treatment is extended over a treatment period of 6 months. The patients enrolling in this study will be participants in the AstraZenenca pivotal Phase III study who are willing to continue the treatment they are receiving in the pivotal study for another 12 weeks. The duration of the Phase III pivotal study is 12 weeks; thus, combined, the entire treatment period for those participating in the current study will be 24 weeks (6 months). 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 is generally safe and well tolerated in the treatment of OIC over a 6-month period.

1.3 Rationale for conducting this study

The goal of this Phase III study to is demonstrate that 6 month administration of NKTR-118 is generally safe and well-tolerated 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 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 6.3.14.3 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 Numeric 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 period of 6 months. Previous studies have administered NKTR-118 for up to 4 weeks, and the planned Phase III study will administer NKTR-118 for 12 weeks. 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 enrollment, Week 12, and Week 14.

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 6.3.14.2 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 and it is also possible that the patient's constipation symptoms could worsen or AEs could occur. Potential risks of receiving placebo or ineffective medication for 6 months in this population are expected to be low given the Phase II study results. Only those patients who have tolerated 3 months of treatment in the pivotal protocol will be randomized. Furthermore, 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. Additional guidance is provided on the use of an enema if bisacodyl is ineffective.

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 for some patients who participate in this study. Participation in the active treatment group may provide symptomatic relief from OIC for the duration of the study. After the end of the study, the patient may be offered an opportunity to participate in a 52-week safety extension 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 compare NKTR-118 12.5 and 25 mg with placebo regarding long-term safety and tolerability in the treatment of OIC using descriptive statistics.

2.2 Secondary objectives

The secondary objectives are to assess the impact of NKTR-118 12.5 and 25 mg on symptoms of constipation and quality of life.

2.3 Exploratory objectives

The exploratory objectives are to assess patient health status index and 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 12-week extension of the Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group 12-week study D3820C00004 to evaluate the safety and tolerability of NKTR-118 12.5 and 25 mg and placebo 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). Patients will continue on their randomized doses from the D3820C00004 study without unblinding. The study duration will be up to 14 weeks, consisting of a 12-week treatment period, and a follow-up visit 2 weeks after the last dose of study drug. Patients who successfully complete the 12-week treatment period may be eligible to participate in a 52-week long-term safety extension study. Up to 630 randomized patients could potentially participate in this study. Approximately 120 centers will participate in the study.

Patients will sign the informed consent at the enrollment visit (Visit 1), which will correspond with the last treatment visit in the previous study D3820C00004. Assessments at Visit 1 will be similar to those at the last treatment visit in the previous study.

To be eligible for the current study, patients must continue to fulfill all inclusion/exclusion (I/E) requirements of study D3820C00004. Demographics, medical and surgical history, and laxative tolerance status will be obtained from study D3820C00004.

Unlike study D3820C00004, the present study will not utilize an eDiary device. The NRS for pain will be completed on a SitePad device at the clinic. Use of bisacodyl as a rescue medication will be assessed by pill count of returned bisacodyl at study visits. In addition, 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.

The first dose of study drug in the current study will be taken by the patient at home on Day 2 (on Day 1 patients will have taken their last dose of study drug for study D3820C00004).

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 recognized that some patients may have their pain managed by personal physicians who are not connected with the study. In these cases, patients will be asked to notify their personal physicians of their participation in the study, and to ask their physicians to notify the study investigator should a change in their pain control regimen be made.

As in study D3820C00004 patients will be prohibited from using any laxatives or other bowel regimens, with the exception of bisacodyl as rescue medication if a bowel movement (BM) has not occurred within at least 72 hours of the last recorded BM.

Unless there is a need for urgent intervention, patients will not be allowed to take any medication for pain control or treatment of constipation, other than their maintenance opioid regimen and approved opioid medication for breakthrough pain, and bisacodyl, 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).

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 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. Any patient who is obstipated and/or has fecal impaction must not be enrolled (see Section 4.2).

Study assessments include:

- Modified Himmelsbach scale to assess centrally mediated opioid withdrawal effects at selected time points throughout the study
- Patient reported outcome (PRO) assessments (Patient Assessment of Constipation Symptoms [PAC-SYM], Patient Assessment of Constipation Quality of Life [PAC-QOL], Euroqol 5 Dimension Instrument [EQ-5D], and NRS [for pain]). The PAC-SYM, PAC-QOL, and EQ-5D, will be completed at selected time points from Visit 1 on. The NRS (for pain) will be completed at enrollment and throughout the study, excluding the follow-up visit (Visit 5). Patients will fill out these questionnaires in the same manner as was done for study D3820C00004, using an electronic device called a SitePad at the study center, and will be reminded that they are to answer the questions on their own, without any help from family or study staff. In addition, for visits after Visit 1, the questionnaires are to be filled out at the start of the relevant visits, prior to any investigations or discussions about their symptoms with the study staff. (An exception to this is made for Visit 1, since only enrolled patients will fill out the questionnaires and interaction with study staff will be necessary to determine whether enrollment criteria have been met.)
- Columbia-Suicide Severity Rating Scale (C-SSRS) throughout the study
- OIC Healthcare Resource Utilization assessed at selected visits.
- Recording of concomitant medications (other than enema rescue medication or opioid medication) throughout the study
- Recording of daily maintenance opioid regimen and opioid medication for breakthrough pain throughout the study
- Recording of AEs throughout the study
- Routine safety laboratories (hematology, chemistry, and total cholesterol) and urinalysis (U/A) and clinical assessments at enrollment and at selected time points throughout the study
- Triplicate ECGs at enrollment and at Week 12; single ECG at follow-up.
- Vital signs and physical examination at enrollment and at selected time points throughout the study

- Pregnancy test for women of childbearing potential (WOCBP) at enrollment and selected time points throughout the study

3.1.1 Visit 1 (Enrollment)/Start of Double-Blind Treatment Period

Patients will be asked to bring prescription(s) and/or clearly labeled bottle(s) of opioid medication with them to Visit 1 for confirmation of their daily maintenance and breakthrough pain opioid dosing regimens. Patients will also be instructed that should they experience a change in their daily maintenance or breakthrough pain opioid 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.

Patients will be reminded that they are not to take any laxative or other bowel regimens including herbal products and prune juice (see prohibited medications, Section 5.6) throughout the 12-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. Bisacodyl for use as rescue medication will be dispensed to patients at each visit, from Visit 1 through Visit 3. Patients will be instructed on the guidelines for rescue bisacodyl use. Patients will be asked to return unused bisacodyl at each subsequent visit. Bisacodyl use will be determined at each visit by counting the number of unused bisacodyl tablets returned.

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 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.

Patients will have taken their last dose of study drug in study D3820C00004 at home on the morning of Visit 1 prior to coming to the clinic and will receive their initial supply of study drug for study D3820C00007 at Visit 1. They will therefore take their first dose of study drug for study D3820C00007 on the morning of Day 2. For subsequent visits through Visit 3, patients will self-administer the study drug in the morning (per their usual routine) prior to coming to the study center. At Visit 4, patients will be asked to hold their morning dose of study drug and bring study drug with them to the visit.

Patients who discontinue prematurely from the study after participating in Visit 1 and receiving at least 1 dose of study drug (starting on Day 2) will be asked to return to the study center for an early termination (ET) visit during which unused study drug will be returned, and assessments normally scheduled for Visit 4 (Day 85) will be obtained. This ET visit should be scheduled as soon as possible after the patient discontinues from the study (see Section 5.8).

The following procedures will be performed at Visit 1:

- Signed informed consent prior to any study-related procedures

- Review of I/E criteria
- Patients will be shown how to complete the NRS (for pain) using the SitePad at the study site, rather than in the eDiary as had been done for study D3820C00004.
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate electronic case report forms (eCRFs). 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 1, they will be asked to bring it to Visit 2.
- Concomitant medications ongoing at the end of the previous study D3820C00004 will be recorded.
- Pain level (NRS) (average pain over the previous 7 days) will be recorded using the SitePad device.
- AEs ongoing at the end of the previous study D3820C00004, as well as resolved AEs meeting medical history criteria, will be recorded as new medical history.
- Study drug will be dispensed.
- Bisacodyl will be dispensed.
- 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 2 will be made. Patients will be instructed to bring study drug and unused bisacodyl with them to the visit.

Data from the following procedures will be obtained from the previous study D3820C00004:

- Demographics
- Medical and surgical history, including OIC history
- Laxative response status (laxative inadequate responder [LIR], laxative adequate responder [LAR], laxative unknown responder [LUR])
- Complete physical examination (including height, weight, body temperature, respiratory rate) (Visit 8 of previous study). An optional rectal examination may be included at the discretion of the investigator.
- PAC-SYM (Visit 8)

- PAC-QOL (Visit 8)
- EQ-5D (Visit 8)
- OIC Healthcare Resource Utilization questionnaire (Visit 8)
- Sitting blood pressure and pulse must be measured (Visit 8). Please see Section 6.3.13.1 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 (Visit 8)
- A urine sample will be collected for the following: urine drug screen (urine toxicology), urine pregnancy test (WOCBP), and U/A (Visit 8). The urine pregnancy test result must be negative before the patient may continue with the visit and dispensing of study drug.
- Blood samples will be collected for laboratory assessments (clinical chemistry including total cholesterol, and hematology) (Visit 8)
- C-SSRS to assess suicidal risk, ideation, and behavior (Visit 8)
- Modified Himmelsbach scale (Visit 8)

3.1.2 Visit 2 (Week 4, Day 29)

Visit 2 will occur on Day 29 (± 3 days). At Visit 2, the following procedures will be performed:

- PAC-SYM will be completed.
- PAC-QOL will be completed.
- EQ-5D will be completed.
- Pain level (NRS) (average pain over the previous 7 days) will be recorded.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.13.1 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.
- C-SSRS to assess suicidal risk, ideation, and behavior will be completed.
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.

- Enema medication will be asked about and recorded on the enema eCRF.
- Use of concomitant medication (other than enema or opioid medication) since Visit 1 will be recorded. (Note: use of bisacodyl will not be asked about and recorded, but will be determined by pill counts of returned bisacodyl and captured on the bisacodyl accountability eCRF).
- AEs since Visit 1 will be recorded.
- Unused study drug will be returned and the number of unused study drug tablets will be recorded. Patient compliance will be determined.
- Unused bisacodyl will be returned and a new supply of bisacodyl will be dispensed.
- Study drug will be dispensed.
- An appointment for Visit 3 will be made. Patients will be instructed to bring study drug and unused bisacodyl with them to the visit.

3.1.2.1 Visit 3 (Week 8, Day 57)

Visit 3 will occur on Day 57 (±3 days). At Visit 3, the following procedures will be performed:

- Pain level (NRS) (average pain over the previous 7 days) will be recorded.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.13.1 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.
- C-SSRS to assess suicidal risk, ideation, and behavior will be completed.
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of enema medication since Visit 2 will be asked about and recorded on the enema eCRF.
- Use of concomitant medication (other than enema or opioid medication) since Visit 2 will be recorded. (Note: use of bisacodyl will not be asked about and recorded, but will be determined by pill counts of returned bisacodyl and captured on the bisacodyl accountability eCRF).
- AEs since Visit 2 will be recorded.
- Unused study drug will be returned and the number of unused study drug tablets will be recorded. Patient compliance will be determined.

- Unused bisacodyl will be returned and a new supply of bisacodyl will be dispensed.
- Study drug will be dispensed.
- An appointment for Visit 4 (Day 85) will be made. Patients will be instructed to bring study drug, and unused bisacodyl with them to the visit. In addition, patients may be asked if they are interested in participating in a 52-week safety extension study. If offered the opportunity to participate in the 52-week extension study, patients will be instructed not to take their study drug at home on the morning of Visit 4 and will also get a reminder phone call prior to Visit 4 regarding the safety extension study. Patients who plan to enter the safety extension study will also be asked to bring prescription(s) and/or clearly labeled bottle(s) of opioid medication with them to Visit 4 for confirmation of their daily maintenance and breakthrough pain opioid dosing regimens.

3.1.2.2 Visit 4 (Week 12, Day 85)

Visit 4 will occur on Day 85 (±3 days), and will be scheduled in the morning. If a patient who plans to enter the 52-week safety extension study accidentally takes study drug at home on the morning of Visit 4, the patient should be rescheduled to return the next morning for all Visit 4 procedures. If a patient accidentally takes study drug at home on the morning of Visit 4 but does not intend to participate in the 52-week safety extension study, he/she can proceed with Visit 4.

For patients who enter the 52-week safety extension study, Visit 4 will also correspond to the randomization visit for the 52-week safety extension study. The order of procedures will be different for patients who enter the 52-week safety extension study (and the order noted for the safety extension study should be followed). However, all Visit 4 assessments listed below are to be collected, even if not required for the 52-week safety extension study.

At Visit 4 the following procedures will be performed**:**

- PAC-SYM will be completed.
- PAC-QOL will be completed.
- EQ-5D will be completed.
- Pain level (NRS) (average pain over the previous 7 days) will be recorded.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Physical examination including weight, body temperature, and respiratory rate will be performed. This may include optional rectal examination at investigator discretion unless patients enter the safety extension study; a rectal examination is mandatory for patients who enter the safety extension study.

- Sitting blood pressure and pulse must be measured. Please see Section 6.3.13.1 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 [including total cholesterol] and hematology) and serum pregnancy test (WOCBP).
- A urine sample will be collected for the following: urine drug screen (urine toxicology) and U/A.
- C-SSRS to assess suicidal risk, ideation, and behavior will be completed.
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of enema medication since Visit 3 will be asked about and recorded on the enema eCRF.
- Use of concomitant medication (other than enema rescue medication or opioid medication) since Visit 3 will be recorded. (Note: use of bisacodyl will not be asked about and recorded, but will be determined by pill counts of returned bisacodyl and captured on the bisacodyl accountability eCRF).
- AEs since Visit 3 will be recorded.
- Modified Himmelsbach scale will be completed.
- Unused bisacodyl will be returned.
- Unused study drug will be returned and the number of unused study drug tablets will be recorded. Patient compliance will be determined.
- An appointment for Visit 5 (Final Visit, Day 99) will be made for patients who do not participate in the 52-week safety extension study.

Following Visit 4, patients may resume any constipation regimen that they and the investigator feel is appropriate, unless they choose to continue in the 52-week safety extension study. Note: Visit 5 is not required for patients who enter the 52-week safety extension study.

3.1.3 Final Visit (Visit 5, Week 14, Day 99)

Visit 5 will occur on Day 99 (±3 days). At Visit 5, the following procedures will be performed:

- PAC-SYM will be completed.
- PAC-QOL will be completed.
- EQ-5D will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse must be measured. Please see Section 6.3.13.1 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 obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology) and serum pregnancy test (WOCBP).
- C-SSRS to assess suicidal risk, ideation, and behavior will be completed.
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of enema rescue medication since Visit 4 will be recorded.
- Use of concomitant medication (including bisacodyl and other laxative medication with the exception of enema) since Visit 4 will be recorded.
- AEs since Visit 4 will be recorded.

Table 1 Study plan

	Enrollment	Treatment Period		Final	
Week	**0**	**W4**	**W8**	**W12**	**+ 2W**
Visits	**1**	**2**	**3**	**4/ET**	**5**
Study Day	**D1**	**D29**	**D57**	**D85[a]**	**D99[b]**
Visit Window (Days)		**±3**	**±3**	**±3**	**±3**
Informed consent [c]	√				
Demographic information	√[d]				
Inclusion/exclusion criteria	√				
Medical and surgical history (including OIC history)	√[d]				
Complete physical examination (weight, temperature, respiratory rate)	√[d.e]			√[e]	
Sitting blood pressure, pulse[m]	√[d]	√	√	√	√
LIR, LAR, LUR status	√[d]				
Pregnancy test for WOCBP[f]	√[d]			√	√
12-lead ECG[g]	√[d]			√	√
Clinical chemistry and hematology	√[d]			√	√
Total cholesterol	√[d]			√	
Urinalysis[h]	√[d]			√	`
Urine drug screen[i]	√[d]			√	
C-SSRS	√[d]	√	√	√	√
Daily maintenance opioid regimen recorded	√	√	√	√	√
Opioid medication for breakthrough pain recorded	√	√	√	√	√
Enema medication recorded		√	√	√	√
Modified Himmelsbach scale	√[d]			√	
PAC-SYM[j]	√[d]	√		√	√
PAC-QOL[j]	√[d]	√		√	√
Pain Level (NRS)[j]	√	√	√	√	
EQ-5D[j]	√[d]	√		√	√
OIC Healthcare Resource Utilization Assessment[j]	√[d]			√	√

Table 1 Study plan

	Enrollment	Treatment Period		Final	
Week	**0**	**W4**	**W8**	**W12**	**+ 2W**
Visits	**1**	**2**	**3**	**4/ET**	**5**
Study Day	**D1**	**D29**	**D57**	**D85[a]**	**D99[b]**
Visit Window (Days)		**±3**	**±3**	**±3**	**±3**
Concomitant medication (other than enema rescue or opioid medication)[k]	√	√	√	√	√
AEs[l]		√	√	√	√
Dispense study drug	√	√	√		
Return unused study drug		√	√	√	
Dispense bisacodyl	√	√	√		
Return unused bisacodyl		√	√	√	
Make appointment for next visit	√	√	√	√	

AEs Adverse events; C-SSRS Columbia Suicide Severity Scale; D Day; ECG electrocardiogram; ePRO electronic patient reported outcome; EQ-5D Euroqol 5 Dimension Instrument; ET early termination; LAR laxative adequate response; LIR laxative inadequate response; LUR laxative unknown response ; OIC opioid-induced constipation; PAC-QOL Patient Assessment of Constipation Quality of Life; PAC-SYM Patient Assessment of Constipation Symptoms; NRS Numeric Rating Scale; WOCBP women of childbearing potential

[a] Week 12 assessments should be performed at the time of early termination for patients who discontinue early, with the exception that patients who do not receive their first dose of study drug in Study D3820C00007 will not be required to have Week 12 assessments.

[b] Patients who enter the 52-week safety extension study do not need to participate in Visit 5.

[c] Informed consent will be collected at Visit 1 for patients who enroll directly from pivotal study D3820C00004.

[d] Demographics, medical and surgical history, and laxative tolerance status will be obtained from the screening visit of study D3820C00004. Complete physical examination, sitting blood pressure and pulse, PAC-SYM, PAC-QOL, EQ-5D, OIC Healthcare Resource Utilization questionnaire, triplicate ECG, urine sample collection (for urine drug screen [urine toxicology], urine pregnancy test [WOCBP], and urinalysis), blood sample collection (for laboratory assessments [clinical chemistry including total cholesterol, and hematology]), C-SSRS, and Modified Himmelsbach scale will all be obtained from Visit 8 of study D3820C00004.

[e] At enrollment (Visit 1) and Week 12 (Visit 4), physical examination may include optional rectal examination at the discretion of the investigator. However at Visit 4 a rectal examination is mandatory for patients who enter the safety extension study.

[f] A urine pregnancy test will be performed at enrollment (Visit 1). If the urine pregnancy test is positive, it is to be followed up with a serum pregnancy test. A serum pregnancy test will be performed at Visit 4 and Visit 5.

[g] A 12-lead ECG will be repeated in triplicate for all patients at enrollment (Visit 1) and Week 12 (Visit 4). A single 12-lead ECG will be performed at the follow-up visit (Visit 5).

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

[i] 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.

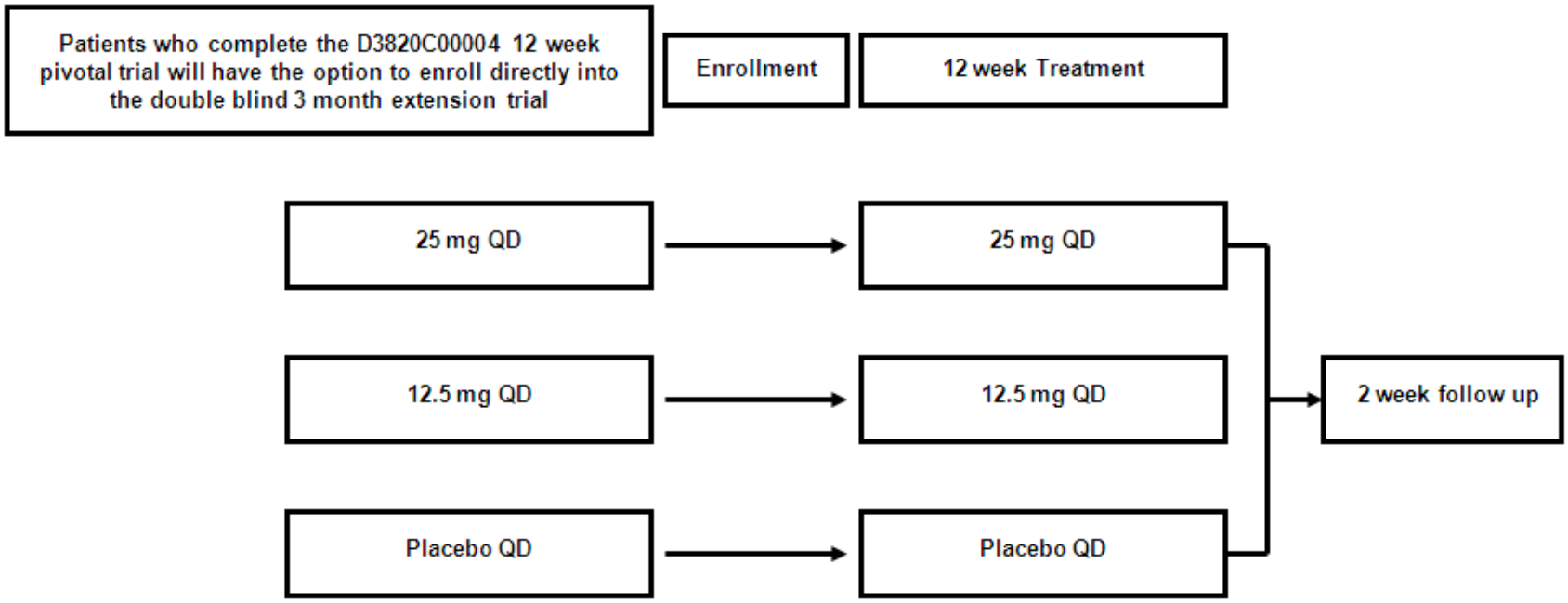
[j] The ePRO questionnaires (PAC-SYM, PAC-QOL, EQ-5D, NRS) are to be completed at the start of relevant visits prior to any investigations or discussions about symptoms with study staff. (An exception to this is made for Visit 1, since interaction with study staff will be necessary to determine whether enrollment criteria have been met. As applicable, the OIC Healthcare Resource Utilization Assessment is to be completed after the ePRO questionnaires, and prior to any investigations or discussions about symptoms with study staff.

[k] Concomitant medications ongoing at the end of the previous study D3820C00004 will be recorded at enrollment. At Visit 5, concomitant medication will include bisacodyl and other laxative medication (with the exception of enema) taken since Visit 4.

[l] AEs ongoing at the end of the previous study D3820C00004, as well as resolved AEs meeting medical history criteria, should be recorded as medical history.

[m] 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 6.3.13.1.

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 12.5 and 25 mg when treatment is extended over a period of 6 months. The patients enrolling in this study will be participants in the AstraZenenca pivotal Phase III study who are willing to continue the treatment they are receiving in the pivotal study for another 12 weeks. Patients will continue on their randomized doses from the pivotal study without unblinding. The duration of the Phase III pivotal study is 12 weeks; thus, combined, the entire treatment period for those participating in the current study will be 24 weeks (6 months).

A placebo comparator (and double-blind design) is chosen to control for normal disease course and other non-specific factors.

The doses of NKTR-118 in the current study (12.5 and 25 mg) were chosen to explore optimal dosing associated with maximal efficacy and minimal side effects. The 12.5 mg dose is included to better understand the minimal effective 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.

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 will continue on their randomized dose from the D3820C00004 study. Interested patients may also have the opportunity to participate in a separate 52-week safety extension study at the completion of the present 12-week safety extension study.

Routine laxative use is prohibited during the treatment period, since these medications could confound the efficacy of NKTR-118. However, patients who do not respond to NKTR-118 or who are receiving placebo 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.

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 at study visits, and specific guidelines for handling possible elevations in liver enzymes are included in the protocol.

4. SUBJECT SELECTION CRITERIA

Each patient should continue to meet all of the inclusion criteria and none of the exclusion criteria for the previous D3820C00004 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. Must have completed the 12-week study D3820C00004 through Visit 8

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

3. Men and women who were between the ages of ≥18 and <85 years at the time of the screening visit for study D3820C00004

4. Continuing to receive 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 E)

5. Willingness to continue abstinence from all laxatives and other bowel regimens including prune juice and herbal products throughout this additional 12-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

6. Male patients who are sexually active must continue to use a double-barrier method of contraception (condom with spermicide) until 12 weeks after their last dose of investigational product (IP). Women of childbearing potential must have a negative pregnancy test and confirmed (by the investigator) continue to use a highly effective form of birth control until 12 weeks after their last dose. Highly effective forms of birth control are listed in Appendix F. 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.

7. Continue to 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 Sitepad device)

8. Outpatient status at enrollment

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 of study D3820C00004 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 had been previously diagnosed by a physician prior to first initiation of opioid therapy and that met the following criteria, were excluded from study D3820C00004 and from the current study:

    - 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 for study D3820C00004 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.

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

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

9. 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

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

11. Patients who had a QTcF >500 msec at the screening visit for study D3820C00004, have a recent history of myocardial infarction within 6 months before enrollment, have symptomatic congestive heart failure, or have any other overt cardiovascular disease.

12. 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 Visit 8 of study D3820C00004 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 for

maintenance treatment of opioid addiction were excluded from study D3820C00004 and are excluded from the present study, however, patients who are receiving methadone for pain management are eligible for participation. The disposition of patients with suspected opiate abuse during the trial will be handled on a case by case basis.

13. Use of prohibited medications as listed in Section 5.6

14. Pregnancy or lactation

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

16. 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)

17. Previous enrollment in the present study or any study with NKTR-118 other than study D3820C00004.

For laboratory test-based exclusion criteria, the investigator must follow the general study discontinuation rules (Section 5.8, Section 6.3.10.2) and adhere to the guidelines describing handling of patients with elevated liver enzymes (Section 6.3.10.2).

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

5. STUDY CONDUCT

5.1 Restrictions during the study

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

5.2 Subject enrollment and randomization

Patients will keep the same randomization number and the same enrollment number that they had in study D3820C00004.

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. Determine patient eligibility. Eligibility will be determined at Visit 1.

If a patient discontinues from participation in the study, then his/her enrollment/randomization code cannot be reused.

5.3 Procedures for handling subjects incorrectly enrolled

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

In cases where patients who do not meet the selection criteria 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

5.4.1 Methods for ensuring blinding

NKTR-118 12.5 and 25 mg tablets will be identical in size and color to their respective placebo tablets. Packaging and labeling of the investigational products (IPs) will be performed in a way to ensure blinding throughout the study. Patients will receive 2 tablets per dose, irrespective of which randomized dose they receive.

No member of the study team in AstraZeneca or its representative, at investigational centers or any contract research organization (CRO) handling data will have access to the randomization scheme during the conduct of the study with the exception of AstraZeneca's Research and Development Supply Chain and Patient Safety. The blinding should remain intact for this study even after unblinding of study D3820C00004.

The randomization schedule for blinding of randomized treatment will be maintained by AstraZeneca and will not be disclosed until after database lock.

5.4.2 Methods for unblinding the study

If a treatment code break is required, this will be done via the interactive voice response system (IVRS). Individual treatment codes, indicating the assigned treatment for each randomized patient, will be available to the investigator(s) or pharmacists from the IVRS. Routines for this will be described in the IVRS user manual that will be provided to each center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. If the treatment code is broken, then the investigator must document and report the action to AstraZeneca or its representative, without revealing the treatment given to the patient to AstraZeneca staff or its representative.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

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 2 bottles of study drug, each containing 35 tablets.

AstraZeneca will provide the study treatment as follows in Table 2**:**

Table 2 Study drug

Investigational product	Dosage form and strength	Manufacturer
NKTR-118	Tablet, 12.5 mg	Pharmaceuticals International, Inc.
NKTR-118	Tablet, 25 mg	Pharmaceuticals International, Inc.
Matching placebo to NKTR-118 12.5 mg	0 mg	Pharmaceuticals International, Inc.
Matching placebo to NKTR-118 25 mg	0 mg	Pharmaceuticals International, Inc.

5.5.2 Doses and treatment regimens

Patients will receive study drug during the 12-week treatment period of the study (Days 2 to 85). Patients will be instructed to take 1 tablet from each bottle 1 hour before eating in the morning.

NKTR-118 or placebo will be administered once daily, as 2 tablets. Patients will receive NKTR-118 12.5 mg, or 25 mg, or placebo, as specified in Table 3.

Table 3 Administration of investigational product

	NKTR-118		
Treatment day	**12.5 mg/day**	**25 mg/day**	**Placebo**
Days 2 to 85	1 x 12.5 mg NKTR-118 tablets 1 x 25 mg placebo tablets	1 x 12.5 mg placebo tablets 1 x 25 mg NKTR-118 tablets	1 x 12.5 mg placebo tablets 1 x 25 mg placebo tablets

5.5.3 Additional study drug

Sites will procure bisacodyl 5 mg tablets for use as laxative rescue medication and will dispense bisacodyl to patients at Visits 1, 2, and 3.

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

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 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)

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 as needed (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 these cases, patients will be asked to notify their personal physicians of their participation in the study, and to ask their physicians to notify the study investigator should a change in their pain control regimen be made.

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

During the treatment period, a 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 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. Any patient who is obstipated and/or has fecal impaction must not be enrolled (see Section 4.2).

During the study, it is advised that the PI be responsible for managing the patient's constipation. Study centers will procure and dispense bisacodyl for use as rescue medication, which will be dispensed to patients at each visit, starting with Visit 1. Patients will be instructed on the guidelines for rescue bisacodyl use. Patients will be asked to return unused bisacodyl at each subsequent visit. Bisacodyl use will be determined at each visit by counting the number of unused bisacodyl tablets returned.

Unless there is a need for urgent intervention, patients will not be allowed to take any additional medication for pain control or treatment of constipation, other than their maintenance opioid regimen and approved opioid medication for breakthrough pain, and bisacodyl, 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). This includes over-the-counter treatments for constipation and pain.

Changes in the opioid regimen may be made to ensure appropriate pain control. Any changes must be recorded in the daily maintenance opioid dosing regimen and/or breakthrough pain medication eCRFs, as appropriate.

The following laxative medications are prohibited on-study; however, they do not constitute an exhaustive list:

- 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

The following opioid antagonists and mixed agonists/antagonists are also prohibited:

- 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:

- 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 section of the eCRF. Compliance with the study drug 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 (2 tablets 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 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. 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 4 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 6.3.10.2. The protocol for handling patients with elevated liver transaminases including guidelines for discontinuing patients is discussed in Section 6.3.10.2).
- Severe non-compliance to the CSP (including dosing regimen with NKTR-118 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)
- 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 assigned dose of 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 6.3.14.2.

Patients who discontinue prematurely from the study after participating in Visit 1 and receiving at least 1 dose of study drug will be asked to return to the study center for an ET visit during which assessments normally scheduled for Visit 4 (Day 85) 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.

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 at the time of the enrollment visit (Visit 1) (refer to the Study Plan, Table 1). Some of these measures will have been obtained in the original pivotal study (D3820C00004) that patients participated in as indicated below:

- Signed informed consent forms (ICFs) will be obtained.
- Demography (date of birth, sex, and race) (obtained from Visit 1 of previous study D3820C00004)
- Review of I/E criteria
- Medical and surgical history (including OIC history) (obtained from Visit 1 of previous study D3820C00004). Any ongoing AEs at the end of the previous study, as well as resolved AEs meeting medical history criteria, should also be entered as medical history in this study.
- Complete physical examination (including height, weight) (obtained from Visit 8 of previous study D3820C00004). May include optional rectal examination at discretion of investigator.
- Vital signs (sitting blood pressure and pulse, body temperature, respiratory rate) (obtained from Visit 8 of previous study D3820C00004)
- LIR, LAR, LUR status (obtained from Visit 1 of previous study D3820C00004)
- PAC-SYM (obtained from Visit 8 of previous study D3820C00004)
- PAC-QOL (obtained from Visit 8 of previous study D3820C00004)
- EQ-5D (obtained from Visit 8 of previous study D3820C00004)
- Pain level (NRS) average over the previous 7 days
- OIC Healthcare Resource Utilization questionnaire (obtained from Visit 8 of previous study D3820C00004)
- Triplicate 12-lead ECG (obtained from Visit 8 of previous study D3820C00004)

- Laboratory assessments (obtained from Visit 8 of previous study D3820C00004)
- Urine drug screen (obtained from Visit 8 of previous study D3820C00004)
- Urine pregnancy test (WOCBP) (obtained from Visit 8 of previous study D3820C00004)
- U/A (obtained from Visit 8 of previous study D3820C00004)
- C-SSRS (obtained from Visit 8 of previous study D3820C00004)
- Modified Himmelsbach scale (obtained from Visit 8 of previous study D3820C00004)
- Concomitant medications ongoing at the end of the previous study D3820C00004
- Daily maintenance opioid dosing regimen and opioid medication for breakthrough pain

6.2.2 Additional procedures including follow-up procedures

Additional procedures (and follow-up procedures) during the visits after enrollment 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 Weeks 4 and 12.
- Mean bisacodyl dose per week for Weeks 4 and 12.
- Change from baseline in the mean NRS pain score for Weeks 4, 8, and 12.
- Observed values and change from baseline in composite score in modified Himmelsbach scale for the evaluation of centrally mediated opioid withdrawal symptoms at Week 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

For patients who do not enroll in an extension study, all AEs will be collected from the time of signature of informed consent to the follow-up visit (Visit 5), 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.

For patients who enroll in an extension study, AEs and SAEs will be collected from the time of signature of informed consent to the last treatment visit (Visit 4), whether or not related to

the IP and must be recorded on the eCRF. Additional AE and SAE reporting will occur in the extension study.

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 collected 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). The 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 #6, 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. Daily maintenance opioid dose and breakthrough opioid pain medication will be recorded on eCRFs at study visits. A home diary will be assigned to each patient to facilitate collection of breakthrough opioid pain usage.

6.3.7 Bisacodyl use

Bisacodyl use will be recorded for each patient on bisacodyl accountability eCRFs at study visits.

6.3.8 NRS

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.

Patients will be asked to complete the NRS at study visits indicating their average pain during the 7 days prior to the visit. The NRS will be completed by patients on the SitePad device provided at the study center. Study staff will provide initial training to patients and will log patients in. 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 1, where some interaction with staff will be necessary in order to ensure that enrollment 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.

6.3.9 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 Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004) and Visit 4 (Week 12). Changes in this scale should generally not be reported as AEs unless standard criteria for AE reporting are otherwise met.

6.3.10 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 4) will be performed as specified in the Study Plan.

Table 4 Laboratory assessments

Hematology	Clinical Chemistry	Urinalysis[f]
B-Hb	S-Albumin	U-Glucose
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]	
B-Monocytes (Absolute and %)	S-Bilirubin, Total	**Urine Drug Screen**
B-Eosinophils (Absolute and %)	BUN	barbiturates
B-Basophils (Absolute and %)	S-Ca	benzodiazepines
B-Platelet count	S-Creatinine	cannabinoids
B- MCV	S-Chloride	cocaine
B- MCH	S-Glucose	methadone
B- MCHC	S-Potassium	methaqualone
B- RDW	S-Sodium	opiates
	Total cholesterol[c]	phencyclidine
	TSH	propoxyphene
	S-Pregnancy test[d]	amphetamine
		tetrahydrocannabinol
	Coagulation	
	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 6.3.10.2).

[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 enrollment (Visit 1) and Week 12 (Visit 4/end of treatment).

[d] A urine pregnancy test will be performed at enrollment (Visit 1); if the urine pregnancy test is positive, it is to be followed up with a serum pregnancy test. A serum pregnancy test will be performed at Visit 4 and Visit 5.

[e] INR is to be assessed during the study if patients meet criteria for significant elevation in liver transaminases (See Section 6.3.10.2).

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

Serum chemistry and hematology tests will be performed on all patients at Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004), Visit 4 (Week 12), and Visit 5 (Week 14, follow-up). Total cholesterol will be assessed at Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004) and Visit 4 (Week 12).

Urine drug screening tests and urinalysis will be performed on all patients at Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004), Visit 4 (Week 12), and anytime during the study, at the discretion of the investigator, to allow appropriate

medical management of the patient. A urine pregnancy test for WOCBP will be performed at Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004). If the urine pregnancy test is positive it is to be followed up with a serum pregnancy test. A serum pregnancy test for WOCBP will be performed at Visit 4 (Week 12) and Visit 5 (Week 14, follow-up).

For blood volume, see Section 7.1.

6.3.10.1 Urine drug screen

As noted above, urine drug screening tests will be performed on all patients at Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004) and Visit 4 (Week 12), and anytime during the study, at the discretion of the investigator, to allow appropriate medical management of the patient. 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.

6.3.10.2 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 G.
- 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.

6.3.11 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) will be performed at Visit 1 (data obtained at the Visit 8 of previous study D3820C00004) and Visit 4. At both visits, this may include an optional rectal examination at the discretion of the investigator, with the exception that at Visit 4 a rectal examination is mandatory for patients who enter the safety extension study.

Significant findings that meet the definition of an AE must be recorded on the AE eCRF.

6.3.12 ECG

6.3.12.1 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 in triplicate at Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004) and Visit 4 (Week 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. A single 12-lead ECG will be performed at Visit 5 (Week 14). The single ECG will be obtained after the patient has been resting in a supine position for at least 10 minutes.

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 ECG 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.

6.3.13 Vital signs

6.3.13.1 Pulse and blood pressure

Blood pressure (sitting) and pulse/heart rate (sitting) must be measured at all study visits (enrollment - data obtained at the Visit 8 of previous study D3820C00004). 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

For management of markedly abnormal heart rates or blood pressures, please refer to Sections 5.8 and 6.3.14.3.

6.3.13.2 Body temperature and respiratory rate

Body temperature and respiratory rate will be measured at Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004) and Visit 4 (Week 12).

6.3.13.3 Weight

Weight will be measured at Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004) and Visit 4 (Week 12).

6.3.14 Other safety assessments

6.3.14.1 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.

6.3.14.2 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.

6.3.14.3 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 6.3.13.1. 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.

6.3.15 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 6.3.14.2)

- 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 (eg, 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 Efficacy

6.4.1 Efficacy variables

The efficacy variables include:

- Change from baseline in PAC-SYM total score and each domain score for Weeks 4, 12, and 14.

- Change from baseline in PAC-QOL total score and each domain score for Weeks 4, 12, and 14.

6.4.1.1 PAC-SYM

The PAC-SYM questionnaire (Frank et al 1999) is a 12-item questionnaire that evaluates the severity of symptoms of constipation in 3 domains (stool, rectal, and abdominal symptoms) on a 5-point Likert scale ranging from 0 (absent) to 4 (very severe) in the 2 weeks (14 days) prior to assessment. The items of the instrument were developed through literature review and patient interviews. The PAC-SYM has been extensively validated for constipation and is available in several languages that facilitate its use in multinational studies. The translations into local languages have been performed according to a linguistic validation process. The questions will take approximately 5 minutes to answer. The patients need to be able to read and to be fluent in the local language. The PAC-SYM will be administered to patients at Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004), Visit 2 (Week 4), Visit 4 (Week 12/early termination), and Visit 5 (Week 14).

The PAC-SYM questionnaire will be completed by patients on the SitePad device provided at the study center. Study staff will log patients in. 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 1, where some interaction with staff will be necessary in order to ensure that enrollment criteria

have been met, patients are to fill out the PAC-SYM questionnaire prior to any interventions or discussions regarding their OIC with the study staff or the investigator.

6.4.1.2 PAC-QOL

The PAC-QOL scale (Marquis et al 2005) is a 28-item self-report instrument designed to evaluate the burden of constipation on patients' everyday functioning and well-being in the 2 weeks (14 days) prior to assessment. Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). The development of the PAC-QOL items was informed by both clinician and patient focus groups and the primary validation study evaluated use of the PAC-QOL in the US, Netherlands, Belgium, Canada, and Australia using French and Dutch translations in addition to the original English language based instrument (Marquis et al 2005). The questions will take approximately 5 minutes to answer. The patients need to be able to read and to be fluent in the local language. The instrument can be used to generate an overall score, but is also reported to assess 4 specific constipation-related domains including: 1) Worries and concerns (11 items), 2) Physical discomfort (4 items), 3) Psychosocial discomfort (8 items), and 4) Satisfaction (5 items). The PAC-QOL will be administered to patients at Visit 1 (enrollment - data obtained at the Visit 8 of previous study D3820C00004), Visit 2 (Week 4), Visit 4 (Week 12/early termination), and Visit 5 (Week 14).

The PAC-QOL questionnaire will be completed by patients on the SitePad device provided at the study center. Study staff will log patients in. 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 1, where some interaction with staff will be necessary in order to ensure that enrollment criteria have been met, patients are to fill out the PAC-QOL questionnaire prior to any interventions or discussions regarding their OIC with the study staff or the investigator.

6.5 Patient reported outcomes (PROs)

The following PROs are utilized in this study:

6.5.1 EQ-5D

See Section 6.9.1.

6.5.2 PAC-SYM

See Section 6.4.1.1.

6.5.3 PAC-QOL

See Section 6.4.1.2.

6.5.4 NRS

See Section 6.3.8.

6.5.5 Administration of PRO questionnaires

The PAC-SYM, PAC-QOL, EQ-5D, and NRS (for pain) will be self-administered using an electronic device (SitePad) at the study center. 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 Visit 1, the questionnaires are 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 Visit 1, since only enrolled patients will fill out the questionnaires and interaction with study staff will be necessary to determine whether enrollment criteria have been met.

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics

The blood sample for genetic research will be obtained from study D3820C00004 (see Section 7.2.1).

6.9 Health economics

6.9.1 EQ-5D

The EQ-5D (EuroQol Group, 1990) is a health utility measure designed to provide an assessment of general health status of the individual. The EQ-5D is a 5-dimension questionnaire. The dimensions consist of mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each item has 3 levels or response options: no problems, some problems, and severe problems. This instrument is extensively validated and is available in several languages that facilitate its use in multinational studies. The translations into local languages have been performed according to a linguistic validation process. The questions will take a few minutes to answer. The patients need to be able to read and to be fluent in the local language. The EQ-5D will be obtained at Visit 1 (enrollment - data from Visit 8 of previous study D3820C00004), Visit 2 (Week 4), Visit 4 (Week 12), and Visit 5 (Week 14) after the administration of the PAC-SYM and PAC-QOL.

The EQ-5D questionnaire will be completed by patients on the SitePad device provided at the study center. Study staff will log patients in and will provide initial training on how to fill out the questionnaire. 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 1, where some interaction with staff will be necessary in order to ensure that enrollment criteria have been met, patients are to fill out the EQ-5D questionnaire prior to any interventions or discussions regarding their OIC with the study staff or the investigator.

6.9.2 OIC Healthcare Resource Utilization Form

Opioid-induced constipation related healthcare resource utilization data will be collected at Visit 2 (Week 4), Visit 4 (Week 12), and Visit 5 (Week 14) through patient interviews. If a patient is taken off the study as a result of a resource utilization (eg, an emergency room [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 ER, 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 questionnaires (eg, PAC-SYM, PAC-QOL, EQ-5D, NRS) in the electronic devices, 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 concomitant medications 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 5 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	3	25.5
	Hematology	4 EDTA	3	12
	Bicarbonate	3.5 SST	3	10.5
Total		16	9	48

EDTA Ethylenediaminetetraacetic acid, SST serum-separating tube

[a] Additional samples may be collected for patients who have elevated liver transaminases (see Section 6.3.10.2), 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. A urine sample from WOCBP will be used to test for pregnancy at Visit 1.

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 Pharmacogenetic samples

No genetic samples will be collected in the current study. Instead, genetic samples collected and stored during study D3820C00004 may be used for future analysis. The data collected in this study may be combined with data from study D3820C00004 in these genetic analyses.

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 (collected in study D3820C00004) 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 Independent Ethics Committee (IEC)/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 IEC/IRB, and to the study site staff.

The opinion of the IEC/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 IEC/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 IEC/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, IECs/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 IEC/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 is 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 IEC/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 IEC/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 IEC/IRB, see Section 8.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's IEC/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 IEC/IRB.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IEC/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 or its representative 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 SitePad 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 IEC/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 [redacted] and to end by [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 for other reasons such as 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 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 the study site, autoqueries that are generated by the eDC system should be addressed by the 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 efficacy variable(s)

11.1.1 PAC-SYM

For the PAC-SYM, each item is scored as 0=absence of symptom, 1=mild, 2=moderate, 3=severe, and 4=very severe. The 12 items of the PAC-SYM are assigned to 3 domains:

- Abdominal symptoms (items 1 to 4)
- Rectal symptoms (items 5 to 7)
- Stool symptoms (items 8 to 12).

Each domain score will be calculated as the mean of the non-missing items for that domain. The total score will be calculated as the mean of all non-missing items. If more than 50% of values for a domain or the total score are missing for a visit, the values for that score will be set to missing.

Change from baseline in the PAC-SYM domain and total scores will be calculated for Weeks 4, 12, and 14 as the post-baseline value minus the baseline value. Negative changes from baseline indicate improvement.

The primary baseline PAC-SYM 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) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline PAC-SYM values will be defined as the data collected at Visit 8 from the previous study D3820C00004 (also defined as Visit 1 of this study).

11.1.2 PAC-QOL

For the PAC-QOL, each of the 28 items is scored from 0 to 4. For items 18, 25, 26, 27, and 28, higher scores represent better outcomes. The scores for these items will be reversed (reversed score=4-original score), so that higher scores represent worse outcomes for all items. The 28-item PAC-QOL is divided into 4 subscales:

- Physical discomfort (items 1 to 4)

- Psychosocial discomfort (items 5 to 12)
- Worries/concerns (items 13 to 23)
- Satisfaction (items 24 to 28).

For each visit, individual subscale scores will be calculated as the mean of the non-missing items for that subscale. The total score will be calculated as the mean of all non-missing items. If more than 50% of values for a subscale score or the total score are missing for a visit, the values for that score will be set to missing.

Change from baseline in the PAC-QOL subscale and total scores will be calculated for Weeks 4, 12, and 14 as the post-baseline value minus the baseline value. Negative changes from baseline indicate improvement.

The primary baseline PAC-QOL 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) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline PAC-QOL values will be defined as the data collected at Visit 8 from the previous study D3820C00004 (also defined as Visit 1 of this study).

11.2 Calculation or derivation of safety variable(s)

11.2.1 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.

11.2.2 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 4, 8, and 12 as the post-baseline value minus the baseline value. Negative changes from baseline indicate improvement.

The NRS (7-Day recall) collected at Visit 1 will serve as the NRS baseline value.

11.2.3 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: enrollment in this study to Week 4 and Week 4 to Week 12, as well as randomization in the previous pivotal study (D3820C00004) to Weeks 4 and 12 in this study.

11.2.4 Mean bisacodyl dose per week

Bisacodyl doses will be recorded for each patient in the eCRF. 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: enrollment to Week 4 and Week 4 to Week 12.

11.2.5 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. Changes from baseline to Week 12 in the modified Himmelsbach scale will be calculated as the post-baseline value minus the baseline value. Negative changes from baseline indicate improvement.

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) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline modified Himmelsbach values will be defined as the data collected at Visit 8 from the previous study D3820C00004 (also defined as Visit 1 of this study).

11.2.6 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 (Weeks 12 and 14) will be calculated as the post-baseline test value minus the baseline test value.

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) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline laboratory values will be

defined as the data collected at Visit 8 from the previous study D3820C00004 (also defined as Visit 1 of this 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.

11.2.7 Physical examination

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

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) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline physical examination results will be defined as the data collected at Visit 8 from the previous study D3820C00004 (also defined as Visit 1 of this study).

11.2.8 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.

The primary baseline weight value will be defined as the latest non-missing value collected prior to the first dose of study drug in the previous pivotal study (D3820C00004) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline weight value will be defined as the data collected at Visit 8 from the previous study D3820C00004 (also defined as Visit 1 of this study).

11.2.9 Body temperature and respiratory rate

Change from baseline to Week 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.

The primary baseline body temperature and respiratory rate 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) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline body temperature and respiratory rate values will be defined as the data collected at Visit 8 from the previous study D3820C00004 (also defined as Visit 1 of this study).

11.2.10 ECG

Changes from baseline to each post-baseline visit (Weeks 12 and 14) for ECG interval data and rate data will be derived by subtracting the baseline value from the final assessment value, where baseline. Markedly abnormal values or changes from baseline will be identified.

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) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline ECG values will be defined as the data collected at Visit 8 from the previous study D3820C00004 (also defined as Visit 1 of this study).

11.2.11 Vital signs

Changes from baseline in vital signs (sitting blood pressure and pulse) at each post-baseline visit (Weeks 4, 8, 12, and 14) will be derived as the value at the visit minus the baseline value for the same assessment. Markedly abnormal values or changes from baseline will be identified.

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) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline vital sign values will be defined as the data collected at Visit 8 from the previous study D3820C00004 (also defined as Visit 1 of this study).

11.2.12 C-SSRS

Occurrence of suicidal behavior after baseline up to the final assessment (Week 14) 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 (Week 14) 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.

The primary baseline C-SSRS 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) (screening, Visit 1 or Week 0, Visit 3), and supportive baseline C-SSRS values will be defined as the data collected at Visit 8 from the previous study D3820C00004 (also defined as Visit 1 of this study).

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 PAC-SYM

See Section 11.1.1.

11.3.2 PAC-QOL

See Section 11.1.2.

11.3.3 NRS for Pain

See Section 11.2.2.

11.3.4 Daily opioid dose

See Section 11.2.3.

11.3.5 Mean Bisacodyl dose per week

See Section 11.2.4.

11.3.6 EQ-5D

See Section 11.6.1.

11.4 Calculation or derivation of PK variables (Not applicable)

11.5 Calculation or derivation of pharmacodynamic (PD) variable(s) – (Not applicable)

11.6 Calculation or derivation of health economic variables

11.6.1 EQ-5D

The weighted health status index scores, derived from the 5 EQ-5D questions, will be calculated, summarized, analyzed, and reported outside of the main study report.

11.6.2 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 (physician or other health care practitioner, urgent care center or hospital ER, inpatient hospital).

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Safety analysis set

The safety analysis set will be the Safety population, defined as all randomized patients who received at least 1 dose of study drug (12.5 mg NKTR-118, 25 mg NKTR-118, or placebo). The safety analysis set will be used to assess safety and tolerability variables.

12.1.2 Efficacy analysis set

The efficacy analysis set will be the modified Intent-to-Treat (ITT) population, defined as all randomized patients who received at least 1 dose of study drug (12.5 mg NKTR-118, 25 mg NKTR-118, or placebo) and have at least 1 post-baseline efficacy assessment.

12.2 Methods of statistical analyses

A comprehensive SAP will be finalized before unblinding of the data.

This is a general evaluation of long-term safety and evaluation. Therefore, no statistical testing will be conducted. Differences between NKTR-118 12.5 and 25 mg and placebo with respect to the evaluation of long-term safety and tolerability will be assessed using descriptive statistics.

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) (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 (Visit 8). Where appropriate, to assess the potential impact of the previous 12 week treatment, the change from baseline in safety parameters will be summarized using both the primary (ie, prior to first dose of study drug in the previous pivotal study) and supportive (final visit of the previous pivotal 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 pivotal study) will also be reported.

Presentation of safety data will include summaries both by individual NKTR-randomized dose group (12.5 and 25 mg) as well as by a total NKTR group, where appropriate.

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 one observation to the numerator of the proportion. The denominator of the proportion will comprise all patients in the Safety population. 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 (eg, after 1 month, after 3 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 unblinding and will also be summarized by each treatment group.

The mean daily opioid dose will be summarized by treatment group for the following intervals: enrollment to Week 4 and Week 4 to Week 12, as well as randomization in the previous pivotal study (D3820C00004) to Weeks 4 and 12 in this study. The mean bisacodyl dose per week will be summarized by treatment group using descriptive statistics for the following intervals: enrollment to Week 4 and Week 4 to Week 12. The observed and change from baseline in composite modified Himmelsbach score will be summarized by treatment group at Week 12 using descriptive statistics. The observed score and change from baseline in NRS pain scores (average in the 7 days prior to the study visit) will be summarized by treatment group for Weeks 4, 8 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 12.5 and 25 mg will be summarized combining the data from the current study with the exposure data from the previous pivotal study (D3820C00004).

Safety parameters may also be summarized by age group, gender, race, region, and response to laxatives (LIR, non-LIR), as appropriate.

12.2.2 Efficacy analyses

Descriptive statistics by treatment group for the PAC-SYM total score and each domain score will be summarized at baseline, Weeks 4, 12, and 14 as well as the change from baseline to each post-dose time point. Descriptive statistics by treatment group for the PAC-QOL total score and each domain score will be summarized at baseline, Weeks 4, 12, and 14 as well as the change from baseline to each post-dose time point.

12.2.3 Health economics

Descriptive statistics for the frequency of responses for each of the 5 EQ-5D questions will be summarized by treatment group for baseline, Weeks 4, 12, and 14. The number and percentage of questionnaires completed at each visit will also be presented.

The percentage of patients with at least 1 healthcare visit will be summarized for each OIC healthcare utilization category (physician or other health care practitioner, urgent care center or hospital ER, inpatient hospital) 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 reason for the visit (eg, enemas, manual disimpactions, treatment of anal fissures, treatment of bowel necrosis, and other) will also be summarized by treatment group using descriptive statistics.

12.2.4 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 will be determined by the number of patients from the previous study D3820C00004 who enroll.

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
[redacted]	North America (NA) Study Physician – Responsible for protocol implementation in US & Canada	[redacted]
[redacted]	Europe Study Physician – Responsible for protocol implementation in Europe	[redacted]
[redacted]	Australia Study Physician - Responsible for protocol implementation in Australia	[redacted]
Quintiles Lifecycle Safety	SAE reporting (US)	[redacted]
Quintiles Lifecycle Safety	SAE reporting (other countries)	Please refer to study-specific Safety Handling Plan

Name	Role in the study	Address & telephone number
Other contact information		
Quintiles Laboratories (QLAB)	Central laboratory	[redacted]
eRT (ECG laboratory)	Central ECG laboratory	[redacted]
Fisher Clinical Services	Packaging and distribution; Study drug return and destruction	[redacted]
Perceptive Informatics	Trial supply management	[redacted]
PHT Corporation	SitePad	[redacted]
Bracket Global	Scale user agreements and acquisitions; Rater training; and translations	[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 #6 (see Section 4.1).

If a patient becomes pregnant during the course of the study, the 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
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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.

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Clinical Study Protocol Appendix C	
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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.

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Clinical Study Protocol Appendix D	
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Appendix D
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
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Clinical Study Protocol Appendix E	
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Appendix E
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 F	
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Appendix F
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 G	
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Appendix G

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