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**A Study to Assess the Tolerability, Safety, and Feasibility of Naloxegol in  
Patients with Cancer and Opioid-Induced Constipation**

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

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| Abbreviation or special term | Explanation                               |
|------------------------------|---|
| AE                           | Adverse event                             |
| ALT                          | Alanine aminotransferase                  |
| AST                          | Aspartate aminotransferase                |
| BM                           | Bowel movement                            |
| BP                           | Blood pressure                            |
| BSS                          | Bristol Stool Scale                       |
| CMP                          | Complete metabolic panel                  |
| COWS                         | Clinical opioid withdrawal scale          |
| eCRF                         | Electronic case report form               |
| CSA                          | Clinical study agreement                  |
| CSP                          | Clinical study protocol                   |
| CSR                          | Clinical study report                     |
| DBP                          | Diastolic blood pressure                  |
| ECG                          | Electrocardiogram                         |
| ECRF                         | Electronic case report form               |
| EDC                          | Electronic data capture                   |
| EU                           | European Union                            |
| FDA                          | Food and Drug Administration              |
| GCP                          | Good clinical practice                    |
| GI                           | Gastrointestinal                          |
| GMP                          | Good manufacturing practices              |
| IB                           | Investigators brochure                    |
| IBS                          | Irritable bowel syndrome                  |
| ICF                          | Informed consent form                     |
| ICH                          | International conference on harmonization |
| I/E                          | Inclusion/exclusion                       |
| IP                           | Investigational product                   |
| IRB                          | Institutional review board                |

|         |  |
|---------|--|
| ITT     | Intent to treat  |
| MedDRA  | Medical dictionary for regulatory activity                                     |
| NRS     | Numeric rating scale   |
| OIC     | Opioid induced constipation  |
| PAC-QOL | Patient assessment of constipation quality of life                             |
| PAC-SYM | Patient assessment of constipation symptoms                                    |
| PI      | Principle investigator   |
| PR      | PR interval – time from onset of P wave to the onset of the QRS complex on ECG |
| PRO     | Patient reported outcome   |
| QD      | Once per day   |
| QRS     | QRS interval – time from beginning to the end of a QRS complex on ECG          |
| QT      | QT interval  |
| QTcF    | Fridericia corrected QT interval   |
| SBM     | Spontaneous bowel movement   |
| SAE     | Serious adverse event  |
| SBP     | Systolic blood pressure  |
| SDV     | Source document verification   |
| SUSAR   | Suspected unexpected serious adverse reaction                                  |
| TEAE    | Treatment emergent adverse event   |
| ULN     | Upper limit of normal  |
| US      | United States  |
| VEGF    | Vascular endothelial growth factor   |
| WOCBP   | Women of child bearing potential   |

## 1. INTRODUCTION

### 1.1 Background

The prevalence of pain in patients with cancer is 30% in all cancer patients, 59% of patients receiving anti-cancer treatment, and 64% to 87% in patients with advanced cancer [1, 2]. Opioids analgesics are the mainstay in the treatment of cancer patients with moderate to severe pain. Following pain management guidelines, opioids can provide adequate pain relief in 75% to 90% of patients with cancer pain [1, 3, 4]. However, opioid use is frequently associated with adverse effects, the most common and debilitating being opioid induced constipation (OIC) [4]. Opioids decrease the secretion of fluids into the gastrointestinal tract, increase constriction of sphincters, and increase non-propulsive activity leading to constipation. Over 64% of cancer patients experience OIC along with the debilitating effects of the cancer itself [5].

There are no set guidelines for the management of OIC, however, current treatment include laxatives, stool softeners, and, if necessary, reflex evacuation via enema. However, in 46% of patients these treatments are not effective [6, 7]. Furthermore, a number of the conventional therapeutic interventions are inconvenient and in some cases impractical. For example, debilitated patients may not be able to self-administer an enema, and a constipated patient with severely inflamed hemorrhoids or neutropenia would not be an ideal candidate for an enema. Although generally well tolerated, side-effects of these various treatments for constipation include bloating, cramps, abdominal pain, nausea, diarrhea, dehydration, and electrolyte imbalances. In addition, prescription and over-the-counter laxatives do not specifically target the opioid mediated mechanisms that are the cause of the constipation. Other treatments available include a subcutaneous injection of methylnaltrexone (approved in US, EU, and Canada for patients with advanced medical illness) and oral lubiprostone (approved in US for treatment of OIC in patients with chronic non-cancer pain). There is a major unmet need for a well-tolerated and efficacious orally-administered treatment option for OIC in cancer patients.

██████████ has developed naloxegol, a peripherally acting  $\mu$ -opioid antagonist, for the treatment of OIC. In the US, naloxegol is approved for the treatment of OIC in adult patients with chronic non-cancer pain. In the EU, naloxegol is approved for the treatment of OIC in adult patients who have had an inadequate response to laxative(s). Naloxegol is a PEGylated derivative of naloxone and is a substrate of the P-gp transporter which limits its ability to cross the blood-brain barrier and enter the central nervous system. In the periphery, naloxegol binds to  $\mu$ -opioid receptors in the GI tract resulting in increased GI motility, hypertonicity and fluid absorption, thereby, targeting the underlying causes of OIC. Previous studies have shown that naloxegol alleviates symptoms of OIC in non-cancer patients while preserving the central analgesic effect of opioid therapy. In Phase III efficacy studies, 25 mg once daily naloxegol was consistently superior to placebo in the number of patients experiencing at least 3 spontaneous bowel movements (SBM) per week and at least 1 SBM increase over baseline for a 12 week period [8, 9]. Further analysis demonstrated the therapeutic effect was not associated with demographic factors, response to previous laxative use, type of opioid, or dose of opioid. These Phase III studies also demonstrated that 25 mg

naloxegol is generally well tolerated and safe in the treatment of OIC in non-cancer patients without reducing opioid-mediated analgesia [8, 9].

As there is a major unmet need for a well-tolerated and efficacious orally-administered treatment option for OIC in cancer patients, this phase IV study of naloxegol has been designed to evaluate its tolerability, safety and feasibility in patients with active cancer, using a design that will concurrently evaluate an efficacy signal and effect size relative to a comparator. Specifically, the study will require a total of 35 days and will have two phases: 1) a 21-day phase with a 7-day baseline assessment followed by a 14-day randomized, double-blind placebo-controlled, two parallel arm design and 2) a 14-day open-label, single arm design for those who complete the first phase. If necessary to arrange visits, the time period for each element of the study can be extended by as many as 3 days.

## **1.2 Research hypothesis**

The primary aim of this study is to test the hypothesis that naloxegol is tolerable and safe for the treatment of OIC in cancer patients with pain. The secondary aims are to determine whether efficacy can be detected compared to controls and whether a controlled study design is feasible in the population with cancer.

## **1.3 Rationale for conducting this study**

Currently naloxegol is approved and marketed for OIC in non-cancer patients in the United States. As described in Section 1.1 patients with cancer pain have an unmet clinical need in the high prevalence of poorly controlled opioid-induced constipation. If naloxegol is found to be safe and effective, it would represent a significant therapeutic advance in the treatment of cancer-related opioid-induced constipation. Because patients with chronic pain in the context of active cancer often require relatively high opioid doses and have more severe medical comorbidities than non-cancer pain patients, a study that confirms the tolerability and safety of naloxegol treatment is needed. By augmenting these aims with a secondary aim focused on efficacy and incorporating design elements that can reveal an efficacy signal, this study has the potential to both confirm safety and provide essential preliminary data for the development of a definitive, adequately powered efficacy trial.

## **1.4 Benefit/risk and ethical assessment**

For a full description of preclinical findings regarding naloxegol, please refer to the Investigator's Brochure (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 clinical laboratory parameters or electrocardiograms (ECGs). Preliminary evaluations of the results indicate that naloxegol does not have cardiac ventricular repolarization effects as assessed by QTcF. Of the 92 healthy volunteers who received naloxegol in Phase I, 2 subjects had a potentially clinically significant decrease in supine BP, 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 naloxegol dose levels of 100 mg, were transient, and resolved spontaneously. In a placebo-controlled Phase I repeated dose study, AEs of dizziness were reported by 66.7% of patients at the highest dose of naloxegol compared with only 25% of patients on placebo. However, dizziness was transient and resolved spontaneously without intervention.

In a Phase II study, in which doses of 5 mg, 25 mg, and 50 mg/day were evaluated against placebo, naloxegol decreased symptoms of OIC as measured by increases in spontaneous bowel movements (SBMs)/week in non-cancer 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 naloxegol studied. Naloxegol was well-tolerated in the Phase II study at 5 and 25 mg/day with the most commonly reported side effects being GI symptoms (abdominal pain, diarrhea, and nausea) in the 50 mg cohort. The frequency of any GI AE was 53% in the 25 mg/day group and 48% in the corresponding placebo group. Most of the AEs were rated mild or moderate. Rare cases of GI perforation associated with the use of methylnaltrexone in OIC have been reported in the post-marketing setting. Such cases of perforation 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, exclusion criteria have been included in this protocol to minimize entry of patients who may be predisposed to GI perforation. In addition, any patient who reports progressive or persistent severe abdominal pain is to be evaluated immediately by the site or otherwise referred for urgent medical assessment. Additional potential risk factors include ovarian cancer or the use of vascular endothelial growth factor (VEGF) inhibitors (eg, bevacizumab, sorafenib). See Section 4.2. No reversal of analgesia was seen at any dose in Phase II trials, as measured by changes in the daily opioid dose or by Numeric Rating Scale (NRS) for pain. Although these data suggest that the risk for reversal of analgesia or precipitation of opioid withdrawal is unlikely, pain will be monitored during this study.

Overall clinical safety data do not indicate that administration of naloxegol has adverse effects on the central nervous, renal, respiratory, or cardiovascular system. However, as summarized above, participation in this study may carry some risks. General safety monitoring, including AEs, vital signs, and clinical laboratory assessments combined with exclusion of patients at higher risk for complications from experimental medication and placebo are in place to minimize any risks. ECGs will also be recorded at visits 1 and 3.

There may be no benefits to patients as a result of participating in this study; alternatively, randomization to the active treatment group may provide symptomatic relief from OIC for the duration of the study. All patients will have the opportunity to take active drug during the 2-week open label phase of the study, provided they meet the relevant eligibility criteria. The results of the study may ultimately help in the development of naloxegol for treatment of OIC in patients experiencing cancer pain.

## **2. STUDY OBJECTIVES**

### **2.1 Primary objective**

The primary objective of this study is to assess the tolerability and safety of repeated doses of naloxegol 25 mg in patients with cancer and refractory OIC.

### **2.2 Secondary objectives**

The secondary objects are:

- To determine whether efficacy of naloxegol 25 mg can be detected compared to placebo control
- To determine whether a controlled study design is feasible in a cancer population
- To compare naloxegol 25 mg and placebo on symptoms associated with constipation and overall quality of life.

### **3. STUDY PLAN AND PROCEDURES**

#### **3.1 Overall study design and flow chart**

This is a multi-center phase IV study which has the evaluation of tolerability and safety as the primary aim and the evaluation of efficacy and feasibility as a secondary aim. It is a randomized, double-blind, placebo-controlled, two parallel arm clinical trial. Placebo will be used as a control to provide evidence of the balance of benefit and risks of a fixed dose of naloxegol 25 mg.

Patients will be recruited from a variety of settings, including outpatient oncology offices, palliative care clinics, and hospice and palliative care sites (home, assisted living facility, or inpatient hospice unit). Home visits are permitted for those subjects who are unable to attend a clinic visit.

Patients will be screened to determine whether they have opioid-treated cancer pain and constipation, and whether they have interest in learning more about the clinical trial. Patients who seek to proceed will provide written informed consent. Consenting patients will undergo pre-randomization study procedures, including a history and physical, a check of laboratory values, an electrocardiogram, and collection of baseline data. This eligibility confirmation/baseline period will last 7 days, after which the patient will be scheduled for the randomization visit if study criteria (including the stability of opioid regimen and constipation criteria) are met.

At the randomization visit, the patient will obtain study drug (naloxegol 25 mg or a placebo) and rescue laxative. Data collected during the 14-day double-blind, randomized, placebo-controlled period will be used to evaluate the tolerability, safety, feasibility, and efficacy of naloxegol 25 mg in the treatment of OIC in cancer patients.

Patients who complete the randomized portion of the study will be able to continue a 14-day open-label extension period, during which treatment will consist of a daily dose of 25 mg naloxegol. After this period, there will be a telephone follow-up at 7 days.

Figure 1

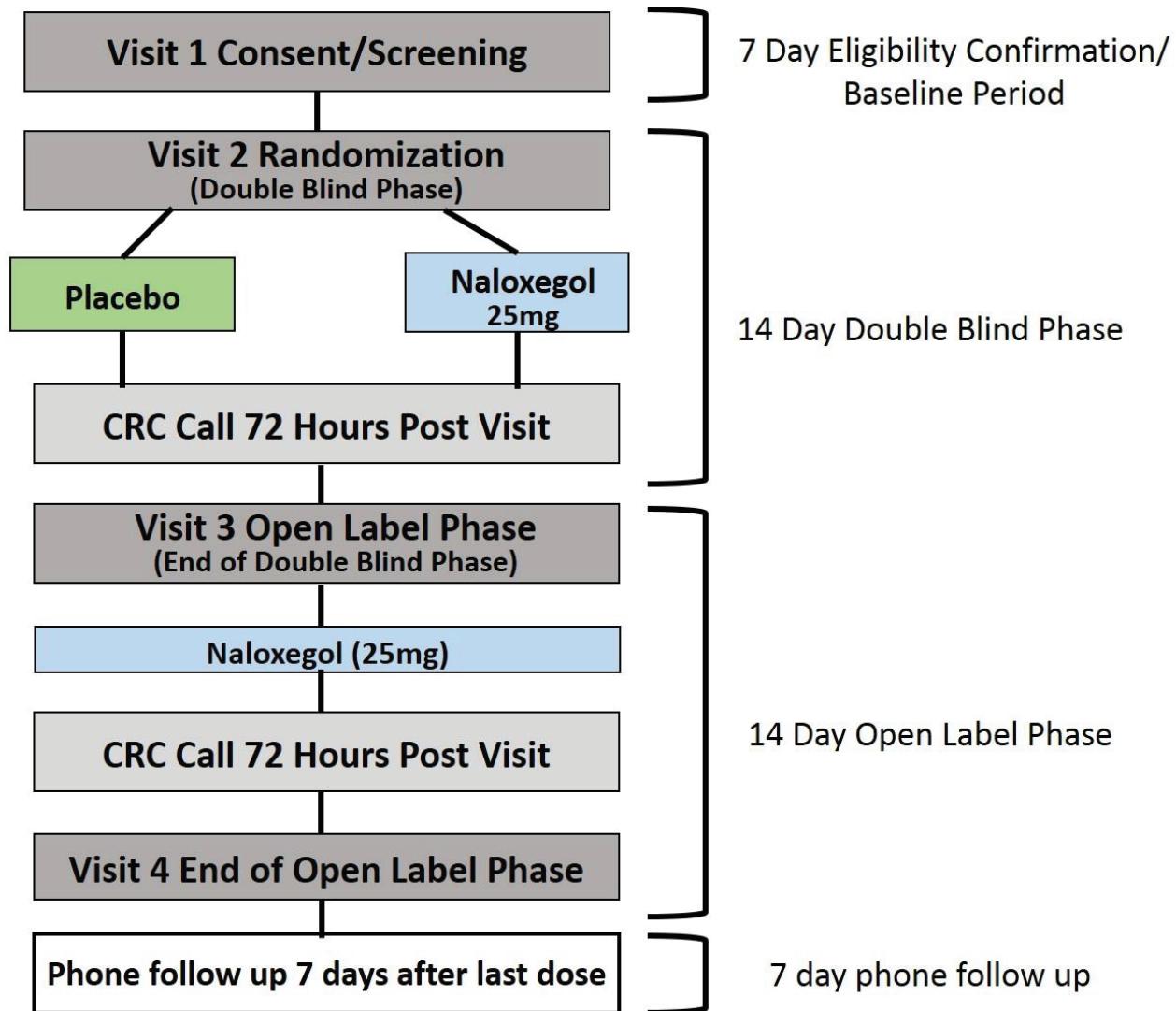


Table 1

14(60)

| Procedure/Scale   | Visit 1   | Visit 2                           | Visit 3                                      | Visit 4                            | Follow up  |
|---|---|-----------------------------------|--|------------------------------------|--|
|   | Consenting/Screening (followed by $\geq$ 7 day baseline data) | Begin Double Blind Treatment      | Completion of RCT/Begin Open Label Treatment | End of Open-label Phase            |  |
|   | day -8  | day 1 (+ $\leq$ 3 days if needed) | day 15 (+ $\leq$ 3 days if needed)           | Day 29 (+ $\leq$ 3 days if needed) | Telephone Contact after 7 days (+ $\leq$ 3 days) |
| Informed Consent  | X   |                                   |  |                                    |  |
| Inclusion and Exclusion                                   | X   |                                   |  |                                    |  |
| Demographic Information                                   | X   |                                   |  |                                    |  |
| Medical History   | X   |                                   |  |                                    |  |
| Complete Physical Exam                                    | X   |                                   |  |                                    |  |
| Brief Physical Exam                                       |   |                                   | As needed                                    |                                    |  |
| Palliative Performance Scale                              | X   |                                   |  |                                    |  |
| Vital Signs & Weight                                      | X   | X (no weight)                     | X (no weight)                                | X (no weight)                      |  |
| Perform or Review 12 lead ECG                             | X   |                                   | X  |                                    |  |
| Blood Sample Collection (CMP, ALT, AST & CBC) (Local Lab) | X   |                                   | X  |                                    |  |
| Urine Pregnancy Test (WOCP)                               | X   |                                   |  |                                    |  |
| Concomitant Medication Review                             | X   | X                                 | X  | X                                  |  |
| Confirm eligibility                                       |   | X                                 |  |                                    |  |
| Query change in medical status                            |   | X                                 | X  |                                    |  |
| Provide Diary & Training                                  | X   | X                                 | X  |                                    |  |
| Provide study drug  |   | X                                 | X  |                                    |  |
| Provide Rescue Medication                                 |   | X                                 | As needed                                    |                                    |  |
| CRC phone call after 72 hrs (+ $\leq$ 3 days if needed)   |   | X                                 | X  |                                    |  |
| Study drug Collection and Accountability                  |   |                                   | X  | X                                  |  |
| Rescue Medication Review & Collection                     |   |                                   | X  | X                                  |  |
| Diary Review  |   | X                                 | X  | X                                  |  |
| Adverse Event Collection & Review                         |   | X                                 | X  | X                                  |  |
| Patient Questionnaires PAC-SYM, PAC-QOL, NRS              |   | X                                 | X  | X                                  |  |

### 3.1.1 Approximate Duration of Patient Participation

All subjects who provide informed consent will participate for a minimum of 1 day and a maximum of 44 days, after which telephone contact will be initiated after 7 days. After providing signed consent, subjects will enter a 7-day period of screening and baseline assessment. This period may be extended by a maximum of 3 days to accommodate the scheduling of the randomization visit (maximum participation Day -8-0). Patients who remain eligible after screening and baseline will be seen, and if eligible to continue, will then be randomized to receive study drug or placebo for 14 days. This period may be extended by a maximum of 3 days to accommodate the scheduling of the subsequent visit (maximum participation in the randomized phase Day 1-14). Patients will continue into open-label phase and receive study drug for an additional 14 days. Again, this period may be extended by a maximum of 3 days to accommodate the scheduling of the end-of-study visit (maximum participation Day 15-29). Following the last visit, a follow-up evaluation by telephone will occur between 7 and 10 days later.

### **3.1.2      Approximate Duration of Study**

This study will be completed in approximately 18 months with about 15.5 months of enrollment.

### **3.1.3      Approximate Number of Subjects**

Approximately 64 patients will be screened to obtain 44 randomly assigned patients. Three sites in the United States will participate. The total enrollment at each site will depend on patient availability and therefore may not be evenly distributed at all sites. Patients who are randomly assigned to study drug but do not take study drug and patients who withdrawal from the study early will not be replaced.

## **3.2      Study Procedures**

### **3.2.1      Visit 1 – Screening/OIC Confirmation**

Visit 1 may take place in an office or the patient's home. The study personnel will perform the following:

- Obtain informed consent
- Record review that establishes adherence to inclusion and exclusion criteria
- Record demographic information (DOB, sex, race, ethnicity)
- Record cancer diagnosis, extent of disease, and status of antineoplastic therapy
- Record pain diagnosis, as known by the patient
- Record other clinically relevant medical comorbidities, active or resolved, or surgical procedures (with dates)
- Record opioid induced constipation diagnosis or symptoms as reported by the patient or identified through medical records consistent with Rome criteria (modified version)
- Record opioid regimen, including baseline drug, dose of baseline drug during the past week, drug for rescue dosing during the past week, number of rescue doses per day during the past week
- Record patient-reported laxative use, including drugs taken, number of days during the past week that each drug was taken, and the dose of each drug taken on the days that it was used
- Record other scheduled medications and doses, and 'as needed' medications and doses during the past week.
- Measure palliative performance status
- Measure sitting blood pressure, pulse and respiratory rate
- Perform a complete physical exam

- Collect blood samples for local laboratory evaluations
- Perform urine pregnancy test (women of child bearing potential only)
- Perform a 12 lead ECG if one has not been performed in the 12 months prior to screening. A copy of a previous tracing must be placed in the source documents
- Dispense and instruct patient and caregiver on the use of the paper diary through the OIC confirmation period

After Visit 1, patients will complete daily diaries to capture baseline values pertaining to OIC and medication taken. Study personnel will contact the patient by telephone as needed to encourage data entry.

The study coordinator will review the data in the daily diaries to confirm subject's eligibility for the study. For the purposes of this review, the measurements recorded on the daily diaries can be conveyed by telephone to the study coordinator, or the diaries can be faxed via secure fax, or scanned and conveyed by secure electronic mail, to the research coordinator. If the subject is eligible for randomization, he or she will be asked to return the diaries at the time of the scheduled Visit 2. Patients who do not proceed to Visit 2 or who drop-out of the study at any time may return the diaries by mail.

A minimum of 7 days of diary data must have been recorded before the patient can be randomized for the study. When this is completed, patients who remain eligible and seek to continue with the study will be scheduled for Visit 2 and randomization will be performed. The study coordinator will contact the randomization coordinator at [REDACTED] and obtain the randomized bottle number for the subject. The study coordinator or authorized staff member will dispense a bottle of study medication according to the bottle number provided. Both the patient and the study coordinator will be blind to the contents of the bottle—either naloxegol 25 mg tablets or placebo tablets. The study coordinator also will receive open-label bisacodyl to be used as a rescue laxative.

### **3.2.2 Visit 2 – Randomization (Part 1 Double Blind Treatment Period)**

Visit 2 may take place in an office or the patient's home. It must occur within 3 days of the end of the baseline period. At Visit 2, the study coordinator will perform the following tasks:

- Review study procedures and confirm eligibility
- Review concomitant medications taken by the patient during the past 48 hours
- Measure sitting blood pressure, pulse, and respiratory rate
- Dispense study medication and instruct the patient (and caregiver, if appropriate) on daily use
- Dispense the rescue laxative and instruct the patient (and caregiver, if appropriate) on use

- Dispense the paper diary and refresh training on daily use.
- Review and record adverse events since visit 1
- Administer the first dose of double-blind study drug and record the time of the dose
- Have patient complete the following validated questionnaires: PAC-SYM, PAC-QOL, and NRS for pain
- Scheduling the next visit for approximately 14 days (+/- 3 days)

After Visit 2, patients will take one dose of study medication (naloxegol or placebo) daily for 14 days and may use rescue laxative as instructed. He or she will again complete the daily diary to capture information about study outcomes. The research coordinator may telephone the patient as needed to answer questions and encourage adherence to study procedures. The research coordinator must contact the patient at 72 hours (+/- 24 hours) after Visit 2.

### **3.2.3 Visit 3 – Open Label Treatment Period (Part 2)**

After 14 days of study drug, the patient will have Visit 3, which must occur within 3 days of the end of the randomized period. At this Visit, the following procedures will be performed:

- Collect and review paper diary and dispense new diary
- Collect empty and unused rescue medication and additional rescue medication may be dispensed as needed.
- Brief physical exam as determined necessary by the investigator
- Collect empty containers and unused study drug and review for compliance
- Dispense open-label medication and instruct patient and caregiver on daily use
- Review and record other scheduled medications and doses, and ‘as needed’ medications and doses
- Collect and record adverse events that have occurred since last visit
- Measure sitting blood pressure, pulse and respiratory rate
- Collect blood samples for local laboratory evaluations
- Obtain 12 lead ECG
- Have patient complete the following validated questionnaires: PAC-SYM, PAC-QOL, and NRS for pain

After Visit 3, patients will take one dose of study medication (naloxegol 25 mg) daily for 14 days and may use rescue laxative as instructed. He or she will again complete the daily diary to capture information about study outcomes. The research coordinator may telephone the patient as needed to answer questions and encourage adherence to study procedures. The research coordinator must contact the patient at 72 hours (+/- 24 hours) after Visit 3.

### **3.2.4 Visit 4 – End of Treatment or Withdrawal**

After 14 days of open-label study drug, the patient will have Visit 4, which must occur within 3 days of the end of the treatment. At this Visit, the following procedures will be performed:

- Collect and review daily paper diary
- Collect empty and unused rescue medication
- Collect empty containers and unused study drug and review for compliance
- Review and record other scheduled medications and doses, and ‘as needed’ medications and doses.
- Collect and record adverse events that have occurred since last visit
- Measure sitting blood pressure, pulse rate, and respiratory rate
- Have patient complete the following validated questionnaires: PAC-SYM, PAC-QOL, and NRS for pain

### **3.2.5 Early Withdrawal**

If the patient begins the randomized phase of the study but withdraws prior to the end of 14 days of treatment, every effort will be made to complete Visit 3. If a visit is not possible, a telephone contact will be attempted, during which information will be elicited about study drug use, change in medical status, other drugs taken and AEs. Pick-up or mailing of the unused study medications and diaries will be arranged.

If the patient begins the open-label extension phase but withdraws prior to the end of 14 days of treatment, every effort will be made to complete Visit 4. If a visit is not possible, a telephone contact will be attempted, during which information will be elicited about study drug use, change in medical status, other drugs taken and AEs. Pick-up or mailing of the unused study medications and diaries will be arranged.

If the patient completes the randomized phase of the study and chooses not to proceed into the open-label extension, the data collected during Visit 3 (completion of RCT) will be used as the end-of-study visit and is not considered an early withdrawal.

### **3.2.6 Follow-Up Phone Calls**

A follow up phone call will occur 7 days after the last dose of study medication to assess for any new or ongoing adverse events.

## **4. SUBJECT SELECTION CRITERIA**

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstance can there be exceptions to this rule. Investigators should keep a record (the patient screening log) of patients who entered screening.

### **4.1 Inclusion criteria**

To be eligible for the study, patients must meet the following criteria:

- Men and women aged 18 or older: Women of child bearing potential must have a negative urine pregnancy test during the Screening/OIC Confirmation/Baseline period, a history of no sexual activity or consistent use of an effective birth control method for at least 12 weeks prior to the study, and agreement that no sexual activity or the method of birth control will be continued during the study and for a period of 8 weeks after it ends; male patients who are sexually active must agree to use a barrier method of contraception (condom with spermicide) from the first dose of IP until 12 weeks after their last dose
- Able to follow instructions in English, give informed consent and to answer patient reported outcomes (PRO) questions by himself/herself; the patient will provide written informed consent before initiation of any study-related procedures
- Active cancer of any type with an investigator-estimated life expectancy  $\geq$  8 weeks and a Palliative Performance Status scale score  $\geq$  30%
- Patients receiving concurrent chemotherapy must have received and recovered from a minimum of 1 cycle of the current chemotherapy regimen upon consenting to the study and be considered stable in the opinion of the investigator
- Chronic cancer-related pain, defined as pain for a minimum of  $\geq$ 2 weeks which on review by the investigator, can be attributed to the neoplasm or its treatment
- Daily treatment with an opioid drug which is taken at a dose equal to or greater than 20 mg morphine or its equivalent for at least one week, with no expectation of a decrease greater than 25% or an increase greater than 100% during the study period.
- Patients may or may not be on a stable laxative regimen, defined as daily use at a stable dose for  $\geq$ 7 days; if the patient is taking a stable dose, he or she must be willing to remain on that regimen for the 7 day confirmation period without titration or adjustments.

History of constipation, defined through history and through participation in the Screening/OIC Confirmation/Baseline period:

- Patient history must include 2 or more of the following during defecations occurring in the two weeks prior to screening:
  - <3 spontaneous bowel movements per week
  - hard/lumpy stools (Bristol Stool Scale Type 1 or 2) in more than 25% of defecations
  - sensation of incomplete evacuation in more than 25% of defecations
  - sensation of anorectal obstruction in more than 25% of defecations
  - Straining during more than 25% of defecations

**Note:** (spontaneous bowel movements (SBMs) are defined as not using a laxative if not already taking daily laxatives, or if taking daily laxatives, not using an additional laxative).

- Confirmation during the 7-day OIC confirmation period must include at least 2 or more of the following symptoms:
  - <3 SBMs per week
  - hard/lumpy stools (Bristol Stool Scale Type 1 or 2) in more than 25% of defecations
  - sensation of incomplete evacuation in more than 25% of defecations
  - sensation of anorectal obstruction in more than 25% of defecations
  - Straining during more than 25% of defecations

## 4.2 Exclusion criteria

Patients must not be enrolled in the study if any of the following exclusion criteria are fulfilled:

- Cancer-related/medical comorbidity-related
  - Patients with a past or current history of intra-abdominal neoplasm AND clinical findings that, on review by the investigator, may increase the risk of bowel perforation
  - An active condition associated with clinically significant brain pathology, including known brain metastases, meningeal metastases, past traumatic brain injury, multiple sclerosis, uncontrolled epilepsy with signs or symptoms of compromised blood brain barrier
  - Patients expected to undergo a first course of a chemotherapy regimen during the study period, patients who received a vinca alkaloid within 2 months, patients who have any history of vinca-associated GI autonomic neuropathy and/or constipation,

- or patients receiving a chemotherapy regimen including a VEGF-inhibitor (e.g., bevacizumab, sorafenib).
- Requiring radiation therapy between the diaphragm and pelvis 2 weeks prior to Visit 1 (screening) and/or during the study
- Any other significant and/or progressive condition (medical, neurological, psychiatric or metabolic) or symptom that could increase the risk of participation in the study or affect the interpretation of study data as determined by the investigator (e.g., uncontrolled hypothyroidism, inadequately controlled clinical depression, poorly controlled seizure disorder)
- Hemorrhagic diathesis
- Expected to have a surgical procedure requiring general anesthesia during the study period
- Other gastrointestinal disorders
  - Medical conditions and treatments, which in the judgment of the investigator, may be associated with diarrhea, intermittent loose stools, or constipation, e.g., active diverticular disease, peritonitis of any cause, inflammatory bowel disease, active irritable bowel syndrome, chronic idiopathic constipation.
  - Any conditions that could affect the absorption or metabolism of the study drug (e.g., malabsorption syndrome, severe liver disease) as judged by the investigator
  - Evidence of fecal impaction either by physical or x-ray exam
  - Known or suspected mechanical GI obstruction
  - Current peritoneal catheter for intra-peritoneal chemotherapy or dialysis
  - Fecal ostomy
  - History of fecal incontinence
  - History of bowel surgery within 60 days of the screening period
  - Any other potential non-opioid cause of bowel dysfunction that in opinion of investigator might be a contributor to the constipation
- Pain-related
  - Receiving opioid medication on less than daily dosing schedule *only*
  - Severe background pain (eg, typical average daily pain intensity rating of 8 to 10 on an 11-point NRS) refractory opioid therapy

- Any of the following findings or conditions between the enrollment and randomization visits:
  - Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $>2.5 \times$  upper limit normal (ULN) and/or serum bilirubin  $>2 \times$  ULN (unless elevation is due to Gilbert's syndrome)
  - Calculated Creatinine clearance  $<30 \text{ ml/min}$
  - A Fridericia corrected QT interval (QTcF)  $> 500 \text{ msec}$  at screening, history of myocardial infarction within 6 months before randomization, symptomatic congestive heart failure despite treatment, unstable angina, or symptomatic peripheral vascular disease
  - Active substance or alcohol use that, in the opinion of the investigator, may compromise patient's ability to comply with the study instructions
  - Use of prohibited medications as listed in Section 5.5
  - Pregnancy or lactation
  - Known history of intolerance or hypersensitivity to alvimopan, methylnaltrexone, or other peripherally acting opioid antagonists or to any other component in the tablets
  - Involvement in the planning and/or conduct of the study (applies to [REDACTED] staff, staff at the study site, and third-party vendors)
  - Any receipt of an investigational medication within 30 days of screening.

## 5. STUDY CONDUCT

### 5.1 Subject recruitment, enrollment and randomization

Potential participants will be identified by the clinical personnel of participating institutions. If the potential study candidate is interested in receiving more information and possibly consenting to the study, the research coordinator will reach out to the patient and provide further information about the study, including its procedures and risk and potential benefits. Patients will be given enough time to ask questions, and consider study participation. If the patient continues to express interest, Visit 1 will be scheduled to obtain a written informed consent before any study-specific procedures are performed.

The consent procedure will take place at the initial part of Visit 1. The research coordinator will review the consent form with the patient, discuss risks and benefits of the study and answer questions. The coordinator will ask brief questions about the study procedures to assure the patient's understanding. After the patient signs the consent form, a copy will be provided to the patient (if a copy can't be obtained, two originals will be signed, one retained by the patient and one by CRC).

Patients who sign the consent form will be considered enrolled in the study. Enrolled patients will be assigned a unique enrollment number. The unique enrollment number is a 4 digit number made up of the site number followed by the patient number. If a patient is discontinued from the study their enrollment number will not be re-used and the patient will not be allowed to re-enter the study.

The consenting patient will participate in the Screening/OIC Confirmation/Baseline period, during which eligibility for randomization will be determined. Patients who are eligible will be enrolled into EDC. If a patient discontinues from participation in the study, then his/her enrollment/randomization code cannot be reused.

### **5.1.1 Procedures for randomization**

Eligible patients will be randomized in blocks to receive either 25 mg naloxegol or placebo in a 1:1 ratio. Bottle numbers will be assigned sequentially as patients become eligible for randomization. The clinical research coordinator will contact the randomization coordinator at [REDACTED] to obtain the bottle number for the subject. Patients who discontinue early from study will not be replaced. If a bottle is allocated incorrectly there will be no attempt to be remedy the error once the study drug has been dispensed.

## **5.2 Procedures for handling subjects incorrectly enrolled, or randomized, or initiated on investigational product**

Patients who fail to meet I/E criteria should not under any circumstances be enrolled or received study drug. If a patient who does not meet selection criteria is randomized in error or is incorrectly started on treatment, a discussion should occur between the medical monitor and the investigator regarding whether to continue or discontinue the patient from treatment.

## **5.3 Blinding and procedures for unblinding the study**

### **5.3.1 Methods for ensuring blinding**

Naloxegol 25 mg and placebo will be identical in size and color. Packaging and labeling of study drug will be in a way to ensure blinding. Patients will receive 1 tablet once per day.

### **5.3.2 Methods for unblinding the study**

The treatment number should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The study site will contact the medical monitor to discuss unblinding. If it is necessary to unblind the subject, the randomization coordinator at [REDACTED] will provide the unblinded drug assignment. The study site will provide documentation of unblinding to [REDACTED]

## 5.4 Treatments

### 5.4.1 Identity of investigational product(s)

Table 2

| Investigational product       | Dosage form and strength | Manufacturer |
|-------------------------------|--------------------------|--------------|
| Naloxegol                     | Tablet 25 mg             | [REDACTED]   |
| Matching Placebo to Naloxegol | Tablet 0 mg              | [REDACTED]   |

### 5.4.2 Doses and treatment regimens

Patients will receive study drug during:

- The 14 day randomized period of the study
- The 14 day open-label period of the study

Patients will be instructed to take 1 tablet, 1 hour before eating in the morning. Naloxegol or placebo will be taken once daily as 1 tablet. Tablets will consist of naloxegol 25 mg or placebo.

### 5.4.3 Additional study drug

Sites will obtain bisacodyl for use as rescue medication and will dispense bisacodyl to patients at Visits 2 and 3.

### 5.4.4 Labeling

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.

[REDACTED] will provide the unblinded study drug (naloxegol 25 mg tablets and identical-appearing placebo tablets) in bulk unlabeled bottles to [REDACTED] who will be responsible for bottling, blinding, and labeling the study medication. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

### 5.4.5 Handling and Storage

The randomization coordinator at [REDACTED] will maintain the unblinded kit log and sequential randomization log for all study sites. When patients become eligible for randomization the study site will contact the randomization coordinator at [REDACTED] to obtain the next sequential bottle number. The study sites will be blinded to the randomized assignments and will only be given the bottle number.

All study drug must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions is specified on the study drug label and in the Investigators' Brochure. All study drug will be stored in original containers and dispensed to the

study patients. The receipt, handling, storage, and dispensing of naloxegol will be in accordance with applicable country regulatory requirements.

## 5.5 Concomitant and post-study treatment(s)

It is recognized that some patients may have their pain managed by personal physicians who are not connected with the study. In these cases, the investigator should notify the patient's personal physicians of the patient's participation in the study, and to ask the physician 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.

Contraceptives (eg, oral contraceptive, implant, dermal contraception, long-term injectable contraceptive, intrauterine device) are allowed.

Patients who were on a maintenance bowel regimen (i.e. regular daily schedule) are allowed to continue on that regimen for the duration of the study. Patients who use laxatives on as needed basis (or those who do not use laxatives) will be required to stop all laxatives and other bowel regimens at randomization for the duration of the study. Bisacodyl will be provided at visit 2 for use during the study. During all treatment periods of the study if after a minimum of 48 hours the patient has not experienced a bowel movement they may take bisacodyl rescue therapy (10 to 15 mg dose). However, in the case the patient is unable to wait 48 hours to receive rescue laxative, rescue laxatives may be administered sooner than 48 hours at the discretion of the investigator. If the patient remains constipated, bisacodyl rescue therapy may be repeated up to 2 additional times, as necessary, each 10 to 15 mg doses administered at 12-hour intervals, or the investigator may prescribe a one-time use of an enema. The timing and administration of any rescue therapy used will be noted and recorded in the diary.

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 diary records. If there is a discrepancy, the patient will be counseled regarding proper documentation of bisacodyl use in the diary.

Patients will be asked to record their daily opioid breakthrough medication use in the paper diary. Changes in the opioid regimen and laxative regimen may occur at the discretion of the investigator to ensure appropriate symptom management throughout the study.

The following laxative medications are prohibited during the study period:

- Lubiprostone (Amitiza®)
- Linaclotide (Linzess)
- Drugs blocking fat absorption with an associated laxative effect
- Prucalopride
- Any agent that is used in an off-label fashion to treat constipation (eg, colchicine, misoprostol, erythromycin, cholinesterase inhibitors such as donezepil)

- Any experimental constipation therapy.

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

- Pentazocine
- Buprenorphine
- Nalbuphine
- Naloxone and other naloxone containing products, such as oxycodone/naloxone combinations (eg, Targin)
- Naltrexone and other naltrexone containing products such as morphine/naltrexone combinations (eg, Embeda)
- Methylnaltrexone (Relistor<sup>®</sup>)
- Alvimopan (Entereg<sup>®</sup>).

The following strong inhibitors of CYP3A4 enzymes and p-glycoprotein (PGP) are prohibited; examples are provided below:

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

Chemotherapy:

- Concurrent chemotherapy is allowed during the study for patients who have received and recovered from at least 1 cycle of the current chemotherapy regimen prior to study entry
- Patients will not be permitted to begin a new chemotherapy regimen during the study period
- 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.

## 5.6 Treatment compliance

Each patient is expected to comply with the treatment regimen and diary recording during the study. The administration of the study drugs should be recorded appropriately by the research coordinator. 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 tables that should have been taken (1 tablet per day). Compliance with the diary will be assessed at each study visit.

### **5.6.1      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. 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. Once monitored, study drug will be destroyed on site in accordance with appropriate regulatory laws.

## **5.7      Discontinuation of investigational product**

Reasons why a subject may discontinue or be withdrawn from the study include but are not limited to AE, subject request, protocol violation, subject noncompliance, and study termination. When a subject discontinues or is withdrawn, the investigator will notify the sponsor, and when possible assessments will be performed, and all study drugs and the diary should be returned by the patient.

### **5.7.1    Procedures for discontinuation of a subject from investigational product**

Participation in the study is voluntary and a patient can withdraw from the study at any time. Besides voluntary withdrawal, a patient can be removed from the study by the investigator for the following reasons.

- Serious adverse event related to the investigational product
- Non-compliance with the study protocol/fails to follow instructions of study personnel
- Closure of the study

If a subject prematurely discontinues from the study, for a reason other than death, after receiving at least one dose of study drug they will be asked to return to the study site to complete all assessments for visit 4 end of treatment visit. This end of treatment visit should be scheduled as soon as possible after the patient discontinues from the study and there will also be a follow-up telephone call approximately 7 days after the patient's last dose of study drug. Any patient who discontinues due to an adverse event will be followed until the event has resolved or is felt to be stable as determined by the investigator.

## **6. COLLECTION OF STUDY VARIABLES**

### **6.1 Recording of data**

The EDC system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs 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. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Patient diaries will be used by patients to collect information regarding BMs, degree of straining, stool consistency (BSS), complete/incomplete evacuation, pain level (NRS), use of bisacodyl laxative rescue medication, and use of opioid medication for breakthrough pain.

The patients will be asked to bring the diary to each visit where the diary will be reviewed for accuracy and completeness.

### **6.2 Efficacy**

#### **6.2.1 PAC-SYM**

The PAC-SYM questionnaire [10] 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 questions will take approximately 5 minutes to answer. The PAC-SYM will be administered to patients at Visits 2,3 and 4.

The PAC-SYM questionnaire will be completed by patients on paper forms provided by the study site. Study staff will provide initial instruction 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 PAC-SYM questionnaire prior to any interventions or discussions regarding their OIC with the study staff or the investigator.

#### **6.2.2 PAC-QOL**

The PAC-QOL scale [11] 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 [11]. The questions will take approximately 5 minutes to answer. 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 questionnaire will be completed by patients on paper forms provided by the study site. Study staff will provide initial instruction 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 PAC-QOL questionnaire prior to any interventions or discussions regarding their OIC with the study staff or the investigator. The PAC-QOL will be administered to patients at Visits 2, 3 and 4.

### **6.2.3      Diary Measurements**

Paper diaries will be provided to each study subject at the screening visit and study staff will instruct the subject on how to complete the diary. Information to be collected daily will include study drug administration, bowel movements, degree of straining, stool consistency (BSS), complete/incomplete evacuation, pain level (NRS), use of bisacodyl laxative rescue medication, and use of opioid medication for breakthrough pain. At each study visit subject diaries will be collected and a new diary will be dispensed. It is the patient's responsibility to complete the diary, however, under extreme circumstances the caregiver may enter the patient's verbal response to the questions directly into the diary. The study staff will transcribe the subject's responses into the EDC.

### **6.2.4      Bowel movements**

All BMs will be recorded in the diary each day as they occur.

### **6.2.5      Stool consistency (Bristol Stool Scale - BSS)**

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

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

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

### **6.2.6 Degree of 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 and recorded in the diary. 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 on 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.

### **6.2.7 Complete/incomplete evacuation**

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

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

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

### **6.2.8 Pain level**

Patients will rate their pain level at the end of each day, using the NRS for pain (see Section 6.3.6).

### **6.2.9 Use of laxative rescue medication**

All bisacodyl laxative rescue medication will be recorded in the diary on the day it was taken (other laxative rescue medication will be recorded on the concomitant medication eCRF page).

### **6.2.10 Use of opioid medication for breakthrough pain**

Opioid medication for breakthrough pain will be recorded in the diary on the day it was taken.

## 6.3 Safety

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

The federal regulations for the protection of human subjects specify that institutions engaged in research with human subjects must have written procedures for ensuring prompt reporting to the IRB, institutional officials, and any supporting department or agency of any unanticipated problems, including adverse events, involving risks to subjects or others.

According to federal regulations, unanticipated problems are considered reportable to the IRB if they meet ALL of the following criteria:

Involve occurrences that are unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and (b) the characteristics of the subject population being studied [Note: adverse events listed in the investigator's brochure would, by definition, not be considered unexpected]; **AND**

- 1) Related to or possibly related to study activities (in this document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); **AND**
- 2) Are significant enough to suggest that the research may place subjects or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm).

While most unanticipated problems involve adverse physical or psychological events, other types of incidents, experiences or outcomes that occur during the conduct of human subject research may also constitute unanticipated problems as well. For example, in some cases of unanticipated problems no harm occurs, but the event places the study participant into an increased risk of harm (for example if breach of confidentiality occurs).

### 6.3.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration 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, electrocardiogram). 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.

Note: Although all AEs must be documented in the study participant's research files (as described below) only some AEs will be determined reportable to the IRB, based on the criteria listed above.

### **6.3.2 Definitions of serious adverse event**

A serious adverse event is an AE occurring during any study phase (ie, screening, double-blind, open label), that fulfils one or more of the following criteria:

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

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to [REDACTED] and [REDACTED].

### **6.3.3 Recording of adverse events**

#### **Time period for collection of adverse events**

All AEs will be collected from the time of signature of informed consent to the follow up visit whether related or not to the IP and must be recorded on the eCRF

#### **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 until resolution or is felt to be stable.

#### **Variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Intensity
- Severity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product
- Action taken with regard to investigational product

- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- 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.

Intensity is defined as follows:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interferences with normal activities)
- severe (incapacitating with ability 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 above. 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 a 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 a SAE.

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes

- Pregnancy exposure to a study drug. If a pregnancy is confirmed, use of the study drug must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male subject, the necessary

information must be collected from the subject, while respecting the confidentiality of the partner.

- Lactation exposure to a test article with or without an AE
- Overdose of study drug as specified in the protocol with or without an AE.
- Inadvertent or accidental exposure to study drug with or without an AE

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 of each AE (ie, their relationship to study drug). Causality will be rated as “related”, “probably related”, “possibly related”, and “unrelated”.

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.”

### **Adverse Events based on signs and symptoms**

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 study drug, 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, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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.

### **Disease progression**

Disease progression can be considered as a worsening of a patient’s condition attributable to the disease for which the study drug is being studied, which in this study refers to the condition of

OIC. Adverse events, which are due to disease (ie, OIC) progression, in the opinion of the investigator, should not be reported as an AE, unless they meet SAE criteria.

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

#### **6.3.4 Reporting of serious adverse events**

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to [REDACTED]. A copy of the MedWatch/AdEERs report must be faxed to [REDACTED] at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to [REDACTED] at the same time.

When reporting to [REDACTED] a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and [REDACTED] ISS reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page to [REDACTED] by email to [REDACTED] or by fax to [REDACTED] (Fax number). Email is the preferred method.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to [REDACTED] within 3 days of site becoming aware preferably using the MedDRA coding language for serious adverse events.

In the case of blinded trials, [REDACTED] will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to [REDACTED] whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

### **6.3.5 Pain and opioid use**

The study drug is an opioid antagonist, and pain opioid use are therefore measured to determine whether the study drug may have an adverse effect on pain management

### **6.3.6 Use of opioid medication for breakthrough pain**

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 diary and the daily maintenance opioid dose will be recorded on the opioid dose eCRF.

### **6.3.7 Numerical Rating Scale of Pain (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 [13]. The NRS rates pain from 0 (no pain) to 10 (worst pain imaginable). The NRS will be recorded each evening via the diary to record the patients' worst pain and average pain during the day.

Patients will rate their pain level at the end of each day, using the NRS for pain. The questions and anchors will be as follows:

“Using a scale of “zero” to “ten”, where zero equals no pain and ten equals the worst pain you can imagine, how would you rate the severity of pain, on average during the past 24 hours?

“Using a scale of “zero” to “ten”, where zero equals no pain and ten equals the worst pain you can imagine, how would you rate the severity of your pain at its worst during the past 24 hours?”

### **6.3.8 Laboratory safety assessment**

Clinical laboratory assessments will be conducted by a local laboratory at each site. Blood samples for determination of clinical chemistry including LFTs and hematology will be taken at the times indicated in the Study Plan (Table 1). Any unscheduled blood draws for laboratory tests should be sent to the local laboratory.

The investigator will obtain normal reference ranges for laboratory tests from the local laboratory. These will be filed in the regulatory binding at the study site.

A urine pregnancy test for all WOCBP will be performed at screening.

### **6.3.9 Handling of subjects with elevated liver transaminases**

Patients who develop ALT or AST  $>2.5 \times$  ULN during the course of the study and have no signs or symptoms of hepatic dysfunction can, at the discretion of the investigator, continue the study drug with close monitoring. Patients with elevated liver enzymes that are felt to be related to study drug will be withdrawn from the study.

### **6.3.10 Physical examination**

A physical examination (weight, 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 to confirm eligibility. Significant findings that are present at the time of screening (Visit 1) must be included in the Medical History/Surgical History eCRF pages. A brief physical exam may be performed at Visit 3 at the discretion of the investigator. At each subsequent visit, the patient will be queried about any adverse events and vital signs will be checked. If the patient reports that there are significant changes, or the vital signs are not in the normal range, this information will be reviewed by the investigator and recorded in the eCRF. Any changes that are potential AEs will be evaluated as previously described.

### **6.3.11 ECG**

Digital ECGs for all patients at all centers will be conducted by the study site. ECGs will be performed at Visit 1 and 3, after the patient has been resting in a supine position for at least 10 minutes. All ECGs will be documented by recording date, time, heart rate, QRS duration, PR interval, RR interval, QT and QTcF.

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.

It is the investigator's judgment whether the findings/results on the ECG assessment are clinically relevant or not and whether the findings will result in the discontinuation of the patient from the study based on the inclusion/exclusion criteria or discontinuation criteria.

### **6.3.12 Vital signs**

Sitting blood pressure, pulse/heart rate, and respiratory rate must be measured at Visits 1, 2, 3 and 4. The patient must be resting at least 5 minutes before measurement and an appropriately sized cuff should be used. Patient's weight and temperature will be measured at the first visit. The measurements will be recorded in eCRF.

### **6.3.13 Other safety assessments**

#### **6.3.13.1 Persistent or progressive severe abdominal pain**

Rare cases of GI perforation associated with the use of methylnaltrexone 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.).

While abdominal pain has been reported in association with naloxegol 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.

#### **6.3.13.2 Blood pressure and heart rate measurements**

Pre-clinical investigations have included a recent dog telemetry study which demonstrated small, transient decreases in blood pressure, left ventricular systolic pressure, cardiac contractility and relaxation indices, as well as increases in heart rate, at blood concentrations about 5 times higher than the maximum dose used in this study (ie, 25 mg). While there have been isolated reports of patients with potentially clinically significant BP decreases in trials of naloxegol, 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 BP at all visits; for specific instructions on methods for measurement, please refer to Section 6.3.12. 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 study drug (see Section 6.3.3).

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.

## **7. ETHICAL AND REGULATORY REQUIREMENTS**

### **7.1 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 Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements.

### **7.2 Ethics and regulatory review**

An Institutional Review Board (IRB) will approve the study protocol and all supporting materials, including all advertising used to recruit patients for the study. The opinion of the IRB should be given in writing. The investigator should submit the written approval to [REDACTED] or its representative before enrollment of any patient into the study. All material used for patient education or advertising will be approved by [REDACTED]. [REDACTED] or its representative will handle the distribution of any of these documents to the national regulatory authorities. [REDACTED] or its representative will provide Regulatory Authorities, IRBs, and PIs with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

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

### **7.3 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 informed consent before conducting any procedure specifically for the study
- Ensure the original, signed consent forms are stored in the Investigator's Study File
- Ensure a copy of the signed consent form 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 consent form that is approved by an IRB.

### **7.4 Changes to the protocol and informed consent form**

Study procedures will not be changed without the mutual agreement of the PI and [REDACTED] and [REDACTED]

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment.

The amendment is to be approved by the IRB before implementation.

[REDACTED] will distribute any subsequent amendments and new versions of the protocol to each PI. If a protocol amendment requires a change to a center's consent form, [REDACTED] and the IRB will approve the revised consent form before the revised form is used.

### **7.5 Audits and inspections**

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

## 8. STUDY MANAGEMENT

### 8.1 Pre-Study Activities

Before the first patient is entered into the study, it is necessary for a representative of [REDACTED] 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 [REDACTED] or its representatives. This will be documented in an agreement between [REDACTED] and the investigator.

### 8.2 Training of study site personnel

Before the first patient is entered into the study, a [REDACTED] representative or its representative will review and discuss the requirements of the protocol and related documents with the investigational staff and also train them in any study-specific procedures.

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).

Monitoring of the study during the study, a [REDACTED] 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.
- 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)

[REDACTED] representatives will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

### **8.3 End of study**

The end of the study is defined as the last visit of the last patient undergoing the study. The study may be terminated at individual centers if the procedures are not being performed according to GCP or if recruitment is slow. [REDACTED] may also terminate the entire study prematurely if concerns for safety arrive within this study or within any other study with naloxegol.

## **9. DATA MANAGEMENT**

### **9.1 Electronic case report form**

The eCRF and the protocol are both confidential. The eCRF will be 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. [REDACTED] will have access to data at all study sites.

All eCRFs are to be completed by an authorized member of the study 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).

### **9.2 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.

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. 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.

### **9.3 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.

## **9.4 Coding**

All AEs and medical/surgical histories recorded in the eCRF will be coded using MedDRA.

## **9.5 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 study files will be stored for 3 years following the study completion as required by the IRB. The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

# **10. EVALUATION AND CALCULATION OF VARIABLES**

## **10.1 Primary aims: tolerability and safety**

The primary aim of this pilot study is to assess the tolerability and safety of naloxegol 25 mg in the management of OIC in the cancer population. The secondary aims are to assess efficacy and feasibility. The primary endpoint for tolerability and safety will be the difference in AEs between study groups. The secondary endpoints for this aim will focus on pain-related variables.

### **10.1.1 Adverse Events**

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

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

$$\text{AE start date} - \text{Date of the first dose of study drug} + 1$$

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

$$\text{AE resolution date} - \text{AE start date} + 1$$

AEs which in the opinion of the investigator are unequivocally due to cancer disease progression will be tabulated separately from all other AEs.

### **10.1.2 Numerical Rating Scale for pain (NRS)**

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 in the paper diary. 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 as the post-baseline value minus the baseline. Negative changes from baseline indicate improvement. Baseline NRS is the mean daily NRS values recorded during the OIC confirmation period.

#### **10.1.3 Daily opioid dose**

Opioid doses will be recorded for each patient, including both the maintenance dose recorded on the eCRF and breakthrough pain medication recorded in the paper diary, 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 as the post-baseline value minus the baseline value. Positive changes from baseline indicate need to increase opioid dose. Baseline daily opioid dose is the mean daily opioid dose recorded during the OIC confirmation period.

#### **10.1.4 Laboratory safety assessments**

Changes from baseline to visit 3 for all patients will be calculated as the post-baseline test value minus the baseline test value. Laboratory test results will also be compared with the laboratory reference ranges, and values that are outside the applicable reference range will be flagged at high or low.

#### **10.1.5 ECG**

Changes from baseline to visit 3 for ECG interval data and rate data will be derived by subtracting the baseline value from the final assessment data. Marked abnormal values or changes from baseline will be identified based on pre-determine criteria.

#### **10.1.6 Vital Signs**

Changes from baseline in vital signs (sitting blood pressure, pulse, and respiratory rate) at post baseline (Visits 2, 3, and 4) will be derived as the value at the visit minus the baseline value for the same assessment.

### **10.2 Secondary aims: efficacy and feasibility**

#### **10.2.1 Calculation or derivation of efficacy variables**

The efficacy assessments of this study include the recording of daily laxation information (date and time of each SBM).

##### **10.2.1.1 SBMs Responder Rate**

A SBM is defined as a BM without rescue laxatives in the previous 24 hours. 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 a patient with  $\geq 3$  SBM in a week and at least one SBM/week increase over baseline for the two weeks during which the study drug is taken. For the purposes of the analysis, the proportion of responders will be evaluated during the randomized period, and also during the extension period. The randomized period permits a comparison of response rates for those who received naloxegol and those who received placebo. The responder rate during the extension period for those patients who entered the extension period after having had placebo will be evaluated as supportive of the response rate determined during the randomized period.

#### **10.2.1.2 Time to First Laxation**

The time to first post-dose SBM will be calculated in hours as:

$$\text{Date/time of first post-dose SBM} - \text{First dose date/time}$$

Response to study drug within the first 24 hours will be assessed using the calculated time to first post-dose SBM.

#### **10.2.1.3 Days with at least 1 SBM**

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

$$(\text{Total number of days with at least 1 SBM during the period of interest}/\text{number of days in the period of interest}) \times 7.$$

#### **10.2.1.4 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 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.

#### **10.2.1.5 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 as the 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 indicated improvement.

#### **10.2.1.6 Days with complete evacuation**

For each BM, the patient will record in the diary 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, multiplied by 100. The percentage of days with complete evacuation will be calculated.

#### **10.2.1.7 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).

The change from baseline in the total score and each construct score will be calculated for visits 3 and 4.

#### **10.2.1.8 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).

The change from baseline in the total score and each construct score will be calculated for visits 3 and 4.

#### **10.2.1.9 Additional Endpoints**

Additional endpoints to be calculated include:

- Doses of rescue laxatives required per week
- Number of enemas required per week
- Number of manual disimpaction procedures required per week

### **10.2.2 Calculation or derivation of feasibility variables**

The study population poses challenges in enrollment and study conduct. This is because most patients receiving daily opioid therapy that have advanced cancer may be medically compromised, have multiple co-morbidities, and burdened by the need for multiple medications. It may be difficult for such ill patients to participate in trials because of poor functional status, fatigue, and the need for frequent clinical visits.

This study will evaluate patient recruitment and retention in a test of an oral therapy requiring one dose per day—25 mg naloxegol. The inclusion criteria are broad and include patients with low

functional status and a short prognosis (2 months). The recruitment goal is to enter 1-2 eligible patients a month at each site into the study.

To evaluate feasibility, the number of patients entering the study per month at each site will be tracked. The retention rate, or the percentage of patients who complete the study, will be calculated for each study site. The goal is a retention rate of 80%. The percentage of screen failures and the percentage of withdrawals will also be calculated.

## **11.0 SAMPLE SIZE DETERMINATION AND STATISTICAL METHODS**

### **11.1 Determination of sample size**

This study has been designed to provide essential information about the potential viability and utility of a definitive adequately-powered superiority trial assessing the ability of naloxegol to provide better efficacy for OIC in cancer patients than current therapies. It is pilot trial with the primary aim of determining safety and tolerability of this drug in the medically ill cancer patient. A secondary aim is to determine whether an efficacy signal can be determined, and if so what the effect size is—information critical to the design of a larger trial. Finally, feasibility, as determined by the ability to recruit and conduct the study according to protocol, is another secondary aim.

As a pilot, sample size determination is not considered to be dispositive of the actual planned recruitment. The study has been planned to screen approximately 64 patients to obtain 44 randomly assigned patients—22 per group. Provided by an ██████████ statistician, this number per group would allow a detection of a group difference of  $0.58 \pm 90\%$  confidence interval at a 70% power and 10% type I error, using a 2 sided tests). This is based off of spontaneous bowel movements per week over 1-4 weeks in the Phase III study of naloxegol 25mg versus placebo in non-cancer patients.

### **11.2 Outcome analyses**

The analysis of the randomized dataset will evaluate an intent-to-treat (ITT) population, defined as all randomized patients participating. These analyses will be complemented by descriptive data from the open-label extension period.

#### **11.2.1 Safety and tolerability analyses**

Adverse events will be classified by body system and preferred team and summarized by the number of patients with events per treatment group. AEs which in the opinion of the investigator are unequivocally due to the progression of a patient's underlying cancer may be analyzed and tabulated separately from other AEs. The number of TEAEs related to the study drug or probably related to the study drug will be compared across active drug and placebo. The number of these AEs mapped to the GI tract will be additionally analyzed. As noted, this analysis will be augmented by descriptive incidence data from the extension period.

The change from baseline in the 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.

All laboratory test results, vital signs (sitting BP and pulse), ECG results, respiratory rate, hematology and blood chemistry will be summarized for each treatment group using descriptive statistics and change from baseline.

### **11.2.2 Efficacy analysis**

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. The proportion of patients who are responders will be compared between treatment groups with a one sample t-test. The proportion of patients who have a laxation response within 24 hours after the 1<sup>st</sup> dose of study drug will be compared between treatment groups with a one sample t-test. Descriptive statistics by treatment group for the mean number of days per week with at least 1 SBM, the mean degree of straining, the mean stool consistency, and the percentage of days with complete evacuation will be summarized for each period (baseline, 2-week treatment period) as well as for the change from baseline to the 2-week treatment period.

Descriptive statistics by treatment group for the total scores and each domain scores of the PAC-SYM and PAC-QOL, as well as rescue laxative use, BSS, straining score and complete evacuation score, will be summarized at baseline (Visit 2), and at Visits 3 and 4. Change from baseline will be described. Group differences will be evaluated using t-tests. The treatment by opioid dose interaction will be assessed using a logistic regression model on the response during the 2-week treatment period, 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. Average daily dose of opioid will include both the maintenance and any breakthrough opioid doses a patient has during each time period. Among patients who undergo increases in their total opioid dose (maintenance + breakthrough), the impact of the increase opioid dose on SBMs/week will be assessed by comparing the difference in SBMs in the 7 day period during the opioid dose increase with the previous 7-day period. Summaries will focus on the largest weekly increase observed during the study. Differences (before and during the increase) will be summarized descriptively. The magnitude of opioid dose increase as defined above will be summarized.

### **11.2.3 Feasibility analysis**

The patient recruitment rate, retention rate, screen failure rate, and withdrawal rate will be compared to previous Phase III studies of naloxegol in patients with non-cancer pain and OIC.

## **12. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR**

### **12.1 Medical emergencies**

The PI is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.2.**

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



## 12.2 Overdose

If an overdose on an [REDACTED] study drug occurs in the course of the study, then investigators or other site personnel inform appropriate [REDACTED] and [REDACTED] representatives **within one 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 [REDACTED] representative works with the [REDACTED] investigator to ensure that all relevant information is provided to the [REDACTED] Patient Safety data entry site.

## 12.3 Pregnancy

All outcomes of pregnancy should be reported to [REDACTED] and [REDACTED] or its representative. 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.

### 12.3.1 Maternal exposure

Requirements for contraception in women of child bearing potential are specified in Inclusion Criteria. If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug 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 [REDACTED] and [REDACTED] 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.

### **12.3.2 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. If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform appropriate [REDACTED] and [REDACTED] 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.

## 13. LIST OF REFERENCES

1. Peng, W.L., et al., *Multidisciplinary management of cancer pain: a longitudinal retrospective study on a cohort of end-stage cancer patients*. J Pain Symptom Manage, 2006. **32**(5): p. 444-52.
2. van den Beuken-van Everdingen, M.H., et al., *Prevalence of pain in patients with cancer: a systematic review of the past 40 years*. Ann Oncol, 2007. **18**(9): p. 1437-49.
3. Zech, D.F., et al., *Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study*. Pain, 1995. **63**(1): p. 65-76.
4. Holzer, P., *Treatment of opioid-induced gut dysfunction*. Expert Opin Investig Drugs, 2007. **16**(2): p. 181-94.
5. Panchal, S.J., P. Muller-Schwefe, and J.I. Wurzelmann, *Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden*. Int J Clin Pract, 2007. **61**(7): p. 1181-7.
6. McNicol, E., et al., *Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review*. J Pain, 2003. **4**(5): p. 231-56.
7. Pappagallo, M., *Incidence, prevalence, and management of opioid bowel dysfunction*. Am J Surg, 2001. **182**(5A Suppl): p. 11S-18S.
8. Chey, W.D., et al., *Naloxegol for opioid-induced constipation in patients with noncancer pain*. N Engl J Med, 2014. **370**(25): p. 2387-96.
9. Webster, L., et al., *Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation*. Aliment Pharmacol Ther, 2014. **40**(7): p. 771-9.
10. Frank, L., et al., *Psychometric validation of a constipation symptom assessment questionnaire*. Scand J Gastroenterol, 1999. **34**(9): p. 870-7.
11. Marquis, P., et al., *Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire*. Scand J Gastroenterol, 2005. **40**(5): p. 540-51.
12. Lewis, S.J. and K.W. Heaton, *Stool form scale as a useful guide to intestinal transit time*. Scand J Gastroenterol, 1997. **32**(9): p. 920-4.
13. Dworkin, R.H., et al., *Core outcome measures for chronic pain clinical trials: IMMPACT recommendations*. Pain, 2005. **113**(1-2): p. 9-19.

## Appendix A - MORPHINE EQUIVALENTS CONVERSION CHART

### 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 <sup>a</sup> | 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 1 mg of parenteral oxymorphone is considered to be equivalent to 15 mg of oral morphine.

<sup>a</sup> For the 72 hr fentanyl patch (25 3g/hr), the equianalgesic daily dose of oral morphine will be considered to be 15 mg every 4 hr OR 45 mg BID of MS-Contin (ie, 90 mg/day of morphine). For transmucosal fentanyl (ie, the fentanyl “lollipop”), an 800 3g dose will be regarded as equivalent to 30 mg of oral morphine.

## Appendix B – PALLIATIVE PERFORMANCE SCALE

| %   | Ambulation        | Activity and Evidence of Disease                          | Self-Care                        | Intake            | Level of Conscious         |
|-----|-------------------|---|----------------------------------|-------------------|----------------------------|
| 100 | Full              | Normal activity, no evidence of disease                   | Full                             | Normal            | Full                       |
| 90  | Full              | Normal activity, some evidence of disease                 | Full                             | Normal            | Full                       |
| 80  | Full              | Normal activity with effort, some evidence of disease     | Full                             | Normal or reduced | Full                       |
| 70  | Reduced           | Unable to do normal work, some evidence of disease        | Full                             | Normal or reduced | Full                       |
| 60  | Reduced           | Unable to do hobby or some housework, significant disease | Occasional assist necessary      | Normal or reduced | Full or confusion          |
| 50  | Mainly sit/lie    | Unable to do any work, extensive disease                  | Considerable assistance required | Normal or reduced | Full or confusion          |
| 40  | Mainly in bed     | Unable to do any work, extensive disease                  | Mainly assistance                | Normal or reduced | Full, drowsy, or confusion |
| 30  | Totally bed bound | Unable to do any work, extensive disease                  | Total care                       | Reduced           | Full, drowsy, or confusion |
| 20  | Totally bed bound | Unable to do any work, extensive disease                  | Total care                       | Minimal sips      | Full, drowsy, or confusion |
| 10  | Totally bed bound | Unable to do any work, extensive disease                  | Total care                       | Mouth care only   | Drowsy or coma             |
| 0   | Death             | —   | —                                | —                 | —                          |

## Appendix C – PAC-SYM

PAC-SYM ©

### PATIENT ASSESSMENT OF CONSTIPATION ©

This questionnaire asks you about your constipation in the **past 2 weeks**. Answer each question according to your symptoms, as accurately as possible. There are no right or wrong answers.

For each symptom below, please indicate how severe your symptoms have been during the past 2 weeks. If you have not had the symptom during the past 2 weeks, check 0. If the symptom seemed mild, check 1. If the

symptom seemed moderate, check 2. If the symptom seemed severe, check 3. If the symptom seemed very severe, check 4. Please be sure to answer every question.

| <b>How severe</b> have each of these symptoms been in the last 2 weeks? | <b>Absent</b><br><b>0</b> | <b>Mild</b><br><b>1</b>  | <b>Moderate</b><br><b>2</b> | <b>Severe</b><br><b>3</b> | <b>Very severe</b><br><b>4</b> |
|---|---------------------------|--------------------------|-----------------------------|---------------------------|--------------------------------|
| 1. discomfort in your abdomen   | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>    | <input type="checkbox"/>  | <input type="checkbox"/>       |
| 2. pain in your abdomen   | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>    | <input type="checkbox"/>  | <input type="checkbox"/>       |
| 3. bloating in your abdomen   | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>    | <input type="checkbox"/>  | <input type="checkbox"/>       |
| 4. stomach cramps   | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>    | <input type="checkbox"/>  | <input type="checkbox"/>       |
| 5. painful bowel movements  | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>    | <input type="checkbox"/>  | <input type="checkbox"/>       |
| 6. rectal burning during or after a bowel movement                      | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>    | <input type="checkbox"/>  | <input type="checkbox"/>       |
| 7. rectal bleeding or tearing during or after a bowel movement          | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>    | <input type="checkbox"/>  | <input type="checkbox"/>       |
| 8. incomplete bowel movement, like you didn't "finish"                  | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>    | <input type="checkbox"/>  | <input type="checkbox"/>       |

|  |                          |                          |                          |                          |                          |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 9. bowel movements that were too hard  | <input type="checkbox"/> |
| 10. bowel movements that were too small  | <input type="checkbox"/> |
| 11. straining or squeezing to try to pass bowel movements                        | <input type="checkbox"/> |
| 12. feeling like you had to pass a bowel movement but you couldn't (false alarm) | <input type="checkbox"/> |

## Appendix D – PAC-QOL

| PAC-QOL ©  |                               |                                   |                               |                               |                              |
|--|-------------------------------|-----------------------------------|-------------------------------|-------------------------------|------------------------------|
| PATIENT ASSESSMENT OF CONSTIPATION   |                               |                                   |                               |                               |                              |
| <p>The following questions are designed to measure the impact constipation has had on your daily life over <b>the past 2 weeks</b>. For each question, please check one box.</p> |                               |                                   |                               |                               |                              |
| <b>The following questions ask about your symptoms related to constipation. During the past 2 weeks, to what extent or <u>intensity</u> have you...</b>                          | <b>Not at all<br/>0</b>       | <b>A little bit<br/>1</b>         | <b>Moderately<br/>2</b>       | <b>Quite a bit<br/>3</b>      | <b>Extremely<br/>4</b>       |
| 1. felt bloated to the point of bursting?  | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
| 2. felt heavy because of your constipation?  | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
|  |                               |                                   |                               |                               |                              |
| <b>The next few questions ask about how constipation affects your <u>daily life</u>. During the past 2 weeks, how much of the time have you...</b>                               | <b>None of the time<br/>0</b> | <b>A little of the time<br/>1</b> | <b>Some of the time<br/>2</b> | <b>Most of the time<br/>3</b> | <b>All of the time<br/>4</b> |
| 3. felt any physical discomfort?   | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
| 4. felt the need to have a bowel movement but not been able to?  | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
| 5. been embarrassed to be with other people?   | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
| 6. been eating less and less because of not being able to have bowel movements?  | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |

| <b>The next few questions ask about how constipation affects your <u>daily life</u>. During the past 2 weeks, to what extent or intensity have you...</b> | Not at all<br>0          | A little bit<br>1         | Moderately<br>2          | Quite a bit<br>3         | Extremely<br>4           |
|---|--------------------------|---------------------------|--------------------------|--------------------------|--------------------------|
|   | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. had to be careful about what you eat?  | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. had a decreased appetite?  | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. been worried about not being able to choose what you eat (for example, at a friend's house)?   | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. been embarrassed about staying in the bathroom for so long when you were away from home?  | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 11. been embarrassed about having to go to the bathroom so often when you were away from home?  | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 12. been worried about having to change your daily routine (for example, traveling, being away from home)?  | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
|   |                          |                           |                          |                          |                          |
| <b>The next few questions ask about your <u>feelings</u> related to constipation. During the past 2 weeks, how much of the time have you...</b>           | None of the time<br>0    | A little of the time<br>1 | Some of the time<br>2    | Most of the time<br>3    | All of the time<br>4     |
|   | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 13. felt irritable because of your condition?   | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 14. been upset by your condition?   | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 15. felt obsessed by your condition?  | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 16. felt stressed by your condition?  | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 17. felt less self-confident because of your condition?   | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 18. felt in control of your situation?  | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

| <b>The next questions ask about your <u>feelings</u> related to constipation. During the past 2 weeks, to what extent or intensity have you...</b>                    | <b>Not at all<br/>0</b>       | <b>A little bit<br/>1</b>         | <b>Moderately<br/>2</b>       | <b>Quite a bit<br/>3</b>      | <b>Extremely<br/>4</b>       |
|---|-------------------------------|-----------------------------------|-------------------------------|-------------------------------|------------------------------|
| 19. been worried about not knowing when you are going to be able to have a bowel movement?  | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
| 20. been worried about not being able to have a bowel movement?   | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
| 21. been more and more bothered by not being able to have a bowel movement?   | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
|   |                               |                                   |                               |                               |                              |
| <b>The next questions ask about your <u>life with constipation</u>. During the past 2 weeks, how much of the time have you...</b>                                     | <b>None of the time<br/>0</b> | <b>A little of the time<br/>1</b> | <b>Some of the time<br/>2</b> | <b>Most of the time<br/>3</b> | <b>All of the time<br/>4</b> |
| 22. been worried that your condition will get worse?  | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
| 23. felt that your body was not working properly?   | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
| 24. had fewer bowel movements than you would like?  | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
|   |                               |                                   |                               |                               |                              |
| <b>The next questions ask about your <u>degree of satisfaction</u> related to constipation. During the past 2 weeks, to what extent or intensity have you been...</b> | <b>Not at all<br/>0</b>       | <b>A little bit<br/>1</b>         | <b>Moderately<br/>2</b>       | <b>Quite a bit<br/>3</b>      | <b>Extremely<br/>4</b>       |
| 25. satisfied with how often you have a bowel movement?   | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
| 26. satisfied with the regularity of your bowel movements?  | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |
| 27. satisfied with the time it takes for food to pass through the intestines?   | <input type="checkbox"/>      | <input type="checkbox"/>          | <input type="checkbox"/>      | <input type="checkbox"/>      | <input type="checkbox"/>     |

28. satisfied with your treatment?

|                          |                          |                          |                          |                          |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|

## Appendix E – NRS Pain Scale

Patients will be asked to grade their average and worst level of pain in the previous 24 hours due to the primary diagnosis at the end of each day.

“Using a scale of “zero” to “ten”, where zero equals no pain and ten equals the worst pain you can imagine, how would you rate the severity of pain, on average during the past 24 hours?

0 \_\_\_\_\_ 1 \_\_\_\_\_ 2 \_\_\_\_\_ 3 \_\_\_\_\_ 4 \_\_\_\_\_ 5 \_\_\_\_\_ 6 \_\_\_\_\_ 7 \_\_\_\_\_ 8 \_\_\_\_\_ 9 \_\_\_\_\_ 10  
*None* *Worst Possible Pain*

“Using a scale of “zero” to “ten”, where zero equals no pain and ten equals the worst pain you can imagine, how would you rate the severity of your pain at its worst during the past 24 hours?”

0 \_\_\_\_\_ 1 \_\_\_\_\_ 2 \_\_\_\_\_ 3 \_\_\_\_\_ 4 \_\_\_\_\_ 5 \_\_\_\_\_ 6 \_\_\_\_\_ 7 \_\_\_\_\_ 8 \_\_\_\_\_ 9 \_\_\_\_\_ 10  
*None* \_\_\_\_\_ *Worst Possible Pain* \_\_\_\_\_