Clinical Study Protocol Amendment

Amendment Number	1
Drug Substance	NKTR-118
Study Code	D3820C00005
Date	
Protocol Dated	

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

Sponsor:

AstraZeneca AB, SE-151 85 Södertälje, Sweden

Centres affected by the Amendment:

All centres.

The protocol for the study is to be amended as follows:

- The list of countries has been expanded to include all potential countries that may participate in this study.
- Text has been added requiring an additional 1 hour post-dose blood pressure and heart rate assessment, and providing additional blood pressure monitoring guidelines including guidance if patients show signs of significant decreases in blood pressure.
- Text has been added requiring all ECGs to be performed in triplicate with the exception of the screening ECG (Visit 1) and final visit ECG (Visit 9) which will be single 12-lead ECGs.
- Text has been added clarifying that no rectal examination is required at Visit 8, unless patients enter the safety extension study in which case a rectal examination is mandatory.

- Text has been added clarifying that in addition to patients recording the timing of any enema use in the eDiary, sites are to record any enema prescription on an enema eCRF

- Removed text specifying that opioid breakthrough pain medication would be captured on an eCRF. Instead, this information will be only be captured in the eDiary. In addition, text was added clarifying that patients would be asked about use of opioid breakthrough pain medication at study visits during the eDiary review. Text has been added clarifying that the eDiary would include the following information for opioid breakthrough pain medication: name of the opioid medication used, dose, route of administration and dosage form.

- Inclusion criterion 4 has been revised to clarify that patients who are receiving only a short acting opioid on an as needed basis that does not follow a fixed schedule, are not eligible for this study (patients who are receiving a short acting opioid PRN on a fixed basis will still be eligible for inclusion).

- Exclusion criterion 3 has been modified to add greater detail regarding irritable bowel syndrome (IBS) exclusion criteria.

- Exclusion criterion 6 has been modified to delete “ventricular arrhythmias” since this is redundant with exclusion criterion 12.

- Text has been added clarifying that methadone use is prohibited and that it can potentially cause QT prolongation.

- Clarification has been added specifying that naloxone containing products and naltrexone containing products are also prohibited during the study.

- Removed text specifying that sites would be provided with containers for packaging bisacodyl.

- Text has been added clarifying that if a patient indicates having had any suicidal behaviour at any visit when the C-SSRS is administered, they should be referred to a mental health professional immediately.

- Criteria for a treatment-emergent AE has been changed to focus on AEs occurring while on study drug.

- Safety analyses have been clarified.

- The 24-hour urgent medical contact number has been updated.

- The following additional minor edits/corrections have been made: abbreviations for diastolic blood pressure (DBP) and systolic blood pressure (SBP) have been added to text and list of abbreviations, abbreviations for EQ-5D (Euroqol 5 Dimension

Instrument) and CRC (colorectal cancer screening) have been corrected in Table 1 (Study Plan)

- Typographical and grammatical errors were corrected.
- Appendix E was amended to require a combination of flexible sigmoidoscopy and double contrast barium as a mandatory screening procedure.
- Headers of Appendices B, C, D, E, and F have been revised to show study number as D3820C00005 instead of D3820C0005 (were missing a "0")

Please note that in text that follows, page numbers refer to the page numbers in the Revised Clinical Study Protocol dated

Section of protocol affected:

Protocol Synopsis, page 2

Previous text:

Study center(s) and number of subjects planned

This will be a multi-center study conducted in Australia, Belgium, Germany, Hungary, and the United States (US). Approximately 1300 patients will be screened to obtain 630 randomized patients (210 per treatment arm). Approximately 120 centers will participate in the study.

Revised text:

Study center(s) and number of subjects planned

This will be a multi-center study **with global participation that may include the following countries:** Australia, Belgium, **Canada, Croatia, the Czech Republic, France,** Germany, Hungary, **Israel, Slovakia, Spain, the United Kingdom (UK),** and the United States (US). Approximately 1300 patients will be screened to obtain 630 randomized patients (210 per treatment arm). Approximately 120 centers will participate in the study.

Section of protocol affected:

Section 3.1, Overall study design and flow chart, page 24

Previous Text:

This is a Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group study of 2 doses of NKTR-118 and placebo. The study duration will be up to 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, during which the diagnosis of OIC and stability of the opioid regimen will be confirmed, 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 will be eligible to participate in a separate safety extension study. Approximately 1300 patients will be

screened to obtain 630 randomized patients at approximately 120 centers in Australia, Belgium, Germany, Hungary, and the US.

Revised Text:

This is a Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group study of 2 doses of NKTR-118 and placebo. **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).** The study duration will be up to 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, during which the diagnosis of OIC and stability of the opioid regimen will be confirmed, 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 will be eligible to participate in a separate safety extension study. Approximately 1300 patients will be screened to obtain 630 randomized patients at approximately 120 centers.

Section of protocol affected:

Section 1.4, Benefit/risk and ethical assessment, pages 21, 22

Previous text:

For a description of pre-clinical findings regarding NKTR-118 please refer to the IB. 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 vital signs, laboratory parameters, or electrocardiograms (ECGs). 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.

Revised text:

For a full description of pre-clinical findings regarding NKTR-118 please refer to the IB. Pre-clinical investigations have included a recent dog telemetry study which demonstrated small, transient decreases in blood pressure, left ventricular systolic pressure, cardiac contractility and relaxation indices, as well as increases in heart rate, at blood concentrations about 5 times higher than the maximum dose used in this study (ie, 25 mg). The clinical significance of this finding is uncertain and follow-up preclinical testing is underway in telemetered dogs with lower doses of NKTR 118. While there have been isolated reports of patients with potentially clinically significant blood pressure decreases in trials of NKTR-118, such cases have also been observed with placebo. No clear or consistent cardiovascular safety signal has been observed in human studies to date (see Section 6.4.13.3 for additional guidance).

In Phase I studies in healthy volunteers, in which single doses up to 1000 mg and repeated doses up to 500 mg/day were administered, there were no clinically significant changes in

laboratory parameters or electrocardiograms (ECGs). **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.

Section of protocol affected:

Section 3.1.1, Visit 1 (Initial screening), page 29

Previous text:

- Sitting blood pressure and pulse will be measured.

Revised text:

- Sitting blood pressure and pulse **must** be measured. **Please see Section 6.4.12.1 for additional details on the protocol-mandated methods for collection of vital signs.**

Sections of protocol affected:

Section 3.1.3.1 Visit 3 (Randomization, Week 0, Day 1), page 34; Section 3.1.3.2, Visit 4 (Week 1, Day 8), page 36; Section 3.1.3.3, Visit 5 (Week 2, Day 15), page 37; Section 3.1.3.4, Visit 6 (Week 4, Day 29), page 38; Section 3.1.3.5, Visit 7 (Week 8, Day 57), page 39; Section 3.1.3.6, Visit 8 (Week 12, Day 85), page 40; Section 3.1.4 Final Visit (Visit 9, Week 14, Day 99), page 42.

Previous text:

- Sitting blood pressure and pulse will be measured.

Revised text:

- Sitting blood pressure and pulse **must** be measured. **Please see Section 6.4.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours and minutes will be recorded for this measurement.**

Section of protocol affected:

Section 3.1.3.1 Visit 3 (Randomization, Week 0, Day 1), page 35

Previous text:

Post-dose:

- Single ECG will be obtained 2 hours after the dose of study drug, before the PK sample is collected.
- Modified Himmelsbach scale will be completed by a clinician 2 hours after patient receives the first dose of study drug.
- Blood sample will be collected for PK measurement 2 hours after the dose of study drug. The PK sampling time in date, hours, and minutes will be recorded accurately.
- Any BM during the 4-hour observation period will be recorded by the patient in the eDiary.
- Study drug will be dispensed and dosing instructions will be provided.
- A new supply of bisacodyl will be dispensed.
- An appointment for Visit 4 (Day 8) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit.

Revised text:

Post-dose:

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

  Please see Section 6.4.12.1 for additional details on the protocol-mandated methods for collection of vital signs. The accurate time in date, hours, and minutes will be recorded for this measurement.

  Additionally, if clinically significant decreases in blood pressure are noted at this post-dose VS measurement, an additional measurement should be taken approximately 2 hours later prior to the patient leaving the clinic (please refer to Section 6.4.12.1 for guidelines on management.)

  In the event of clinically significant findings compared to the pre-dose measurements (per the judgment of the Investigator or delegate) please refer to Sections 5.8 and 6.4.13.3.

- **Triplicate 12-lead ECGs** will be obtained 2 hours after the dose of study drug, before the PK sample is collected.

- Modified Himmelsbach scale will be completed by a clinician 2 hours after patient receives the first dose of study drug.
- Blood sample will be collected for PK measurement 2 hours after the dose of study drug. The PK sampling time in date, hours, and minutes will be recorded accurately.
- Any BM during the 4-hour observation period will be recorded by the patient in the eDiary.
- Study drug will be dispensed and dosing instructions will be provided.
- A new supply of bisacodyl will be dispensed.
- An appointment for Visit 4 (Day 8) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit.

Section of protocol affected:

Section 3.1.3.3 Visit 5 (Week 2, Day 15), page 37; Section 3.1.3.4 Visit 6 (Week 4, Day 29), page 38; Section 3.1.3.5 Visit 7 (Week 8, Day 57), page 39.

Previous text:

- Single 12-lead ECG will be obtained.

Revised text:

- **Triplicate** 12-lead ECG will be obtained.

Section of protocol affected:

Table 1, Study Plan, Footnote "i", page 45

Previous text:

[i] At randomization (Visit 3) a 12-lead ECG will be repeated in triplicate pre-dose, and a single ECG will be obtained 2 hours post-dose. Triplicate ECGs will also be obtained at Week 1 (Visit 4) and Week 12 (Visit 8). Single 12-lead ECGs will be obtained at Weeks 2 (Visit 5), 4 (Visit 6), 8 (Visit 7), and 14 (Visit 9).

Revised text:

[i] **A single** 12-lead ECG will be **obtained at screening (Visit 1) and at Week 14 (Visit 9). At randomization (pre- and post-dose) and at all other visits, a 12-lead ECG will be repeated in triplicate.**

Section of protocol affected:

Table 1, Study Plan, New Footnote "u", page 45

Previous text:

"Sitting blood pressure, pulse" had no footnote

Revised text:

u **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 6.4.12.1. At Visit 3, patients will have blood pressure and pulse measured pre-dose as well as 1 hour post-dose (for practical purposes, this can be performed within a window from 1 hour to 90 minutes post-dose). If clinically significant decreases in blood pressure are noted at this post-dose measurement, an additional measurement should be taken approximately 2 hours later, prior to the patient leaving the clinic. In the event of clinically significant findings compared to the pre-dose measurement (per the judgment of the investigator or delegate), please refer to Sections 5.8, 6.4.12.1, and 6.4.13.3 for additional guidelines on management.**

Section of protocol affected:

Section 6.4.11.1 Resting 12-lead ECG, page 79

Previous text:

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 at screening, randomization, and all study visits after randomization. Digital ECGs will be obtained after the patient has been resting in a supine position for at least 10 minutes. At Visit 3 (randomization), patients will receive a triplicate ECG pre-dose and a single ECG 2 hours after the dose of study drug. Triplicate ECGs will also be performed at Visit 4 (Week 1) and Visit 8 (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. Single 12-lead ECGs will be performed at Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), and Visit 9 (Week 14).

Revised text:

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 at screening, randomization, and all study visits after randomization. Digital ECGs will be obtained after the patient has been resting in a supine position for at least 10 minutes. **Single 12-lead ECGs will be performed at screening (Visit 1) and at Week 14 (Visit 9). At randomization (pre- and post-dose) and at all other study visits, triplicate ECGs will be performed**. 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.

Section of protocol affected:

Section 5.8, Discontinuation from study, pages 61, 62

Previous text:

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 6.4.9.2. The protocol for handling patients with elevated liver transaminases including guidelines for discontinuing patients is discussed in Section 6.4.9.2).
- ECG evidence of QT prolongation (QTcF >500 ms, or an increase of QTcF >60 ms above baseline to a value >480 ms on the12-lead ECG, confirmed on a repeat 12-lead ECG taken after waiting at least 5 minutes after the original finding of prolonged QTc)
- 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 that would not be consistent with continuation in the study, as determined by the investigator, AstraZeneca, or its representative, or the patient.
- Safety reasons as judged by the investigator

- Patient becomes pregnant
- Significantly worsened OIC refractory to medical treatment as judged by the investigator (including failure of the laxative rescue regimen either before or after randomization)
- The patient is unable to comply with the restrictions on the use of concomitant medications as detailed in Section 5.6 (in such cases the investigator should consult with the study physician before discontinuing the patient).
- The patient is unable to tolerate the assigned dose of the study drug.

Revised text:

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 6.4.9.2. The protocol for handling patients with elevated liver transaminases including guidelines for discontinuing patients is discussed in Section 6.4.9.2).
- ECG evidence of QT prolongation (QTcF >500 ms, or an increase of QTcF >60 ms above baseline to a value >480 ms on the12-lead ECG, confirmed on a repeat 12-lead ECG taken after waiting at least 5 minutes after the original finding of prolonged QTc)
- 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 either before or after randomization)
- The patient is unable to comply with the restrictions on the use of concomitant medications as detailed in Section 5.6 (in such cases the investigator should consult with the study physician before discontinuing the patient).
- The patient is unable to tolerate the assigned dose of the study drug.

Section of protocol affected:

Section 6.2.1, Screening and demographic measurements, page 63

Previous text:

The following data will be collected and recorded on the appropriate sections of the eCRF at the time of the screening visit (Visit 1) (refer to the Study Plan, Table 1):

- Vital signs (sitting blood pressure and pulse, body temperature, respiratory rate)

Revised text:

The following data will be collected and recorded on the appropriate sections of the eCRF at the time of the screening visit (Visit 1) (refer to the Study Plan, Table 1):

- Vital signs (sitting blood pressure and pulse, body temperature, respiratory rate). **Please refer to Section 6.4.12.1 for proper methodology of vital sign assessment.**

Section of protocol affected:

Section 6.4.12.1, pages 80, 81

Previous text:

Blood pressure (sitting) and pulse/heart rate (sitting) will be measured at all study visits except Visit 2 (start of OIC confirmation period). An appropriately sized cuff will be used to obtain systolic and diastolic blood pressure.

Revised text:

Blood pressure (sitting) and pulse/heart rate (sitting) **must** be measured **at all study visits**. **The following measures should be employed consistently for every measurement:**

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

Note: at Visit 3 (randomization) care should be taken to record heart rate and blood pressure, which at this visit should be performed pre-dose and 1 hour post-dose (for practical purposes, this can be performed and recorded within a window from 1 hour to 90 minutes post-dose). If clinically significant BP decreases (in the judgment of the investigator or delegate) are noted at the 1-hour post-dose measurement, the BP should be repeated approximately 2 hours later before the patient leaves the clinic to ensure that the BP is within normal limits for that patient (in the judgment of the investigator or delegate). If the BP value is still significantly low by the time of potential discharge, the investigator should consider discontinuing the patient from the study (see Sections 5.8 and 6.3.13.3), although it is recommended that the investigator consult with the Study Physician prior to discontinuing the patient.

For management of markedly abnormal heart rates or blood pressures, please refer to Sections 5.8 and 6.4.13.3.

Section of protocol affected:

Section 6.4.13.3 Blood pressure and heart rate measurements (new section has been added), page 82

Previous text:

New section added

Revised text:

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 6.4.12.1. For specific instructions regarding the potential need for discontinuation based on sustained clinically significant vital sign abnormalities, please refer to Section 5.8. It should be noted that vital sign abnormalities should generally be reported as AEs only if they fulfill AE criteria proper or are the reason for discontinuation of treatment with the IP (see Section 6.4.4).

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.

Section of protocol affected:

Section 6.4.14, Safety specific areas of interest, pages 82, 83

Previous text:

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 6.4.13.2).

The topics listed above, as well as other topics which may be subsequently determined by AstraZeneca, may be subject to enhanced surveillance activities and/or an adjudication team process (note: any case reports of bowel perforation and related events will be subject to an

external adjudication process). 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.

Revised text:

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 6.4.13.2)
- **Cardiovascular type events (including, but not limited to, abnormalities in blood pressure and heart rate)**

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

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

Section of protocol affected:

Section 3.1.3.6, Visit 8 (Week 12, Day 85), page 40

Previous text:

- Physical examination including weight, body temperature, and respiratory rate.

Revised text:

- Physical examination including weight, body temperature, and respiratory rate **(no rectal examination required unless patients enter the safety extension study; a rectal examination is mandatory for patients who enter the safety extension study.**

Section of protocol affected:

Table 1, Study Plan, Footnote "f", page 45

Previous text:

[f] Visit 1: physical examination will include rectal examination, as well as height, weight, temperature, respiratory rate; Visit 3 (Randomization): targeted physical examination (lungs, cardiovascular, abdomen) with weight, collected, may include optional rectal examination at the discretion of the investigator, if necessary to ensure the safety of the patient; Visit 8 (end-of-treatment): physical examination including weight, temperature, respiratory rate (no rectal examination).

Revised text:

[f] Visit 1: physical examination will include rectal examination, as well as height, weight, temperature, respiratory rate; Visit 3 (Randomization): targeted physical examination (lungs, cardiovascular, abdomen) with weight collected, may include optional rectal examination at the discretion of the investigator, if necessary to ensure the safety of the patient; Visit 8 (end-of-treatment): physical examination including weight, temperature, respiratory rate (no rectal examination **required unless patients enter the safety extension study; a rectal examination is mandatory for patients who enter the safety extension study)**.

Section of protocol affected:

Section 3.1, Overall study design and flow chart, pages 26, 27

Previous text:

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. If these secondary interventions fail, the patient should be discontinued from the study (or excluded from the study if the patient fails the rescue regimen prior to randomization) 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 randomized (see Section 4.2).

Revised text:

If after a minimum of 72 hours, the patient has not experienced a BM, he/she may take bisacodyl rescue therapy (10 to 15 mg dose, ie, 2 to 3 bisacodyl tablets at a time). If the patient remains constipated, bisacodyl rescue therapy may be repeated up to 2 additional times, as necessary, each 10 to 15 mg dose separated by 12 hour intervals. It is recommended

that the bisacodyl tablets be taken either at bedtime or before breakfast. If after 3 doses of bisacodyl rescue therapy, the patient still has not experienced a BM, the investigator may prescribe one-time use of an enema. **The timing of administration of this therapy will be noted and recorded in the eDiary. 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 (or excluded from the study if the patient fails the rescue regimen prior to randomization) 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 randomized (see Section 4.2).

Section of protocol affected:

Section 5.6, Concomitant and post-study treatment(s), page 57

Previous text:

Patients may take laxatives during the screening period of the study, but must discontinue use of laxatives at least 24 hours prior to the start of the OIC confirmation period. During the OIC confirmation period and 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 two additional times, as necessary, each 10 to 15 mg dose separated by 12 hour intervals. It is recommended that the bisacodyl tablets be taken either at bedtime or before breakfast. If after 3 doses of bisacodyl rescue therapy, the patient still has not experienced a BM, the investigator may prescribe one-time use of an enema. The timing of administration of this therapy will be noted and recorded in the eDiary. If these secondary interventions fail, the patient should be discontinued from the study (or excluded from the study if the patient fails the rescue regimen prior to randomization) 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 randomized (see Section 4.2).

Revised text:

Patients may take laxatives during the screening period of the study, but must discontinue use of laxatives at least 24 hours prior to the start of the OIC confirmation period. During the OIC confirmation period and 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 two additional times, as necessary, each 10 to 15 mg dose separated by 12 hour intervals. It is recommended that the bisacodyl tablets be taken either at bedtime or before breakfast. If after 3 doses of bisacodyl rescue therapy, the patient still has not experienced a BM, the investigator may prescribe one-time use of an enema. The timing of administration of this therapy will be noted and recorded in the eDiary.

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 (or excluded from the study if the patient fails the rescue regimen prior to randomization) 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 randomized (see Section 4.2).

Section of protocol affected:

Section 3.1, Overall study design and flow chart, page 28

Previous text:

Additional Assessments:

- Recording of concomitant medications (other than laxative rescue medication and opioid medication for breakthrough pain) throughout the study
- Recording of opioid medication for breakthrough pain throughout the study – specific information regarding timing of breakthrough pain medication is captured in the eDiary. Information regarding breakthrough pain medication is also collected on electronic case report forms (eCRFs) and recorded in the eDiary to allow for daily recording of dosing.

Revised text:

Additional Assessments:

- Recording of concomitant medications (other than **opioid medication or** laxative rescue medication) throughout the study

Section of protocol affected:

Section 3.1.1 Visit 1 (Initial screening), page 29, 30

Previous text:

The following additional procedures will be performed at Visit 1:

- Daily maintenance and breakthrough pain opioid dosing regimens over the 60 days before enrollment will be asked about and recorded on the appropriate eCRFs. The daily opioid and breakthrough pain dosing regimens will be confirmed by prescription or clearly labeled bottles of opioid medication. Information from the breakthrough pain medication eCRF will be recorded in the eDiary to allow for daily recording of dosing.

Revised text:

The following additional procedures will be performed at Visit 1:

- Daily maintenance opioid dosing regimen over the 60 days before enrollment will be asked about and recorded on the appropriate eCRF. The daily opioid dosing regimen will be confirmed by prescription or clearly labeled bottles of opioid medication.

- **Information regarding breakthrough pain medication will be entered in the eDiary to allow for daily recording of dosing. The breakthrough pain opioid dosing regimen will be confirmed by prescription or clearly labeled bottles of opioid medication.**

Section of protocol affected:

Section 3.1.2 Visit 2 (OIC confirmation), page 31

Previous text:

For patients who continue in the study:

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

Revised text:

For patients who continue in the study:

- Daily maintenance opioid dosing regimen will be asked about and recorded on the appropriate eCRF.

Section of protocol affected:

Section 3.1.3.1, Visit 3 (Randomization, Week 0, Day 1), pages 33, 34

Previous text:

Pre-dose

- The eDiary (including proper documentation of bisacodyl and enema use) will be reviewed with the patient, and instruction on proper completion of the eDiary will be reviewed.

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

Revised text:

- The eDiary (including proper documentation of bisacodyl, enema, **and opioid breakthrough pain medication use**) will be reviewed with the patient, and instruction on proper completion of the eDiary will be reviewed.

- Daily maintenance opioid dosing regimen will be asked about and recorded on the appropriate eCRF.

Sections of protocol affected:

Section 3.1.3.2 Visit 4 (Week 1, Day 8), page 36; Section 3.1.3.3 Visit 5 (Week 2, Day 15), page 37; Section 3.1.3.4 Visit 6 (Week 4, Day 29), page 38; Section 3.1.3.5 Visit 7 (Week 8, Day 57), page 39

Previous text:

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

- eDiary (including proper documentation of bisacodyl and enema use) review

Revised text:

- Daily maintenance opioid dosing regimen will be asked about and recorded on the appropriate eCRF.

- eDiary (including proper documentation of bisacodyl, enema, **and opioid breakthrough pain medication use**) review

Sections of protocol affected:

Section 3.1.3.6 Visit 8 (Week 12, Day 85), page 41

Previous text:

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

- eDiary (including proper documentation of bisacodyl and enema use) review and return of the eDiary device

Revised text:

- Daily maintenance opioid dosing regimen will be asked about and recorded on the appropriate eCRF.

- eDiary (including proper documentation of bisacodyl, enema, **and opioid breakthrough pain medication use**) review and return of the eDiary device

Section of protocol affected:

Section 3.1.4, Final Visit (Visit 9, Week 14, Day 99), page 42

Previous text:

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

Revised text:

- Daily maintenance opioid dosing regimen will be asked about and recorded on the appropriate eCRF.

Section of protocol affected:

Section 5.6, Concomitant and post-study treatment(s), page 58

Previous text:

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.

Revised text:

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 **eCRF** and/or **eDiary (opioid** breakthrough pain medication), as appropriate.

Section of protocol affected:

Section 6.2.1, Screening and demographic measurements, page 63

Previous text:

The following data will be collected and recorded on the appropriate sections of the eCRF at the time of the screening visit (Visit 1) (refer to the Study Plan, Table 1):

- Prior and current medications (including opioid dose and laxative use)

- Daily maintenance and breakthrough pain opioid dosing regimen.

Revised text:

The following data will be collected and recorded on the appropriate sections of the eCRF at the time of the screening visit (Visit 1) (refer to the Study Plan, Table 1):

- Prior and current medications (including laxative use)
- Daily maintenance opioid dosing regimen.

Section of protocol affected:

Section 6.3.2.7 Use of opioid medication for breakthrough pain, page 69

Previous text:

Opioid medication for breakthrough pain will be recorded in the eDiary at the time the medication is taken. Breakthrough pain medication will also be reviewed at study visits and recorded on a breakthrough pain medication eCRF; this information will be recorded in the eDiary to facilitate daily recording of dosing.

Revised text:

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

Section of protocol affected:

Section 6.4.6 Daily opioid dose, page 74

Previous text:

Opioid doses will be recorded for each patient and the daily opioid dose in morphine equivalents will be calculated. Breakthrough pain medication will be recorded in the eDiary, and the daily maintenance opioid dose will be recorded on the maintenance opioid dose eCRF. Breakthrough pain medication will also be reviewed at study visits and recorded on a breakthrough pain medication eCRF; this information will be recorded in the eDiary to facilitate daily recording of dosing.

Revised text:

Opioid doses will be recorded for each patient and the daily opioid dose in morphine equivalents will be calculated. Breakthrough pain medication will be recorded in the eDiary, and the daily maintenance opioid dose will be recorded on the maintenance opioid dose eCRF.

Section of protocol affected:

Section 6.1, Recording of data, page 62

Previous text:

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

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA).

The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

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

Revised text:

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

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

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

Section of protocol affected:

Section 4.1, Inclusion criteria, (Inclusion criterion 4), page 49

Previous text:

Receiving a stable maintenance opioid regimen consisting of a total daily dose of 30 mg to 1000 mg of oral morphine, or equianalgesic amount(s) of 1 or more other opioid therapies (see Appendix H) for a minimum of 4 weeks prior to screening for non-cancer-related pain with no anticipated change in opioid dose requirement over the proposed study period as a result of disease progression. The opioid regimen should be confirmed by a prescription or clearly labeled medication bottle. Regimen stability will be confirmed during the 2-week OIC

confirmation period. Patients will be disqualified from randomization if they consume >4 additional breakthrough pain medication doses per day for more than 3 days during the 2-week OIC confirmation period, or if their long-acting maintenance opioid dose was modified during this same period. The use of additional doses of opioids for breakthrough pain will be captured in the eDiary during the 2-week OIC confirmation period. Patients who are receiving only short-acting opioids will be allowed in the study if they are receiving doses according to a fixed schedule. Patients who are receiving only a short-acting opioid on an as-needed (PRN) basis are not eligible for this study. Intrathecal dosing is permitted as long as the patient is taking another orally dosed opioid that meets the dosing and duration criteria defined above.

Revised text:

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

Section of protocol affected:

Section 4.2, Exclusion criteria (Exclusion criterion 3), page 50

Previous text:

Medical conditions and treatments associated with diarrhea, intermittent loose stools, or constipation, which could confound the interpretation of the results, eg, fecal incontinence, irritable bowel syndrome (physician-diagnosed), or chronic idiopathic constipation.

Revised text:

Medical conditions and treatments associated with diarrhea, intermittent loose stools, or constipation, which could confound the interpretation of the results, eg, fecal incontinence or chronic idiopathic constipation. **In addition, patients having irritable bowel syndrome (IBS) that has been previously diagnosed by a physician prior to first initiation of opioid therapy and that meets the following criteria, would be excluded:**

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

Section of protocol affected:

Section 4.2, Exclusion criteria (Exclusion criterion 6), page 51

Previous text:

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, ventricular arrhythmias, poorly controlled seizure disorder)

Revised text:

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)

Section of protocol affected:

Section 4.2, Exclusion criteria (Exclusion criterion 13), page 52

Previous text:

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

Revised text:

Active substance or alcohol use that in the opinion of the investigator, may compromise patient's ability to comply with the study instructions. Patients with a positive urine drug screen at the screening visit for cocaine, or amphetamine (unless verified by prescription that

the patient is receiving amphetamine for treatment of Attention-Deficit Hyperactivity Disorder or other neuropsychiatric condition) will be excluded. Patients **receiving** methadone will be excluded. The disposition of patients with suspected opiate abuse during the trial will be handled on a case by case basis.

Section of protocol affected:

Section 5.6 Concomitant and post-study treatment(s), page 60

Previous text:

Drugs that may prolong the QT interval are also prohibited. Common examples of such drugs are listed in Appendix J. This list should not be considered comprehensive. Therefore investigators need to use their judgment when reviewing the medication list from individual patients and restrict patients who must stay on drugs that may increase the QT interval.

Revised text:

Drugs that may prolong the QT interval are also prohibited. Common examples of such drugs are listed in Appendix J. **Please note that methadone is included in this category of prohibited drugs.** This list should not be considered comprehensive. Therefore investigators need to use their judgment when reviewing the medication list from individual patients and restrict patients who must stay on drugs that may increase the QT interval.

Section of protocol affected:

Section 5.6 Concomitant and post-study treatment(s), page 59

Previous text:

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

- Pentazocine
- Buprenorphine
- Nalbuphine
- Naloxone
- Naltrexone
- Methylnaltrexone (Relistor®)
- Alvimopan (Entereg®)

Revised text:

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®)

Section of protocol affected:

Section 5.5.3 Additional study drug, page 56

Previous text:

Sites will procure bisacodyl 5 mg tablets for use as laxative rescue medication and will dispense bisacodyl to patients at Visits 2, 3, 4, 5, 6, and 7. Containers for the procured bisacodyl will be provided to the sites (see Section 5.6).

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

Revised text:

Sites will procure bisacodyl 5 mg tablets for use as laxative rescue medication and will dispense bisacodyl to patients at Visits 2, 3, 4, 5, 6, and 7.

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

Section of protocol affected:

Section 6.4.13.1 C-SSRS, page 81

Previous text:

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 suicidal ideation or having a rating of type 4 or 5 on the C-SSRS suicidal ideation scale at any visit when the C-SSRS is administered, 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.

Revised text:

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 visit when the C-SSRS is administered **or indicates having had any suicidal behaviour on the scale**, 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.

Section of protocol affected:

Section 11.2.1, Adverse Events, page 99

Previous text:

A treatment-emergent adverse event (TEAE) is defined as any AE that started on or after the first dose of study drug up to 30 days after 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.

Revised text:

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.**

Section of protocol affected:

Section 11.2.9, ECG, page 101

Previous text:

Changes from baseline to each post-baseline visit (Weeks 1, 2, 4, 8, 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 is the latest non-missing value collected prior to the first dose of study drug (Visit 1 or 3). Marked abnormal values or changes from baseline will be identified based on pre-determined criteria.

Revised text:

Changes from baseline to each post-baseline visit (**Week 0 [2 hours post-dose],** Weeks 1, 2, 4, 8, 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 is the latest non-missing value collected prior to the first dose of study drug (Visit 1 or 3). Marked abnormal values or changes from baseline will be identified based on pre-determined criteria.

Section of protocol affected:

Section 11.2.10, Vital Signs, page 101

Previous text:

Changes from baseline in vital signs (sitting blood pressure and pulse) at each post-baseline visit (Weeks 1, 2, 4, 8, 12, and 14) will be derived as the value at the visit minus the baseline value for the same assessment, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 3).

Revised text:

Changes from baseline in vital signs (sitting blood pressure and pulse) at each post-baseline visit (**Week 0 [1 hour post-dose]**, Weeks 1, 2, 4, 8, 12, and 14) will be derived as the value at the visit minus the baseline value for the same assessment, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 3).

Section of protocol affected:

Section 12.2, Methods of statistical analysis, page 104

Previous text:

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

For the by-visit assessments, baseline will be defined as the latest non-missing value collected prior to the first dose of study drug (screening, Visit 1 or Week 0, Visit 2).

For the eDiary assessments, baseline will be defined as the values observed during the OIC confirmation period, which are the last 14 days prior to randomization (as defined in Section 3.1.2).

Descriptive statistics for continuous data will include n, mean, median, standard deviation, minimum, and maximum values. Descriptive statistics for categorical data will include n, frequency, and percentage.

To control the overall type I error rate to be ≤ 0.05 for the multiple comparisons in the primary and the key secondary endpoints, a Multiple Testing Procedure (MTP) with Bonferroni-Holm over Groups, and Fixed-Sequence within groups will be applied. Specifically, there will be 2 groups defined by the doses of 12.5 and 25 mg, and within each group there will be a pre-defined fixed-sequence MTP of comparisons of the key secondary endpoints vs placebo (ie, responder analysis in LIR subgroup, responder analysis for the 12-week treatment period, and regularity analysis) at level of $\alpha/2$. If the null hypotheses for 1 dose group can be rejected entirely (ie, significant difference between active vs placebo for all 4 endpoints at $\alpha=0.025$), one will increase the level to α (ie, 0.05) for the other group. This amounts to using Bonferroni-Holm over groups, and fix-sequence within groups. This multiplicity adjustment method follows the general results described by Bretz (Bretz et al 2009) and by Burman (Burman et al 2009).

No other correction to the reported p-values will be made for the analysis of additional secondary measures. Where appropriate, 95% confidence intervals (CIs) will be presented.

Revised text:

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

For the by-visit assessments, baseline will be defined as the latest non-missing value collected prior to the first dose of study drug (screening, Visit 1 or Week 0, **Visit 3**).

For the eDiary assessments, baseline will be defined as the values observed during the OIC confirmation period, which are the last 14 days prior to randomization (as defined in Section 3.1.2).

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.

To control the overall type I error rate to be ≤ 0.05 for the multiple comparisons in the primary and the key secondary endpoints, a Multiple Testing Procedure (MTP) with Bonferroni-Holm over Groups, and Fixed-Sequence within groups will be applied. Specifically, there will be 2 groups defined by the doses of 12.5 and 25 mg, and within each group there will be a pre-defined fixed-sequence MTP of comparisons of the key secondary endpoints vs placebo (ie, responder analysis in LIR subgroup, responder analysis for the 12-week treatment period, and regularity analysis) at level of α/2. If the null hypotheses for 1 dose group can be rejected entirely (ie, significant difference between active vs placebo for all 4 endpoints at α=0.025), one will increase the level to α (ie, 0.05) for the other group. This amounts to using Bonferroni-Holm over groups, and fix-sequence within groups. This multiplicity adjustment method follows the general results described by Bretz (Bretz et al 2009) and by Burman (Burman et al 2009).

No other correction to the reported p-values will be made for the analysis of additional secondary measures. Where appropriate, 95% confidence intervals (CIs) will be presented.

Section of protocol affected:

Section 12.2.4, Safety analyses, pages 107, 108

Previous text:

Treatment-emergent AEs will be coded using the MedDRA dictionary. 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. Treatment-emergent AEs will also be summarized by intensity and separately, by causality. 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 will be summarized in a similar manner than TEAEs.

Treatment-emergent AEs, SAEs, TEAEs leading to death, and ~~TE~~AEs leading to study discontinuation will be tabulated for each treatment group. Commonly occurring TEAEs, ie, those which occur in 5% or more of the patients in either treatment group, will be summarized using descriptive statistics. Descriptive statistics for time to onset and duration of select TEAEs will be summarized by treatment group. Treatment-emergent AEs that could potentially be indicative of centrally mediated opioid withdrawal will be identified prior to unblinding and will also be summarized by each treatment group. Evaluation of GI-related symptoms will be conducted at baseline, treatment-emergent GI AEs will be summarized by treatment group.

The observed composite modified Himmelsbach score will be summarized by treatment group at baseline, 2 hours after first dose of study drug, and Weeks 1, 4, and 12 using descriptive statistics. The change from baseline in the composite modified Himmelsbach score, mean daily opioid dose, and mean NRS pain scores (average and worst per day) will be summarized by treatment group, and tested within each treatment group using one-sample t-tests to determine where the change is significantly different from zero. The interpretations in change from baseline within each treatment or difference between treatment groups for these parameters are important to be made clinically.

All laboratory test results, vital signs, 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. Shifts from baseline to each post-baseline visit in the frequency of laboratory values outside of the clinically significant reference range will be presented by treatment group. The incidence of potentially clinically significant laboratory results 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. The incidence of markedly abnormal values and changes from baseline in the ECG parameters will be summarized by treatment group.

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.

Revised text:

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 observed composite modified Himmelsbach score will be summarized by treatment group at baseline, 2 hours after first dose of study drug, and Weeks 1, 4, and 12 using descriptive statistics. The change from baseline in the composite modified Himmelsbach score, mean daily opioid dose, and mean NRS pain scores (average and worst per day) will be summarized by treatment group, and tested within each treatment group using one-sample t-tests to determine where the change is significantly different from zero. The interpretations in change from baseline within each treatment or difference between treatment groups for these parameters are important to be made clinically.

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.

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.

Section of protocol affected:

Section 13.1, Medical emergencies and AstraZeneca contacts, page 109

Previous text:

Name	Role in the study	Address & telephone number
Dr.	North America (NA) Study Physician – Responsible for protocol implementation in US & Canada	
Dr.	Europe Study Physician – Responsible for protocol implementation in Europe	

Revised text:

Name	Role in the study	Address & telephone number
	– Responsible	

Changes to Appendices:

- Appendix E has been revised to clarify that patients with **high risk for CRC** must have had colonoscopy **or** (double contrast barium enema **AND** flexible sigmoidoscopy), or virtual colonoscopy at least within 5 years from the screening visit or they are not eligible to participate in the study. (previous text had only specified that patients with **high risk for CRC** must have had colonoscopy, double contrast barium enema, flexible sigmoidoscopy, or virtual colonoscopy at least within 5 years from the screening visit).

- Appendix J has been revised to include methadone as a drug that prolongs the QT interval

- Headers of Appendices B, C, D, E, and F have been revised to show study number as D3820C00005 instead of D3820C0005 (were missing a "0")

Reasons for Amendment:

- Given that late availability of IP for countries other than the US may influence which countries participate in the study, the list of countries has been expanded to include all potential countries that may participate. This will prevent a delay in finalization of the protocol, and avoid the necessity of creating a new protocol amendment for each new country that may be added.

- The additional 1 hour post-dose blood pressure and heart rate assessment added at randomization, and additional blood pressure monitoring guidelines including guidance if patients show signs of significant decreases in blood pressure were prompted by 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 5 times higher than the maximum dose used in this study.

- It was decided to collect all ECGs during the treatment period in triplicate to allow more precise analysis of any potential effects of NKTR-118 on ECG parameters.

- A mandatory rectal examination is required for patients who roll over into the 52-week safety extension study, because this is a requirement for patients entering the safety extension study, and Visit 8 corresponds to the first visit of the extension study for roll-over patients.

- An enema eCRF has been added to facilitate more precise collection of enema use.

- It was decided not to record opioid breakthrough pain medication on an eCRF in order to avoid potential reconciliation difficulties between opioid breakthrough pain medication recorded in the eDiary and on the opioid breakthrough pain medication eCRF. It was also determined that the eDiary can include all of the necessary information required to fully capture opioid breakthrough pain medication use including dosage and name of medication.

- Clarification regarding allowable PRN short acting opioid use was made in response to feedback at the Investigator Meeting that many patients receive short acting opioids on a fixed basis although their prescription may initially have been written for PRN use. The intent of this change was to clarify this point and allow these patients to participate in the study.

- In response to feedback at the Investigator Meeting, greater detail regarding IBS exclusion criteria was added to clarify how to handle this complex medical condition.

- Exclusion criterion 6 has been modified to delete “ventricular arrhythmias” since this is redundant with exclusion criterion 12.

- Because the QT prolongation potential of NKTR-118 has not been definitely excluded by a thorough QT study in humans, drugs that could potentially impact on QT prolongation (including methadone, recently identified) are excluded.

- It was clarified that combination products containing naloxone or naltrexone should be excluded because these drugs are opioid antagonists and could potentially induce a withdrawal reaction.

- Due to a requirement for labeling when re-packaging bisacodyl and additional logistics required to support this, it was decided that containers for re-packaging bisacodyl would not be provided to sites.

- Protocol clarification regarding handling reported suicidal behaviour on the C-SSRS was added following consultation with Dr. Posner, who developed the C-SSRS.

- Criteria for a treatment-emergent AE has been changed to focus on AEs occurring while on study drug. A separate set of analyses will be performed for AEs that occur after the termination of experimental treatment (i.e. during the follow-up period). This delineation between AEs occurring during the drug exposure and those following removal of the drug will be more precise in separating treatment-emergent AEs and those AEs that potentially result from removal of drug exposure (withdrawal) or recurrence of OIC.

- Safety analyses have been clarified. Changes to the text were made to further clarify analytic procedures for handling of safety data outliers (ie,. shift analyses), adverse event pooling, and safety areas of special interest.

- Appendix E was amended to require a combination of flexible sigmoidoscopy and double contrast barium as a mandatory screening procedure because by itself flexible sigmoidoscopy is not sufficient for colorectal cancer screening as it will not visualize most of the colon.

Persons who initiated the Amendment:

AstraZeneca Clinical Project Team

Clinical Study Protocol

Drug Substance	NKTR-118
Study Code	D3820C00004
Edition Number	1.0
Date	

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

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

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

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 Study to Assess the Efficacy and Safety of NKTR-118 in Patients with Non-Cancer-Related Pain and Opioid-Induced Constipation (OIC)

National Co-ordinating Investigator

Study center(s) and number of subjects planned

This will be a multi-center study conducted in Canada, Slovakia, the United Kingdom (UK), and the United States (US). Approximately 1300 patients will be screened to obtain 630 randomized patients (210 per treatment arm). Approximately 120 centers will participate in the study.

Study period		Phase of development
Estimated date of first patient enrolled	1st Quarter 2011	III
Estimated date of last patient completed	1st Quarter 2012	

Objectives

Primary objective:

- To compare the efficacy of NKTR-118 12.5 and 25 mg with placebo in the treatment of patients who have opioid-induced constipation (OIC).

Secondary objectives:

- To compare NKTR-118 12.5 and 25 mg with placebo on the daily signs and symptoms associated with OIC (straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and quality of life.

Safety objectives:

- To assess the safety and tolerability of NKTR-118 12.5 and 25 mg, when used for the treatment of OIC.

Exploratory objectives:

- To characterize the pharmacokinetics (PK) of NKTR-118 and the covariate effect in the targeted disease population.
- To explore the NKTR-118 exposure-response relationship.
- To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to NKTR-118.
- To assess patient health status index and healthcare resource utilization.
- To assess patients' willingness to take the study drug again.

Study design

This is a Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy and safety of NKTR-118 12.5 and 25 mg in the treatment of OIC in patients with non-cancer-related pain. Patients who successfully complete the 12-week treatment period will be eligible to participate in a separate safety extension study.

Target subject population

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

Confirmed OIC is defined as:

- Documented <3 SBMs/week on average over the 2-week OIC confirmation period. Patients with uneven distribution of SBMs across the 2-week OIC confirmation period (0 SBMs in 1 week with ≥4 SBMs in the other week) will be excluded. In addition to the SBM frequency criterion, patients must report ≥1 of the following symptoms in at least 25% of the BMs recorded in the electronic diary (eDiary)

during the OIC confirmation period: Bristol Stool Scale (BSS) stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM. Patients who have 0 BMs over the 2-week OIC confirmation period will not be randomized.

In addition, a minimum of 50% of patients are to meet criteria for being laxative inadequate responders (LIR).

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 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, during which the diagnosis of OIC and stability of opioid regimen will be confirmed, a 12-week treatment period, and a follow-up visit 2 weeks after the last dose of study drug.

Outcome variable(s):

Primary efficacy variable: Response (responder/non-responder) to study drug during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.

- **Key secondary efficacy variables:**

  - Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks

  - Response (responder/non-responder) to study drug over the entire 12 week treatment period, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 75% of the weeks

  - Regularity during the first 4 weeks of treatment, where regularity is measured as the mean number of days per week with at least 1 SBM during Weeks 1 to 4

  Additional secondary efficacy variables:

  - Change from baseline in the SBMs/week for Weeks 1 to 4 and 1 to 12

  - Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours

- Mean number of days per week with at least 1 SBM for Weeks 1 to 12
- Change from baseline in the mean degree of straining for Weeks 1 to 4 and 1 to 12
- Change from baseline in the mean stool consistency (BSS) for Weeks 1 to 4 and 1 to 12
- Percentage of days with complete evacuation for Weeks 1 to 4 and 1 to 12
- Mean bisacodyl dose per week for Weeks 1 to 4 and 1 to 12
- Change from baseline in Patient Assessment of Constipation Symptoms (PAC-SYM) total score and each domain score for Weeks 2, 4, 8, and 12
- Change from baseline in Patient Assessment of Constipation Quality of Life (PAC-QOL) total score and each domain score for Weeks 4 and 12

- **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 the mean daily opioid dose for Weeks 1 to 4 and 1 to 12
  - Change from baseline in the mean Numeric Rating Scale (NRS) pain score for Weeks 1 to 4 and 1 to 12
  - Observed values and change from baseline in composite score in modified Himmelsbach scale for the evaluation of centrally mediated opioid withdrawal symptoms at 2 hours after first dose of study drug, and at Weeks 1, 4, and 12
  - Changes in vital signs and physical examination
  - Changes in laboratory assessments (ie, chemistry, hematology, and urinalysis [U/A])
  - Changes in electrocardiograms (ECGs)

- **Pharmacokinetics**

  Pharmacokinetics parameters of NKTR-118 will be estimated for individual patients (when possible). These parameters include:

  – oral clearance (CL/F)

  – absorption rate constant (Ka) and

  – area under plasma concentration-time curve from zero to time 24 hours (AUC [0-24])

- **Health economics**

  – Data on the Euroqol 5 Dimension (EQ-5D) questionnaire for Weeks 4 and 12.

  – Data on OIC healthcare resource utilization will be captured at the site for economic modelling purposes

  – Willingness to Take Drug Again questionnaire for Week 12

Statistical methods

The efficacy analysis set will be the Intent-to-Treat (ITT) population, defined as all randomized patients who received at least 1 dose of study drug and have at least 1 post-baseline efficacy assessment. The safety analysis set will be the Safety population, defined as all randomized patients who received at least 1 dose of study drug.

The primary analysis will be made comparing the response rate of Weeks 1 to 4 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by response to laxatives at baseline (LIR, laxative adequate responder [LAR], laxative unknown responder [LUR]).

The following will be categorized as key secondary endpoints:

1. Comparison of the response rate of Weeks 1 to 4 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo in the LIR subgroup. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using Chi-Square tests.

2. Comparison of the response rate of Weeks 1 to 12 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. The response rate for each treatment

group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using CMH tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

3. Comparison of the regularity during the first 4 weeks of treatment of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. Differences between treatment groups in the mean number of days per week with at least 1 SBM will be analyzed using analysis of covariance (ANCOVA), with treatment group and response to laxatives at baseline as fixed effects, and the mean number of days per week with at least 1 SBM during the baseline period as a covariate.

To control the overall type I error rate to be ≤ 0.05 for the multiple comparisons in the primary and the key secondary endpoints, a Multiple Testing Procedure (MTP) with Bonferroni-Holm over Groups, and Fixed-Sequence within groups will be applied. Specifically, there will be 2 groups defined by the doses of 12.5 and 25 mg, and within each group there will be a pre-defined fixed-sequence MTP of comparisons of the key secondary endpoints (ie, responder analysis in LIR subgroup, responder analysis for the 12-week treatment period, and regularity analysis) at level of $\alpha/2$. If the null hypotheses for 1 dose group can be rejected entirely (ie, significant difference between active vs placebo for all 4 endpoints at $\alpha=0.025$), one will increase the level to α (ie, 0.05) for the other group. This amounts to using Bonferroni-Holm over groups, and fix-sequence within groups. This multiplicity adjustment method follows the general results described by Bretz (Bretz et al 2009) and by Burman (Burman et al 2009).

A sample size of 105 patients per group would be needed to detect a difference of 25% in response rate (60% on NKTR and 35% on placebo), with power=90%, $\alpha=0.025$ and 2-sided test. In order to provide an adequate power to detect a treatment difference in the LIR subgroup (assuming LIR is 50% of the total study population), it is recommended that 210 patients per group (total 630 patients for 3 treatment groups) be randomized to the study. The assumptions on expected response rate were referenced from the NKTR-118 Phase II study and from other similar drugs.

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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 6.4.2)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of Covariance
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 hepatits C virus
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC (0-24)	Area under plasma concentration-time curve from zero to time 24 hours
AZDD	AstraZeneca Drug Dictionary
B	Blood
BIL	Bilirubin
BM	Bowel movement
BSS	Bristol Stool Scale
BUN	Blood urea nitrogen
Ca	Calcium
CI	Confidence interval
CK	Creatine kinase
CMH	Cochran-Mantel-Haenszel
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

Abbreviation or special term	Explanation
CSP	Clinical study protocol
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical study report
CYP3A4	Cytochrome P450 3A4
DEA	Drug Enforcement Administration
dECG	Digital electrocardiogram
DES	(Patient safety) data entry site
DM	Data management
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
EBV VCA IgM + EBNA IgG	Immunoglobulin M antibody to Epstein Barr virus viral capsid antigen + Immunoglobulin G antibody to Epstein Barr virus nuclear antigen
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid
ePRO	Electronic patient reported outcome
EQ-5D	Euroqol 5 Dimension Instrument
eRT	eResearch Technology
ET	Early termination
FIT	Fecal immunochemical test
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practices
GRand	AstraZeneca's Global Randomization system
H	High
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCV RNA	Hepatitis C virus ribonucleic acid
HDPE	High-density polyethylene
IB	Investigator's Brochure

Abbreviation or special term	Explanation
ICF	Informed consent form
ICH	International Conference on Harmonisation
I/E	Inclusion/exclusion
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
Ka	Absorption rate constant
L	Low
LAR	Laxative Adequate Responder
LIR	Laxative inadequate Responder
LUR	Laxative Unknown Responder
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MTP	Multiple Testing Procedure
NA	North America
NONMEM	Nonlinear mixed effect modeling
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
PK	Pharmacokinetics
POPPK	Population PK

Abbreviation or special term	Explanation
PP	Per protocol (population)
PR	(PR interval) The time from the onset of the P wave to the onset of the QRS complex on an electrocardiogram.
PRMP	Patient risk management plan
PRN	As occasion requires
PRO	Patient reported outcome
PT	Prothrombin time
QD	Every day
QLAB	Quintiles Laboratories
QRS	(QRS interval) The time from the beginning to the end of a QRS complex on an electrocardiogram.
QT	(QT interval) The time from the onset of the QRS complex to the end of the T wave on an electrocardiogram.
QTc	Corrected QT interval
QTcF	Fridericia corrected QT interval
RDW	Red blood cell distribution width
RR	(RR interval)
S	Serum
SAE	Serious adverse event (see definition in Section 6.4.3)
SAP	Statistical Analysis Plan
SBM	Spontaneous bowel movement
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
UBC	United BioSource Corporation
UK	United Kingdom
ULN	Upper limit of normal
US	United States

Abbreviation or special term	Explanation
WBC	White blood cell
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

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

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

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

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

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

Based on the above, it is appropriate to proceed with a Phase III study in the target population, that is, patients receiving opioid therapy for non-cancer-related pain who are experiencing OIC. This study will evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of 2 dose levels of NKTR-118. 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 useful in the treatment of OIC.

1.3 Rationale for conducting this study

The goal of this Phase III study to is demonstrate that NKTR-118 is well-tolerated and efficacious in the treatment of OIC in patients taking opioids for their non-cancer-related pain. NKTR-118 is expected to reverse 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. 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 vital signs, laboratory parameters, or electrocardiograms (ECGs). In a Phase I repeated dose study, adverse events (AEs) of dizziness were reported by 4/6 patients at the highest dose of NKTR-118 compared with 2/8 placebo patients. All events of dizziness were transient and resolved spontaneously without the need for any intervention.

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

NKTR-118 was well-tolerated in the Phase II study at 5 and 25 mg/day with the most commonly reported side effects being GI in nature (abdominal pain, diarrhea, and nausea) and most frequent in the 50 mg cohort. The frequency of any GI AE was 53% in the 25 mg/day

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

As summarized above, participation in this study may carry risks. New risks may be discovered when more patients are exposed to NKTR-118. 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. Because a thorough QT study has not yet been conducted, ECGs will be recorded and submitted for centralized analysis at screening, randomization (pre-dose and post-dose), and at each visit thereafter. In addition, individuals at high risk for arrhythmias are excluded from participation until the effect of NKTR-118 on QT interval in humans has been assessed.

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 6.4.13.2 for additional guidance.

To be able to determine scientifically if there is medical benefit from NKTR-118, this study has been designed as a monotherapy study with a placebo treatment arm. A dose range of 12.5 to 25 mg will be tested. 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. A rescue

medication is incorporated in the study design by use of bisacodyl if no SBM has occurred within at least 72 hours since the previous one. Further guidance is provided on the use of an enema if bisacodyl is ineffective. The risks of receiving placebo or ineffective medication in this population are expected to be low given the Phase II study results.

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

There may be benefits to patients as a result of participating in this study. Randomization to the active treatment group may provide symptomatic relief from OIC for the duration of the study. After the end of the study, the patient will be offered an opportunity to participate in a 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 the efficacy of NKTR-118 12.5 and 25 mg with placebo in the treatment of patients who have OIC.

2.2 Secondary objectives

The secondary objectives are to compare NKTR-118 12.5 and 25 mg with placebo on the daily signs and symptoms associated with OIC (straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and quality of life.

2.3 Safety objectives

The safety objectives are to assess the safety and tolerability of NKTR-118 when used for the treatment of OIC.

2.4 Exploratory objectives

The exploratory objectives are to characterize the PK of NKTR-118 and the covariate effect in the targeted disease population, explore the NKTR-118 exposure-response relationship, collect and store deoxyribonucleic acid (DNA) for future exploratory research, assess patient health status index and healthcare resource utilization, and assess patients' willingness to take the study drug again.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group study of 2 doses of NKTR-118 and placebo. The study duration will be up to 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, during which the diagnosis of OIC and stability of the opioid regimen will be confirmed, 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 will be eligible to participate in a separate safety extension study. Approximately 1300 patients will be screened to obtain 630 randomized patients at approximately 120 centers in Canada, Slovakia, the UK, and the US.

Patients will sign the informed consent at the initial screening visit (Visit 1), within 14 days prior to entering the OIC confirmation period. Screening assessments will include review of inclusion/exclusion (I/E) criteria, collection of demographic information, and assessment of routine safety laboratory parameters (hematology and chemistry), ECG, urine pregnancy test for women of childbearing potential (WOCBP), urinalysis (U/A), urine drug screen, medical and surgical history, prior and concomitant medications, daily opioid use, laxative use, physical examination including rectal examination and vital signs, and the Columbia-Suicide Severity Rating Scale (C-SSRS). At the screening visit patients must also adhere to the colorectal cancer (CRC) screening criteria outlined in Appendix E. This includes provision of a stool sample for fecal immunochemical testing (FIT) for some patients, and patients at high risk for CRC providing documentation of negative colonoscopy or other appropriate imaging measures performed within 5 years of the screening visit. At screening, patients will receive an electronic diary (eDiary) device and training on how to record information using the device. Patients will be required to record information using the device during a pilot training period, to last a minimum of 5 consecutive days (see Section 3.1.1).

In addition, laxative response status will be determined at the screening visit (Visit 1) based on response to a questionnaire (See Section 6.2.2 and Appendix F). On the basis of physician assessment, patients will be grouped into 1 of 3 categories: patients who had adequate response to laxatives (Laxative Adequate Responder [LAR]), patients who had inadequate response to laxatives (Laxative Inadequate Responder [LIR]), and those patients whose laxative responder status could not be confirmed due to lack or infrequent use of laxatives in the 2 weeks before screening (Laxative Unknown Responder [LUR]).

Once patients have met initial screening requirements (including self-reported active symptoms of OIC at screening [<3 SBMs/week and ≥1 reported symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction in at least 25% of bowel movements (BMs) over the previous 4 weeks]), and have completed at least 5 days of recording using the eDiary device, they will return for Visit 2. At Visit 2, the eDiary

recording will be reviewed with the patient and instructions regarding proper recording will be repeated. Patients who experienced difficulty using the device will have the opportunity to have any questions answered. Daily opioid use, use of other medications, and AEs will also be collected at Visit 2. Bisacodyl for use as a rescue medication will be dispensed to patients at Visit 2, and at each visit thereafter until Visit 8. Confirmation of OIC will be established between Visits 2 and 3.

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

Confirmed OIC is defined as:

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

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

Randomization will occur at the onset of the 12-week double-blind treatment period at Visit 3. Patients will be stratified based on their response to laxative use (LIR, LAR, LUR), and randomly assigned to 1 of the 3 treatment groups in a 1:1:1 ratio, with a minimum of 50% of patients enrolled in the LIR category. Patients will be randomly assigned in a 1:1:1 ratio (approximately 210 patients per treatment arm) to receive placebo, or NKTR-118 at a dose of 12.5 or 25 mg every day (QD).

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.

During the OIC confirmation and treatment periods of the study, patients will be required to stop all laxatives and other bowel regimens, and may use only bisacodyl as rescue medication if a BM has not occurred within at least 72 hours of the last recorded BM.

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. If these secondary interventions fail, the patient should be discontinued from the study (or excluded from the study if the patient fails the rescue regimen prior to randomization) 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 randomized (see Section 4.2).

Study assessments include:

Electronic Diary (eDiary) Assessments: (collected daily starting with pilot training during the screening period through the end of randomized treatment).

- Date and time of BMs (recorded at the time of each BM)
- Stool consistency (BSS) (recorded at the time of each BM)
- Straining (recorded at the time of each BM)
- Complete/incomplete evacuation (recorded at the time of each BM)
- Pain level (NRS) recorded each evening
- Date and time of use of laxative rescue medication (bisacodyl or enema) recorded at the time that medication is taken

- Date and time of use of opioid medication for breakthrough pain recorded at the time that medication is taken

Additional Assessments:

- 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 [EQ-5D], and Willingness to Take Drug Again questionnaire). The PAC-SYM, PAC-QOL, and EQ-5D, will be completed at selected time points from Visit 3 on; the Willingness to Take Drug Again questionnaire will be completed at Visit 8. At Visit 3, patients will receive training on filling out these questionnaires using an electronic device called a SitePad at the study center, and will be instructed that they are to answer the questions on their own, without any help from family or study staff. In addition, for visits after Visit 3, 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 3, since only randomized patients will fill out the questionnaires and interaction with study staff will be necessary to determine whether randomization criteria have been met.)

- C-SSRS throughout the study

- OIC Healthcare Resource Utilization assessed from Visit 4 through Visit 9

- Recording of concomitant medications (other than laxative rescue medication and opioid medication for breakthrough pain) throughout the study

- Recording of opioid medication for breakthrough pain throughout the study – specific information regarding timing of breakthrough pain medication is captured in the eDiary. Information regarding breakthrough pain medication is also collected on electronic case report forms (eCRFs) and recorded in the eDiary to allow for daily recording of dosing.

- Recording of AEs throughout the study

- Recording of daily maintenance opioid regimen throughout the study

- Routine safety laboratories (hematology, chemistry, and total cholesterol) and U/A and clinical assessments at screening and at selected time points throughout the study

- ECG at screening and at selected time points throughout the study

- Vital signs and physical examination at screening and at selected time points throughout the study
- Pregnancy test for WOCBP at screening and selected time points throughout the study
- PK sampling throughout the study starting with Visit 3
- Genetic sampling (optional; for patients who consent, collected once after randomization, preferably at Visit 3)

3.1.1 Visit 1 (Initial screening)

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.

At Visit 1, each patient's laxative response status will be determined based on 4 questions which explore the frequency of laxative use, constipation symptom severity, and laxative side-effects during the previous 2 weeks. The patients will be classified as LIR, LAR, or LUR based on their answers. The LIR/LAR/LUR algorithm is presented in more detail in Section 6.2.2 and in Appendix F.

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

- Patients will receive the eDiary recording device and detailed instructions for its use. The eDiary is to be completed for at least 5 consecutive days of pilot training and will be used to collect daily information regarding BMs, straining, stool consistency, complete/incomplete evacuation, pain level, use of laxative rescue medication, and use of opioid medication for breakthrough pain. However, the pilot period will not be counted towards the 14 day OIC confirmation period, which begins at Visit 2.

The following additional procedures will be performed at Visit 1:

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

- Review of inclusion and exclusion criteria including review of CRC screening requirements
- FIT test or verification of previous imaging study, if required
- Review of medical and surgical history (including OIC history)
- Complete physical examination (including rectal examination, height, weight, body temperature, respiratory rate)
- Sitting blood pressure and pulse will be measured.
- Single 12-lead ECG will be obtained.
- Urine sample will be collected for urine drug screen (urine toxicology), to test for pregnancy (WOCBP), and for U/A.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- C-SSRS to assess suicidal risk, ideation, and behavior
- Modified Himmelsbach scale will be completed.
- Daily maintenance and breakthrough pain opioid dosing regimens over the 60 days before enrollment will be asked about and recorded on the appropriate eCRFs. The daily opioid and breakthrough pain dosing regimens will be confirmed by prescription or clearly labeled bottles of opioid medication. Information from the breakthrough pain medication eCRF will be recorded in the eDiary to allow for daily recording of dosing
- Use of prior/concomitant medication will be recorded. Prior medications taken up to 60 days before enrollment will be recorded.
- An appointment for Visit 2 will be made. Patients will be instructed to bring the eDiary with them to the visit.

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

3.1.2 Visit 2 (OIC confirmation)

Visit 2 will occur 5 to 14 days after Visit 1, as soon as all initial screening assessments have taken place, results have been reviewed by the investigator, eligibility determined, and a

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

At Visit 2, patients who failed initial screening requirements will return the eDiary, be asked if any AEs have occurred since Visit 1, will be administered the C-SSRS, and will be discontinued from the study. Patients who are discontinued from the study prior to randomization will be considered to be screen failures.

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

Patients will be asked to discontinue all laxative and other bowel regimens including herbal products and prune juice (see prohibited medications, Section 5.6) throughout the 2-week OIC confirmation period and 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 2 through Visit 7. Patients will be instructed on the guidelines for rescue bisacodyl use. Patients will be asked to return unused bisacodyl at each subsequent visit. Documentation of bisacodyl use will be reviewed with the patient at each visit by comparing returned bisacodyl with eDiary records. If there is a discrepancy, the patient will be counseled regarding proper documentation of bisacodyl use in the eDiary. If a patient does not experience a BM following bisacodyl rescue, the investigator may prescribe one-time use of an enema. The timing of administration of this therapy will be noted. If these secondary interventions fail, the patient should be excluded from the study and referred for additional medical evaluation. Since the patient is excluded from the study, the investigator should recommend initiation of any therapy deemed most appropriate. Any patient who is obstipated and/or has fecal impaction must not be randomized (see Section 4.2).

The following additional procedures will be performed at Visit 2:

For patients who do not continue in the study:

- AEs since Visit 1 will be recorded.
- The eDiary device will be returned.
- C-SSRS to assess suicidal risk, ideation, and behavior

For patients who continue in the study:

- AEs since Visit 1 will be recorded.
- Use of concomitant medication (other than opioid medication) since Visit 1 will be recorded. Use of laxatives will be recorded on the concomitant medication eCRF.
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Bisacodyl will be dispensed.
- An appointment for Visit 3 (Week 1, Day 1) will be made. Patients will be instructed to bring the eDiary recording device and unused bisacodyl with them to the visit.

3.1.3 Double-blind treatment period (Visits 3, 4, 5, 6, 7, 8)

During the double-blind treatment period, patients will be required to continue daily eDiary recording of BMs along with ratings of straining, stool consistency (BSS), and complete/incomplete stool evacuation as each BM occurs, pain level (NRS scale) recorded each evening, use of laxative rescue medication, and use of opioid medication for breakthrough pain. Patients will be instructed that they are to complete the eDiary every day, including days that they have study visits. Compliance with the eDiary will be assessed remotely by the site at least every 48 hours to confirm that the patient is entering data. The patient will be phoned if any data are missing. Patients will also be asked to bring the eDiary recording device with them to each visit, during which their recordings and proper use of the device will be reviewed.

Patients will be asked to bring their bottles of study drug with them to each visit, so that unused study drug tablets can be counted and recorded, and compliance can be determined. Patients should be reminded of the importance of adherence to the study dosing regimen.

Patients will also be instructed that should they experience a change in their daily maintenance or breakthrough pain opioid 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.

Bisacodyl for use as rescue medication will be dispensed to patients at each visit. Patients will be asked to return unused bisacodyl at each subsequent visit. Documentation of bisacodyl use will be reviewed with the patient at each visit by comparing returned bisacodyl with eDiary records. If there is a discrepancy, the patient will be counseled regarding proper documentation of bisacodyl use in the eDiary.

Patients will receive their first dose of study drug at the study center at Visit 3. For subsequent visits through Visit 8, patients will self-administer the study drug in the morning (per their usual routine) prior to coming to the study center.

Patients who discontinue prematurely from the study after participating in Visit 3 and receiving at least 1 dose of study drug will be asked to return to the study center for an early termination (ET) visit during which unused study drug and the eDiary will be returned, and assessments normally scheduled for Visit 8 (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).

3.1.3.1 Visit 3 (Randomization, Week 0, Day 1)

Visit 3 will occur 14 days (-1 day to +3 days) after Visit 2, at the completion of the OIC confirmation period. A minimum of 11 days of eDiary data collection must have been recorded since the start of the OIC confirmation period before the patient can be randomized for the study.

Visit 3 will be scheduled in the morning. Patients will be required to remain at the study center for a minimum of 4 hours after receiving the study drug, for observation (see Section 6.4.13.2 regarding abdominal pain), PK sampling, and completion of the modified Himmelsbach scale. A light breakfast (eg, skim or lowfat milk, cereal, fruits, coffee, tea) will be allowed; however, a minimum of 4 hours must have passed after breakfast and before the study drug can be given at Visit 3. No food or snacks are allowed for 1 hour after dosing.

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

Patients who cannot appropriately use the eDiary device (greater than 25% of the data are missing), will be considered for exclusion from the study.

Patients who continue in the study will also complete electronic PRO (ePRO) assessments (PAC-SYM, PAC-QOL, EQ-5D) after randomization. Patients will receive training from study staff regarding how to enter the data electronically using an electronic device called a SitePad provided at the study center. Training procedures will be documented separately from this CSP. Patients will be instructed to answer the questions on their own, without help from others (family, friends, or study staff).

At Visit 3, the following procedures will be performed:

For patients who do not continue in the study:

- AEs that occurred since Visit 2 will be recorded.
- The eDiary device will be returned.

- C-SSRS to assess suicidal risk, ideation, and behavior
- Unused bisacodyl will be returned.

For patients who continue in the study:

Pre-dose:

- I/E criteria will be reviewed with the patient.
- The eDiary (including proper documentation of bisacodyl and enema use) will be reviewed with the patient, and instruction on proper completion of the eDiary will be reviewed.
- Patients will receive training on how to fill out ePRO assessments using the SitePad at the study site.
- PAC-SYM will be completed.
- PAC-QOL will be completed.
- EQ-5D will be completed.
- Sitting blood pressure and pulse will be measured.
- Targeted physical examination (lungs, cardiovascular, abdomen) with weight. Special emphasis should be placed on the pre-randomization abdominal examination so as not to enroll any patients with an acute abdominal process (see Section 4.2). At the discretion of the investigator, a rectal examination may be performed at this time, if necessary to ensure the safety of the patient.
- 12-lead ECG after resting for 10 minutes, with triplicate ECGs collected over a 5-minute period
- Urine sample will be collected for urine pregnancy test (WOCBP). The urine pregnancy test result must be negative before the patient may continue with the visit and administration of study drug.
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 2 will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior
- AEs since Visit 2 will be recorded.

- Modified Himmelsbach scale will be completed by a clinician before the patient receives the first dose of study drug.
- Patients who continue to meet I/E criteria (including confirmation of stability of the dose of the opioid) and who meet OIC criteria will be randomized to a treatment arm using the Interactive Voice Response System (IVRS).
- Unused bisacodyl will be returned.
- Weight will be assessed.
- Blood samples will be collected for laboratory assessments (clinical chemistry [including total cholesterol] and hematology).
- Blood sample will be collected for genetic sampling (if genetic informed consent signed). It is preferred that the blood sample for genetic analysis be collected at Visit 3; however, it may be collected at any visit during the study after the patient is randomized.

Dose:

- First dose of double-blind study drug will be administered at the study center and the patient observed for at least 4 hours. The accurate dose time in date, hours, and minutes will be recorded.

Post-dose:

- Single ECG will be obtained 2 hours after the dose of study drug, before the PK sample is collected.
- Modified Himmelsbach scale will be completed by a clinician 2 hours after patient receives the first dose of study drug.
- Blood sample will be collected for PK measurement 2 hours after the dose of study drug. The PK sampling time in date, hours, and minutes will be recorded accurately.
- Any BM during the 4-hour observation period will be recorded by the patient in the eDiary.
- Study drug will be dispensed and dosing instructions will be provided.
- A new supply of bisacodyl will be dispensed.
- An appointment for Visit 4 (Day 8) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit.

3.1.3.2 Visit 4 (Week 1, Day 8)

Visit 4 will occur on Day 8 (±1 day). At Visit 4, the following procedures will be performed. (Note: The OIC Healthcare Resource Utilization questionnaire will be administered starting on Visit 4):

- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse will be measured.
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- Blood sample will be collected for PK measurement. The PK sampling time in date, hours, and minutes will be recorded accurately. The accurate last 2 dose times of study drug in date, hours, and minutes will be collected. Any missing dose of study drug in the previous 5 days will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 3 will be recorded.
- Patient will bring unused study drug to visit and number of unused study drug tablets will be recorded in order to determine patient compliance.
- AEs since Visit 3 will be recorded.
- Modified Himmelsbach scale will be completed.
- Unused bisacodyl will be returned and a new supply of bisacodyl will be dispensed.
- eDiary (including proper documentation of bisacodyl and enema use) review
- An appointment for Visit 5 (Day 15) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit.

3.1.3.3 Visit 5 (Week 2, Day 15)

Visit 5 will occur on Day 15 (±1 day). At Visit 5, the following procedures will be performed:

- PAC-SYM will be completed.

- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse will be measured.
- Single 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- Blood sample will be collected for PK measurement. The PK sampling time in date, hours, and minutes will be recorded accurately. The accurate last 2 dose times of study drug in date, hours, and minutes will be collected. Any missing dose of study drug in the previous 5 days will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 4 will be recorded.
- Patient will bring unused study drug to visit and number of unused study drug tablets will be recorded in order to determine patient compliance.
- AEs since Visit 4 will be recorded.
- Unused bisacodyl will be returned and a new supply of bisacodyl will be dispensed.
- eDiary (including proper documentation of bisacodyl and enema use) review
- An appointment for Visit 6 (Day 29) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit.

3.1.3.4 Visit 6 (Week 4, Day 29)

Visit 6 will occur on Day 29 (±3 days). At Visit 6, 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 will be measured.
- Single 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology) and serum pregnancy test (WOCBP).
- Blood sample will be collected for PK measurement. The PK sampling time in date, hours, and minutes will be recorded accurately. The accurate last 2 dose times of study drug in date, hours, and minutes will be collected. Any missing dose of study drug in the previous 5 days will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 5 will be recorded.
- AEs since Visit 5 will be recorded.
- Modified Himmelsbach scale will be completed.
- Unused bisacodyl will be returned and a new supply of bisacodyl will be dispensed.
- eDiary (including proper documentation of bisacodyl and enema use) review
- Unused study drug will be returned and the number of unused study drug tablets will be recorded. Patient compliance will be determined.
- Study drug will be dispensed.
- An appointment for Visit 7 (Day 57) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit.

3.1.3.5 Visit 7 (Week 8, Day 57)

Visit 7 will occur on Day 57 (±3 days). At Visit 7, the following procedures will be performed:

- PAC-SYM will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse will be measured.

- Single 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology) and serum pregnancy test (WOCBP).
- Blood sample will be collected for PK measurement. The PK sampling time in date, hours, and minutes will be recorded accurately. The accurate last 2 dose times of study drug in date, hours, and minutes will be collected. Any missing dose of study drug in the previous 5 days will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 6 will be recorded.
- AEs since Visit 6 will be recorded.
- Unused bisacodyl will be returned and a new supply of bisacodyl will be dispensed.
- eDiary (including proper documentation of bisacodyl and enema use) review
- Unused study drug will be returned and the number of unused study drug tablets will be recorded. Patient compliance will be determined.
- Study drug will be dispensed.
- An appointment for Visit 8 (Day 85) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit. In addition, patients will be asked if they are interested in participating in a safety extension study. It is also recommended that patients get a reminder phone call prior to Visit 8 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 8 for confirmation of their daily maintenance and breakthrough pain opioid dosing regimens.

3.1.3.6 Visit 8 (Week 12, Day 85)

Visit 8 will occur on Day 85 (±3 days). At Visit 8 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.
- Willingness to Take Drug Again questionnaire will be completed
- Physical examination including weight, body temperature, and respiratory rate
- Sitting blood pressure and pulse will be measured.
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry [including total cholesterol] and hematology).
- Blood sample will be collected for PK measurement. The PK sampling time in date, hours, and minutes will be recorded accurately. The accurate last 2 dose times of study drug in date, hours, and minutes will be collected. Any missing dose of study drug in the previous 5 days will be recorded.
- Urine sample will be collected for U/A, urine drug screen (urine toxicology), and urine pregnancy test (WOCBP).
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 7 will be recorded.
- AEs since Visit 7 will be recorded.
- Modified Himmelsbach scale will be completed.
- eDiary (including proper documentation of bisacodyl and enema use) review, and return of the eDiary device
- 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 9 (Final Visit, Day 99) will be made for patients who do not participate in the safety extension study.

Following Visit 8, patients may resume any constipation regimen that they and the investigator feel is appropriate, unless they choose to continue in the safety extension study. Note: Visit 9 is not required for patients who enter the safety extension study.

3.1.4 Final Visit (Visit 9, Week 14, Day 99)

Visit 9 will occur on Day 99 (±3 days). At Visit 9, the following procedures will be performed:

- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse will be measured.
- 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
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (including bisacodyl and enema) since Visit 8 will be recorded.
- AEs since Visit 8 will be recorded.

Table 1 Study plan

	Screening	OIC Confirmation	Treatment Period					Final	
Week	**-4 to -2[a]**	**-2 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**14**
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET**	**9**
Study Day	**-28 to -14**	**-14 to -1**	**D1[b]**	**D8**	**D15**	**D29**	**D57**	**D85[c]**	**D99[d]**
Visit Window (Days)			**-1 to +3**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**
Informed consent & genetic informed consent[e]	√								
Randomization			√						
Demographic information	√								
Inclusion/exclusion criteria	√		√						
CRC risk factor evaluation (including FIT as necessary)	√								
Medical and surgical history (including OIC history)	√								
Complete physical examination (including height, weight, temperature, respiratory rate)[f]	√		(√)[f]					√	
Sitting blood pressure, pulse	√		√	√	√	√	√	√	√
LIR, LAR, LUR status[g]	√								
Pregnancy test for WOCBP[h]	√		√			√	√	√	√
12-lead ECG[i]	√		√	√	√	√	√	√	√
Clinical chemistry and hematology[j]	√		√	√	√	√	√	√	√
Total cholesterol			√					√	
Urinalysis[k]	√							√	`
Urine drug screen[l]	√							√	
Genetic sampling[e]			√						
PK sampling[m]			√	√	√	√	√	√	
C-SSRS	√	√	√	√	√	√	√	√	√
Opioid regimen recorded (maintenance and breakthrough)	√	√	√	√	√	√	√	√	√
Modified Himmelsbach scale[n]	√		√	√		√		√	
PAC-SYM[o]			√		√	√	√	√	

Table 1 Study plan

	Screening	OIC Confirmation	Treatment Period					Final	
Week	**-4 to -2[a]**	**-2 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**14**
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET**	**9**
Study Day	**-28 to -14**	**-14 to -1**	**D1[b]**	**D8**	**D15**	**D29**	**D57**	**D85[c]**	**D99[d]**
Visit Window (Days)			**-1 to +3**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**
PAC-QOL[o]			√			√		√	
EQ-5D[o]			√			√		√	
OIC Healthcare Resource Utilization Assessment[o]				√	√	√	√	√	√
Prior/concomitant medication (other than laxative rescue medication and opioid medication)[p]	√	√	√	√	√	√	√	√	√
eDiary device dispensed	√								
eDiary ([daily]: BM, straining, complete/incomplete evacuation, stool consistency (BSS), pain level [NRS], laxative rescue medication [bisacodyl, enema], opioid medication for breakthrough pain)[q]	√ ◄----------	----------	----------	----------	----------	----------	----------►	√	
eDiary (including proper documentation of bisacodyl and enema use) review		√	√	√	√	√	√	√	
eDiary device returned		√[r]	√[r]					√	
AEs		√[s]	√[s]	√	√	√	√	√	√
Return unused study drug[t]				√	√	√	√	√	
Dispense study drug			√			√	√		
Dispense bisacodyl		√	√	√	√	√	√		
Return unused bisacodyl			√	√	√	√	√	√	
Willingness to Take Drug Again questionnaire[o]								√	
Make appointment for next visit	√	√	√	√	√	√	√	√	

AEs Adverse events; BSS Bristol Stool Scale; CRC colorectal screening; C-SSRS Columbia Suicide Severity Scale; D Day; ECG electrocardiogram; eDiary electronic diary; ePRO electronic patient reported outcome; EQ-5D European Quality of Life; ET early termination; FIT fecal immunochemical test; 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; PK pharmacokinetic; SBM spontaneous bowel movement; NRS Numeric Rating Scale; WOCBP women of childbearing potential

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

[b] A minimum of 11 days of eDiary data collection must have occurred since the start of the OIC confirmation period before the patient can be randomized.

Day 1 visit requires 4-hour post-dose in-office stay.

[c] Day 85 assessments should be performed at the time of early termination for patients who discontinue early, with the exception that patients who discontinue prior to Visit 3 (randomization) will not be required to have Day 85 assessments.

[d] Patients who enter the safety extension study do not need to participate in Visit 9.

[e] Genetic informed consent does not need to be obtained at enrollment, but must be obtained before any blood sample for genetic analysis is collected. It is preferred that blood samples for genetic testing be collected at Visit 3, but blood samples may be collected at any visit from Visit 3 through Visit 9.

[f] Visit 1: physical examination will include rectal examination, as well as height, weight, temperature, respiratory rate; Visit 3 (Randomization): targeted physical examination (lungs, cardiovascular, abdomen) with weight, collected, may include optional rectal examination at the discretion of the investigator, if necessary to ensure the safety of the patient; Visit 8 (end-of-treatment): physical examination including weight, temperature, respiratory rate (no rectal examination).

[g] Determined based on self reported laxative use over the 2 weeks prior to the screening visit, continued constipation symptoms, and laxative side effects.

[h] Urine pregnancy tests will be performed at screening (Visit 1), randomization (Visit 3), and Week 12 (Visit 8). Any positive urine pregnancy test is to be followed up with a serum pregnancy test. Serum pregnancy tests will be performed at Week 4 (Visit 6), Week 8 (Visit 7), and Week 14 (Visit 9).

[i] At randomization (Visit 3) a 12-lead ECG will be repeated in triplicate pre-dose, and a single ECG will be obtained 2 hours post-dose. Triplicate ECGs will also be obtained at Week 1 (Visit 4) and Week 12 (Visit 8). Single 12-lead ECGs will be obtained at Weeks 2 (Visit 5), 4 (Visit 6), 8 (Visit 7), and 14 (Visit 9)

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

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

[l] If, in the opinion of the investigator, a patient is undergoing opiate withdrawal or significant exacerbation of pain, the investigator is to conduct a repeat urine drug screen to rule out noncompliance with the opioid regimen as an explanation for withdrawal or pain.

[m] PK sample collection during the Day 1 visit will be 2 hours after the dose of study drug. One PK sample will be collected at each visit specified for PK collection. The PK sampling time in date, hours, and minutes will be recorded accurately. For the Day 1 visit, the dose time in date, hours, and minutes will be recorded accurately. For subsequent specified visits, the accurate last 2 dose times of study drug in date, hours, and minutes will be recorded. Any missing dose in the 5 days before each specified PK visit will be recorded.

[n] Completed before the first dose and 2 hours after the first dose during Visit 3.

[o] The ePRO questionnaires (PAC-SYM, PAC-QOL, EQ-5D) 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 3, since only randomized patients will fill out the questionnaires and interaction with study staff will be necessary to determine whether randomization criteria have been met. As applicable, the OIC Healthcare Resource Utilization Assessment is to be completed after the ePRO questionnaires, and prior to any investigations or discussions about symptoms with study staff.

[p] Prior medications will be collected from 60 days before screening. At Visit 9, concomitant medication will include laxative rescue medication taken since Visit 8.

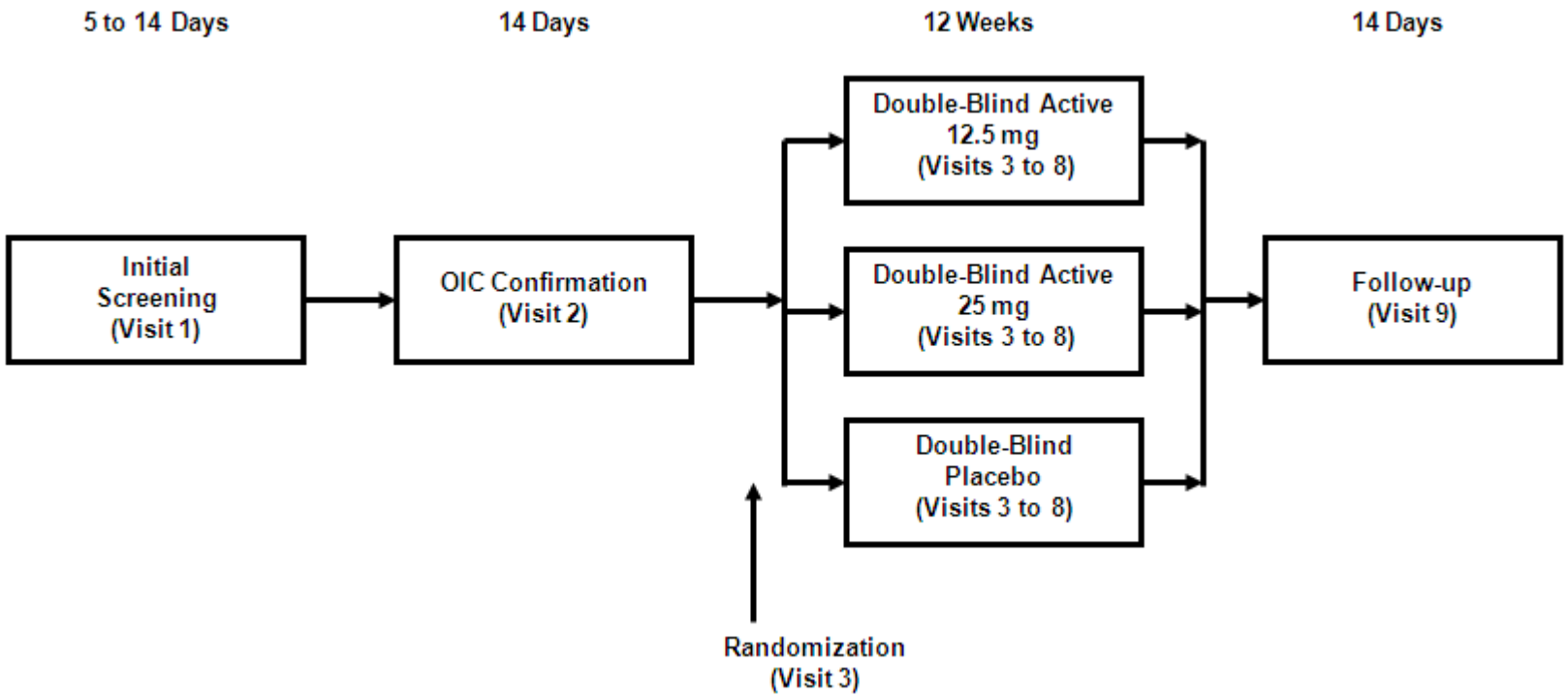
[q] eDiary assessments collected daily by the patient, eDiary pilot training will begin at Visit 1.

[r] Patients who do not meet initial screening criteria will return the eDiary device at Visit 2; patients who do not meet OIC confirmation criteria, or who continue to have difficulty using the eDiary recording device, will return the eDiary device at Visit 3.

[s] For patients who fail initial screening, AEs will be collected at Visit 2. For patients who fail OIC confirmation, AEs will be collected at Visit 3.

[t] Patients will be asked to bring the study drug with them to Visits 4 through 8 (to assess compliance); unused study drug will be returned/collected at Visits 6, 7, and 8.

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 confirm the effect of NKTR-118 on SBMs/week and symptoms of constipation in patients with confirmed OIC. A placebo comparator (and double-blind design) is chosen to control for normal disease course and other non-specific factors.

The assessment of constipation in this study is based on the Rome III criteria, reflecting standard practice (Longstreth et al 2006). Spontaneous BM frequency is a well-recognized primary endpoint, commonly employed in pharmaceutical research and the academic literature.

Patients with varying response to laxatives (LIR, LAR, LUR) are included in this study; however, a minimum of 50% of patients will have laxative inadequate response. Laxative inadequate responders are an important subpopulation with high unmet medical need for a chronic oral treatment option. Planned secondary analyses focus on the response to NKTR-118 in the LIR population only.

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 Phase II study consisted almost exclusively of patients who did not have cancer-related pain, and the present study is an attempt to replicate and extend those findings. Furthermore, it is likely that the AE profile in a non-cancer pain population is different from that of patients with cancer.

The present study includes a screening period (up to 2 weeks), a 2-week OIC confirmation period to confirm the diagnosis of OIC, a 12-week treatment period, and a follow-up visit 2 weeks after last dose of study drug. During the screening period, patients will receive instruction on using the eDiary device and will have the opportunity to practice using the device for at least 5 days. This training is included to minimize patient error in using the device. During the 2-week OIC confirmation period, patients will have additional time to become proficient using the device. The 12-week treatment period is longer than the 4-week treatment period employed in the Phase II study and will provide longer term safety and

efficacy data. Interested patients will also have the opportunity to participate in a separate safety extension study at the completion of the present study.

Laxative use is prohibited during the OIC confirmation and treatment periods, 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 reverse the symptoms of OIC by blocking the peripheral effects of opioid medication without inducing central opioid withdrawal symptoms or interfering with analgesia. Although there was no indication of opioid withdrawal symptoms or reversal of analgesia in the Phase II study, the current study includes the modified Himmelsbach scale to assess withdrawal symptoms, and the NRS along with ongoing assessment of daily opioid dose to assess pain.

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

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

4. SUBJECT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

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

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

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

3. Self-reported active symptoms of OIC at screening (<3 SBMs/week and experiencing ≥1 reported symptom of hard/lumpy stools, straining, or sensation of

incomplete evacuation/anorectal obstruction in at least 25% of BMs over the previous 4 weeks); **and**

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

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

5. Willingness to stop all laxatives and other bowel regimens including prune juice and herbal products throughout the 2-week OIC confirmation period and the 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. Patients must comply with CRC screening criteria as specified in Appendix E.

7. Male patients who are sexually active must use a double-barrier method of contraception (condom with spermicide) from the first dose of investigational product (IP) until 12 weeks after their last dose. Women of childbearing potential must have a negative pregnancy test and confirmed (by the investigator) use of a highly effective form of birth control for 12 weeks before enrollment and until 12 weeks after their last dose. Highly effective forms of birth control are listed in Appendix I. Women of non-childbearing potential can participate in this study without adherence to the pregnancy precautions. Women of non-childbearing

potential are defined as women who are either permanently sterilized (hysterectomy or bilateral oophorectomy or bilateral salpingectomy) or are postmenopausal. Any woman who is older than 57 years of age is considered postmenopausal. In addition, women who are older than 50 years of age and amenorrheic with at least 12 months having passed since the last menses (after cessation of all exogenous hormone treatments), are also considered postmenopausal.

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

9. Outpatient status at enrollment and randomization

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

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

4.2 Exclusion criteria

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

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

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

3. Medical conditions and treatments associated with diarrhea, intermittent loose stools, or constipation, which could confound the interpretation of the results, eg, fecal incontinence, irritable bowel syndrome (physician-diagnosed), or chronic idiopathic constipation.

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

period or expected surgical procedure of the abdomen during the study participation period would be excluded.

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

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

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

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

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

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

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

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

12. Patients who are at increased risk for ventricular arrhythmia, including those that have a prior history of serious ventricular arrhythmia, family history of sudden

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

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

14. Use of prohibited medications as listed in Section 5.6

15. Pregnancy or lactation

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

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

18. Previous randomization in the present study or any study with NKTR-118

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

20. Any receipt of an investigational medication within 30 days of screening

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

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

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

5. STUDY CONDUCT

5.1 Restrictions during the study

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

5.2 Subject enrollment and randomization

The Principal Investigator (PI) or other qualified designee will:

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

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

3. Determine patient eligibility. Eligibility will be determined after the screening and OIC confirmation periods, upon completion of the OIC confirmation period (see Sections 4.1 and 4.2).

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

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

5.2.1 Procedures for randomization

Randomization codes will be distributed and communicated to study sites by use of an IVRS. Randomization will be stratified by response to laxatives (LIR, LAR, LUR) during the 2 weeks prior to screening. The randomization procedure will be structured to ensure that a minimum of 50% of patients are LIR.

Eligible patients will be randomized in balanced blocks to receive NKTR-118 12.5 mg, NKTR-118 25 mg, or matching placebo in a 1:1:1 ratio. The actual treatment given to individual patients will be determined by a randomization scheme that has been loaded into the IVRS database. The randomization scheme will be produced by a computer software program called GRand (AstraZeneca's Global Randomization system) that incorporates a standard procedure for generating random numbers. If a patient is discontinued from the study, his/her patient number or enrollment number will not be reused, and the patient will not be allowed to re-enter the study. Randomized patients who discontinue early from the study will not be replaced.

Randomization codes will be assigned strictly sequentially within the response to laxative categories as patients become eligible for randomization.

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

Entry of incorrect stratification information into the IVRS will not disqualify a patient from continuation in the study.

5.3 Procedures for handling subjects incorrectly enrolled

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

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

5.4 Blinding and procedures for unblinding the study

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 Investigational Products and Patient Safety.

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 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 except for the futility analysis 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 1 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

Treatment day	NKTR-118 12.5 mg/day	NKTR-118 25 mg/day	Placebo
Days 1 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 2, 3, 4, 5, 6, and 7. Containers for the procured bisacodyl will be provided to the sites (see Section 5.6).

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 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.

Patients may take laxatives during the screening period of the study, but must discontinue use of laxatives at least 24 hours prior to the start of the OIC confirmation period. During the OIC confirmation period and 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 two additional times, as necessary, each 10 to 15 mg dose separated by 12 hour intervals. It is recommended that the bisacodyl tablets be taken either at bedtime or before breakfast. If after 3 doses of bisacodyl rescue therapy, the patient still has not experienced a BM, the investigator may prescribe one-time use of an enema. The timing of administration of this therapy will be noted and recorded in the eDiary. If these secondary interventions fail, the patient should be discontinued from the study (or excluded from the study if the patient fails the rescue regimen prior to randomization) 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 randomized (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 2. Patients will be instructed on the guidelines for rescue bisacodyl use. Patients will be asked to return unused bisacodyl at each subsequent visit. Documentation of bisacodyl use will be reviewed with the patient at each visit by comparing returned bisacodyl with eDiary records. If there is a

discrepancy, the patient will be counseled regarding proper documentation of bisacodyl use in the eDiary.

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
- Naltrexone
- 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

Drugs that may prolong the QT interval are also prohibited. Common examples of such drugs are listed in Appendix J. This list should not be considered comprehensive. Therefore investigators need to use their judgment when reviewing the medication list from individual patients and restrict patients who must stay on drugs that may increase the QT interval.

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 and eDiary recording 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). Compliance with the eDiary will be assessed remotely by the site at least every 48 hours to confirm that the patient is entering data. The patient will be phoned if any information is found to be missing.

5.7.1 Accountability

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.

5.8 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 8 assessments will be performed. Adverse events will be followed up (see Sections 6.4.4 and 6.4.5); and all study drugs and the eDiary device 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 6.4.9.2. The protocol for handling patients with elevated liver transaminases including guidelines for discontinuing patients is discussed in Section 6.4.9.2).
- ECG evidence of QT prolongation (QTcF >500 ms, or an increase of QTcF >60 ms above baseline to a value >480 ms on the12-lead ECG, confirmed on a repeat 12-lead ECG taken after waiting at least 5 minutes after the original finding of prolonged QTc)
- 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 that would not be consistent with continuation in the study, as determined by the investigator, AstraZeneca, or its representative, or the patient.
- Safety reasons as judged by the investigator
- Patient becomes pregnant
- Significantly worsened OIC refractory to medical treatment as judged by the investigator (including failure of the laxative rescue regimen either before or after randomization)
- The patient is unable to comply with the restrictions on the use of concomitant medications as detailed in Section 5.6 (in such cases the investigator should consult with the study physician before discontinuing the patient).
- The patient is unable to tolerate the 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 6.4.13.2.

Patients who discontinue prematurely from the study after participating in Visit 3 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 8 (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.

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

6.2 Data collection and enrollment

6.2.1 Screening and demographic measurements

The following data will be collected and recorded on the appropriate sections of the eCRF at the time of the screening visit (Visit 1) (refer to the Study Plan, Table 1):

- Signed informed consent forms (ICFs) will be obtained.
- Signed genetic informed consent (may be signed at a subsequent visit)
- Demography (date of birth, sex, and race)
- Review of I/E criteria

- Review of medical and surgical history (including OIC history)
- FIT test or verification of previous imaging study, if required
- Complete physical examination (including rectal examination, height, and weight)
- Vital signs (sitting blood pressure and pulse, body temperature, respiratory rate)
- Determination of LIR, LAR, LUR status
- 12-lead ECG
- Laboratory assessments
- Urine drug screen
- Urine pregnancy test (WOCBP)
- U/A
- C-SSRS
- Modified Himmelsbach scale
- Prior and current medications (including opioid dose and laxative use)
- eDiary device training and distribution
- Daily maintenance and breakthrough pain opioid dosing regimen.

6.2.2 Definitions for laxative responder status

One of the main goals of the study is to determine whether NKTR-118 is efficacious in patients who have had inadequate response to laxatives previously. For the purpose of identifying those patients, at Visit 1, each patient's laxative response status will be determined based on 4 questions which explore the frequency of laxative use, constipation symptom severity, and laxative side-effects during the previous 2 weeks. The patients will be classified as LIR, LAR, or LUR based on their answers. Patients who report having used laxatives over the previous 2 weeks will be asked about the frequency of laxative use (total days used) and constipation symptom severity.

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

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

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

6.2.3 Additional procedures including follow-up procedures

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

6.3 Efficacy

6.3.1 Efficacy variables

The primary efficacy endpoint is response (responder/non-responder) to study drug during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.

The key secondary efficacy endpoints (or outcome variables) supporting the primary objective, and included in the multiplicity adjustment, are:

- Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.

- Response (responder/non-responder) to study drug over the entire 12 week treatment period, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 75% of the weeks.

- Regularity during the first 4 weeks of treatment, where regularity is measured as the mean number of days per week with at least 1 SBM during Weeks 1 to 4.

Additional secondary efficacy variables include:

- Change from baseline in the SBMs/week for Weeks 1 to 4 and 1 to 12.

- Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours.

- Mean number of days per week with at least 1 SBM for Weeks 1 to 12

- Change from baseline in the mean degree of straining for Weeks 1 to 4 and 1 to 12.

- Change from baseline in the mean stool consistency (BSS) for Weeks 1 to 4 and 1 to 12.
- Percentage of days with complete evacuation for Weeks 1 to 4 and 1 to 12.
- Mean bisacodyl dose per week for Weeks 1 to 4 and 1 to 12
- Change from baseline in PAC-SYM total score and each domain score for Weeks 2, 4, 8, and 12.
- Change from baseline in PAC-QOL total score and each domain score for Weeks 4 and 12.
- Willingness to Take Drug Again questionnaire for Week 12.

6.3.1.1 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 3 (randomization), Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), and Visit 8 (Week 12).

The PAC-SYM 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 3, where some interaction with staff will be necessary in order to ensure that randomization 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.

6.3.1.2 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 3 (randomization), Week 4 (Visit 6), and Week 12 (Visit 8).

The PAC-QOL 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 3, where some interaction with staff will be necessary in order to ensure that randomization 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.

6.3.1.3 Willingness to Take Drug Again Questionnaire

The Willingness to Take Drug Again questionnaire will consist of a yes/no question regarding the patient's willingness to take study drug again. The Willingness to Take Drug Again questionnaire will be completed at Visit 8 (Week 12). The Willingness to Take Drug Again 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. Patients are to fill out the Willingness to Take Drug Again questionnaire prior to any interventions or discussions regarding their OIC with the study staff or the investigator.

6.3.2 Measurements recorded in eDiary

Patients will be supplied with a handheld eDiary for pilot training, the OIC confirmation period, and the treatment period. At Visit 1, all patients will be carefully instructed and trained on how to fill in the eDiary and how to handle the device. Written information will be supplied to each patient. The patients must understand and be willing to use the eDiary and be instructed on how and where to request help if problems occur. If a patient does not fill out the eDiary, there will be a reminder prompt at the end of the day informing the patient that no data has been recorded and to confirm that they have not had any BMs that day. Additional reminder prompts for data consistency will also be included (eg, if a patient records 2 BMs, but fills out the symptom data only once, he/she will be prompted at the end of the day to fill out the symptom data for the other BM).

The eDiary will be completed each day from the evening of Visit 1 to the morning of Visit 8, including days of study visits. The eDiary will include the following daily recordings:

- Date and time of BM (recorded at the time of each BM)
- Stool consistency (BSS) (recorded at the time of each BM)
- Straining (recorded at the time of each BM)

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

6.3.2.1 Bowel movements

All BMs will be recorded as they occur.

6.3.2.2 Stool consistency (Bristol Stool Scale)

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

The BSS is a medical aid designed to classify the form of human feces into 7 categories. It was developed by Heaton at the University of Bristol and was first published in the Scandinavian Journal of Gastroenterology in 1997 (Lewis and Heaton 1997). The form of the stool depends on the time it spends in the colon. The 7 stool types are:

1. Separate hard lumps, like nuts (hard to pass)
2. Sausage-shaped, but lumpy
3. Like sausage, but with cracks on its surface
4. Like a sausage or snake, smooth and soft
5. Soft blobs with clear cut edges (passed easily)
6. Fluffy pieces with ragged edges, a mushy stool
7. Watery, no solid pieces.

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

6.3.2.3 Straining

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

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

Patients will be asked to respond on a 5 point Likert scale choosing one of the following options:

1=Not at all

2=A little bit

3=A moderate amount

4=A great deal

5=An extreme amount.

6.3.2.4 Complete/incomplete evacuation

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

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

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

6.3.2.5 Pain level

Patients will rate their pain level at the end of each day, using the NRS for pain (see Section 6.4.7).

6.3.2.6 Use of laxative rescue medication

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

6.3.2.7 Use of opioid medication for breakthrough pain

Opioid medication for breakthrough pain will be recorded in the eDiary at the time the medication is taken. Breakthrough pain medication will also be reviewed at study visits and recorded on a breakthrough pain medication eCRF; this information will be recorded in the eDiary to facilitate daily recording of dosing.

6.4 Safety

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

6.4.1 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.
- Change from baseline in the mean daily opioid dose for Weeks 1 to 4 and 1 to 12.
- Change from baseline in the mean Numeric Rating Scale (NRS) pain score for Weeks 1 to 4 and 1 to 12.
- Observed values and change from baseline in composite score in modified Himmelsbach scale for the evaluation of centrally mediated opioid withdrawal symptoms at 2 hours after first dose of study drug, and at Weeks 1, 4, and 12.
- Changes in vital signs and physical examination.
- Changes in laboratory assessments (ie, chemistry, hematology, and U/A).
- Changes in ECGs.

6.4.2 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.

6.4.3 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 or incapacity

- 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.

6.4.4 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 9), 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 8), 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 6.4.3. 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 6.4.5. Suicidal thoughts and preparation for suicide should also be regarded as AEs. All events of suicidality will be monitored via the C-SSRS.

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

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

Causality collection

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

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

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

Adverse events based on signs and symptoms

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

Adverse events based on examinations and tests

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

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

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

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

Underlying disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease, or it may be considered normal fluctuation in symptoms. The development of pain due to progression of the underlying condition responsible for the patient's pain should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study, unless they meet serious criteria (ie, hospitalization).

6.4.5 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.

6.4.6 Daily Opioid Dose

Opioid doses will be recorded for each patient and the daily opioid dose in morphine equivalents will be calculated. Breakthrough pain medication will be recorded in the eDiary, and the daily maintenance opioid dose will be recorded on the maintenance opioid dose eCRF. Breakthrough pain medication will also be reviewed at study visits and recorded on a breakthrough pain medication eCRF; this information will be recorded in the eDiary to facilitate daily recording of dosing.

6.4.7 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). The NRS will be recorded each evening via the eDiary to record the patients' worst pain and average pain during the day. Changes in this scale should generally not be reported as AEs unless standard criteria for AE reporting are otherwise met.

6.4.8 Modified Himmelsbach Scale

Patients are rated by examination for symptoms of opioid withdrawal using the modified Himmelsbach scale. The modified Himmelsbach scale will be administered by a clinician at the study site. Patients will be rated with respect to the following symptoms as observed at the time of the assessment: yawning, lacrimation, rhinorrhea, perspiration, tremor, mydriasis, piloerection, and restlessness. The signs will be quantified on a scale of 0 to 3, with 0=none, 1=mild, 2=moderate, 3=severe. (Himmelsbach 1941; Culpepper-Morgan et al 1992, Webster et al 2008). To ensure adequate inter-rater agreement, raters will undergo training on proper scoring using the modified Himmelsbach scale and will receive certification provided by United BioSource Corporation (UBC). The modified Himmelsbach scale will be administered at Visit 1 (screening), Visit 3 (randomization), Visit 4 (Week 1), Visit 6 (Week 4), and Visit 8 (Week 12). Changes in this scale should generally not be reported as AEs unless standard criteria for AE reporting are otherwise met.

6.4.9 Laboratory safety assessment

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

The following clinical laboratory tests (chemistry, hematology, and U/A shown in Table 4) will be performed as specified in the Study Plan.

Table 4 Laboratory assessments

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

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

[a] A separate protocol is outlined regarding additional laboratory tests for elevated liver transaminases (see Section 6.4.9.2).

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

[c] Total cholesterol will be assessed at randomization (Visit 3) and Week 12 (Visit 8/end of treatment).

[d] Serum pregnancy tests will be performed at Week 4 (Visit 6), Week 8 (Visit 7), and Week 14 (Visit 9); urine pregnancy tests will be performed at screening (Visit 1), randomization (Visit 3), and Week 12 (Visit 8). Any positive urine pregnancy test is to be followed up with a serum pregnancy test.

[e] PT/INR is assessed only at screening in order to calculate Child-Pugh classification. INR is also to be assessed during the study if patients meet criteria for significant elevation in liver transaminases (See Section 6.4.9.2).

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

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

Serum chemistry and hematology tests will be performed on all patients at Visit 1 (screening), Visit 3 (randomization), Visit 4 (Week 1), Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), Visit 8 (Week 12), and Visit 9 (Week 14, follow-up). Total cholesterol will be assessed at Visit 3 (randomization) and Visit 8 (Week 12).

Urine drug screening tests will be performed on all patients at Visit 1 (screening) and Visit 8 (Week 12). Urinalysis (and urine pregnancy tests for all WOCBP) will be performed at Visit 1 (screening) and Visit 8 (Week 12). A urine pregnancy test will also be performed at Visit 3 (randomization). Any positive urine pregnancy test is to be followed up with a serum pregnancy test. Serum pregnancy tests for WOCBP will be performed at Visit 6 (Week 4), Visit 7 (Week 8), and Visit 9 (Week 14, follow-up).

For blood volume, see Section 7.1.

6.4.9.1 Urine drug screen

As noted above, urine drug screening tests will be performed on all patients at Visit 1 and Visit 8 (Week 12). 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.

6.4.9.2 Handling of subjects with elevated liver transaminases

The investigator will be alerted from the central laboratory regarding patients developing ALT or AST >3 x ULN during the study, ie, all values above >3 x 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 >3 x 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 >3 x ULN but ≤8 x 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 >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN AND (total bilirubin >2 x ULN or INR >1.5)
- ALT or AST >3 x 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.

6.4.10 Physical examination

A complete physical examination (general appearance, skin, neck, [including thyroid], eyes, ears, nose, throat, chest, lungs, heart, abdomen, back, lymph nodes, extremities, and basic nervous system evaluation) will be performed at Visit 1 and Visit 8. At Visit 1, this will include rectal examination. A targeted physical examination (lungs, cardiovascular, abdomen) will be performed at Visit 3 (see Section 3.1.3.1). This may include a rectal examination, at the discretion of the investigator, if necessary to ensure the safety of the patient.

Significant findings that are present at the time of screening (Visit 1) must be included in the appropriate medical history/surgical history eCRF pages. Significant findings made after the screening visit (Visit 1) that meet the definition of an AE must be recorded on the AE eCRF.

6.4.10.1 CRC Risk Factor Evaluation

The patients must comply with the CRC screening criteria as specified in Appendix E. These criteria are modified from American College of Gastroenterology Guidelines for Colorectal Cancer Screening (Rex et al 2000, Rex et al 2009) and are intended to make a reasonable and practical good faith effort to rule out underlying colorectal malignancy as a potential contributor to constipation symptoms and to avoid enrolling patients with underlying malignancy into prolonged clinical trials. Patients are classified into high and average CRC risk groups based on their family history. Further division is made based on age, race, and previous diagnostic evaluation for CRC. A FIT test is required for those who are ≥50 years of

age and at average risk for CRC, unless they provide verification of negative colonoscopy, flexible sigmoidoscopy, barium enema study, or virtual colonoscopy. For more details, please refer to Appendix E.

6.4.11 ECG

6.4.11.1 Resting 12-lead ECG

Digital ECGs (dECG) for all patients at all centers will be conducted at the center using a machine provided by the central ECG laboratory and will be transmitted to the central ECG laboratory. The ECG machine will also print off 2 copies of the ECG by default, 1 copy that can be provided to the central ECG laboratory for digitization and analysis if necessary. Digital ECGs will be performed at screening, randomization, and all study visits after randomization. Digital ECGs will be obtained after the patient has been resting in a supine position for at least 10 minutes. At Visit 3 (randomization), patients will receive a triplicate ECG pre-dose and a single ECG 2 hours after the dose of study drug. Triplicate ECGs will also be performed at Visit 4 (Week 1) and Visit 8 (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. Single 12-lead ECGs will be performed at Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), and Visit 9 (Week 14).

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. Discontinuation criteria include QTcF >500 ms or change from baseline >60 ms with a QTcF interval exceeding 480 ms (see Section 5.8).

6.4.12 Vital signs

6.4.12.1 Pulse and blood pressure

Blood pressure (sitting) and pulse/heart rate (sitting) will be measured at all study visits except Visit 2 (start of OIC confirmation period). An appropriately sized cuff will be used to obtain systolic and diastolic blood pressure.

6.4.12.2 Body temperature and respiratory rate

Body temperature and respiratory rate will be measured at Visit 1 (screening) and Visit 8 (Week 12).

6.4.12.3 Weight

Weight will be measured at Visit 1 (screening), Visit 3 (randomization), and Visit 8 (Week 12).

6.4.13 Other safety assessments

6.4.13.1 C-SSRS

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

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

If a patient indicates having suicidal ideation or having a rating of type 4 or 5 on the C-SSRS suicidal ideation scale at any visit when the C-SSRS is administered, 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.

6.4.13.2 Persistent or Progressive Severe Abdominal Pain

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

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

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

6.4.14 Safety Specific Areas of Interest

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

- Opioid withdrawal
- Abuse liability
- Bowel perforation type events (eg, ischemic colitis) (see Section 6.4.13.2).

The topics listed above, as well as other topics which may be subsequently determined by AstraZeneca, may be subject to enhanced surveillance activities and/or an adjudication team process (note: any case reports of bowel perforation and related events will be subject to an external adjudication process). 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.

6.5 Patient reported outcomes (PROs)

See Section 6.3.2 for PROs in the eDiary. In addition, 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 6.3.1.1.

6.5.3 PAC-QOL

See Section 6.3.1.2.

6.5.4 Willingness to Take Drug Again

See Section 6.3.1.3.

6.5.5 Administration of PRO questionnaires

The NRS (for pain) and BSS will be administered in the eDiary. The PAC-SYM, PAC-QOL, EQ-5D, and Willingness to Take Drug Again questionnaire will be self-administered using an electronic device (SitePad) at the study center. At Visit 3, patients will receive training from study staff regarding how to enter the data electronically using the SitePad device provided at the study center. Training procedures will be documented separately from this CSP. 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 3, 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 3, since only randomized patients will fill out the questionnaires and interaction with study staff will be necessary to determine whether randomization criteria have been met.

6.6 Pharmacokinetics

Blood samples will be taken at specified visits. The actual date and time of the sample collection (in date, hour and minute) must be recorded on the appropriate eCRF page.

6.6.1 Collection of samples

Venous blood samples (6 mL) will be taken at the times specified in Table 1. Individual venipunctures for each time point may be performed or an in-dwelling catheter may be used. If the study site chooses to use an in-dwelling catheter, the first 1 mL of blood will be discarded and the catheter flushed with saline following the sampling. Heparin may not be used to flush the catheter.

Six milliliter (6 mL) samples of whole blood will be collected into ethylenediaminetetraacetic acid (EDTA) spray-dried tubes for the determination of NKTR-118 in human plasma. All samples will be immediately placed on ice until centrifugation, which will begin within 30 minutes of sample collection. The sample will be centrifuged for 10 minutes at 2°C to 8°C at 1500Xg. The resulting plasma will be divided into 2 transfer tubes (2.0 mL Microcentrifuge Micro Tubes-Sterilized, Cat #4204S, Bio Plas, Inc., USA, or a tube approved by AstraZeneca) and immediately frozen upright at or below 20°C within 15 minutes of plasma preparation and kept frozen at this temperature before, during, and after transport to the designated laboratory. One of the samples will be retained at the study site. This retention sample will be retained until the analysis is completed on the original sample and it has been determined that the retention sample can be destroyed.

It is important that the time and date of the PK sample collection be recorded in the eCRF.

Plasma samples will be shipped on a monthly basis.

For blood volume, see Section 7.1.

6.6.2 Labeling of NKTR-118 plasma samples

Freezer compatible labels will be applied to the plasma sample tubes. The labels should contain the following information:

Study Number: D3820C00004

Patient Number

Treatment Period

Week Number

Visit Number

Analyte: NKTR-118

Matrix: Plasma

6.6.3 Shipment of NKTR-118 plasma samples

All plasma samples accompanied by the sample shipment logs will be shipped via an agreed upon courier. The frozen samples must be packed securely to avoid breakage during transit, should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples remain frozen for at least 72 hours to allow for delays in the shipment. All applicable shipping regulations must be followed. Documentation sufficient to identify each sample must be included with the shipment.

Samples should only be shipped on Monday through Wednesday. Do not ship on or within 2 days prior to a legal holiday.

Plasma samples should be shipped according to guidelines in the Laboratory Manual.

6.6.4 Determination of drug concentration

Samples for determination of NKTR-118 concentrations in plasma will be analyzed by on behalf of AstraZeneca. Full details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

No samples from patients with placebo treatment will be analyzed unless anomalous results are seen in the patients with active treatment.

Additional analyses may be conducted on the biological samples to further investigate reproducibility of incurred samples. Any results from such analyses will be included in the bioanalytical study contribution report.

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics

See Appendix D for details on pharmacogenetic sampling.

6.8.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from patients post-randomization. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may discontinue due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 3 (randomization), it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1.

6.9 Health economics

6.9.1 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 administered to patients at Visit 3 (randomization), Visit 6 (Week 4), and Visit 8 (Week 12) 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 3, where some interaction with staff will be necessary in order to ensure that randomization 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 4 (Week 1), Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), Visit 8 (Week 12), and Visit 9 (Week 14) through patient interviews. If a patient is taken off the study as a result of a resource utilization (eg, an ER visit for manual disimpaction), the data should be recorded in the OIC healthcare resource utilization form prior to discontinuation. A health care resource utilization form will be used to collect information on whether the patient had any contact or

visited with a health care provider (physician or other health care practitioner, urgent care center or hospital emergency room, or inpatient hospital) for the management of their OIC, including the details of the type and number of visits, as well as the reason for the visit (such as the use of enemas, manual disimpaction, and treatment of anal fissures).

As applicable, the interview will be conducted after the patient completes filling out the PRO questionnaires (eg, PAC-SYM, PAC-QOL, EQ-5D) 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	8	68
	Hematology	4 EDTA	8	32
	Bicarbonate	3.5 SST	8	28
	Coagulation (PT/INR)	4.5 Sodium Citrate	1	4.5
Pharmacokinetic		6 EDTA	6	36
Pharmacogenetics		10 EDTA	1	10
Total		36.5	31	178.5

EDTA Ethylenediaminetetraacetic acid, SST serum-separating tube
[a] Additional samples may be collected for patients who have elevated liver transaminases (see Section 6.4.9.2), who require repeat laboratory testing at screening, or who require a serum pregnancy test.

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

7.2 Handling, storage, and destruction of biological samples

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

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

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

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Samples will be disposed of after the CSR has been finalized, unless retained for future analyses, see below.

Key samples for metabolites analysis may be retained at the CRO to be determined on behalf of Clinical Pharmacology & Drug Metabolism and Pharmacokinetics (DMPK), Wilmington, AstraZeneca for a maximum of 1 year following the finalization of the CSR. The results from such analysis will be reported in a separate report.

Additional NKTR-118 analyses will be conducted on the biological samples to investigate the reproducibility of the analytical results in incurred samples. Any results from such analyses will only be used to confirm the reproducibility of the method and will be reported in a separate table in the bioanalytical study contribution report.

7.2.2 Pharmacogenetic samples

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

7.3 Labeling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

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

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

The PI:

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

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

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

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

8.3 Ethics and regulatory review

An 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(s) is/are stored in the investigator's Study File.
- Ensure a copy of the signed and dated ICF is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an 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 eDiary recording device, and other system(s) utilized.

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

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

9.3 Monitoring of the study

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

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

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

9.3.1 Source data

Refer to the CSA for location of the source data.

9.4 Study agreements

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

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

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

- Signed CSA between AstraZeneca and the PI/study center
- Signed CSP and other agreements between AstraZeneca and the PI/study center
- Written approval of the study by the 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 1st Quarter 2011 and to end by 1st Quarter 2012.

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

10. DATA MANAGEMENT BY ASTRAZENECA

10.1 Electronic case report form

The eCRF and the protocol are both confidential. The eCRF will be created by the 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 Spontaneous bowel movements (SBMs) per week

A SBM is defined as a BM without the use of rescue laxatives administered in the previous 24 hours. Patients will use electronic hand-held (eDiary) devices to enter daily information related to laxative rescue medication, use of opioid medication for breakthrough pain, date and time of BMs and their associated characteristics (straining, stool consistency, completion of evacuation). Days with no BMs should be recorded as zero, rather than missing. This diary data will be used to identify SBMs. The weekly SBM frequency within each time period will be calculated for each patient as:

(total number of SBMs during the time period of interest/number of days) x 7

where the denominator is the number of days during the time period in which the patient records data. If less than 4 days of data are recorded within a particular week, the data for that week will be considered insufficient and the rate will be set to missing for that week.

A responder is defined as a patient with at least 3 SBMs/week and at least a 1 SBM/week increase over baseline for at least 75% of the weeks (eg, 3 out of 4 weeks). A patient who does not meet these criteria will be deemed a non-responder.

Baseline SBMs/week is calculated as:

(total number of SBMs during the 14-day OIC confirmation period/number of days in the OIC confirmation period in which the patient records data) x 7.

If more that 14 days of data are collected during the OIC confirmation period, data from the last 14 days prior to randomization will be used in the calculation of baseline SBMs/week.

Response will be assessed for Weeks 1 to 4 and 1 to 12.

Change from baseline in the mean number of SBMs/week will be calculated for Weeks 1, 2, 3, 4, 1 to 4, and 1 to 12 as the post-baseline value minus the baseline value, such that the change represents the increase in SBMs/week.

11.1.2 Time to first post-dose laxation

Time to first post-dose laxation without the use of rescue laxatives within the last 24 hours will be calculated in hours as:

> Date/Time of first post-dose laxation without rescue – First dose date/time.

Patients who do not have any post-dose laxation without the use of rescue laxatives within the last 24 hours will have their data censored at their last visit date or date of discontinuation from study drug. The censored value will be calculated as:

> Date/Time of last study visit or discontinuation of study drug – First dose date/time.

Response to study drug within the first 12 hours will be assessed using the calculated time to first post-dose laxation without the use of rescue laxatives.

11.1.3 Days with at least 1 SBM

The mean number of days per week with at least 1 SBM will be calculated as:

> (total number of days with at least 1 SBM during the period of interest/number of days in the period of interest) x 7.

The mean number of days per week with at least 1 SBM will be assessed for Weeks 1 to 4 and 1 to 12.

11.1.4 Days with complete evacuation

For each BM, a patient will record in the eDiary whether or not they had complete evacuation (ie, no stool in their rectum that they could not empty out).

The percentage of days with complete evacuation will be calculated as the number of days with complete evacuation within the interval of interest divided by the total number of days in the interval. The percentage of days with complete evacuation will be calculated for Weeks 1 to 4 and 1 to 12.

11.1.5 Degree of straining

The mean degree of straining for an interval will be calculated as the sum of the straining values for the interval divided by the number of BMs recorded within the interval. Change

from baseline in the mean degree of straining will be calculated for Weeks 1 to 4 and 1 to 12 post-baseline value minus the baseline value, where baseline is the mean degree of straining recorded during the OIC confirmation period. Negative changes from baseline indicate improvement.

11.1.6 Bristol Stool Scale

The mean daily BSS score for an interval will be calculated as the sum of daily values for the interval divided by the number of days within the interval in which the data were collected. Change from baseline in the mean BSS score will be calculated for Weeks 1 to 4 and 1 to 12 as the post-baseline value minus the baseline value, where baseline is the mean daily BSS score recorded during the OIC confirmation period. Positive changes from baseline indicate improvement.

11.1.7 Mean Bisacodyl dose per week

Bisacodyl doses will be recorded for each patient in the eDiary. 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 Weeks 1 to 4 and 1 to 12.

11.1.8 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 2, 4, 8, and 12 as the post-baseline value minus the baseline value, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 3). Negative changes from baseline indicate improvement.

11.1.9 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 and 12 as the post-baseline value minus the baseline value, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 3). Negative changes from baseline indicate improvement.

11.1.10 Willingness to Take Drug Again

Willingness to take drug again (yes/no) will be recorded at the end of the 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 30 days after 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.

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 daily pain rating based on the 11-point NRS for pain ranging from 0 (no pain) to 10 (worst imaginable pain) will be entered by patients the same time every day using the eDiary. Both the average pain rating over the previous 24 hours and the worst pain experiences over the previous 24 hours will be recorded. The mean daily NRS for an interval will be calculated

as the sum of daily values for the interval divided by the number of days within the interval in which the data were collected. Change from baseline in mean daily NRS values will be calculated for Weeks 1 to 4 and 1 to 12 as the post-baseline value minus the baseline value, where baseline is the mean daily NRS values recorded during the OIC confirmation period. Negative changes from baseline indicate improvement.

11.2.3 Daily opioid dose

Opioid doses will be recorded for each patient, including both the maintenance dose recorded on the eCRF and rescue medication recorded in the eDiary, and the daily opioid dose in morphine equivalents (mg/day) will be calculated. 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. Change from baseline in mean daily opioid dose will be calculated for Weeks 1 to 4 and 1 to 12 as the post-baseline value minus the baseline value, where baseline is the mean daily opioid dose recorded during the OIC confirmation period. Positive changes from baseline indicate need to increase opioid dose.

11.2.4 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 50% of the 8 signs are missing at a visit, the composite score will be set to missing. Changes from baseline to 2 hours after first dose of study drug, and Weeks 1, 4, and 12 in the modified Himmelsbach scale will be calculated as the post-baseline value minus the baseline value, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 3). Negative changes from baseline indicate improvement.

11.2.5 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 1, 2, 4, 8, 12, and 14) will be calculated as the post-baseline test value minus the baseline test value, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 1 or 3).

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, potentially clinically significant laboratory results will be flagged. The criteria for potentially clinically significant laboratory results will be outlined in the SAP.

11.2.6 Physical examination

Change from baseline to Week 12 for physical examination will be reported, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 1).

11.2.7 Weight

Change from baseline to Week 12 for weight will be calculated as the visit assessment minus the baseline value, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 1 or 3 [for weight]).

11.2.8 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, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 1).

11.2.9 ECG

Changes from baseline to each post-baseline visit (Weeks 1, 2, 4, 8, 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 is the latest non-missing value collected prior to the first dose of study drug (Visit 1 or 3). Marked abnormal values or changes from baseline will be identified based on pre-determined criteria.

11.2.10 Vital signs

Changes from baseline in vital signs (sitting blood pressure and pulse) at each post-baseline visit (Weeks 1, 2, 4, 8, 12, and 14) will be derived as the value at the visit minus the baseline value for the same assessment, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 3).

11.2.11 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.

For the C-SSRS, baseline defined as the latest non-missing value collected prior to the first dose of study drug (Visit 1 or 3).

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 Degree of straining

See Section 11.1.5.

11.3.2 Bristol Stool Scale

See Section 11.1.6.

11.3.3 PAC-SYM

See Section 11.1.8.

11.3.4 PAC-QOL

See Section 11.1.9.

11.3.5 Willingness to Take Drug Again

See Section 11.1.10.

11.3.6 NRS for Pain

See Section 11.2.2.

11.3.7 Daily opioid dose

See Section 11.2.3.

11.3.8 EQ-5D

See Section 11.6.1.

11.4 Calculation or derivation of PK variables

Samples for PK determination of NKTR-118 will be analyzed by a certified laboratory using validated bioanalytical methods. Full details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

The plasma concentration data of NKTR-118 will be listed, summarized on the basis of time intervals, and plotted in scattering with time relative to the immediately preceding NKTR-118 dosing time.

A separate population PK (POPPK) analysis of NKTR-118 concentrations in patients with OIC will be performed using non-linear mixed-effects modelling technique with NONMEM (version 6 or later), for the data collected in this study and other studies where appropriate. The effect of covariates such as age, sex, and body mass index on plasma exposures of NKTR-118 will be explored. Population mean and post hoc Bayesian individual estimates of the PK parameters for NKTR-118 will be estimated. Summaries of individual predictions of exposure metrics may be listed and the relationship between predicted individual exposure metrics and response will be explored. The outcome from this analysis will be reported separately from the CSR.

11.5 Calculation or derivation of pharmacodynamic (PD) variable(s)

11.5.1 Calculation or derivation of the relationship between PK and PD variables

The POPPK model will be used to predict the individual and population plasma concentrations at the time of each efficacy and/or adverse outcome assessment to develop the quantitative relationship between NKTR-118 exposure and response. Initial plots of efficacy and/or adverse endpoints versus concentration will help elucidate the nature of the concentration-response relationship, while hysteresis plots will help assess any delays between changes in concentration and response. The outcome from this analysis will be reported separately from the CSR.

11.5.2 Population analysis of PK/PD variables

The POPPK model will be used to construct a PK/response model as functions of time, treatment, and relevant patient covariates. Initially, exploratory plots of the response endpoints against measures of drug exposure will be constructed in order to evaluate the strength and temporal association of various possible relationships. Next nonlinear mixed-effects models will be constructed describing the time course of changes in response endpoints in addition to the variability between and within patients, and the uncertainty in these parameters. The outcome from this analysis will be reported separately from the CSR.

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 emergency room, inpatient hospital).

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

The efficacy analysis set will be the 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 one post-baseline efficacy assessment.

Select efficacy analyses (to be specified in the SAP), will be repeated on the Per Protocol (PP) population. The PP population is defined as all patients in the ITT population without significant protocol violations or deviations. Patients included in the PP population will be determined prior to unblinding of the study.

12.1.2 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).

12.2 Methods of statistical analyses

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

For the by-visit assessments, baseline will be defined as the latest non-missing value collected prior to the first dose of study drug (screening, Visit 1 or Week 0, Visit 2).

For the eDiary assessments, baseline will be defined as the values observed during the OIC confirmation period, which are the last 14 days prior to randomization (as defined in Section 3.1.2).

Descriptive statistics for continuous data will include n, mean, median, standard deviation, minimum, and maximum values. Descriptive statistics for categorical data will include n, frequency, and percentage.

To control the overall type I error rate to be ≤ 0.05 for the multiple comparisons in the primary and the key secondary endpoints, a Multiple Testing Procedure (MTP) with Bonferroni-Holm over Groups, and Fixed-Sequence within groups will be applied. Specifically, there will be 2 groups defined by the doses of 12.5 and 25 mg, and within each group there will be a pre-defined fixed-sequence MTP of comparisons of the key secondary endpoints vs placebo (ie, responder analysis in LIR subgroup, responder analysis for the 12-week treatment period, and regularity analysis) at level of $\alpha/2$. If the null hypotheses for 1 dose group can be rejected entirely (ie, significant difference between active vs placebo for all 4 endpoints at $\alpha=0.025$), one will increase the level to α (ie, 0.05) for the other group. This amounts to using Bonferroni-Holm over groups, and fix-sequence within groups. This multiplicity adjustment method follows the general results described by Bretz (Bretz et al 2009) and by Burman (Burman et al 2009).

No other correction to the reported p-values will be made for the analysis of additional secondary measures. Where appropriate, 95% confidence intervals (CIs) will be presented.

12.2.1 Primary analysis

The primary analysis will be made comparing the response rate of Weeks 1 to 4 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

12.2.2 Key secondary analysis

1. Comparison of the response rate of Weeks 1 to 4 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo in the LIR subgroup. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using Chi-Square tests.

2. Comparison of the response rate of Weeks 1 to 12 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using CMH tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

3. Comparison of the regularity during the first 4 weeks of treatment of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. Differences between treatment groups in the mean number of days per week with at least 1 SBM will be analyzed using analysis of covariance (ANCOVA), with treatment group and response to laxatives at baseline as fixed effects, and the mean number of days per week with at least 1 SBM during the baseline period as a covariate.

12.2.3 Additional secondary analysis

Additional secondary endpoints will be either analyzed or summarized descriptively.

Response rate for Weeks 1 to 4 and 1 to 12 will also be summarized for subgroups of interest (eg, age, gender, race, response to laxatives (LIR, non-LIR [LAR, LUR combined], LAR, LUR).

The treatment by opioid dose interaction will be assessed using a logistic regression model on the response for Week 1 to 4 and Weeks 1 to 12, to determine whether opioid dose (a continuous variable) is a significant factor in treatment response for the duration of the treatment period. To help visualize the effect, a plot of response by the opioid dose will be generated. The relationship between response within the first 12 hours of treatment (ie, at

least 1 SBM within the first 12 hours of treatment) and the response during Weeks 1 to 4, as well as during the entire study (Weeks 1 to 12) will be assessed within each treatment group using Chi-Square tests, for both the ITT population as well as the LIR subgroup.

Differences between treatment groups in the mean number of days per week with at least 1 SBM for Weeks 1 to 12 will be analyzed using ANCOVA, with treatment group and response to laxatives at baseline as fixed effects, and the mean number of days per week with at least 1 SBM during the baseline period as a covariate.

Change from baseline in SBMs/week for Weeks 1, 2, 3, and 4 will be analyzed using mixed model repeated measures (MMRM) (Lewis and Heaton 1997) to compare the treatment groups of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. Change from baseline in SBMs/week for Weeks 1 to 4 and 1 to 12 will also be analyzed using ANCOVA, with treatment group and response to laxatives at baseline as fixed effects, and the SBMs/week during the baseline period as a covariate.

Change from baseline in SBMs/week will also be summarized descriptively within the response to laxative subgroups (LIR, LAR, LUR, non-LIR) for each treatment group.

Treatment group differences within the subgroup of LIR patients with inadequate response from 2 laxatives will be assessed in the Integrated Summary of Efficacy based on pooling of the 2 pivotal Phase III studies for the outcome variables of response rate and change from baseline in the SBMs/week. Response rate and change from baseline in SBMs/week for this subgroup will be presented descriptively in the study report.

Treatment comparisons of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo, for the time to first laxation without laxative use in the previous 24 hours will be analyzed using log rank tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

Descriptive statistics by treatment group for the mean degree of straining, the mean stool constituency, and the percentage of days with complete evacuation will be summarized for each period (baseline, Weeks 1 to 4, Weeks 1 to 12) as well a for the change from baseline to Weeks 1 to 4 and 1 to 12. Differences between NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo in the change from baseline in these outcome variables will be analyzed using ANCOVA, with treatment group and response to laxatives at baseline as fixed effects, and the associated baseline value as a covariate.

The mean bisacodyl dose per week will be summarized by treatment group using descriptive statistics for Weeks 1 to 4 and 1 to 12.

Descriptive statistics by treatment group for the PAC-SYM total score and each domain score will be summarized at baseline, Weeks 2, 4, 8, and 12 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, and 12 as well as the change from baseline to each post-dose time point.

Treatment comparisons of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo in the change from baseline for each of the PAC-SYM domain scores and the PAC-QOL Satisfaction domain score will be analyzed at each post-dose time point using ANCOVA, with treatment group and response to laxatives at baseline as fixed effects, and the associated baseline value as a covariate.

Descriptive statistics for the Willingness to Take Drug Again questionnaire will be summarized by treatment group.

12.2.4 Safety analyses

Treatment-emergent AEs will be coded using the MedDRA dictionary. 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. Treatment-emergent AEs will also be summarized by intensity and separately, by causality. 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 will be summarized in a similar manner than TEAEs.

Treatment-emergent AEs, SAEs, TEAEs leading to death, and TEAEs leading to study discontinuation will be tabulated for each treatment group. Commonly occurring TEAEs, ie, those which occur in 5% or more of the patients in either treatment group, will be summarized using descriptive statistics. Descriptive statistics for time to onset and duration of select TEAEs will be summarized by treatment group. Treatment-emergent AEs that could potentially be indicative of centrally mediated opioid withdrawal will be identified prior to unblinding and will also be summarized by each treatment group. Evaluation of GI-related symptoms will be conducted at baseline, treatment-emergent GI AEs will be summarized by treatment group.

The observed composite modified Himmelsbach score will be summarized by treatment group at baseline, 2 hours after first dose of study drug, and Weeks 1, 4, and 12 using descriptive statistics. The change from baseline in the composite modified Himmelsbach score, mean daily opioid dose, and mean NRS pain scores (average and worst per day) will be summarized by treatment group, and tested within each treatment group using one-sample t-tests to determine where the change is significantly different from zero. The interpretations in change from baseline within each treatment or difference between treatment groups for these parameters are important to be made clinically.

All laboratory test results, vital signs, 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. Shifts from baseline to each post-baseline visit in the frequency of laboratory values outside of the clinically significant reference range will be presented by treatment group. The incidence of potentially clinically significant laboratory results 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. The incidence of markedly abnormal values and changes from baseline in the ECG parameters will be summarized by treatment group.

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.

12.2.5 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, and 12. 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 emergency room, 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.

12.2.6 Pharmacokinetic analyses

See Section 11.4.

12.2.7 Interim analyses

A futility analysis is proposed at the time when 180 LIR patients (approximately 60 LIR patients per treatment group) are randomized in both of the 2 pivotal Phase III studies combined and have completed the first 4 weeks of double-blind treatment. An independent statistician (not otherwise involved in the study and located in a different geographical location than the project statisticians) will perform this analysis. The stopping rule (ie, futility) will be if the difference in the response rate (primary efficacy endpoint) for both 12.5 mg and 25 mg of NKTR-118 as compared to placebo is less than or equal to 5 percentage points (ie, NKTR-118 response rate - placebo response rate $\leq$ 5%). Under this condition, the probability of at least one of the NKTR-118 doses having a statistically significant effect over placebo at the end of the study is approximately 0.07.

12.3 Determination of sample size

A sample size of 105 patients per group would be needed to detect a difference of 25% in response rate (60% on NKTR and 35% on placebo), with power=90%, alpha=0.025, and 2-sided test. In order to provide an adequate power to detect a treatment difference in LIR

subgroup (assuming LIR is 50% of the total study population), it is recommended that 210 patients per group (total 630 patients for 3 treatment groups) be randomized to the study. The assumptions on expected response rate were referenced from the NKTR-118 Phase II study and from other similar drugs.

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 6.4.5.**

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

Name	Role in the study	Address & telephone number
Q Pharmacovigilance	SAE reporting (other countries)	Please refer to study-specific Safety Handling Plan

Name	Role in the study	Address & telephone number
Other contact information		

Name	Role in the study	Address & telephone number

13.2 Overdose

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

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

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

For recording purposes:

- If an overdose is reported during the course of a study, the patient is evaluated by the investigator/site staff to determine whether an SAE, non-serious AE, or no symptoms have been experienced after the overdose has been taken.
- If the patient experiences an overdose with an associated SAE, the investigator/site staff will capture details of the SAE and associated information on OVERDOSE, AELOG, and SAE modules in the eCRF.
- If the patient experiences an overdose with an associated non-serious AE, the investigator/site staff will capture details of the non-serious AE and associated information on OVERDOSE and AELOG modules in the eCRF.
- If the patient experiences an overdose with no symptoms, the investigator/site staff will capture details of the overdose and associated information on OVERDOSE module only in the eCRF.
- The OVERDOSE module (found in Module Package Library) is the preferred way of collecting overdose information. If the OVERDOSE module cannot be used, for

example, if a CRO is managing the study and is unable to use the module, the Clinical Study Overdose template, may be used. This form is also used if the overdose occurred in a person not enrolled in the study, eg, accidental ingestion by a relative of the patient.

For reporting purposes:

- If an overdose occurs in the course of an AstraZeneca study, the investigators/site staff inform appropriate AstraZeneca representatives immediately, but no later than the end of the next business day of when he or she becomes aware of it.
- The designated AstraZeneca representative or its representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety Data Entry Site (DES).
- The following timelines will apply on reports of overdose:
  - Fatal/life-threatening SAEs are sent to DES within 1 calendar day of initial notification of the overdose.
  - Other SAEs are sent to DES within 4 calendar days of initial notification of the overdose.
  - Overdoses with no symptoms or with associated non-serious AEs are sent to DES within 5 calendar days of initial notification of the overdose.

13.3 Pregnancy

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

13.3.1 Maternal exposure

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

If a patient becomes pregnant during the course of the study, 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 6.4.5 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 6.4.5 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 A	
Drug Substance	NKTR-118
Study Code	D3820C00004
Edition Number	1.0
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

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

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

(Day Month Year)

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

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

ASTRAZENECA SIGNATURE(S)

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SIGNATURE OF NATIONAL CO-ORDINATING INVESTIGATOR

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Clinical Study Protocol Appendix B

Drug Substance	NKTR-118
Study Code	D3820C00004
Edition Number	1.0
Date	

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	
Drug Substance	NKTR-118
Study Code	D3820C00004
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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.

Clinical Study Protocol Appendix D	
Drug Substance	NKTR-118
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Appendix Date	

Appendix D
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

1. BACKGROUND AND RATIONALE

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

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

2. GENETIC RESEARCH OBJECTIVES

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

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

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

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

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

- Previous allogeneic bone marrow transplant

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

3.1.4 Discontinuation of subjects from this genetic research

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

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

3.2 Collection of samples for genetic research

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

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

3.3 Coding and storage of DNA samples

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

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

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

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

4. ETHICAL AND REGULATORY REQUIREMENTS

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

4.1 Informed consent

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

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

4.2 Subject data protection

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

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

5. DATA MANAGEMENT

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

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

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

7. LIST OF REFERENCES

Not applicable.

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Clinical Study Protocol Appendix E	
Drug Substance	NKTR-118
Study Code	D3820C00004
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Date	

Appendix E
Guidelines for Required Colorectal Cancer Screening

1. GUIDELINES FOR REQUIRED COLORECTAL CANCER SCREENING

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

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

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

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

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

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

2. LIST OF REFERENCES

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

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

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

1. GUIDELINES FOR DETERMINATION OF LAXATIVE RESPONSE STATUS

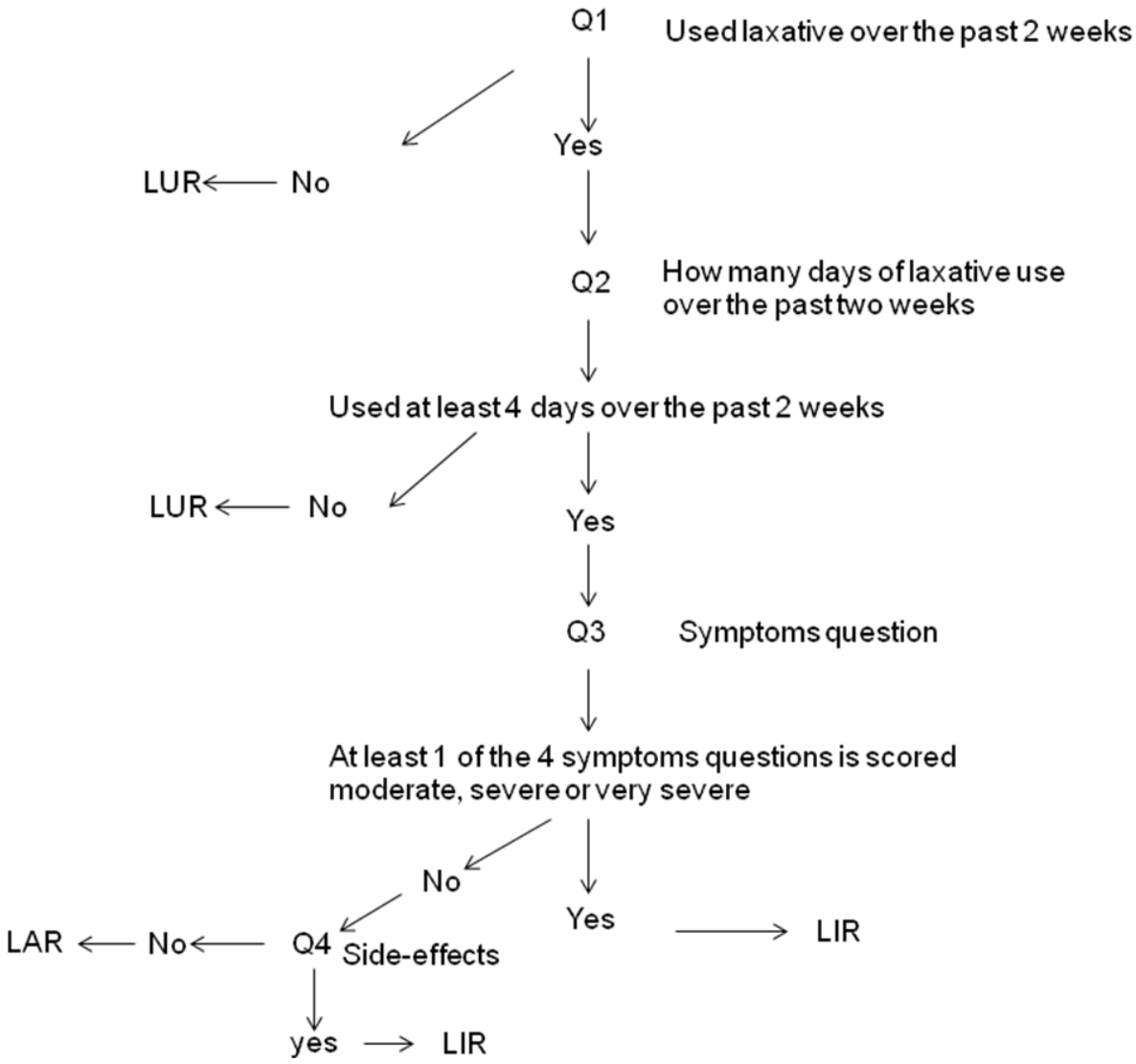
At the Screening visit, each patient's laxative response status will be determined based on 4 questions which explore the frequency of laxative use, constipation symptom severity, and laxative side-effects during the previous 2 weeks. The patients will be classified as LIR, LAR, or LUR based on their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

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

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

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

Figure 1 Determination of Laxative Response Status



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Clinical Study Protocol Appendix G	
Drug Substance	NKTR-118
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Date	

Appendix G
Child-Pugh Classification

1. CRITERIA FOR CHILD-PUGH CLASSIFICATION

Table 1 Criteria for Child-Pugh Classification

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

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

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

2. LIST OF REFERENCES

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

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Clinical Study Protocol Appendix H	
Drug Substance	NKTR-118
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Appendix H
Morphine Equivalents Conversion Chart

1. MORPHINE EQUIVALENTS CONVERSION CHART

Table 1 Dose Equivalents for Opioid Analgesics

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

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

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

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Clinical Study Protocol Appendix I

Drug Substance	NKTR-118
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Appendix I
Highly Effective Forms of Birth Control

1. HIGHLY EFFECTIVE FORMS OF BIRTH CONTROL

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

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

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

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

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Clinical Study Protocol Appendix J	
Drug Substance	NKTR-118
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Date	

Appendix J
Drugs that prolong QT/QTc interval

1. DRUGS THAT PROLONG QT/QTC INTERVAL

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

Table 1 Drugs that Prolong QT/QTc Interval

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

Clinical Study Protocol

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

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

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

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 Study to Assess the Efficacy and Safety of NKTR-118 in Patients with Non-Cancer-Related Pain and Opioid-Induced Constipation (OIC)

National Co-ordinating Investigator

Study center(s) and number of subjects planned

This will be a multi-center study conducted in Australia, Belgium, Germany, Hungary, and the United States (US). Approximately 1300 patients will be screened to obtain 630 randomized patients (210 per treatment arm). Approximately 120 centers will participate in the study.

Study period		Phase of development
Estimated date of first patient enrolled	1st Quarter 2011	III
Estimated date of last patient completed	1st Quarter 2012	

Objectives

Primary objective:

- To compare the efficacy of NKTR-118 12.5 and 25 mg with placebo in the treatment of patients who have opioid-induced constipation (OIC).

Secondary objectives:

- To compare NKTR-118 12.5 and 25 mg with placebo on the daily signs and symptoms associated with OIC (straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and quality of life.

Safety objectives:

- To assess the safety and tolerability of NKTR-118 12.5 and 25 mg, when used for the treatment of OIC.

Exploratory objectives:

- To characterize the pharmacokinetics (PK) of NKTR-118 and the covariate effect in the targeted disease population.
- To explore the NKTR-118 exposure-response relationship.
- To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to NKTR-118.
- To assess patient health status index and healthcare resource utilization.
- To assess patients' willingness to take the study drug again.

Study design

This is a Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy and safety of NKTR-118 12.5 and 25 mg in the treatment of OIC in patients with non-cancer-related pain. Patients who successfully complete the 12-week treatment period will be eligible to participate in a separate safety extension study.

Target subject population

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

Confirmed OIC is defined as:

- Documented <3 SBMs/week on average over the 2-week OIC confirmation period. Patients with uneven distribution of SBMs across the 2-week OIC confirmation period (0 SBMs in 1 week with ≥4 SBMs in the other week) will be excluded. In addition to the SBM frequency criterion, patients must report ≥1 of the following symptoms in at least 25% of the BMs recorded in the electronic diary (eDiary)

during the OIC confirmation period: Bristol Stool Scale (BSS) stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM. Patients who have 0 BMs over the 2-week OIC confirmation period will not be randomized.

In addition, a minimum of 50% of patients are to meet criteria for being laxative inadequate responders (LIR).

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 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, during which the diagnosis of OIC and stability of opioid regimen will be confirmed, a 12-week treatment period, and a follow-up visit 2 weeks after the last dose of study drug.

Outcome variable(s):

Primary efficacy variable: Response (responder/non-responder) to study drug during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.

- **Key secondary efficacy variables:**

  - Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks

  - Response (responder/non-responder) to study drug over the entire 12 week treatment period, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 75% of the weeks

  - Regularity during the first 4 weeks of treatment, where regularity is measured as the mean number of days per week with at least 1 SBM during Weeks 1 to 4

  Additional secondary efficacy variables:

  - Change from baseline in the SBMs/week for Weeks 1 to 4 and 1 to 12

  - Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours

- Mean number of days per week with at least 1 SBM for Weeks 1 to 12
- Change from baseline in the mean degree of straining for Weeks 1 to 4 and 1 to 12
- Change from baseline in the mean stool consistency (BSS) for Weeks 1 to 4 and 1 to 12
- Percentage of days with complete evacuation for Weeks 1 to 4 and 1 to 12
- Mean bisacodyl dose per week for Weeks 1 to 4 and 1 to 12
- Change from baseline in Patient Assessment of Constipation Symptoms (PAC-SYM) total score and each domain score for Weeks 2, 4, 8, and 12
- Change from baseline in Patient Assessment of Constipation Quality of Life (PAC-QOL) total score and each domain score for Weeks 4 and 12

- **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 the mean daily opioid dose for Weeks 1 to 4 and 1 to 12
  - Change from baseline in the mean Numeric Rating Scale (NRS) pain score for Weeks 1 to 4 and 1 to 12
  - Observed values and change from baseline in composite score in modified Himmelsbach scale for the evaluation of centrally mediated opioid withdrawal symptoms at 2 hours after first dose of study drug, and at Weeks 1, 4, and 12
  - Changes in vital signs and physical examination
  - Changes in laboratory assessments (ie, chemistry, hematology, and urinalysis [U/A])
  - Changes in electrocardiograms (ECGs)

- **Pharmacokinetics**

  Pharmacokinetics parameters of NKTR-118 will be estimated for individual patients (when possible). These parameters include:

  - oral clearance (CL/F)
  - absorption rate constant (Ka) and
  - area under plasma concentration-time curve from zero to time 24 hours (AUC [0-24])

- **Health economics**

  - Data on the Euroqol 5 Dimension (EQ-5D) questionnaire for Weeks 4 and 12.
  - Data on OIC healthcare resource utilization will be captured at the site for economic modelling purposes
  - Willingness to Take Drug Again questionnaire for Week 12

Statistical methods

The efficacy analysis set will be the Intent-to-Treat (ITT) population, defined as all randomized patients who received at least 1 dose of study drug and have at least 1 post-baseline efficacy assessment. The safety analysis set will be the Safety population, defined as all randomized patients who received at least 1 dose of study drug.

The primary analysis will be made comparing the response rate of Weeks 1 to 4 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by response to laxatives at baseline (LIR, laxative adequate responder [LAR], laxative unknown responder [LUR]).

The following will be categorized as key secondary endpoints:

1. Comparison of the response rate of Weeks 1 to 4 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo in the LIR subgroup. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using Chi-Square tests.

2. Comparison of the response rate of Weeks 1 to 12 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. The response rate for each treatment

group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using CMH tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

3. Comparison of the regularity during the first 4 weeks of treatment of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. Differences between treatment groups in the mean number of days per week with at least 1 SBM will be analyzed using analysis of covariance (ANCOVA), with treatment group and response to laxatives at baseline as fixed effects, and the mean number of days per week with at least 1 SBM during the baseline period as a covariate.

To control the overall type I error rate to be ≤ 0.05 for the multiple comparisons in the primary and the key secondary endpoints, a Multiple Testing Procedure (MTP) with Bonferroni-Holm over Groups, and Fixed-Sequence within groups will be applied. Specifically, there will be 2 groups defined by the doses of 12.5 and 25 mg, and within each group there will be a pre-defined fixed-sequence MTP of comparisons of the key secondary endpoints (ie, responder analysis in LIR subgroup, responder analysis for the 12-week treatment period, and regularity analysis) at level of $\alpha/2$. If the null hypotheses for 1 dose group can be rejected entirely (ie, significant difference between active vs placebo for all 4 endpoints at $\alpha=0.025$), one will increase the level to α (ie, 0.05) for the other group. This amounts to using Bonferroni-Holm over groups, and fix-sequence within groups. This multiplicity adjustment method follows the general results described by Bretz (Bretz et al 2009) and by Burman (Burman et al 2009).

A sample size of 105 patients per group would be needed to detect a difference of 25% in response rate (60% on NKTR and 35% on placebo), with power=90%, $\alpha=0.025$ and 2-sided test. In order to provide an adequate power to detect a treatment difference in the LIR subgroup (assuming LIR is 50% of the total study population), it is recommended that 210 patients per group (total 630 patients for 3 treatment groups) be randomized to the study. The assumptions on expected response rate were referenced from the NKTR-118 Phase II study and from other similar drugs.

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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 6.4.2)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of Covariance
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 hepatits C virus
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC (0-24)	Area under plasma concentration-time curve from zero to time 24 hours
AZDD	AstraZeneca Drug Dictionary
B	Blood
BIL	Bilirubin
BM	Bowel movement
BSS	Bristol Stool Scale
BUN	Blood urea nitrogen
Ca	Calcium
CI	Confidence interval
CK	Creatine kinase
CMH	Cochran-Mantel-Haenszel
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

Abbreviation or special term	Explanation
CSP	Clinical study protocol
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical study report
CYP3A4	Cytochrome P450 3A4
DEA	Drug Enforcement Administration
dECG	Digital electrocardiogram
DES	(Patient safety) data entry site
DM	Data management
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
EBV VCA IgM + EBNA IgG	Immunoglobulin M antibody to Epstein Barr virus viral capsid antigen + Immunoglobulin G antibody to Epstein Barr virus nuclear antigen
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid
ePRO	Electronic patient reported outcome
EQ-5D	Euroqol 5 Dimension Instrument
eRT	eResearch Technology
ET	Early termination
FIT	Fecal immunochemical test
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practices
GRand	AstraZeneca's Global Randomization system
H	High
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCV RNA	Hepatitis C virus ribonucleic acid
HDPE	High-density polyethylene
IB	Investigator's Brochure

Abbreviation or special term	Explanation
ICF	Informed consent form
ICH	International Conference on Harmonisation
I/E	Inclusion/exclusion
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
Ka	Absorption rate constant
L	Low
LAR	Laxative Adequate Responder
LIR	Laxative inadequate Responder
LUR	Laxative Unknown Responder
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MTP	Multiple Testing Procedure
NA	North America
NONMEM	Nonlinear mixed effect modeling
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
PK	Pharmacokinetics
POPPK	Population PK

Abbreviation or special term	Explanation
PP	Per protocol (population)
PR	(PR interval) The time from the onset of the P wave to the onset of the QRS complex on an electrocardiogram.
PRMP	Patient risk management plan
PRN	As occasion requires
PRO	Patient reported outcome
PT	Prothrombin time
QD	Every day
QLAB	Quintiles Laboratories
QRS	(QRS interval) The time from the beginning to the end of a QRS complex on an electrocardiogram.
QT	(QT interval) The time from the onset of the QRS complex to the end of the T wave on an electrocardiogram.
QTc	Corrected QT interval
QTcF	Fridericia corrected QT interval
RDW	Red blood cell distribution width
RR	(RR interval)
S	Serum
SAE	Serious adverse event (see definition in Section 6.4.3)
SAP	Statistical Analysis Plan
SBM	Spontaneous bowel movement
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
UBC	United BioSource Corporation
UK	United Kingdom
ULN	Upper limit of normal
US	United States

Abbreviation or special term	Explanation
WBC	White blood cell
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

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

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

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

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

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

Based on the above, it is appropriate to proceed with a Phase III study in the target population, that is, patients receiving opioid therapy for non-cancer-related pain who are experiencing OIC. This study will evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of 2 dose levels of NKTR-118. 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 useful in the treatment of OIC.

1.3 Rationale for conducting this study

The goal of this Phase III study to is demonstrate that NKTR-118 is well-tolerated and efficacious in the treatment of OIC in patients taking opioids for their non-cancer-related pain. NKTR-118 is expected to reverse 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. 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 vital signs, laboratory parameters, or electrocardiograms (ECGs). In a Phase I repeated dose study, adverse events (AEs) of dizziness were reported by 4/6 patients at the highest dose of NKTR-118 compared with 2/8 placebo patients. All events of dizziness were transient and resolved spontaneously without the need for any intervention.

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

NKTR-118 was well-tolerated in the Phase II study at 5 and 25 mg/day with the most commonly reported side effects being GI in nature (abdominal pain, diarrhea, and nausea) and most frequent in the 50 mg cohort. The frequency of any GI AE was 53% in the 25 mg/day

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

As summarized above, participation in this study may carry risks. New risks may be discovered when more patients are exposed to NKTR-118. 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. Because a thorough QT study has not yet been conducted, ECGs will be recorded and submitted for centralized analysis at screening, randomization (pre-dose and post-dose), and at each visit thereafter. In addition, individuals at high risk for arrhythmias are excluded from participation until the effect of NKTR-118 on QT interval in humans has been assessed.

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 6.4.13.2 for additional guidance.

To be able to determine scientifically if there is medical benefit from NKTR-118, this study has been designed as a monotherapy study with a placebo treatment arm. A dose range of 12.5 to 25 mg will be tested. 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. A rescue

medication is incorporated in the study design by use of bisacodyl if no SBM has occurred within at least 72 hours since the previous one. Further guidance is provided on the use of an enema if bisacodyl is ineffective. The risks of receiving placebo or ineffective medication in this population are expected to be low given the Phase II study results.

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

There may be benefits to patients as a result of participating in this study. Randomization to the active treatment group may provide symptomatic relief from OIC for the duration of the study. After the end of the study, the patient will be offered an opportunity to participate in a 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 the efficacy of NKTR-118 12.5 and 25 mg with placebo in the treatment of patients who have OIC.

2.2 Secondary objectives

The secondary objectives are to compare NKTR-118 12.5 and 25 mg with placebo on the daily signs and symptoms associated with OIC (straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and quality of life.

2.3 Safety objectives

The safety objectives are to assess the safety and tolerability of NKTR-118 when used for the treatment of OIC.

2.4 Exploratory objectives

The exploratory objectives are to characterize the PK of NKTR-118 and the covariate effect in the targeted disease population, explore the NKTR-118 exposure-response relationship, collect and store deoxyribonucleic acid (DNA) for future exploratory research, assess patient health status index and healthcare resource utilization, and assess patients' willingness to take the study drug again.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a Phase III, multi-center, double-blind, randomized, placebo-controlled, parallel group study of 2 doses of NKTR-118 and placebo. The study duration will be up to 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, during which the diagnosis of OIC and stability of the opioid regimen will be confirmed, 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 will be eligible to participate in a separate safety extension study. Approximately 1300 patients will be screened to obtain 630 randomized patients at approximately 120 centers in Australia, Belgium, Germany, Hungary, and the US.

Patients will sign the informed consent at the initial screening visit (Visit 1), within 14 days prior to entering the OIC confirmation period. Screening assessments will include review of inclusion/exclusion (I/E) criteria, collection of demographic information, and assessment of routine safety laboratory parameters (hematology and chemistry), ECG, urine pregnancy test for women of childbearing potential (WOCBP), urinalysis (U/A), urine drug screen, medical and surgical history, prior and concomitant medications, daily opioid use, laxative use, physical examination including rectal examination and vital signs, and the Columbia-Suicide Severity Rating Scale (C-SSRS). At the screening visit patients must also adhere to the colorectal cancer (CRC) screening criteria outlined in Appendix E. This includes provision of a stool sample for fecal immunochemical testing (FIT) for some patients, and patients at high risk for CRC providing documentation of negative colonoscopy or other appropriate imaging measures performed within 5 years of the screening visit. At screening, patients will receive an electronic diary (eDiary) device and training on how to record information using the device. Patients will be required to record information using the device during a pilot training period, to last a minimum of 5 consecutive days (see Section 3.1.1).

In addition, laxative response status will be determined at the screening visit (Visit 1) based on response to a questionnaire (See Section 6.2.2 and Appendix F). On the basis of physician assessment, patients will be grouped into 1 of 3 categories: patients who had adequate response to laxatives (Laxative Adequate Responder [LAR]), patients who had inadequate response to laxatives (Laxative Inadequate Responder [LIR]), and those patients whose laxative responder status could not be confirmed due to lack or infrequent use of laxatives in the 2 weeks before screening (Laxative Unknown Responder [LUR]).

Once patients have met initial screening requirements (including self-reported active symptoms of OIC at screening [<3 SBMs/week and ≥1 reported symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction in at least 25% of bowel movements (BMs) over the previous 4 weeks]), and have completed at least 5 days of recording using the eDiary device, they will return for Visit 2. At Visit 2, the eDiary

recording will be reviewed with the patient and instructions regarding proper recording will be repeated. Patients who experienced difficulty using the device will have the opportunity to have any questions answered. Daily opioid use, use of other medications, and AEs will also be collected at Visit 2. Bisacodyl for use as a rescue medication will be dispensed to patients at Visit 2, and at each visit thereafter until Visit 8. Confirmation of OIC will be established between Visits 2 and 3.

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

Confirmed OIC is defined as:

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

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

Randomization will occur at the onset of the 12-week double-blind treatment period at Visit 3. Patients will be stratified based on their response to laxative use (LIR, LAR, LUR), and randomly assigned to 1 of the 3 treatment groups in a 1:1:1 ratio, with a minimum of 50% of patients enrolled in the LIR category. Patients will be randomly assigned in a 1:1:1 ratio (approximately 210 patients per treatment arm) to receive placebo, or NKTR-118 at a dose of 12.5 or 25 mg every day (QD).

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.

During the OIC confirmation and treatment periods of the study, patients will be required to stop all laxatives and other bowel regimens, and may use only bisacodyl as rescue medication if a BM has not occurred within at least 72 hours of the last recorded BM.

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. If these secondary interventions fail, the patient should be discontinued from the study (or excluded from the study if the patient fails the rescue regimen prior to randomization) 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 randomized (see Section 4.2).

Study assessments include:

Electronic Diary (eDiary) Assessments: (collected daily starting with pilot training during the screening period through the end of randomized treatment).

- Date and time of BMs (recorded at the time of each BM)
- Stool consistency (BSS) (recorded at the time of each BM)
- Straining (recorded at the time of each BM)
- Complete/incomplete evacuation (recorded at the time of each BM)
- Pain level (NRS) recorded each evening
- Date and time of use of laxative rescue medication (bisacodyl or enema) recorded at the time that medication is taken

- Date and time of use of opioid medication for breakthrough pain recorded at the time that medication is taken

Additional Assessments:

- 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 [EQ-5D], and Willingness to Take Drug Again questionnaire). The PAC-SYM, PAC-QOL, and EQ-5D, will be completed at selected time points from Visit 3 on; the Willingness to Take Drug Again questionnaire will be completed at Visit 8. At Visit 3, patients will receive training on filling out these questionnaires using an electronic device called a SitePad at the study center, and will be instructed that they are to answer the questions on their own, without any help from family or study staff. In addition, for visits after Visit 3, 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 3, since only randomized patients will fill out the questionnaires and interaction with study staff will be necessary to determine whether randomization criteria have been met.)

- C-SSRS throughout the study

- OIC Healthcare Resource Utilization assessed from Visit 4 through Visit 9

- Recording of concomitant medications (other than laxative rescue medication and opioid medication for breakthrough pain) throughout the study

- Recording of opioid medication for breakthrough pain throughout the study – specific information regarding timing of breakthrough pain medication is captured in the eDiary. Information regarding breakthrough pain medication is also collected on electronic case report forms (eCRFs) and recorded in the eDiary to allow for daily recording of dosing.

- Recording of AEs throughout the study

- Recording of daily maintenance opioid regimen throughout the study

- Routine safety laboratories (hematology, chemistry, and total cholesterol) and U/A and clinical assessments at screening and at selected time points throughout the study

- ECG at screening and at selected time points throughout the study

- Vital signs and physical examination at screening and at selected time points throughout the study
- Pregnancy test for WOCBP at screening and selected time points throughout the study
- PK sampling throughout the study starting with Visit 3
- Genetic sampling (optional; for patients who consent, collected once after randomization, preferably at Visit 3)

3.1.1 Visit 1 (Initial screening)

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.

At Visit 1, each patient's laxative response status will be determined based on 4 questions which explore the frequency of laxative use, constipation symptom severity, and laxative side-effects during the previous 2 weeks. The patients will be classified as LIR, LAR, or LUR based on their answers. The LIR/LAR/LUR algorithm is presented in more detail in Section 6.2.2 and in Appendix F.

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

- Patients will receive the eDiary recording device and detailed instructions for its use. The eDiary is to be completed for at least 5 consecutive days of pilot training and will be used to collect daily information regarding BMs, straining, stool consistency, complete/incomplete evacuation, pain level, use of laxative rescue medication, and use of opioid medication for breakthrough pain. However, the pilot period will not be counted towards the 14 day OIC confirmation period, which begins at Visit 2.

The following additional procedures will be performed at Visit 1:

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

- Review of inclusion and exclusion criteria including review of CRC screening requirements
- FIT test or verification of previous imaging study, if required
- Review of medical and surgical history (including OIC history)
- Complete physical examination (including rectal examination, height, weight, body temperature, respiratory rate)
- Sitting blood pressure and pulse will be measured.
- Single 12-lead ECG will be obtained.
- Urine sample will be collected for urine drug screen (urine toxicology), to test for pregnancy (WOCBP), and for U/A.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- C-SSRS to assess suicidal risk, ideation, and behavior
- Modified Himmelsbach scale will be completed.
- Daily maintenance and breakthrough pain opioid dosing regimens over the 60 days before enrollment will be asked about and recorded on the appropriate eCRFs. The daily opioid and breakthrough pain dosing regimens will be confirmed by prescription or clearly labeled bottles of opioid medication. Information from the breakthrough pain medication eCRF will be recorded in the eDiary to allow for daily recording of dosing
- Use of prior/concomitant medication will be recorded. Prior medications taken up to 60 days before enrollment will be recorded.
- An appointment for Visit 2 will be made. Patients will be instructed to bring the eDiary with them to the visit.

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

3.1.2 Visit 2 (OIC confirmation)

Visit 2 will occur 5 to 14 days after Visit 1, as soon as all initial screening assessments have taken place, results have been reviewed by the investigator, eligibility determined, and a

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

At Visit 2, patients who failed initial screening requirements will return the eDiary, be asked if any AEs have occurred since Visit 1, will be administered the C-SSRS, and will be discontinued from the study. Patients who are discontinued from the study prior to randomization will be considered to be screen failures.

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

Patients will be asked to discontinue all laxative and other bowel regimens including herbal products and prune juice (see prohibited medications, Section 5.6) throughout the 2-week OIC confirmation period and 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 2 through Visit 7. Patients will be instructed on the guidelines for rescue bisacodyl use. Patients will be asked to return unused bisacodyl at each subsequent visit. Documentation of bisacodyl use will be reviewed with the patient at each visit by comparing returned bisacodyl with eDiary records. If there is a discrepancy, the patient will be counseled regarding proper documentation of bisacodyl use in the eDiary. If a patient does not experience a BM following bisacodyl rescue, the investigator may prescribe one-time use of an enema. The timing of administration of this therapy will be noted. If these secondary interventions fail, the patient should be excluded from the study and referred for additional medical evaluation. Since the patient is excluded from the study, the investigator should recommend initiation of any therapy deemed most appropriate. Any patient who is obstipated and/or has fecal impaction must not be randomized (see Section 4.2).

The following additional procedures will be performed at Visit 2:

For patients who do not continue in the study:

- AEs since Visit 1 will be recorded.
- The eDiary device will be returned.
- C-SSRS to assess suicidal risk, ideation, and behavior

For patients who continue in the study:

- AEs since Visit 1 will be recorded.
- Use of concomitant medication (other than opioid medication) since Visit 1 will be recorded. Use of laxatives will be recorded on the concomitant medication eCRF.
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Bisacodyl will be dispensed.
- An appointment for Visit 3 (Week 1, Day 1) will be made. Patients will be instructed to bring the eDiary recording device and unused bisacodyl with them to the visit.

3.1.3 Double-blind treatment period (Visits 3, 4, 5, 6, 7, 8)

During the double-blind treatment period, patients will be required to continue daily eDiary recording of BMs along with ratings of straining, stool consistency (BSS), and complete/incomplete stool evacuation as each BM occurs, pain level (NRS scale) recorded each evening, use of laxative rescue medication, and use of opioid medication for breakthrough pain. Patients will be instructed that they are to complete the eDiary every day, including days that they have study visits. Compliance with the eDiary will be assessed remotely by the site at least every 48 hours to confirm that the patient is entering data. The patient will be phoned if any data are missing. Patients will also be asked to bring the eDiary recording device with them to each visit, during which their recordings and proper use of the device will be reviewed.

Patients will be asked to bring their bottles of study drug with them to each visit, so that unused study drug tablets can be counted and recorded, and compliance can be determined. Patients should be reminded of the importance of adherence to the study dosing regimen.

Patients will also be instructed that should they experience a change in their daily maintenance or breakthrough pain opioid 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.

Bisacodyl for use as rescue medication will be dispensed to patients at each visit. Patients will be asked to return unused bisacodyl at each subsequent visit. Documentation of bisacodyl use will be reviewed with the patient at each visit by comparing returned bisacodyl with eDiary records. If there is a discrepancy, the patient will be counseled regarding proper documentation of bisacodyl use in the eDiary.

Patients will receive their first dose of study drug at the study center at Visit 3. For subsequent visits through Visit 7, patients will self-administer the study drug in the morning (per their usual routine) prior to coming to the study center. At Visit 8, 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 3 and receiving at least 1 dose of study drug will be asked to return to the study center for an early termination (ET) visit during which unused study drug and the eDiary will be returned, and assessments normally scheduled for Visit 8 (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).

3.1.3.1 Visit 3 (Randomization, Week 0, Day 1)

Visit 3 will occur 14 days (-1 day to +3 days) after Visit 2, at the completion of the OIC confirmation period. A minimum of 11 days of eDiary data collection must have been recorded since the start of the OIC confirmation period before the patient can be randomized for the study.

Visit 3 will be scheduled in the morning. Patients will be required to remain at the study center for a minimum of 4 hours after receiving the study drug, for observation (see Section 6.4.13.2 regarding abdominal pain), PK sampling, and completion of the modified Himmelsbach scale. A light breakfast (eg, skim or lowfat milk, cereal, fruits, coffee, tea) will be allowed; however, a minimum of 4 hours must have passed after breakfast and before the study drug can be given at Visit 3. No food or snacks are allowed for 1 hour after dosing.

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

Patients who cannot appropriately use the eDiary device (greater than 25% of the data are missing), will be considered for exclusion from the study.

Patients who continue in the study will also complete electronic PRO (ePRO) assessments (PAC-SYM, PAC-QOL, EQ-5D) after randomization. Patients will receive training from study staff regarding how to enter the data electronically using an electronic device called a SitePad provided at the study center. Training procedures will be documented separately from this CSP. Patients will be instructed to answer the questions on their own, without help from others (family, friends, or study staff).

At Visit 3, the following procedures will be performed:

For patients who do not continue in the study:

- AEs that occurred since Visit 2 will be recorded.

- The eDiary device will be returned.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Unused bisacodyl will be returned.

For patients who continue in the study:

Pre-dose:

- I/E criteria will be reviewed with the patient.
- The eDiary (including proper documentation of bisacodyl and enema use) will be reviewed with the patient, and instruction on proper completion of the eDiary will be reviewed.
- Patients will receive training on how to fill out ePRO assessments using the SitePad at the study site.
- PAC-SYM will be completed.
- PAC-QOL will be completed.
- EQ-5D will be completed.
- Sitting blood pressure and pulse will be measured.
- Targeted physical examination (lungs, cardiovascular, abdomen) with weight. Special emphasis should be placed on the pre-randomization abdominal examination so as not to enroll any patients with an acute abdominal process (see Section 4.2). At the discretion of the investigator, a rectal examination may be performed at this time, if necessary to ensure the safety of the patient.
- 12-lead ECG after resting for 10 minutes, with triplicate ECGs collected over a 5-minute period
- Urine sample will be collected for urine pregnancy test (WOCBP). The urine pregnancy test result must be negative before the patient may continue with the visit and administration of study drug.
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 2 will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior

- AEs since Visit 2 will be recorded.
- Modified Himmelsbach scale will be completed by a clinician before the patient receives the first dose of study drug.
- Patients who continue to meet I/E criteria (including confirmation of stability of the dose of the opioid) and who meet OIC criteria will be randomized to a treatment arm using the Interactive Voice Response System (IVRS).
- Unused bisacodyl will be returned.
- Weight will be assessed.
- Blood samples will be collected for laboratory assessments (clinical chemistry [including total cholesterol] and hematology).
- Blood sample will be collected for genetic sampling (if genetic informed consent signed). It is preferred that the blood sample for genetic analysis be collected at Visit 3; however, it may be collected at any visit during the study after the patient is randomized.

Dose:

- First dose of double-blind study drug will be administered at the study center and the patient observed for at least 4 hours. The accurate dose time in date, hours, and minutes will be recorded.

Post-dose:

- Single ECG will be obtained 2 hours after the dose of study drug, before the PK sample is collected.
- Modified Himmelsbach scale will be completed by a clinician 2 hours after patient receives the first dose of study drug.
- Blood sample will be collected for PK measurement 2 hours after the dose of study drug. The PK sampling time in date, hours, and minutes will be recorded accurately.
- Any BM during the 4-hour observation period will be recorded by the patient in the eDiary.
- Study drug will be dispensed and dosing instructions will be provided.
- A new supply of bisacodyl will be dispensed.

- An appointment for Visit 4 (Day 8) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit.

3.1.3.2 Visit 4 (Week 1, Day 8)

Visit 4 will occur on Day 8 (±1 day). At Visit 4, the following procedures will be performed. (Note: The OIC Healthcare Resource Utilization questionnaire will be administered starting on Visit 4):

- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse will be measured.
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- Blood sample will be collected for PK measurement. The PK sampling time in date, hours, and minutes will be recorded accurately. The accurate last 2 dose times of study drug in date, hours, and minutes will be collected. Any missing dose of study drug in the previous 5 days will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 3 will be recorded.
- Patient will bring unused study drug to visit and number of unused study drug tablets will be recorded in order to determine patient compliance.
- AEs since Visit 3 will be recorded.
- Modified Himmelsbach scale will be completed.
- Unused bisacodyl will be returned and a new supply of bisacodyl will be dispensed.
- eDiary (including proper documentation of bisacodyl and enema use) review
- An appointment for Visit 5 (Day 15) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit.

3.1.3.3 Visit 5 (Week 2, Day 15)

Visit 5 will occur on Day 15 (±1 day). At Visit 5, the following procedures will be performed:

- PAC-SYM will be completed.
- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse will be measured.
- Single 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology).
- Blood sample will be collected for PK measurement. The PK sampling time in date, hours, and minutes will be recorded accurately. The accurate last 2 dose times of study drug in date, hours, and minutes will be collected. Any missing dose of study drug in the previous 5 days will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 4 will be recorded.
- Patient will bring unused study drug to visit and number of unused study drug tablets will be recorded in order to determine patient compliance.
- AEs since Visit 4 will be recorded.
- Unused bisacodyl will be returned and a new supply of bisacodyl will be dispensed.
- eDiary (including proper documentation of bisacodyl and enema use) review
- An appointment for Visit 6 (Day 29) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit.

3.1.3.4 Visit 6 (Week 4, Day 29)

Visit 6 will occur on Day 29 (±3 days). At Visit 6, 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 will be measured.
- Single 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology) and serum pregnancy test (WOCBP).
- Blood sample will be collected for PK measurement. The PK sampling time in date, hours, and minutes will be recorded accurately. The accurate last 2 dose times of study drug in date, hours, and minutes will be collected. Any missing dose of study drug in the previous 5 days will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 5 will be recorded.
- AEs since Visit 5 will be recorded.
- Modified Himmelsbach scale will be completed.
- Unused bisacodyl will be returned and a new supply of bisacodyl will be dispensed.
- eDiary (including proper documentation of bisacodyl and enema use) review
- Unused study drug will be returned and the number of unused study drug tablets will be recorded. Patient compliance will be determined.
- Study drug will be dispensed.
- An appointment for Visit 7 (Day 57) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit.

3.1.3.5 Visit 7 (Week 8, Day 57)

Visit 7 will occur on Day 57 (±3 days). At Visit 7, the following procedures will be performed:

- PAC-SYM will be completed.
- OIC Healthcare Resource Utilization questionnaire will be complete d.
- Sitting blood pressure and pulse will be measured.
- Single 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology) and serum pregnancy test (WOCBP).
- Blood sample will be collected for PK measurement. The PK sampling time in date, hours, and minutes will be recorded accurately. The accurate last 2 dose times of study drug in date, hours, and minutes will be collected. Any missing dose of study drug in the previous 5 days will be recorded.
- C-SSRS to assess suicidal risk, ideation, and behavior
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 6 will be recorded.
- AEs since Visit 6 will be recorded.
- Unused bisacodyl will be returned and a new supply of bisacodyl will be dispensed.
- eDiary (including proper documentation of bisacodyl and enema use) review
- Unused study drug will be returned and the number of unused study drug tablets will be recorded. Patient compliance will be determined.
- Study drug will be dispensed.
- An appointment for Visit 8 (Day 85) will be made. Patients will be instructed to bring the eDiary, study drug, and unused bisacodyl with them to the visit. In addition, patients will be asked if they are interested in participating in a safety extension study. Patients will be instructed not to take their study drug at home on the morning of Visit 8. Patients will also get a reminder phone call prior to Visit 8 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 8 for confirmation of their daily maintenance and breakthrough pain opioid dosing regimens.

3.1.3.6 Visit 8 (Week 12, Day 85)

Visit 8 will occur on Day 85 (±3 days), and will be scheduled in the morning. If a patient who plans to enter the safety extension study accidentally takes study drug at home on the morning of Visit 8, the patient should be rescheduled to return the next morning for all Visit 8 procedures. If a patient accidentally takes study drug at home on the morning of Visit 8 but does not intend to participate in the safety extension study, he/she can proceed with Visit 8.

For patients who enter the safety extension study, Visit 8 will also correspond to the randomization visit for the safety extension study. The order of procedures will be different for patients who enter the safety extension study (and the order noted for the safety extension study should be followed). However, all Visit 8 assessments listed below are to be collected, even if not required for the safety extension study.

At Visit 8 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.
- Willingness to Take Drug Again questionnaire will be completed
- Physical examination including weight, body temperature, and respiratory rate
- Sitting blood pressure and pulse will be measured.
- Triplicate 12-lead ECG will be obtained.
- Blood samples will be collected for laboratory assessments (clinical chemistry [including total cholesterol] and hematology).
- Blood sample will be collected for PK measurement. The PK sampling time in date, hours, and minutes will be recorded accurately. The accurate last 2 dose times of study drug in date, hours, and minutes will be collected. Any missing dose of study drug in the previous 5 days will be recorded.
- Urine sample will be collected for U/A, urine drug screen (urine toxicology), and urine pregnancy test (WOCBP).
- C-SSRS to assess suicidal risk, ideation, and behavior

- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (other than laxative rescue medication or opioid medication) since Visit 7 will be recorded.
- AEs since Visit 7 will be recorded.
- Modified Himmelsbach scale will be completed.
- eDiary (including proper documentation of bisacodyl and enema use) review, and return of the eDiary device
- 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 9 (Final Visit, Day 99) will be made for patients who do not participate in the safety extension study.

Following Visit 8, patients may resume any constipation regimen that they and the investigator feel is appropriate, unless they choose to continue in the safety extension study. Note: Visit 9 is not required for patients who enter the safety extension study.

3.1.4 Final Visit (Visit 9, Week 14, Day 99)

Visit 9 will occur on Day 99 (±3 days). At Visit 9, the following procedures will be performed:

- OIC Healthcare Resource Utilization questionnaire will be completed.
- Sitting blood pressure and pulse will be measured.
- 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
- Daily maintenance and breakthrough pain opioid dosing regimens will be asked about and recorded on the appropriate eCRFs.
- Use of concomitant medication (including bisacodyl and enema) since Visit 8 will be recorded.

- AEs since Visit 8 will be recorded.

Table 1 Study plan

	Screening	OIC Confirmation	Treatment Period					Final	
Week	**-4 to -2[a]**	**-2 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**14**
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET**	**9**
Study Day	**-28 to -14**	**-14 to -1**	**D1[b]**	**D8**	**D15**	**D29**	**D57**	**D85[c]**	**D99[d]**
Visit Window (Days)			**-1 to +3**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**
Informed consent & genetic informed consent[e]	√								
Randomization			√						
Demographic information	√								
Inclusion/exclusion criteria	√		√						
CRC risk factor evaluation (including FIT as necessary)	√								
Medical and surgical history (including OIC history)	√								
Complete physical examination (including height, weight, temperature, respiratory rate)[f]	√		(√)[f]					√	
Sitting blood pressure, pulse	√		√	√	√	√	√	√	√
LIR, LAR, LUR status[g]	√								
Pregnancy test for WOCBP[h]	√		√			√	√	√	√
12-lead ECG[i]	√		√	√	√	√	√	√	√
Clinical chemistry and hematology[j]	√		√	√	√	√	√	√	√
Total cholesterol			√					√	
Urinalysis[k]	√							√	`
Urine drug screen[l]	√							√	
Genetic sampling[e]			√						
PK sampling[m]			√	√	√	√	√	√	
C-SSRS	√	√	√	√	√	√	√	√	√
Opioid regimen recorded (maintenance and breakthrough)	√	√	√	√	√	√	√	√	√
Modified Himmelsbach scale[n]	√		√	√		√		√	
PAC-SYM[o]			√		√	√	√	√	

Table 1 Study plan

	Screening	OIC Confirmation	Treatment Period					Final	
Week	**-4 to -2**[a]	**-2 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**14**
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET**	**9**
Study Day	**-28 to -14**	**-14 to -1**	**D1**[b]	**D8**	**D15**	**D29**	**D57**	**D85**[c]	**D99**[d]
Visit Window (Days)			**-1 to +3**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**
PAC-QOL[o]			√			√		√	
EQ-5D[o]			√			√		√	
OIC Healthcare Resource Utilization Assessment[o]				√	√	√	√	√	√
Prior/concomitant medication (other than laxative rescue medication and opioid medication)[p]	√	√	√	√	√	√	√	√	√
eDiary device dispensed	√								
eDiary ([daily]: BM, straining, complete/incomplete evacuation, stool consistency (BSS), pain level [NRS], laxative rescue medication [bisacodyl, enema], opioid medication for breakthrough pain)[q]	√	◄------	------	------	------	------	------►	√	
eDiary (including proper documentation of bisacodyl and enema use) review		√	√	√	√	√	√	√	
eDiary device returned		√[r]	√[r]					√	
AEs		√[s]	√[s]	√	√	√	√	√	√
Return unused study drug[t]				√	√	√	√	√	
Dispense study drug			√			√	√		
Dispense bisacodyl		√	√	√	√	√	√		
Return unused bisacodyl			√	√	√	√	√	√	
Willingness to Take Drug Again questionnaire[o]								√	
Make appointment for next visit	√	√	√	√	√	√	√	√	

AEs Adverse events; BSS Bristol Stool Scale; CRC colorectal screening; C-SSRS Columbia Suicide Severity Scale; D Day; ECG electrocardiogram; eDiary electronic diary; ePRO electronic patient reported outcome; EQ-5D European Quality of Life; ET early termination; FIT fecal immunochemical test; 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; PK pharmacokinetic; SBM spontaneous bowel movement; NRS Numeric Rating Scale; WOCBP women of childbearing potential

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

[b] A minimum of 11 days of eDiary data collection must have occurred since the start of the OIC confirmation period before the patient can be randomized.

Day 1 visit requires 4-hour post-dose in-office stay.

[c] Day 85 assessments should be performed at the time of early termination for patients who discontinue early, with the exception that patients who discontinue prior to Visit 3 (randomization) will not be required to have Day 85 assessments.

[d] Patients who enter the safety extension study do not need to participate in Visit 9.

[e] Genetic informed consent does not need to be obtained at enrollment, but must be obtained before any blood sample for genetic analysis is collected. It is preferred that blood samples for genetic testing be collected at Visit 3, but blood samples may be collected at any visit from Visit 3 through Visit 9.

[f] Visit 1: physical examination will include rectal examination, as well as height, weight, temperature, respiratory rate; Visit 3 (Randomization): targeted physical examination (lungs, cardiovascular, abdomen) with weight collected, may include optional rectal examination at the discretion of the investigator, if necessary to ensure the safety of the patient; Visit 8 (end-of-treatment): physical examination including weight, temperature, respiratory rate (no rectal examination).

[g] Determined based on self reported laxative use over the 2 weeks prior to the screening visit, continued constipation symptoms, and laxative side effects.

[h] Urine pregnancy tests will be performed at screening (Visit 1), randomization (Visit 3), and Week 12 (Visit 8). Any positive urine pregnancy test is to be followed up with a serum pregnancy test. Serum pregnancy tests will be performed at Week 4 (Visit 6), Week 8 (Visit 7), and Week 14 (Visit 9).

[i] At randomization (Visit 3) a 12-lead ECG will be repeated in triplicate pre-dose, and a single ECG will be obtained 2 hours post-dose. Triplicate ECGs will also be obtained at Week 1 (Visit 4) and Week 12 (Visit 8). Single 12-lead ECGs will be obtained at Weeks 2 (Visit 5), 4 (Visit 6), 8 (Visit 7), and 14 (Visit 9)

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

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

[l] If, in the opinion of the investigator, a patient is undergoing opiate withdrawal or significant exacerbation of pain, the investigator is to conduct a repeat urine drug screen to rule out noncompliance with the opioid regimen as an explanation for withdrawal or pain.

[m] PK sample collection during the Day 1 visit will be 2 hours after the dose of study drug. One PK sample will be collected at each visit specified for PK collection. The PK sampling time in date, hours, and minutes will be recorded accurately. For the Day 1 visit, the dose time in date, hours, and minutes will be recorded accurately. For subsequent specified visits, the accurate last 2 dose times of study drug in date, hours, and minutes will be recorded. Any missing dose in the 5 days before each specified PK visit will be recorded.

[n] Completed before the first dose and 2 hours after the first dose during Visit 3.

[o] These ePRO questionnaires (PAC-SYM, PAC-QOL, EQ-5D) 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 3, since only randomized patients will fill out the questionnaires and interaction with study staff will be necessary to determine whether randomization criteria have been met. As applicable, the OIC Healthcare Resource Utilization Assessment is to be completed after the ePRO questionnaires, and prior to any investigations or discussions about symptoms with study staff.

[p] Prior medications will be collected from 60 days before screening. At Visit 9, concomitant medication will include laxative rescue medication taken since Visit 8.

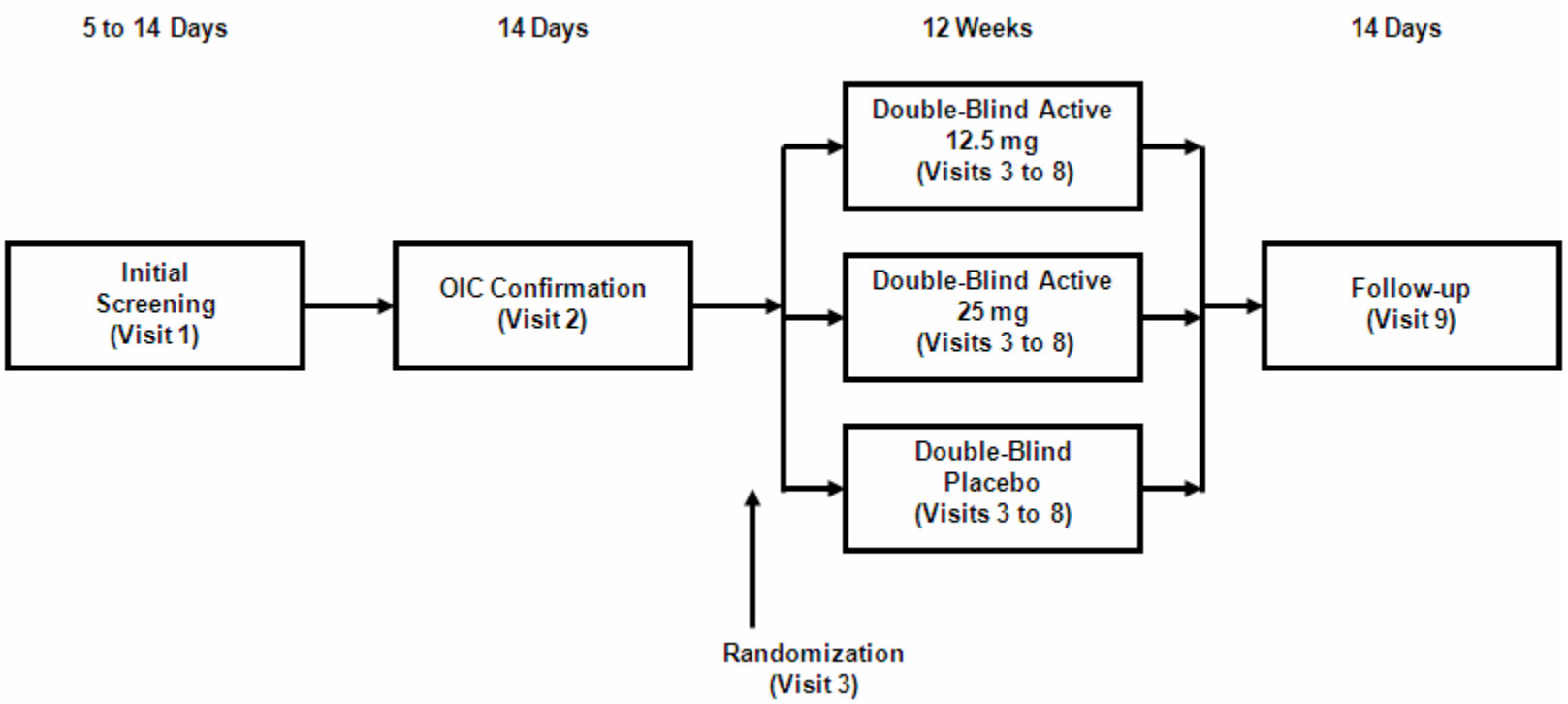
[q] eDiary assessments collected daily by the patient, eDiary pilot training will begin at Visit 1.

[r] Patients who do not meet initial screening criteria will return the eDiary device at Visit 2; patients who do not meet OIC confirmation criteria, or who continue to have difficulty using the eDiary recording device, will return the eDiary device at Visit 3.

[s] For patients who fail initial screening, AEs will be collected at Visit 2. For patients who fail OIC confirmation, AEs will be collected at Visit 3.

[t] Patients will be asked to bring the study drug with them to Visits 4 through 8 (to assess compliance); unused study drug will be returned/collected at Visits 6, 7, and 8.

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 confirm the effect of NKTR-118 on SBMs/week and symptoms of constipation in patients with confirmed OIC. A placebo comparator (and double-blind design) is chosen to control for normal disease course and other non-specific factors.

The assessment of constipation in this study is based on the Rome III criteria, reflecting standard practice (Longstreth et al 2006). Spontaneous BM frequency is a well-recognized primary endpoint, commonly employed in pharmaceutical research and the academic literature.

Patients with varying response to laxatives (LIR, LAR, LUR) are included in this study; however, a minimum of 50% of patients will have laxative inadequate response. Laxative inadequate responders are an important subpopulation with high unmet medical need for a chronic oral treatment option. Planned secondary analyses focus on the response to NKTR-118 in the LIR population only.

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 Phase II study consisted almost exclusively of patients who did not have cancer-related pain, and the present study is an attempt to replicate and extend those findings. Furthermore, it is likely that the AE profile in a non-cancer pain population is different from that of patients with cancer.

The present study includes a screening period (up to 2 weeks), a 2-week OIC confirmation period to confirm the diagnosis of OIC, a 12-week treatment period, and a follow-up visit 2 weeks after last dose of study drug. During the screening period, patients will receive instruction on using the eDiary device and will have the opportunity to practice using the device for at least 5 days. This training is included to minimize patient error in using the device. During the 2-week OIC confirmation period, patients will have additional time to become proficient using the device. The 12-week treatment period is longer than the 4-week treatment period employed in the Phase II study and will provide longer term safety and

efficacy data. Interested patients will also have the opportunity to participate in a separate safety extension study at the completion of the present study.

Laxative use is prohibited during the OIC confirmation and treatment periods, 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 reverse the symptoms of OIC by blocking the peripheral effects of opioid medication without inducing central opioid withdrawal symptoms or interfering with analgesia. Although there was no indication of opioid withdrawal symptoms or reversal of analgesia in the Phase II study, the current study includes the modified Himmelsbach scale to assess withdrawal symptoms, and the NRS along with ongoing assessment of daily opioid dose to assess pain.

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

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

4. SUBJECT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

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

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

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

3. Self-reported active symptoms of OIC at screening (<3 SBMs/week and experiencing ≥1 reported symptom of hard/lumpy stools, straining, or sensation of

incomplete evacuation/anorectal obstruction in at least 25% of BMs over the previous 4 weeks); **and**

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

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

5. Willingness to stop all laxatives and other bowel regimens including prune juice and herbal products throughout the 2-week OIC confirmation period and the 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. Patients must comply with CRC screening criteria as specified in Appendix E.

7. Male patients who are sexually active must use a double-barrier method of contraception (condom with spermicide) from the first dose of investigational product (IP) until 12 weeks after their last dose. Women of childbearing potential must have a negative pregnancy test and confirmed (by the investigator) use of a highly effective form of birth control for 12 weeks before enrollment and until 12 weeks after their last dose. Highly effective forms of birth control are listed in Appendix I. Women of non-childbearing potential can participate in this study without adherence to the pregnancy precautions. Women of non-childbearing

potential are defined as women who are either permanently sterilized (hysterectomy or bilateral oophorectomy or bilateral salpingectomy) or are postmenopausal. Any woman who is older than 57 years of age is considered postmenopausal. In addition, women who are older than 50 years of age and amenorrheic with at least 12 months having passed since the last menses (after cessation of all exogenous hormone treatments), are also considered postmenopausal.

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

9. Outpatient status at enrollment and randomization

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

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

4.2 Exclusion criteria

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

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

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

3. Medical conditions and treatments associated with diarrhea, intermittent loose stools, or constipation, which could confound the interpretation of the results, eg, fecal incontinence, irritable bowel syndrome (physician-diagnosed), or chronic idiopathic constipation.

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

period or expected surgical procedure of the abdomen during the study participation period would be excluded.

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

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

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

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

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

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

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

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

12. Patients who are at increased risk for ventricular arrhythmia, including those that have a prior history of serious ventricular arrhythmia, family history of sudden

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

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

14. Use of prohibited medications as listed in Section 5.6

15. Pregnancy or lactation

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

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

18. Previous randomization in the present study or any study with NKTR-118

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

20. Any receipt of an investigational medication within 30 days of screening

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

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

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

5. STUDY CONDUCT

5.1 Restrictions during the study

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

5.2 Subject enrollment and randomization

The Principal Investigator (PI) or other qualified designee will:

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

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

3. Determine patient eligibility. Eligibility will be determined after the screening and OIC confirmation periods, upon completion of the OIC confirmation period (see Sections 4.1 and 4.2).

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

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

5.2.1 Procedures for randomization

Randomization codes will be distributed and communicated to study sites by use of an IVRS. Randomization will be stratified by response to laxatives (LIR, LAR, LUR) during the 2 weeks prior to screening. The randomization procedure will be structured to ensure that a minimum of 50% of patients are LIR.

Eligible patients will be randomized in balanced blocks to receive NKTR-118 12.5 mg, NKTR-118 25 mg, or matching placebo in a 1:1:1 ratio. The actual treatment given to individual patients will be determined by a randomization scheme that has been loaded into the IVRS database. The randomization scheme will be produced by a computer software program called GRand (AstraZeneca's Global Randomization system) that incorporates a standard procedure for generating random numbers. If a patient is discontinued from the study, his/her patient number or enrollment number will not be reused, and the patient will not be allowed to re-enter the study. Randomized patients who discontinue early from the study will not be replaced.

Randomization codes will be assigned strictly sequentially within the response to laxative categories as patients become eligible for randomization.

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

Entry of incorrect stratification information into the IVRS will not disqualify a patient from continuation in the study.

5.3 Procedures for handling subjects incorrectly enrolled

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

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

5.4 Blinding and procedures for unblinding the study

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 Investigational Products and Patient Safety.

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 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 except for the futility analysis 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 1 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

Treatment day	NKTR-118 12.5 mg/day	NKTR-118 25 mg/day	Placebo
Days 1 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 2, 3, 4, 5, 6, and 7. Containers for the procured bisacodyl will be provided to the sites (see Section 5.6).

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 United Kingdom (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 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.

Patients may take laxatives during the screening period of the study, but must discontinue use of laxatives at least 24 hours prior to the start of the OIC confirmation period. During the OIC confirmation period and 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 two additional times, as necessary, each 10 to 15 mg dose separated by 12 hour intervals. It is recommended that the bisacodyl tablets be taken either at bedtime or before breakfast. If after 3 doses of bisacodyl rescue therapy, the patient still has not experienced a BM, the investigator may prescribe one-time use of an enema. The timing of administration of this therapy will be noted and recorded in the eDiary. If these secondary interventions fail, the patient should be discontinued from the study (or excluded from the study if the patient fails the rescue regimen prior to randomization) 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 randomized (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 2. Patients will be instructed on the guidelines for rescue bisacodyl use. Patients will be asked to return unused bisacodyl at each subsequent visit. Documentation of bisacodyl use will be reviewed with the patient at each visit by comparing returned bisacodyl with eDiary records. If there is a

discrepancy, the patient will be counseled regarding proper documentation of bisacodyl use in the eDiary.

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
- Naltrexone
- 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

Drugs that may prolong the QT interval are also prohibited. Common examples of such drugs are listed in Appendix J. This list should not be considered comprehensive. Therefore investigators need to use their judgment when reviewing the medication list from individual patients and restrict patients who must stay on drugs that may increase the QT interval.

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 and eDiary recording 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). Compliance with the eDiary will be assessed remotely by the site at least every 48 hours to confirm that the patient is entering data. The patient will be phoned if any information is found to be missing.

5.7.1 Accountability

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.

5.8 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 8 assessments will be performed. Adverse events will be followed up (see Sections 6.4.4 and 6.4.5); and all study drugs and the eDiary device 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 6.4.9.2. The protocol for handling patients with elevated liver transaminases including guidelines for discontinuing patients is discussed in Section 6.4.9.2).
- ECG evidence of QT prolongation (QTcF >500 ms, or an increase of QTcF >60 ms above baseline to a value >480 ms on the12-lead ECG, confirmed on a repeat 12-lead ECG taken after waiting at least 5 minutes after the original finding of prolonged QTc)
- 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 that would not be consistent with continuation in the study, as determined by the investigator, AstraZeneca, or its representative, or the patient.
- Safety reasons as judged by the investigator
- Patient becomes pregnant
- Significantly worsened OIC refractory to medical treatment as judged by the investigator (including failure of the laxative rescue regimen either before or after randomization)
- The patient is unable to comply with the restrictions on the use of concomitant medications as detailed in Section 5.6 (in such cases the investigator should consult with the study physician before discontinuing the patient).
- The patient is unable to tolerate the 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 6.4.13.2.

Patients who discontinue prematurely from the study after participating in Visit 3 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 8 (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.

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

6.2 Data collection and enrollment

6.2.1 Screening and demographic measurements

The following data will be collected and recorded on the appropriate sections of the eCRF at the time of the screening visit (Visit 1) (refer to the Study Plan, Table 1):

- Signed informed consent forms (ICFs) will be obtained.
- Signed genetic informed consent (may be signed at a subsequent visit)
- Demography (date of birth, sex, and race)
- Review of I/E criteria

- Review of medical and surgical history (including OIC history)
- FIT test or verification of previous imaging study, if required
- Complete physical examination (including rectal examination, height, and weight)
- Vital signs (sitting blood pressure and pulse, body temperature, respiratory rate)
- Determination of LIR, LAR, LUR status
- 12-lead ECG
- Laboratory assessments
- Urine drug screen
- Urine pregnancy test (WOCBP)
- U/A
- C-SSRS
- Modified Himmelsbach scale
- Prior and current medications (including opioid dose and laxative use)
- eDiary device training and distribution
- Daily maintenance and breakthrough pain opioid dosing regimen.

6.2.2 Definitions for laxative responder status

One of the main goals of the study is to determine whether NKTR-118 is efficacious in patients who have had inadequate response to laxatives previously. For the purpose of identifying those patients, at Visit 1, each patient's laxative response status will be determined based on 4 questions which explore the frequency of laxative use, constipation symptom severity, and laxative side-effects during the previous 2 weeks. The patients will be classified as LIR, LAR, or LUR based on their answers. Patients who report having used laxatives over the previous 2 weeks will be asked about the frequency of laxative use (total days used) and constipation symptom severity.

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

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

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

6.2.3 Additional procedures including follow-up procedures

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

6.3 Efficacy

6.3.1 Efficacy variables

The primary efficacy endpoint is response (responder/non-responder) to study drug during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.

The key secondary efficacy endpoints (or outcome variables) supporting the primary objective, and included in the multiplicity adjustment, are:

- Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.

- Response (responder/non-responder) to study drug over the entire 12 week treatment period, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 75% of the weeks.

- Regularity during the first 4 weeks of treatment, where regularity is measured as the mean number of days per week with at least 1 SBM during Weeks 1 to 4.

Additional secondary efficacy variables include:

- Change from baseline in the SBMs/week for Weeks 1 to 4 and 1 to 12.

- Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours.

- Mean number of days per week with at least 1 SBM for Weeks 1 to 12

- Change from baseline in the mean degree of straining for Weeks 1 to 4 and 1 to 12.

- Change from baseline in the mean stool consistency (BSS) for Weeks 1 to 4 and 1 to 12.
- Percentage of days with complete evacuation for Weeks 1 to 4 and 1 to 12.
- Mean bisacodyl dose per week for Weeks 1 to 4 and 1 to 12
- Change from baseline in PAC-SYM total score and each domain score for Weeks 2, 4, 8, and 12.
- Change from baseline in PAC-QOL total score and each domain score for Weeks 4 and 12.
- Willingness to Take Drug Again questionnaire for Week 12.

6.3.1.1 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 3 (randomization), Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), and Visit 8 (Week 12).

The PAC-SYM 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 3, where some interaction with staff will be necessary in order to ensure that randomization 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.

6.3.1.2 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 3 (randomization), Week 4 (Visit 6), and Week 12 (Visit 8).

The PAC-QOL 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 3, where some interaction with staff will be necessary in order to ensure that randomization 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.

6.3.1.3 Willingness to Take Drug Again Questionnaire

The Willingness to Take Drug Again questionnaire will consist of a yes/no question regarding the patient's willingness to take study drug again. The Willingness to Take Drug Again questionnaire will be completed at Visit 8 (Week 12). The Willingness to Take Drug Again 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. Patients are to fill out the Willingness to Take Drug Again questionnaire prior to any interventions or discussions regarding their OIC with the study staff or the investigator.

6.3.2 Measurements recorded in eDiary

Patients will be supplied with a handheld eDiary for pilot training, the OIC confirmation period, and the treatment period. At Visit 1, all patients will be carefully instructed and trained on how to fill in the eDiary and how to handle the device. Written information will be supplied to each patient. The patients must understand and be willing to use the eDiary and be instructed on how and where to request help if problems occur. If a patient does not fill out the eDiary, there will be a reminder prompt at the end of the day informing the patient that no data has been recorded and to confirm that they have not had any BMs that day. Additional reminder prompts for data consistency will also be included (eg, if a patient records 2 BMs, but fills out the symptom data only once, he/she will be prompted at the end of the day to fill out the symptom data for the other BM).

The eDiary will be completed each day from the evening of Visit 1 to the morning of Visit 8, including days of study visits. The eDiary will include the following daily recordings:

- Date and time of BM (recorded at the time of each BM)
- Stool consistency (BSS) (recorded at the time of each BM)
- Straining (recorded at the time of each BM)

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

6.3.2.1 Bowel movements

All BMs will be recorded as they occur.

6.3.2.2 Stool consistency (Bristol Stool Scale)

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

The BSS is a medical aid designed to classify the form of human feces into 7 categories. It was developed by Heaton at the University of Bristol and was first published in the Scandinavian Journal of Gastroenterology in 1997 (Lewis and Heaton 1997). The form of the stool depends on the time it spends in the colon. The 7 stool types are:

1. Separate hard lumps, like nuts (hard to pass)
2. Sausage-shaped, but lumpy
3. Like sausage, but with cracks on its surface
4. Like a sausage or snake, smooth and soft
5. Soft blobs with clear cut edges (passed easily)
6. Fluffy pieces with ragged edges, a mushy stool
7. Watery, no solid pieces.

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

6.3.2.3 Straining

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

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

Patients will be asked to respond on a 5 point Likert scale choosing one of the following options:

1=Not at all

2=A little bit

3=A moderate amount

4=A great deal

5=An extreme amount.

6.3.2.4 Complete/incomplete evacuation

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

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

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

6.3.2.5 Pain level

Patients will rate their pain level at the end of each day, using the NRS for pain (see Section 6.4.7).

6.3.2.6 Use of laxative rescue medication

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

6.3.2.7 Use of opioid medication for breakthrough pain

Opioid medication for breakthrough pain will be recorded in the eDiary at the time the medication is taken. Breakthrough pain medication will also be reviewed at study visits and recorded on a breakthrough pain medication eCRF; this information will be recorded in the eDiary to facilitate daily recording of dosing.

6.4 Safety

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

6.4.1 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.
- Change from baseline in the mean daily opioid dose for Weeks 1 to 4 and 1 to 12.
- Change from baseline in the mean Numeric Rating Scale (NRS) pain score for Weeks 1 to 4 and 1 to 12.
- Observed values and change from baseline in composite score in modified Himmelsbach scale for the evaluation of centrally mediated opioid withdrawal symptoms at 2 hours after first dose of study drug, and at Weeks 1, 4, and 12.
- Changes in vital signs and physical examination.
- Changes in laboratory assessments (ie, chemistry, hematology, and U/A).
- Changes in ECGs.

6.4.2 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.

6.4.3 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 or incapacity

- 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.

6.4.4 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 9), 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 8), 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 6.4.3. 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 6.4.5. Suicidal thoughts and preparation for suicide should also be regarded as AEs. All events of suicidality will be monitored via the C-SSRS.

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

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

Causality collection

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

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

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

Adverse events based on signs and symptoms

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

Adverse events based on examinations and tests

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

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

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

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

Underlying disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease, or it may be considered normal fluctuation in symptoms. The development of pain due to progression of the underlying condition responsible for the patient's pain should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study, unless they meet serious criteria (ie, hospitalization).

6.4.5 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.

6.4.6 Daily Opioid Dose

Opioid doses will be recorded for each patient and the daily opioid dose in morphine equivalents will be calculated. Breakthrough pain medication will be recorded in the eDiary, and the daily maintenance opioid dose will be recorded on the maintenance opioid dose eCRF. Breakthrough pain medication will also be reviewed at study visits and recorded on a breakthrough pain medication eCRF; this information will be recorded in the eDiary to facilitate daily recording of dosing.

6.4.7 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). The NRS will be recorded each evening via the eDiary to record the patients' worst pain and average pain during the day. Changes in this scale should generally not be reported as AEs unless standard criteria for AE reporting are otherwise met.

6.4.8 Modified Himmelsbach Scale

Patients are rated by examination for symptoms of opioid withdrawal using the modified Himmelsbach scale. The modified Himmelsbach scale will be administered by a clinician at the study site. Patients will be rated with respect to the following symptoms as observed at the time of the assessment: yawning, lacrimation, rhinorrhea, perspiration, tremor, mydriasis, piloerection, and restlessness. The signs will be quantified on a scale of 0 to 3, with 0=none, 1=mild, 2=moderate, 3=severe. (Himmelsbach 1941; Culpepper-Morgan et al 1992, Webster et al 2008). To ensure adequate inter-rater agreement, raters will undergo training on proper scoring using the modified Himmelsbach scale and will receive certification provided by United BioSource Corporation (UBC). The modified Himmelsbach scale will be administered at Visit 1 (screening), Visit 3 (randomization), Visit 4 (Week 1), Visit 6 (Week 4), and Visit 8 (Week 12). Changes in this scale should generally not be reported as AEs unless standard criteria for AE reporting are otherwise met.

6.4.9 Laboratory safety assessment

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

The following clinical laboratory tests (chemistry, hematology, and U/A shown in Table 4) will be performed as specified in the Study Plan.

Table 4 Laboratory assessments

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

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

[a] A separate protocol is outlined regarding additional laboratory tests for elevated liver transaminases (see Section 6.4.9.2).

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

[c] Total cholesterol will be assessed at randomization (Visit 3) and Week 12 (Visit 8/end of treatment).

[d] Serum pregnancy tests will be performed at Week 4 (Visit 6), Week 8 (Visit 7), and Week 14 (Visit 9); urine pregnancy tests will be performed at screening (Visit 1), randomization (Visit 3), and Week 12 (Visit 8). Any positive urine pregnancy test is to be followed up with a serum pregnancy test.

[e] PT/INR is assessed only at screening in order to calculate Child-Pugh classification. INR is also to be assessed during the study if patients meet criteria for significant elevation in liver transaminases (See Section 6.4.9.2).

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

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

Serum chemistry and hematology tests will be performed on all patients at Visit 1 (screening), Visit 3 (randomization), Visit 4 (Week 1), Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), Visit 8 (Week 12), and Visit 9 (Week 14, follow-up). Total cholesterol will be assessed at Visit 3 (randomization) and Visit 8 (Week 12).

Urine drug screening tests will be performed on all patients at Visit 1 (screening) and Visit 8 (Week 12). Urinalysis (and urine pregnancy tests for all WOCBP) will be performed at Visit 1 (screening) and Visit 8 (Week 12). A urine pregnancy test will also be performed at Visit 3 (randomization). Any positive urine pregnancy test is to be followed up with a serum pregnancy test. Serum pregnancy tests for WOCBP will be performed at Visit 6 (Week 4), Visit 7 (Week 8), and Visit 9 (Week 14, follow-up).

For blood volume, see Section 7.1.

6.4.9.1 Urine drug screen

As noted above, urine drug screening tests will be performed on all patients at Visit 1 and Visit 8 (Week 12). 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.

6.4.9.2 Handling of subjects with elevated liver transaminases

The investigator will be alerted from the central laboratory regarding patients developing ALT or AST >3 x ULN during the study, ie, all values above >3 x 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 >3 x 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 >3 x ULN but ≤8 x 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 >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN AND (total bilirubin >2 x ULN or INR >1.5)
- ALT or AST >3 x 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.

6.4.10 Physical examination

A complete physical examination (general appearance, skin, neck, [including thyroid], eyes, ears, nose, throat, chest, lungs, heart, abdomen, back, lymph nodes, extremities, and basic nervous system evaluation) will be performed at Visit 1 and Visit 8. At Visit 1, this will include rectal examination. A targeted physical examination (lungs, cardiovascular, abdomen) will be performed at Visit 3 (see Section 3.1.3.1). This may include a rectal examination, at the discretion of the investigator, if necessary to ensure the safety of the patient.

Significant findings that are present at the time of screening (Visit 1) must be included in the appropriate medical history/surgical history eCRF pages. Significant findings made after the screening visit (Visit 1) that meet the definition of an AE must be recorded on the AE eCRF.

6.4.10.1 CRC Risk Factor Evaluation

The patients must comply with the CRC screening criteria as specified in Appendix E. These criteria are modified from American College of Gastroenterology Guidelines for Colorectal Cancer Screening (Rex et al 2000, Rex et al 2009) and are intended to make a reasonable and practical good faith effort to rule out underlying colorectal malignancy as a potential contributor to constipation symptoms and to avoid enrolling patients with underlying malignancy into prolonged clinical trials. Patients are classified into high and average CRC risk groups based on their family history. Further division is made based on age, race, and previous diagnostic evaluation for CRC. A FIT test is required for those who are ≥50 years of

age and at average risk for CRC, unless they provide verification of negative colonoscopy, flexible sigmoidoscopy, barium enema study, or virtual colonoscopy. For more details, please refer to Appendix E.

6.4.11 ECG

6.4.11.1 Resting 12-lead ECG

Digital ECGs (dECG) for all patients at all centers will be conducted at the center using a machine provided by the central ECG laboratory and will be transmitted to the central ECG laboratory. The ECG machine will also print off 2 copies of the ECG by default, 1 copy that can be provided to the central ECG laboratory for digitization and analysis if necessary. Digital ECGs will be performed at screening, randomization, and all study visits after randomization. Digital ECGs will be obtained after the patient has been resting in a supine position for at least 10 minutes. At Visit 3 (randomization), patients will receive a triplicate ECG pre-dose and a single ECG 2 hours after the dose of study drug. Triplicate ECGs will also be performed at Visit 4 (Week 1) and Visit 8 (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. Single 12-lead ECGs will be performed at Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), and Visit 9 (Week 14).

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. Discontinuation criteria include QTcF >500 ms or change from baseline >60 ms with a QTcF interval exceeding 480 ms (see Section 5.8).

6.4.12 Vital signs

6.4.12.1 Pulse and blood pressure

Blood pressure (sitting) and pulse/heart rate (sitting) will be measured at all study visits except Visit 2 (start of OIC confirmation period). An appropriately sized cuff will be used to obtain systolic and diastolic blood pressure.

6.4.12.2 Body temperature and respiratory rate

Body temperature and respiratory rate will be measured at Visit 1 (screening) and Visit 8 (Week 12).

6.4.12.3 Weight

Weight will be measured at Visit 1 (screening), Visit 3 (randomization), and Visit 8 (Week 12).

6.4.13 Other safety assessments

6.4.13.1 C-SSRS

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

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

If a patient indicates having suicidal ideation or having a rating of type 4 or 5 on the C-SSRS suicidal ideation scale at any visit when the C-SSRS is administered, 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.

6.4.13.2 Persistent or Progressive Severe Abdominal Pain

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

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

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

6.4.14 Safety Specific Areas of Interest

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

- Opioid withdrawal
- Abuse liability
- Bowel perforation type events (eg, ischemic colitis) (see Section 6.4.13.2).

The topics listed above, as well as other topics which may be subsequently determined by AstraZeneca, may be subject to enhanced surveillance activities and/or an adjudication team process (note: any case reports of bowel perforation and related events will be subject to an external adjudication process). 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.

6.5 Patient reported outcomes (PROs)

See Section 6.3.2 for PROs in the eDiary. In addition, 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 6.3.1.1.

6.5.3 PAC-QOL

See Section 6.3.1.2.

6.5.4 Willingness to Take Drug Again

See Section 6.3.1.3.

6.5.5 Administration of PRO questionnaires

The NRS (for pain) and BSS will be administered in the eDiary. The PAC-SYM, PAC-QOL, EQ-5D, and Willingness to Take Drug Again questionnaire will be self-administered using an electronic device (SitePad) at the study center. At Visit 3, patients will receive training from study staff regarding how to enter the data electronically using the SitePad device provided at the study center. Training procedures will be documented separately from this CSP. 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 3, 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 3, since only randomized patients will fill out the questionnaires and interaction with study staff will be necessary to determine whether randomization criteria have been met.

6.6 Pharmacokinetics

Blood samples will be taken at specified visits. The actual date and time of the sample collection (in date, hour and minute) must be recorded on the appropriate eCRF page.

6.6.1 Collection of samples

Venous blood samples (6 mL) will be taken at the times specified in Table 1. Individual venipunctures for each time point may be performed or an in-dwelling catheter may be used. If the study site chooses to use an in-dwelling catheter, the first 1 mL of blood will be discarded and the catheter flushed with saline following the sampling. Heparin may not be used to flush the catheter.

Six milliliter (6 mL) samples of whole blood will be collected into ethylenediaminetetraacetic acid (EDTA) spray-dried tubes for the determination of NKTR-118 in human plasma. All samples will be immediately placed on ice until centrifugation, which will begin within 30 minutes of sample collection. The sample will be centrifuged for 10 minutes at 2°C to 8°C at 1500Xg. The resulting plasma will be divided into 2 transfer tubes (2.0 mL Microcentrifuge Micro Tubes-Sterilized, Cat #4204S, Bio Plas, Inc., USA, or a tube approved by AstraZeneca) and immediately frozen upright at or below 20°C within 15 minutes of plasma preparation and kept frozen at this temperature before, during, and after transport to the designated laboratory. One of the samples will be retained at the study site. This retention sample will be retained until the analysis is completed on the original sample and it has been determined that the retention sample can be destroyed.

It is important that the time and date of the PK sample collection be recorded in the eCRF.

Plasma samples will be shipped on a monthly basis.

For blood volume, see Section 7.1.

6.6.2 Labeling of NKTR-118 plasma samples

Freezer compatible labels will be applied to the plasma sample tubes. The labels should contain the following information:

Study Number: D3820C00005

Patient Number

Treatment Period

Week Number

Visit Number

Analyte: NKTR-118

Matrix: Plasma

6.6.3 Shipment of NKTR-118 plasma samples

All plasma samples accompanied by the sample shipment logs will be shipped via an agreed upon courier. The frozen samples must be packed securely to avoid breakage during transit, should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples remain frozen for at least 72 hours to allow for delays in the shipment. All applicable shipping regulations must be followed. Documentation sufficient to identify each sample must be included with the shipment.

Samples should only be shipped on Monday through Wednesday. Do not ship on or within 2 days prior to a legal holiday.

Plasma samples should be shipped according to guidelines in the Laboratory Manual.

6.6.4 Determination of drug concentration

Samples for determination of NKTR-118 concentrations in plasma will be analyzed by Covance (Indianapolis, IN) on behalf of AstraZeneca. Full details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

No samples from patients with placebo treatment will be analyzed unless anomalous results are seen in the patients with active treatment.

Additional analyses may be conducted on the biological samples to further investigate reproducibility of incurred samples. Any results from such analyses will be included in the bioanalytical study contribution report.

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics

See Appendix D for details on pharmacogenetic sampling.

6.8.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from patients post-randomization. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may discontinue due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 3 (randomization), it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1.

6.9 Health economics

6.9.1 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 administered to patients at Visit 3 (randomization), Visit 6 (Week 4), and Visit 8 (Week 12) 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 3, where some interaction with staff will be necessary in order to ensure that randomization 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 4 (Week 1), Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), Visit 8 (Week 12), and Visit 9 (Week 14) through patient interviews. If a patient is taken off the study as a result of a resource utilization (eg, an ER visit for manual disimpaction), the data should be recorded in the OIC healthcare resource utilization form prior to discontinuation. A health care resource utilization form will be used to collect information on whether the patient had any contact or

visited with a health care provider (physician or other health care practitioner, urgent care center or hospital emergency room, or inpatient hospital) for the management of their OIC, including the details of the type and number of visits, as well as the reason for the visit (such as the use of enemas, manual disimpaction, and treatment of anal fissures).

As applicable, the interview will be conducted after the patient completes filling out the PRO questionnaires (eg, PAC-SYM, PAC-QOL, EQ-5D) 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	8	68
	Hematology	4 EDTA	8	32
	Bicarbonate	3.5 SST	8	28
	Coagulation (PT/INR)	4.5 Sodium Citrate	1	4.5
Pharmacokinetic		6 EDTA	6	36
Pharmacogenetics		10 EDTA	1	10
Total		36.5	31	178.5

EDTA Ethylenediaminetetraacetic acid, SST serum-separating tube

[a] Additional samples may be collected for patients who have elevated liver transaminases (see Section 6.4.9.2), who require repeat laboratory testing at screening, or who require a serum pregnancy test.

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

7.2 Handling, storage, and destruction of biological samples

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

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

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

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Samples will be disposed of after the CSR has been finalized, unless retained for future analyses, see below.

Key samples for metabolites analysis may be retained at the CRO to be determined on behalf of Clinical Pharmacology & Drug Metabolism and Pharmacokinetics (DMPK), Wilmington, AstraZeneca for a maximum of 1 year following the finalization of the CSR. The results from such analysis will be reported in a separate report.

Additional NKTR-118 analyses will be conducted on the biological samples to investigate the reproducibility of the analytical results in incurred samples. Any results from such analyses will only be used to confirm the reproducibility of the method and will be reported in a separate table in the bioanalytical study contribution report.

7.2.2 Pharmacogenetic samples

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

7.3 Labeling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

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

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

The PI:

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

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

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

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

8.3 Ethics and regulatory review

An 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(s) is/are stored in the investigator's Study File.
- Ensure a copy of the signed and dated ICF is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an 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 eDiary recording device, and other system(s) utilized.

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

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

9.3 Monitoring of the study

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

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

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

9.3.1 Source data

Refer to the CSA for location of the source data.

9.4 Study agreements

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

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

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

- Signed CSA between AstraZeneca and the PI/study center
- Signed CSP and other agreements between AstraZeneca and the PI/study center
- Written approval of the study by the 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 1st Quarter 2011 and to end by 1st Quarter 2012.

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

10. DATA MANAGEMENT BY ASTRAZENECA

10.1 Electronic case report form

The eCRF and the protocol are both confidential. The eCRF will be created by the 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 Spontaneous bowel movements (SBMs) per week

A SBM is defined as a BM without the use of rescue laxatives administered in the previous 24 hours. Patients will use electronic hand-held (eDiary) devices to enter daily information related to laxative rescue medication, use of opioid medication for breakthrough pain, date and time of BMs and their associated characteristics (straining, stool consistency, completion of evacuation). Days with no BMs should be recorded as zero, rather than missing. This diary data will be used to identify SBMs. The weekly SBM frequency within each time period will be calculated for each patient as:

(total number of SBMs during the time period of interest/number of days) x 7

where the denominator is the number of days during the time period in which the patient records data. If less than 4 days of data are recorded within a particular week, the data for that week will be considered insufficient and the rate will be set to missing for that week.

A responder is defined as a patient with at least 3 SBMs/week and at least a 1 SBM/week increase over baseline for at least 75% of the weeks (eg, 3 out of 4 weeks). A patient who does not meet these criteria will be deemed a non-responder.

Baseline SBMs/week is calculated as:

(total number of SBMs during the 14-day OIC confirmation period/number of days in the OIC confirmation period in which the patient records data) x 7.

If more that 14 days of data are collected during the OIC confirmation period, data from the last 14 days prior to randomization will be used in the calculation of baseline SBMs/week.

Response will be assessed for Weeks 1 to 4 and 1 to 12.

Change from baseline in the mean number of SBMs/week will be calculated for Weeks 1, 2, 3, 4, 1 to 4, and 1 to 12 as the post-baseline value minus the baseline value, such that the change represents the increase in SBMs/week.

11.1.2 Time to first post-dose laxation

Time to first post-dose laxation without the use of rescue laxatives within the last 24 hours will be calculated in hours as:

> Date/Time of first post-dose laxation without rescue – First dose date/time.

Patients who do not have any post-dose laxation without the use of rescue laxatives within the last 24 hours will have their data censored at their last visit date or date of discontinuation from study drug. The censored value will be calculated as:

> Date/Time of last study visit or discontinuation of study drug – First dose date/time.

Response to study drug within the first 12 hours will be assessed using the calculated time to first post-dose laxation without the use of rescue laxatives.

11.1.3 Days with at least 1 SBM

The mean number of days per week with at least 1 SBM will be calculated as:

> (total number of days with at least 1 SBM during the period of interest/number of days in the period of interest) x 7.

The mean number of days per week with at least 1 SBM will be assessed for Weeks 1 to 4 and 1 to 12.

11.1.4 Days with complete evacuation

For each BM, a patient will record in the eDiary whether or not they had complete evacuation (ie, no stool in their rectum that they could not empty out).

The percentage of days with complete evacuation will be calculated as the number of days with complete evacuation within the interval of interest divided by the total number of days in the interval. The percentage of days with complete evacuation will be calculated for Weeks 1 to 4 and 1 to 12.

11.1.5 Degree of straining

The mean degree of straining for an interval will be calculated as the sum of the straining values for the interval divided by the number of BMs recorded within the interval. Change

from baseline in the mean degree of straining will be calculated for Weeks 1 to 4 and 1 to 12 post-baseline value minus the baseline value, where baseline is the mean degree of straining recorded during the OIC confirmation period. Negative changes from baseline indicate improvement.

11.1.6 Bristol Stool Scale

The mean daily BSS score for an interval will be calculated as the sum of daily values for the interval divided by the number of days within the interval in which the data were collected. Change from baseline in the mean BSS score will be calculated for Weeks 1 to 4 and 1 to 12 as the post-baseline value minus the baseline value, where baseline is the mean daily BSS score recorded during the OIC confirmation period. Positive changes from baseline indicate improvement.

11.1.7 Mean Bisacodyl dose per week

Bisacodyl doses will be recorded for each patient in the eDiary. 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 Weeks 1 to 4 and 1 to 12.

11.1.8 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 2, 4, 8, and 12 as the post-baseline value minus the baseline value, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 3). Negative changes from baseline indicate improvement.

11.1.9 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 and 12 as the post-baseline value minus the baseline value, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 3). Negative changes from baseline indicate improvement.

11.1.10 Willingness to Take Drug Again

Willingness to take drug again (yes/no) will be recorded at the end of the 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 30 days after 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.

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 daily pain rating based on the 11-point NRS for pain ranging from 0 (no pain) to 10 (worst imaginable pain) will be entered by patients the same time every day using the eDiary. Both the average pain rating over the previous 24 hours and the worst pain experiences over the previous 24 hours will be recorded. The mean daily NRS for an interval will be calculated

as the sum of daily values for the interval divided by the number of days within the interval in which the data were collected. Change from baseline in mean daily NRS values will be calculated for Weeks 1 to 4 and 1 to 12 as the post-baseline value minus the baseline value, where baseline is the mean daily NRS values recorded during the OIC confirmation period. Negative changes from baseline indicate improvement.

11.2.3 Daily opioid dose

Opioid doses will be recorded for each patient, including both the maintenance dose recorded on the eCRF and rescue medication recorded in the eDiary, and the daily opioid dose in morphine equivalents (mg/day) will be calculated. 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. Change from baseline in mean daily opioid dose will be calculated for Weeks 1 to 4 and 1 to 12 as the post-baseline value minus the baseline value, where baseline is the mean daily opioid dose recorded during the OIC confirmation period. Positive changes from baseline indicate need to increase opioid dose.

11.2.4 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 50% of the 8 signs are missing at a visit, the composite score will be set to missing. Changes from baseline to 2 hours after first dose of study drug, and Weeks 1, 4, and 12 in the modified Himmelsbach scale will be calculated as the post-baseline value minus the baseline value, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 3). Negative changes from baseline indicate improvement.

11.2.5 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 1, 2, 4, 8, 12, and 14) will be calculated as the post-baseline test value minus the baseline test value, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 1 or 3).

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, potentially clinically significant laboratory results will be flagged. The criteria for potentially clinically significant laboratory results will be outlined in the SAP.

11.2.6 Physical examination

Change from baseline to Week 12 for physical examination will be reported, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 1).

11.2.7 Weight

Change from baseline to Week 12 for weight will be calculated as the visit assessment minus the baseline value, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 1 or 3 [for weight]).

11.2.8 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, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 1).

11.2.9 ECG

Changes from baseline to each post-baseline visit (Weeks 1, 2, 4, 8, 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 is the latest non-missing value collected prior to the first dose of study drug (Visit 1 or 3). Marked abnormal values or changes from baseline will be identified based on pre-determined criteria.

11.2.10 Vital signs

Changes from baseline in vital signs (sitting blood pressure and pulse) at each post-baseline visit (Weeks 1, 2, 4, 8, 12, and 14) will be derived as the value at the visit minus the baseline value for the same assessment, where baseline is the latest non-missing value collected prior to the first dose of study drug (Visit 3).

11.2.11 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.

For the C-SSRS, baseline defined as the latest non-missing value collected prior to the first dose of study drug (Visit 1 or 3).

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 Degree of straining

See Section 11.1.5.

11.3.2 Bristol Stool Scale

See Section 11.1.6.

11.3.3 PAC-SYM

See Section 11.1.8.

11.3.4 PAC-QOL

See Section 11.1.9.

11.3.5 Willingness to Take Drug Again

See Section 11.1.10.

11.3.6 NRS for Pain

See Section 11.2.2.

11.3.7 Daily opioid dose

See Section 11.2.3.

11.3.8 EQ-5D

See Section 11.6.1.

11.4 Calculation or derivation of PK variables

Samples for PK determination of NKTR-118 will be analyzed by a certified laboratory using validated bioanalytical methods. Full details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

The plasma concentration data of NKTR-118 will be listed, summarized on the basis of time intervals, and plotted in scattering with time relative to the immediately preceding NKTR-118 dosing time.

A separate population PK (POPPK) analysis of NKTR-118 concentrations in patients with OIC will be performed using non-linear mixed-effects modelling technique with NONMEM (version 6 or later), for the data collected in this study and other studies where appropriate. The effect of covariates such as age, sex, and body mass index on plasma exposures of NKTR-118 will be explored. Population mean and post hoc Bayesian individual estimates of the PK parameters for NKTR-118 will be estimated. Summaries of individual predictions of exposure metrics may be listed and the relationship between predicted individual exposure metrics and response will be explored. The outcome from this analysis will be reported separately from the CSR.

11.5 Calculation or derivation of pharmacodynamic (PD) variable(s)

11.5.1 Calculation or derivation of the relationship between PK and PD variables

The POPPK model will be used to predict the individual and population plasma concentrations at the time of each efficacy and/or adverse outcome assessment to develop the quantitative relationship between NKTR-118 exposure and response. Initial plots of efficacy and/or adverse endpoints versus concentration will help elucidate the nature of the concentration-response relationship, while hysteresis plots will help assess any delays between changes in concentration and response. The outcome from this analysis will be reported separately from the CSR.

11.5.2 Population analysis of PK/PD variables

The POPPK model will be used to construct a PK/response model as functions of time, treatment, and relevant patient covariates. Initially, exploratory plots of the response endpoints against measures of drug exposure will be constructed in order to evaluate the strength and temporal association of various possible relationships. Next nonlinear mixed-effects models will be constructed describing the time course of changes in response endpoints in addition to the variability between and within patients, and the uncertainty in these parameters. The outcome from this analysis will be reported separately from the CSR.

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 emergency room, inpatient hospital).

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

The efficacy analysis set will be the 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 one post-baseline efficacy assessment.

Select efficacy analyses (to be specified in the SAP), will be repeated on the Per Protocol (PP) population. The PP population is defined as all patients in the ITT population without significant protocol violations or deviations. Patients included in the PP population will be determined prior to unblinding of the study.

12.1.2 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).

12.2 Methods of statistical analyses

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

For the by-visit assessments, baseline will be defined as the latest non-missing value collected prior to the first dose of study drug (screening, Visit 1 or Week 0, Visit 2).

For the eDiary assessments, baseline will be defined as the values observed during the OIC confirmation period, which are the last 14 days prior to randomization (as defined in Section 3.1.2).

Descriptive statistics for continuous data will include n, mean, median, standard deviation, minimum, and maximum values. Descriptive statistics for categorical data will include n, frequency, and percentage.

To control the overall type I error rate to be ≤ 0.05 for the multiple comparisons in the primary and the key secondary endpoints, a Multiple Testing Procedure (MTP) with Bonferroni-Holm over Groups, and Fixed-Sequence within groups will be applied. Specifically, there will be 2 groups defined by the doses of 12.5 and 25 mg, and within each group there will be a pre-defined fixed-sequence MTP of comparisons of the key secondary endpoints vs placebo (ie, responder analysis in LIR subgroup, responder analysis for the 12-week treatment period, and regularity analysis) at level of $\alpha/2$. If the null hypotheses for 1 dose group can be rejected entirely (ie, significant difference between active vs placebo for all 4 endpoints at $\alpha=0.025$), one will increase the level to α (ie, 0.05) for the other group. This amounts to using Bonferroni-Holm over groups, and fix-sequence within groups. This multiplicity adjustment method follows the general results described by Bretz (Bretz et al 2009) and by Burman (Burman et al 2009).

No other correction to the reported p-values will be made for the analysis of additional secondary measures. Where appropriate, 95% confidence intervals (CIs) will be presented.

12.2.1 Primary analysis

The primary analysis will be made comparing the response rate of Weeks 1 to 4 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

12.2.2 Key secondary analysis

1. Comparison of the response rate of Weeks 1 to 4 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo in the LIR subgroup. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using Chi-Square tests.

2. Comparison of the response rate of Weeks 1 to 12 of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using CMH tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

3. Comparison of the regularity during the first 4 weeks of treatment of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. Differences between treatment groups in the mean number of days per week with at least 1 SBM will be analyzed using analysis of covariance (ANCOVA), with treatment group and response to laxatives at baseline as fixed effects, and the mean number of days per week with at least 1 SBM during the baseline period as a covariate.

12.2.3 Additional secondary analysis

Additional secondary endpoints will be either analyzed or summarized descriptively.

Response rate for Weeks 1 to 4 and 1 to 12 will also be summarized for subgroups of interest (eg, age, gender, race, response to laxatives (LIR, non-LIR [LAR, LUR combined], LAR, LUR).

The treatment by opioid dose interaction will be assessed using a logistic regression model on the response for Week 1 to 4 and Weeks 1 to 12, to determine whether opioid dose (a continuous variable) is a significant factor in treatment response for the duration of the treatment period. To help visualize the effect, a plot of response by the opioid dose will be generated. The relationship between response within the first 12 hours of treatment (ie, at

least 1 SBM within the first 12 hours of treatment) and the response during Weeks 1 to 4, as well as during the entire study (Weeks 1 to 12) will be assessed within each treatment group using Chi-Square tests, for both the ITT population as well as the LIR subgroup.

Differences between treatment groups in the mean number of days per week with at least 1 SBM for Weeks 1 to 12 will be analyzed using ANCOVA, with treatment group and response to laxatives at baseline as fixed effects, and the mean number of days per week with at least 1 SBM during the baseline period as a covariate.

Change from baseline in SBMs/week for Weeks 1, 2, 3, and 4 will be analyzed using mixed model repeated measures (MMRM) (Lewis and Heaton 1997) to compare the treatment groups of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. Change from baseline in SBMs/week for Weeks 1 to 4 and 1 to 12 will also be analyzed using ANCOVA, with treatment group and response to laxatives at baseline as fixed effects, and the SBMs/week during the baseline period as a covariate.

Change from baseline in SBMs/week will also be summarized descriptively within the response to laxative subgroups (LIR, LAR, LUR, non-LIR) for each treatment group.

Treatment group differences within the subgroup of LIR patients with inadequate response from 2 laxatives will be assessed in the Integrated Summary of Efficacy based on pooling of the 2 pivotal Phase III studies for the outcome variables of response rate and change from baseline in the SBMs/week. Response rate and change from baseline in SBMs/week for this subgroup will be presented descriptively in the study report.

Treatment comparisons of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo, for the time to first laxation without laxative use in the previous 24 hours will be analyzed using log rank tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

Descriptive statistics by treatment group for the mean degree of straining, the mean stool constituency, and the percentage of days with complete evacuation will be summarized for each period (baseline, Weeks 1 to 4, Weeks 1 to 12) as well a for the change from baseline to Weeks 1 to 4 and 1 to 12. Differences between NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo in the change from baseline in these outcome variables will be analyzed using ANCOVA, with treatment group and response to laxatives at baseline as fixed effects, and the associated baseline value as a covariate.

The mean bisacodyl dose per week will be summarized by treatment group using descriptive statistics for Weeks 1 to 4 and 1 to 12.

Descriptive statistics by treatment group for the PAC-SYM total score and each domain score will be summarized at baseline, Weeks 2, 4, 8, and 12 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, and 12 as well as the change from baseline to each post-dose time point.

Treatment comparisons of NKTR-118 12.5 mg vs placebo and NKTR-118 25 mg vs placebo in the change from baseline for each of the PAC-SYM domain scores and the PAC-QOL Satisfaction domain score will be analyzed at each post-dose time point using ANCOVA, with treatment group and response to laxatives at baseline as fixed effects, and the associated baseline value as a covariate.

Descriptive statistics for the Willingness to Take Drug Again questionnaire will be summarized by treatment group.

12.2.4 Safety analyses

Treatment-emergent AEs will be coded using the MedDRA dictionary. 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. Treatment-emergent AEs will also be summarized by intensity and separately, by causality. 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 will be summarized in a similar manner than TEAEs.

Treatment-emergent AEs, SAEs, TEAEs leading to death, and TEAEs leading to study discontinuation will be tabulated for each treatment group. Commonly occurring TEAEs, ie, those which occur in 5% or more of the patients in either treatment group, will be summarized using descriptive statistics. Descriptive statistics for time to onset and duration of select TEAEs will be summarized by treatment group. Treatment-emergent AEs that could potentially be indicative of centrally mediated opioid withdrawal will be identified prior to unblinding and will also be summarized by each treatment group. Evaluation of GI-related symptoms will be conducted at baseline, treatment-emergent GI AEs will be summarized by treatment group.

The observed composite modified Himmelsbach score will be summarized by treatment group at baseline, 2 hours after first dose of study drug, and Weeks 1, 4, and 12 using descriptive statistics. The change from baseline in the composite modified Himmelsbach score, mean daily opioid dose, and mean NRS pain scores (average and worst per day) will be summarized by treatment group, and tested within each treatment group using one-sample t-tests to determine where the change is significantly different from zero. The interpretations in change from baseline within each treatment or difference between treatment groups for these parameters are important to be made clinically.

All laboratory test results, vital signs, 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. Shifts from baseline to each post-baseline visit in the frequency of laboratory values outside of the clinically significant reference range will be presented by treatment group. The incidence of potentially clinically significant laboratory results 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. The incidence of markedly abnormal values and changes from baseline in the ECG parameters will be summarized by treatment group.

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.

12.2.5 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, and 12. 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 emergency room, 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.

12.2.6 Pharmacokinetic analyses

See Section 11.4.

12.2.7 Interim analyses

A futility analysis is proposed at the time when 180 LIR patients (approximately 60 LIR patients per treatment group) are randomized in both of the 2 pivotal Phase III studies combined and have completed the first 4 weeks of double-blind treatment. An independent statistician (not otherwise involved in the study and located in a different geographical location than the project statisticians) will perform this analysis. The stopping rule (ie, futility) will be if the difference in the response rate (primary efficacy endpoint) for both 12.5 mg and 25 mg of NKTR-118 as compared to placebo is less than or equal to 5 percentage points (ie, NKTR-118 response rate - placebo response rate $\leq$ 5%). Under this condition, the probability of at least one of the NKTR-118 doses having a statistically significant effect over placebo at the end of the study is approximately 0.07.

12.3 Determination of sample size

A sample size of 105 patients per group would be needed to detect a difference of 25% in response rate (60% on NKTR and 35% on placebo), with power=90%, alpha=0.025, and 2-sided test. In order to provide an adequate power to detect a treatment difference in LIR

subgroup (assuming LIR is 50% of the total study population), it is recommended that 210 patients per group (total 630 patients for 3 treatment groups) be randomized to the study. The assumptions on expected response rate were referenced from the NKTR-118 Phase II study and from other similar drugs.

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 6.4.5.**

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

Name	Role in the study	Address & telephone number

Name	Role in the study	Address & telephone number
Q		
Q Pharmacovigilance	SAE reporting (other countries)	Please refer to study-specific Safety Handling Plan
Other contact information		

Name	Role in the study	Address & telephone number
	Scale user agreements and acquisitions; Rater training; and translations	

13.2 Overdose

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

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

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

For recording purposes:

- If an overdose is reported during the course of a study, the patient is evaluated by the investigator/site staff to determine whether an SAE, non-serious AE, or no symptoms have been experienced after the overdose has been taken.
- If the patient experiences an overdose with an associated SAE, the investigator/site staff will capture details of the SAE and associated information on OVERDOSE, AELOG, and SAE modules in the eCRF.
- If the patient experiences an overdose with an associated non-serious AE, the investigator/site staff will capture details of the non-serious AE and associated information on OVERDOSE and AELOG modules in the eCRF.
- If the patient experiences an overdose with no symptoms, the investigator/site staff will capture details of the overdose and associated information on OVERDOSE module only in the eCRF.
- The OVERDOSE module (found in Module Package Library) is the preferred way of collecting overdose information. If the OVERDOSE module cannot be used, for

example, if a CRO is managing the study and is unable to use the module, the Clinical Study Overdose template, may be used. This form is also used if the overdose occurred in a person not enrolled in the study, eg, accidental ingestion by a relative of the patient.

For reporting purposes:

- If an overdose occurs in the course of an AstraZeneca study, the investigators/site staff inform appropriate AstraZeneca representatives immediately, but no later than the end of the next business day of when he or she becomes aware of it.
- The designated AstraZeneca representative or its representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety Data Entry Site (DES).
- The following timelines will apply on reports of overdose:
  - Fatal/life-threatening SAEs are sent to DES within 1 calendar day of initial notification of the overdose.
  - Other SAEs are sent to DES within 4 calendar days of initial notification of the overdose.
  - Overdoses with no symptoms or with associated non-serious AEs are sent to DES within 5 calendar days of initial notification of the overdose.

13.3 Pregnancy

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

13.3.1 Maternal exposure

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

If a patient becomes pregnant during the course of the study, 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 6.4.5 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 6.4.5 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 A

Drug Substance	NKTR-118
Study Code	D3820C00005
Edition Number	1.0
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

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

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

ASTRAZENECA SIGNATURE(S)

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

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

SIGNATURE OF NATIONAL CO-ORDINATING INVESTIGATOR

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

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

Clinical Study Protocol Appendix B

Drug Substance	NKTR-118
Study Code	D3820C0005
Edition Number	1.0
Date	

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

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Clinical Study Protocol Appendix D

Drug Substance	NKTR-118
Study Code	D3820C0005
Appendix Edition Number	1.0
Appendix Date	

Appendix D
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

1. BACKGROUND AND RATIONALE

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

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

2. GENETIC RESEARCH OBJECTIVES

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

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

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

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

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

- Previous allogeneic bone marrow transplant

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

3.1.4 Discontinuation of subjects from this genetic research

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

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

3.2 Collection of samples for genetic research

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

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

3.3 Coding and storage of DNA samples

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

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

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

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

4. ETHICAL AND REGULATORY REQUIREMENTS

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

4.1 Informed consent

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

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

4.2 Subject data protection

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

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

5. DATA MANAGEMENT

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

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

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

7. LIST OF REFERENCES

Not applicable.

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Clinical Study Protocol Appendix E	
Drug Substance	NKTR-118
Study Code	D3820C0005
Edition Number	1.0
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Appendix E
Guidelines for Required Colorectal Cancer Screening

1. GUIDELINES FOR REQUIRED COLORECTAL CANCER SCREENING

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

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

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

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

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

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

2. LIST OF REFERENCES

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

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

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Clinical Study Protocol Appendix F

Drug Substance	NKTR-118
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Edition Number	1.0
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Appendix F
Guidelines for Determination of Laxative Response Status

1. GUIDELINES FOR DETERMINATION OF LAXATIVE RESPONSE STATUS

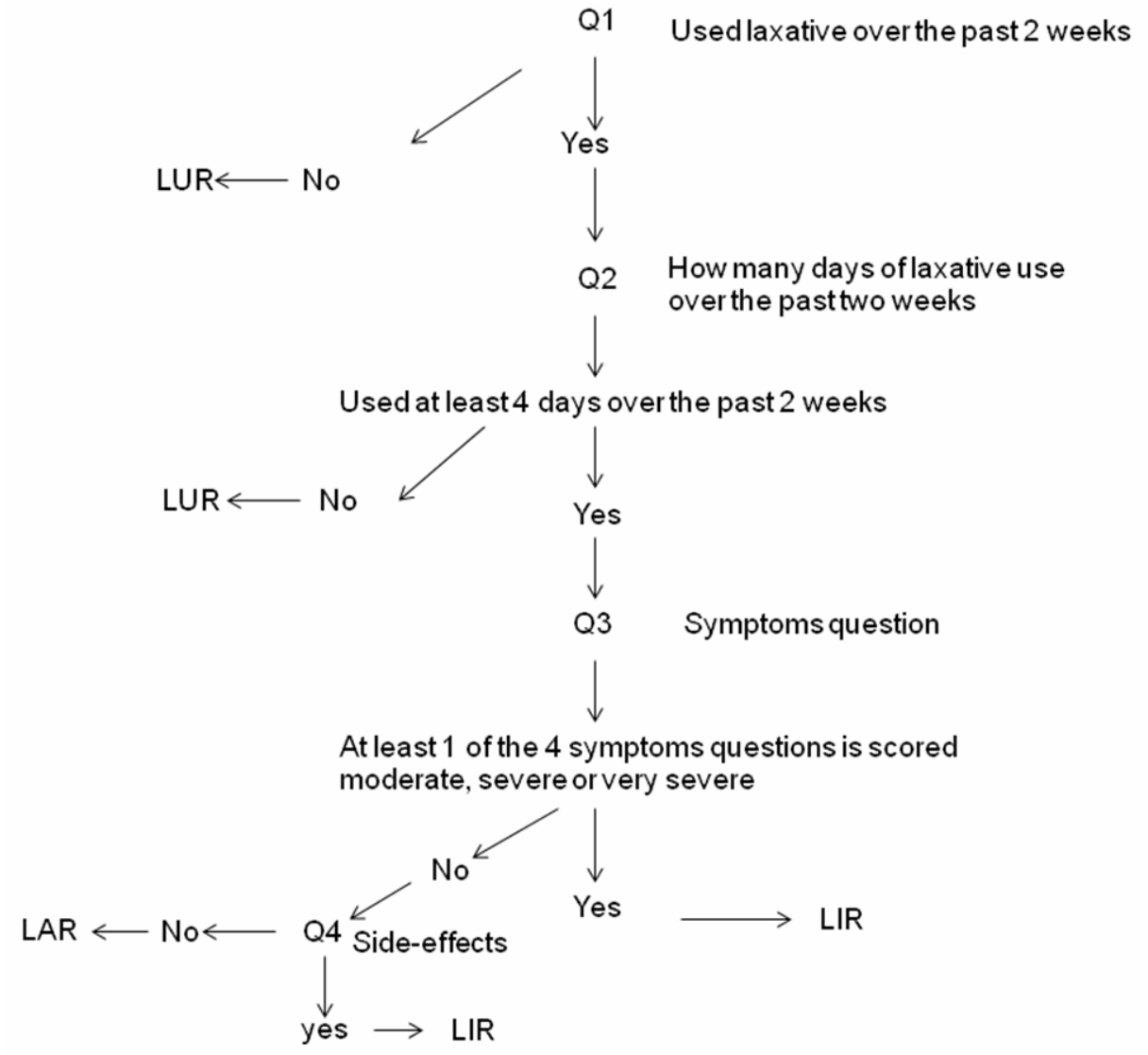
At the Screening visit, each patient's laxative response status will be determined based on 4 questions which explore the frequency of laxative use, constipation symptom severity, and laxative side-effects during the previous 2 weeks. The patients will be classified as LIR, LAR, or LUR based on their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

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

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

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

Figure 1 Determination of Laxative Response Status



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Clinical Study Protocol Appendix G

Drug Substance	NKTR-118
Study Code	D3820C00005
Edition Number	1.0
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Appendix G
Child-Pugh Classification

1. CRITERIA FOR CHILD-PUGH CLASSIFICATION

Table 1 Criteria for Child-Pugh Classification

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

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

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

2. LIST OF REFERENCES

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

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Clinical Study Protocol Appendix H	
Drug Substance	NKTR-118
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Date	

Appendix H
Morphine Equivalents Conversion Chart

1. MORPHINE EQUIVALENTS CONVERSION CHART

Table 1 Dose Equivalents for Opioid Analgesics

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

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

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

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Clinical Study Protocol Appendix I

Drug Substance	NKTR-118
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Edition Number	1.0
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Appendix I
Highly Effective Forms of Birth Control

1. HIGHLY EFFECTIVE FORMS OF BIRTH CONTROL

1. Total sexual abstinence (for the total duration of the trial including the followup period)

2. Vasectomized sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia)

3. Tubal occlusion

4. Intra-uterine Device (provided that coils are copper-banded)

5. Levonorgestrel Intrauterine System (e.g. Mirena)

6. Medroxyprogesterone injections (Depo-Provera)

7. Etonogestrel implants (Implanon, Norplan)

8. Normal and low dose combined oral pills

9. Norelgestromin / ethinylestradiol transdermal system

10. Intravaginal device (e.g., ethinylestradiol and etonogestrel)

11. Cerazette (desogestrel)

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

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

1. Triphasic combined oral contraceptives

2. All progesterone only pills, except Cerazette

3. All barrier methods, if intended to be used alone

4. Non-copper containing IUDs

5. Fertility awareness methods

6. Coitus interruptus

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Clinical Study Protocol Appendix J	
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Date	

Appendix J
Drugs that prolong QT/QTc interval

1. DRUGS THAT PROLONG QT/QTC INTERVAL

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

Table 1 Drugs that Prolong QT/QTc Interval

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