



A Phase II, Randomized, Single Center, Pilot Feasibility Study to Evaluate Naloxegol
for Opioid-Induced Constipation in Cancer Patients

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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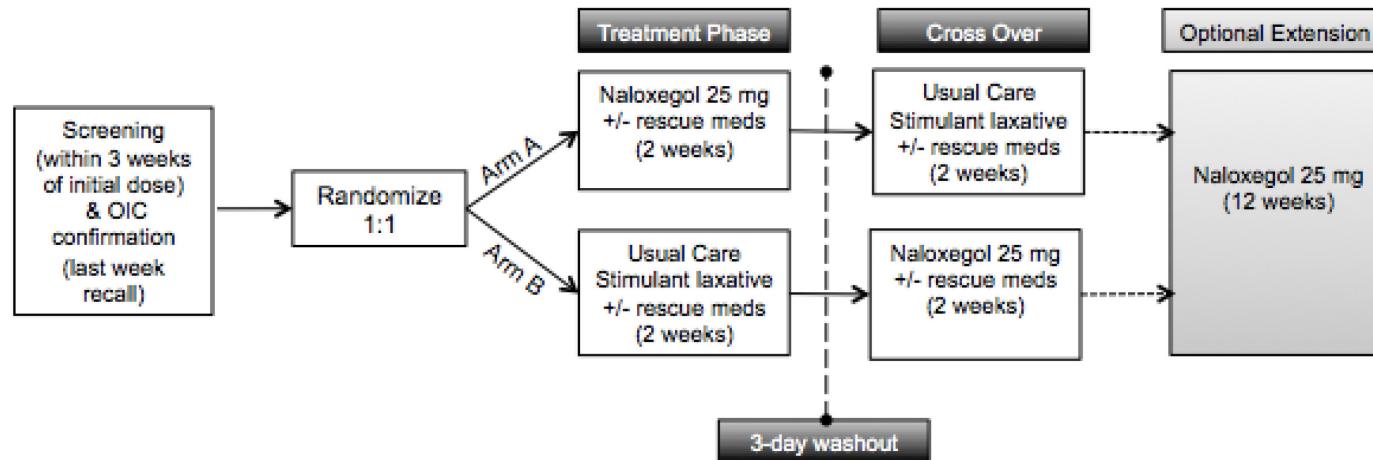
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LIST OF ABBREVIATIONS

AdEERS	Adverse Event Expedited Reporting System
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BPI-sf	Brief Pain Inventory-Short Form
BSS	Bristol Stool Scale
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDPE	High-Density Polyethylene Bottles
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protections Program
ICH	International Conference on Harmonization
IDS	Investigational Drug Services
IRB	Institutional Review Board
ISS	Investigator-Sponsored Study
MedDRA	Medical Dictionary for Medical Activities
NCI	National Cancer Institute
NOEL	No Adverse Effect Level
OIC	Opioid-induced Constipation
PAC-SYM	Patient Assessment of Constipation Symptoms
PAC-QOL	Patient Assessment of Constipation Quality of Life
P-gp	P-glycoprotein
PO.	Per os/by mouth/orally
PRN	Pro re nata/As needed
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
ULN	Upper Limit of Normal
UPR	Unanticipated Problems involving Risk to subjects or others

STUDY SCHEMA



STUDY SUMMARY

Title	A Phase II, Randomized, Single Center, Pilot Feasibility Study to Evaluate Naloxegol for Opioid-Induced Constipation in Cancer Patients
Short Title	Naloxegol in Cancer Opioid-Induced Constipation
Phase	II
Methodology	Single-center, randomized, open-label crossover study
Study Duration	The anticipated total duration of this study is 1 year.
Study Center(s)	University of California, San Diego Moores Cancer Center
Objectives	<p>The primary objective of this study is to evaluate the feasibility of naloxegol 25mg in the treatment of opioid-induced constipation (OIC) in comparison to usual care.</p> <p>We hypothesize that feasibility, defined as more than 70% of selected study subjects completing all study related procedures, will be achieved.</p> <p>Secondary Objectives include:</p> <ul style="list-style-type: none"> • To determine the effect of naloxegol versus usual care on OIC as defined by ≤ 3 bowel movements per week. • To evaluate naloxegol versus usual care on stool quality using the Bristol Stool Scale (BSS). • To evaluate the occurrence of adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. • To evaluate health related quality of life utilizing the Patient Assessment of Constipation Symptoms (PAC-SYM), Patient Assessment of Constipation Quality of Life (PAC-QOL). • To evaluate changes in patient-reported pain using the Brief Pain Inventory Short Form (BPI-sf). <p>Exploratory Objectives include:</p> <ul style="list-style-type: none"> • To evaluate laxative compliance with weekly pill counts. • To evaluate healthcare resource utilization as defined by the number of emergency room visits, hospitalizations, telephone encounters, and EPIC mychart encounters regarding signs/symptoms associated with constipation between the two arms. • To determine patient preference to continue naloxegol in the optional 12-week extension.
Number of Subjects	60
Diagnosis and Main Inclusion Criteria	<p>Patient with a histologically confirmed cancer diagnosis and documented, confirmed OIC defined as ≤ 3 bowel movements and/or Bristol Stool Scale (BSS) rated 1-2 in more than 25% of defecations ¹ over a 1-week OIC confirmation period at any time during screening and prior to initial treatment period Day 1.</p> <p>Key Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Male or female adults ≥ 18 years of age. 2. Eastern Cooperative Oncology Group (ECOG) ≤ 3. 3. Glomerular filtration rate (GFR) ≥ 30 ml/min/1.73m² by Modification of Diet in Renal Disease (MDRD) 4. Corrected serum calcium level ≤ 10.5 mg/dL. 5. Estimated life expectancy ≥ 6 months. 6. Negative pregnancy test prior to initiating study treatment for females of childbearing potential.

	<p>Key Exclusion Criteria</p> <ol style="list-style-type: none"> 1. Patients receiving the following medications within 3 days of Study Day 1 and/or are planned to receive throughout the duration of the study period: opioid antagonist, mixed antagonist, a strong CYP3A4 and/or P-glycoprotein (P-gp) inhibitor, a moderate CYP3A4 and/or P-gp inhibitor, and/or a strong CYP3A4 inducer. 2. Patient currently receiving or planned to receive concurrent total parenteral nutrition. 3. Concurrent use of metoclopramide or use within 24 hours prior to study treatment (given elimination $t_{1/2}$ 6 hours). 4. Patients at high risk for bowel perforation. 5. Constipation that was not primarily caused by opioids in the investigator's medical opinion. 6. A condition that may have affected the permeability of the blood-brain barrier (e.g., known brain metastases, meningeal metastases, brain injury, multiple sclerosis, recent brain injury, uncontrolled epilepsy) 7. Patient has clinically active diverticular disease. 8. Past medical history of irritable bowel syndrome, signs of active gastrointestinal (GI) bleeding, acute surgical abdomen, bowel stents, indwelling peritoneal catheter, mechanical GI obstruction, fecal impaction, or fecal ostomy. 9. Patient has motility/neurologic disorders including autonomic failure (spinal cord lesions, tumor invasion of nerves) and/or poorly controlled endocrine/metabolic disorders (hypercalcemia, hypokalemia, diabetes, hypothyroidism), as determined by the investigator. 10. Uncontrolled cancer pain despite analgesic therapy 11. Pregnant or lactating female; men planning to father a child or women planning a pregnancy while taking study drug or within 28 days after the last dose of study drug
Study Product(s), Dose, Route, Regimen	Naloxegol (MOVANTIK™) is a round, bi-convex, white film-coated tablet. Subjects will receive 25 mg of naloxegol once daily, as an oral tablet (PO). Subjects will take naloxegol one hour before eating in the morning.
Duration of administration	Subjects will receive naloxegol or usual care for a 2-week initial treatment period followed by 3-day washout period, then a 2-week crossover treatment period where subjects will receive naloxegol or usual care. Treatment assignment during the initial and crossover treatment periods will be dictated by the randomization arm. Subjects will also have the option to participate in a 12-week extension phase of naloxegol.
Reference therapy	Usual care in the palliative care clinic: stimulant laxative prophylaxis (up to 8 tablets/day of senna or up to 30mg/day of bisacodyl) and/or constipation treatment (osmotic laxative such as polyethylene glycol plus stimulant laxative).
Statistical Methodology	The primary aim of this study is feasibility - specifically, feasibility will be defined as completion of all study drugs over 4 weeks. For the primary aim we believe an acceptable completion rate would be at least 70%. Assuming a true completion rate of 85% (H_A), a sample size of 50 patients would have an 80% power to show that the true rate is at least 70% (H_0), using a one-sided binomial exact test with $\alpha=0.05$. Any dropout after the initiation of study treatment will be categorized as non-completion of study drugs. Thus we plan to recruit until 50 subjects have begun study treatment.

	<p>Safety endpoints will be evaluated by monitoring adverse events adverse events from clinical and laboratory reporting, using the NCI-CTCAE. Trends in the distribution and severity of adverse events across the study groups will be assessed by examining the count of total adverse events and count of adverse events at each severity level over the course of the 2 weeks for the initial treatment and over the 2 weeks of the crossover treatment phases of the study.</p> <p>Secondary outcome measures are the effect of naloxegol versus usual care on; bowel movements per week, stool quality using the BSS,² occurrence and grade of adverse events using the NCI CTCAE version 4.03,³ health related quality of life utilizing the PAC-SYM⁴ & PAC-QOL,⁵ and changes in patient reported pain using the Brief Pain Inventory.⁶ For variables in the secondary aim, we plan to use generalized linear mixed effects models (GLM) to determine the impact of naloxegol on each endpoint over the course of 2 weeks for the initial treatment and crossover treatment phases of the study, achieved by treating the crossover arm as a time-dependent covariate. Within the GLM model; count of bowel movements per week will be assessed using a Poisson model. Stool quality (BSS, 7 point Likert-type scale), PAC-SYM (5 point Likert-scale), and PAC-QoL (5 point Likert-scale) will be assessed using an ordinal logistic model. The two parts of the BPI-sf (Intensity of pain and inference of pain) are calculated as the mean of several questions; as such they will be assessed as a continuous outcome with possible transformation for skewness if necessary. To control for the multiple comparisons a Bonferroni-Holm (e.g. Stepwise Bonferroni) method will be applied to the combined secondary and exploratory analyses, using an omnibus $\alpha = 0.05$.</p> <p>Exploratory aims include laxative compliance (weekly pill counts), healthcare resource utilization (per electronic medical record evaluation of emergency room visits, hospitalizations, telephone encounters, and Mychart encounters), and patient preference (as evidenced by patient desire to continue naloxegol optional 12-week extension).</p> <p>For analysis of differences in weekly pill counts between naloxegol and usual care, we plan to use a generalized linear mixed effects model to determine the impact of naloxegol on weekly pill counts, over the course of 2 weeks for the initial treatment and crossover treatment phases of the study, achieved by treating the arms as a time-dependent covariate. Within this model the weekly pill counts will be assessed using a Poisson model. Count of healthcare utilization resource, will be the sum of total utilizations (summed separately for each of the two weeks for initial treatment and cross over phase). Differences in healthcare utilization between the arms will be determined by fitting a Poisson regression model (or negative binomial in the case of over dispersion) of treatment arm on bi-weekly utilization count. We will examine patient preference by calculating a 95% confidence interval for the proportion of patients who wish to continue the optional 12-week extension.</p>
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SCHEDULE OF EVENTS

	Screening (<21 days)	Initial Treatment Period (2 weeks)				Washout Period (3 days)	Crossover Treatment Period (2 weeks)				Optional Extension Period (up to 12 weeks)	End of Study Visit (28d ± 7d from last study treatment)	
		Day 1 (+/- 3)	Days 2-7 (+/- 3)	Day 8 (+/- 3)	Days 9-14 (+/- 3)		Day 18 (+/- 3)	Days 19-24 (+/- 3)	Day 25 (+/- 3)	Days 26-31 (+/- 3)	Days 32-116 (+/- 3)		
Informed consent	X												
Medical/surgical history, including OIC history	X												
Demographics	X												
Eligibility criteria	X												
Opioid-induced constipation confirmation ¹	X												
1:1 randomization ¹		X											
Physical exam	X	X					X			X ²		X ²	
Vital signs	X	X					X			X ²		X ²	
Height, weight	X	X					X			X ²		X ²	
Eastern Cooperative Oncology Group (ECOG) Performance status	X	X					X			X ²		X ²	
Concomitant medications ³	X	X	X	X	X	X	X	X	X	X			
Serious Adverse Events with AEs ⁹		X	X	X	X	X	X	X	X	X		X	
Pregnancy test (if applicable) ⁴	X												
Complete blood count (differential, platelets)	X	X					X			X ²		X ²	
Comprehensive metabolic panel	X	X					X			X ²		X ²	
Study drug dispensing		X					X			X ⁶			
Study drug							X			X ⁶		X	

	Screening (≤21 days)	Initial Treatment Period (2 weeks)				Washout Period (3 days)	Crossover Treatment Period (2 weeks)				Optional Extension Period (up to 12 weeks)		End of Study Visit (28d + 7d from last study treatment)
		Day 1 (+/- 3)	Days 2-7 (+/- 3)	Day 8 (+/- 3)	Days 9-14 (+/- 3)	Days 15- 17	Day 18 (+/- 3)	Days 19-24 (+/- 3)	Day 25 (+/- 3)	Days 26-31 (+/- 3)	Days 32-116 (+/- 3)	Weekly (Days 32, 39, 46...109) (+/- 3)	
accountability													
Patient study drug diary		X	X	X	X		X	X	X	X	X ⁶		
Pill count ⁷				X		X			X			X	X
Patient Assessment of Constipation Symptoms (PAC-SYM)	X ⁵	X		X			X		X			X ⁸	X
Patient Assessment of Constipation Quality of Life (PAC-QOL)	X ⁵	X					X					X ⁸	X
Brief Pain Inventory Short Form (BPI-sf)	X	X	X	X	X	X	X	X	X	X		X ⁸	X
Bristol Stool Scale (BSS)	X	X	X	X	X	X	X	X	X	X			
Patient medication use diary ³		X	X	X	X	X	X	X	X	X			
Patient bowel movement diary		X	X	X	X	X	X	X	X	X			

1. Randomization will occur within 3 days of initial treatment day. Prior to randomization, patients will be asked to confirm whether they have experienced OIC during the past week (See Section 5.1.4 for definition).
2. During the optional extension period, physical exam, ECOG performance status, vital signs, height and weight, and laboratory tests will be performed once at the beginning of the treatment period (Day 32). Thereafter, these procedures will be performed according to routine frequency for the participant's oncology care. If these procedures are performed as part of routine oncology care, results will be collected for the study. At the end of study visit, if these procedures are performed as part of participant's routine oncology care, results will be collected for the study
3. To include a record of opioid medication use, over-the-counter analgesic medication use, rescue laxative use, and all other over-the-counter prn medications.
4. Females of childbearing potential only; to be performed within 72 hours of initial treatment day.
5. To be completed up to 2 weeks prior to initial treatment day
6. Patients will be dispensed a 28-day supply of naloxegol at a time during the optional extension phase. During the extension phase, patients will be asked to return to clinic for a new supply of naloxegol, return of any unused naloxegol, review of the previous month's study drug diary, and pill count on Days 32, 60 and 88 of the extension period
7. The study coordinator will perform weekly reminder calls to the participant to review requirements for completing patient questionnaires and diaries and to perform pill counts if no in-person visit has occurred with the patient during a previous week.
8. To be completed every 28 days during the optional extension period at the time of study drug supply refill.
9. National Cancer Institute **Common Terminology Criteria for Adverse Events (CTCAE) v4.3** will be used to assess, monitor, and grade AEs.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Opioid-Induced Constipation

Despite being a very effective therapy in the treatment of cancer pain, opioids cause several undesired side effects. The most common of these side effects is opioid-induced constipation (OIC) in 40-90% of patients taking opioids.⁷ OIC results from the binding of opioid agonists to μ -opioid (pronounced “mu”) receptors located in the enteric nervous system, which leads to increased non-propulsive contracts and inhibition of water and electrolyte secretion. Opioids also delay gastric emptying, increase pyloric tone, delay transit throughout the small and large intestines, increase resting anal sphincter pressure, and decrease secretion of electrolytes and water into the intestinal lumen.⁸ OIC can cause intense abdominal pain, nausea, and vomiting and, if untreated, can result in emergency department evaluation and even hospitalization.⁹ Consequently, once a patient has experienced OIC, adherence to opioids decreases with subsequent influences on quality of life.

Constipation is defined as difficult defecation with reduced number of bowel movements experienced outside the normal elimination patterns of an individual. A proper constipation history includes more than simply asking when a patient’s last bowel movement occurred. The clinician needs to inquire regarding changes from the patient’s normal stool pattern and characteristics of the stool over time. Although opioids are a very common cause of constipation, a thorough history should include information regarding other potential causes of constipation including: altered diet (dehydration, decreased oral intake), decreased physical activity, medications (5-HT₃ receptor antagonists, calcium or aluminum-containing antacids, calcium channel blockers, anticholinergics, iron, and select chemotherapeutic agents), mechanical obstruction (intrinsic or extrinsic compression by masses), motility/neurologic disorders (autonomic failure, spinal cord lesions, tumor invasion of nerves), endocrine/metabolic disorders (hypercalcemia, hypokalemia, hypothyroidism).¹⁰

Opioid-Induced Constipation Treatment

Treatment of OIC includes both prophylaxis and therapeutic treatment. Since opioids have the unintended consequence of slowing bowel motility, prophylaxis should begin at the initiation of an opioid regimen. Constipation prophylaxis can be approached in a stepwise additive fashion with stimulant laxatives such as senna (1-8 tabs/day) and bisacodyl (maximum 30 mg/day) as the agents of choice. However, patients must titrate these stimulant laxatives based on diet, exercise, fluid intake, and concomitant medication use. Consequently, titrating stimulant laxatives can result in under or overtreatment and be quite burdensome to patients.

Ideally, OIC is prevented, but when it does occur in spite of prophylaxis, it can be effectively treated with the addition of other classes of laxatives (e.g. osmotics, softeners). However, the most specific drug class to specifically reverse OIC is the peripherally acting μ -opioid antagonists. For example, methylnaltrexone (Relistor[®]) is a subcutaneous injection and treatment of OIC in patients with advanced medical illness¹¹ and alvimopan (Entereg[®]) has restricted approval for shortening the course of postoperative ileus.¹² Naloxegol (Movantik[®]), the most recently approved oral, peripherally acting, pegylated derivative of the μ -opioid receptor antagonist naloxone, has been evaluated in non-cancer pain and shown to reduce constipation without reducing opioid-mediated analgesia.¹³ With 25mg of oral naloxegol versus placebo subjects experienced an approximate 15% improvement in response rate (defined as at least 3 spontaneous bowel movements per week and at least one spontaneous bowel movement per week increase over baseline for at least 9 out of the 12 treatment weeks and 3

out of the last 4 treatment weeks during the double-blind treatment period.¹³

Opioid-Induced Constipation Management by UCSD Palliative Care Team

Given the vast majority of the patients evaluated by the UCSD Moores Cancer Center Palliative Care service have cancer-related pain and are taking opioids, we systematically educate our patients about the role of stimulant laxatives (i.e. up to 8 tablets/day of senna or up to 30mg/day of bisacodyl) in the prophylaxis of OIC. For treatment of OIC in spite of stimulant laxative optimization, we generally recommend the addition of an osmotic laxative such as polyethylene glycol. Suppositories and enemas are usually avoided given many of our cancer patients are receiving chemotherapy. In general, the rectal route is avoided in cancer patients at risk for neutropenia given theoretical concerns of bacterial translocation.

In review of our outpatient cancer patients over a two-month period (February to March 2015), there were 218 outpatient palliative care encounters at the Moores Cancer Center. Of these encounters, 103 were unique patients with 68 new consults. All patients routinely completed a standardized Likert scale rating 11 symptoms, including constipation. Cancer types included breast, GI, genitourinary, gynecologic, hematologic, head and neck, neurologic, sarcoma, and thoracic cancers. The median patient reported constipation score was 4.2 (0-10) with a median follow up of 27 days. On average, patients reported a 17% decrease in constipation on a Likert scale by the first follow-up visit with usual care. By the second follow-up visit, there was a reduction in constipation of 30%. Overall, patients tolerate the scheduled stimulant laxatives with or without the osmotic laxative well. However, the major complaint of patients in the management of OIC is the need to constantly titrate their stimulant laxative based on diet, water intake, chemotherapy, opioid-use, and medication side effect (e.g. 5HT₃ antagonists).

1.2 Study Agent(s)

For a detailed description of pre-clinical findings regarding naloxegol, please refer to the Investigator Brochure. In brief, the mechanism of action of naloxegol has been characterized via *in vitro* binding assays. Naloxegol binds to μ -, δ - and κ -opioid receptors and was shown to be a full and competitive antagonist at human μ -opioid receptors, with no significant agonist efficacy. *In vitro* data indicate that naloxegol is a substrate for CYP3A4 and the P-gp transporter, and that CYP3A is the major CYP enzyme responsible for the metabolism of naloxegol. Naloxegol is also a substrate of the P-gp transporter, which plays a role in limiting central nervous system access of naloxegol. Safety pharmacology studies have examined potential effects on the central nervous, cardiovascular, GI, respiratory, and renal systems. According to the Investigator Brochure, no safety concerns for naloxegol were identified in such studies regarding central nervous, respiratory, or renal system functions. Effects on the GI system were evaluated by measuring effects on gastric emptying and small intestinal transport in conscious rats. Exposures at no adverse effect level (NOELs) were 15x and 112x the human exposure, respectively. Given the high exposures at which they occurred, these effects were considered not likely to be related to the primary pharmacology of the compound. Effects on the cardiovascular system were assessed using conscious dog telemetry. No drug related changes in cardiovascular parameters were observed at systemic exposure comparable to human exposures at the recommended human dose. Naloxegol poses no genotoxic risk to humans based on the genotoxicity studies and was not carcinogenic in the mouse.

Clinical effects of naloxegol have been studied in Phase I, Phase II and Phase III trials. In a Phase IIb study in patients with OIC, mean naloxegol C_{max} and AUC₀₋₂₄ were similar between Day 1 and Day 28, with 70.6 ng/mL vs. 81.1 ng/mL for C_{max}, and 328 vs. 335 ng·h/mL for AUC₀₋₂₄, respectively, following oral 25 mg once daily. The mean exposure values were comparable to

those observed in healthy volunteers. Mean T_{max} was less than 1.7 hours across dose groups and dosing days, indicating naloxegol was rapidly absorbed. Mean terminal half-life values were similar across dose levels (5 to 50 mg), ranging from 14.1 to 20.3 hours. The primary route of naloxegol elimination is via hepatic metabolism, with renal excretion playing a minimal role. Naloxegol is a sensitive substrate of CYP3A4 enzyme and a substrate of P-gp transporter, and CYP3A4 is the major CYP enzyme responsible for the metabolism of naloxegol. Concomitant use with dual P-gp or strong CYP3A4 inhibitors, or moderate CYP3A4 inhibitors, significantly increases naloxegol plasma concentrations (**Appendices B and C**). Conversely, concomitant use with a strong CYP3A4 inducer results in decreased plasma concentration.

Two multi-center, placebo-controlled 12-week, intent-to-treat, Phase III studies have been completed to evaluate naloxegol efficacy in the treatment of OIC. The primary endpoint in both studies was the proportion of patients who showed a pre-specified response, defined as at least 3 spontaneous bowel movements per week and at least a 1 spontaneous bowel movements per week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period. Symptom ratings for straining, stool consistency, and complete bowel movements were consistent with improvements in spontaneous bowel movement frequency and latency. In both studies, for the naloxegol 25 mg group compared with placebo, the primary and all key secondary endpoints achieved statistical significance with $p<0.025$ in each case. Compared to placebo, naloxegol 25 mg/day had a higher percentage of patients responding (40-44% vs. 29%), shorter median time to first post-dose spontaneous bowel movement (6-12 vs. 36-37), and greater improvement in OIC symptoms. In terms of safety data from these Phase III studies, the incidence of severe adverse events (SAEs) was similar across treatment groups. Pneumonia was the most frequently reported SAE overall, with no notable imbalance in frequency across treatment groups.

1.3 Other Agents

Usual Care

Usual care at the UCSD Moores Cancer Center palliative care clinic includes the use of stimulant laxative prophylaxis (up to 8 tablets/day of senna or up to 30mg/day of bisacodyl) and/or constipation treatment (primarily osmotic laxatives such as polyethylene glycol plus stimulant laxatives). Stimulant laxatives (senna or bisacodyl) are used daily regardless of bowel movement as prophylaxis of OIC. If OIC occurs despite optimal dosing of stimulant laxative, then a standard dose of polyethylene glycol (17 grams per day) is used for treatment of OIC until it resolves.

1.4 Rationale

OIC is a common symptom in patients with cancer-related pain and requires burdensome self-titration of laxatives for prophylaxis and treatment. Consequently, naloxegol may have an important role in this setting. Naloxegol has been evaluated in relieving OIC with cancer patients in a randomized, double blind, placebo-controlled trial over 4 weeks with a 12-week extension phase. However, accrual was challenging and the trial was closed early.¹⁴ Given the complexity of cancer and its treatment, a key first step is to determine if evaluating naloxegol versus standard of care is feasible in the management of OIC in this setting.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the feasibility of naloxegol 25mg in the treatment of OIC in comparison to usual care.

We hypothesize that feasibility, defined as more than 70% of selected study subjects completing all study related procedures, will be achieved.

2.2 Secondary Objectives

1. To determine the frequency of naloxegol versus usual care on OIC as defined by ≤ 3 bowel movements per week.
2. To evaluate naloxegol versus usual care on stool quality using the Bristol Stool Scale (BSS).²
3. To describe the adverse events associated with naloxegol when administered daily in this patient population and to compare the adverse events associated with Naloxegol with adverse events observed with usual care, using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.³
4. To evaluate health related quality of life utilizing the Patient Assessment of Constipation Symptoms (PAC-SYM)⁴ and Patient Assessment of Constipation Quality of Life (PAC-QOL).⁵
5. To evaluate changes in patient reported pain using the Brief Pain Inventory-Short Form (BPI-sf).⁶

2.3 Exploratory Objectives

1. To evaluate laxative compliance with weekly pill counts.
2. To evaluate healthcare resource utilization as defined by the number of emergency room visits, hospitalizations, telephone encounters, and EPIC mychart encounters regarding signs/symptoms associated with constipation between the two arms.
3. To determine patient preference to continue naloxegol in the optional 12-week extension.

2.4 Endpoints

The primary endpoint on this study is defined as completion of all study drug over the first 4 weeks of study treatment (initial and crossover treatment phases).

Secondary endpoints include number of bowel movements per week, as captured on the Patient bowel movement diary (**Appendix F**), stool quality as measured by the Bristol Stool Scale (**Appendix G**), safety defined as the rate of drug-related adverse events experienced assessed according to the NCI's CTCAE v4.03 toxicity criteria, and health related quality of life and pain measures as assessed by the PAC-SYM, PAC-QOL, and BPI-sf, within the first 4 weeks of study treatment (see **section 9.3.3**).

Exploratory endpoints will include drug administration compliance as measured by weekly pill counts by a member of the study team, healthcare resource utilization as defined by the number of number of emergency room visits, hospitalizations, telephone encounters, and EPIC mychart

encounters related to signs and symptoms of constipation, and patient preference (yes/no) for naloxegol to treat OIC as defined by choice of participation in the optional extension phase of the study.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

1. Patient has the ability to understand and the willingness to sign a written informed consent.
2. Histologically confirmed cancer diagnosis.
3. Documented, confirmed OIC defined ≤ 3 bowel movements and/or Bristol Stool Scale (BSS) 1-2 (**Appendix G**) more than 25% of defecations¹ per week over a 1-week OIC confirmation period at any time during screening and prior to initial treatment period Day 1.
4. Patient is ≥ 18 years of age.
5. Both men and women of all races and ethnic groups are eligible for this trial.
6. ECOG Performance Status ≤ 3 (see **Appendix A**).
7. Patient has adequate organ function as defined below:
 - The estimated glomerular filtration rate (GFR) greater than or equal to 30 ml/min/1.73m² by Modification of Diet in Renal Disease (MDRD) Study equation.
 - Corrected serum calcium ≤ 10.5 mg/dL
8. Females of child-bearing potential and men with partners of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 28 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
Female:
 - No child bearing potential, including:
 - Post-menopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months)
 - Surgically Sterile - undergone a hysterectomy or bilateral oophorectomy
 - With child bearing potential, must have
 - Negative pregnancy test within 72 hours prior to initiating study drug dosing
 - Agree to use barrier contraceptives throughout the study
- Male:
 - Surgically sterile
 - Non-sterile: Agree to use barrier contraceptives throughout the study during intercourse with a female partner
9. Patient has an estimated life expectancy ≥ 6 months in the opinion of the investigator.
10. Patient is able to swallow and retain oral medication.

3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Patient has received any of the following agents within 3 days prior to Study Day 1 and/or are planned to receive throughout the duration of the study: opioid antagonist and mixed agonist/antagonist (e.g. pentazocine, buprenorphine, nalbuphine, naloxone/naloxone combinations, naltrexone/naltrexone combinations, methylnaltrexone, alvimopan), a strong CYP3A4 and/or P-gp inhibitor, a moderate CYP3A4 and/or P-gp inhibitor, and/or a strong CYP3A4 inducer (see **Appendices B and C**).
2. Patient currently receiving or planned to receive concurrent total parenteral nutrition.
3. Patient currently receiving or planned to receive concurrent use of metoclopramide (or other GI prokinetic agents which can potentially slow the GI tract motilities) or use within 24 hours prior to study treatment (elimination $t_{1/2}$ 6 hours).
4. Patient is at high risk for bowel perforation.
5. Patient has constipation that was not primarily caused by opioids, as determined by the investigator.
6. Patient has a condition that may have affected the permeability of the blood-brain barrier (e.g., known brain metastases, meningeal metastases, brain injury, multiple sclerosis, recent brain injury, uncontrolled epilepsy).
7. Patient has clinically active diverticular disease.
8. Patient has a history of irritable bowel syndrome, signs of active GI bleeding, acute surgical abdomen, bowel stents, indwelling peritoneal catheter, mechanical GI obstruction, fecal impaction, or fecal ostomy.
9. Patient has motility/neurologic disorders including autonomic failure (spinal cord lesions, tumor invasion of nerves) and/or poorly controlled endocrine/metabolic disorders (hypercalcemia, hypokalemia, diabetes, hypothyroidism), as determined by the investigator.
10. Patient has uncontrolled cancer pain despite analgesic therapy.
11. Patient has a severe organ impairment or uncontrolled medical disorder that would, in the investigator's opinion, impair the ability to receive study treatment (i.e., uncontrolled diabetes, severe acute or chronic renal failure, severe pulmonary disease, severe hepatic impairment or active, uncontrolled infection, psychiatric illness/social situations that would limit compliance with study requirements).
12. Patient has any other condition that, in the opinion of the investigator, may impact the absorption of oral medications.
13. Patient is pregnant or nursing. There is a potential for congenital abnormalities and for this regimen to harm nursing infants.

4.0 TREATMENT PLAN

4.1 Study Design

This is a single center, randomized, open-label crossover study. We anticipate recruitment of approximately 60 total study participants at the UCSD Moores Cancer Center. Study participants will be recruited across all oncology disease teams. Potential participants will be identified in weekly palliative care or disease team patient triage meetings.

In order to meet eligibility for participation, a patient must be ≥ 18 years old, have histologically confirmed cancer, an ECOG performance status ≤ 3 , serum creatinine $\leq 1.5 \times$ institution's ULN, corrected serum calcium level ≤ 10.5 mg/dL, and life expectancy ≥ 6 months. Qualifying subjects must have documented, confirmed OIC which is defined as ≤ 3 bowel movements and/or Bristol Stool Scale (BSS) 1-2 more than 25% of defecations¹ during the preceding week.

Patients will be excluded if constipation is not primarily due to treatment with opioids or if they have signs or symptoms of a mechanical GI obstruction, fecal impaction, acute surgical abdomen, fecal ostomy, indwelling peritoneal catheter, bowel stents, signs of active GI bleeding, or are high risk for bowel perforation. Any patient with a past medical history of irritable bowel syndrome, motility/neurologic disorder, poorly controlled endocrine/metabolic disorder, any condition that may have affected the permeability of the blood-brain barrier, and/or uncontrolled cancer pain despite analgesic therapy will also be excluded from participation. Finally, in order to participate, patients cannot receive concurrent total parenteral nutrition and/or metoclopramide, and must discontinue use of the following medications within 3 days of Study Day 1: opioid antagonist, mixed antagonist, a strong CYP3A4 and/or P-gp inhibitor, a moderate CYP3A4 and/or P-gp inhibitor, and/or a strong CYP3A4 inducer (**Appendices B,C**).

The primary objective of this study is to evaluate the feasibility of naloxegol 25mg in the treatment of OIC in comparison to usual care, defined as completion of all study drug over 4 weeks, including initial and crossover treatment phases.

Secondary objectives will seek to determine the effect of naloxegol versus usual care on OIC, to evaluate naloxegol versus usual care on stool quality (BSS), to describe the adverse events associated with naloxegol when administered daily in this patient population (NCI CTCAE v4.03), to evaluate health related quality of life (PAC-SYM and PAC-QOL), and to evaluate changes in patient reported pain (BPI-sf).

Exploratory objectives will evaluate laxative compliance, healthcare resource utilization, and patient preference to continue naloxegol in the optional 12-week extension period.

Following informed consent, patients will have the following procedures completed to confirm eligibility: physical exam with vital signs, height, and weight, ECOG performance status, complete blood count, comprehensive metabolic panel, and a serum pregnancy test (women of child-bearing potential only). During this screening period, patients will also complete baseline PAC-SYM, PAC-QOL and BPI-sf questionnaires. To confirm OIC, patients will be asked about their frequency of bowel movements in the last week and asked to recall the average BSS that they have experienced. Upon confirmation of all eligibility criteria and within 72 hours of the initial dose of study treatment, patients will be randomized in a 1:1 ratio to either Arm A or Arm B by block randomization. Randomization will be performed by CTRI using a randomization package in the software R (blockrand)^{15,16}. The CTRI office will provide the study coordinator with prestuffed envelopes numbered 1-62. In the envelope, a paper will indicate the treatment assignment. One envelope will be assigned to each patient by the study coordinator in order of accrual. The number on the envelope will become the patient number and will be the identification number on all study documents. Individual patient randomization arm must be assigned prior to the patient being treated on study. The study coordinator will contact IDS once subject randomization arm has been confirmed.

REGIMENT DESCRIPTION				
Treatment Phase	Arm A	Arm B	Schedule	Cycle Length
Initial	Single 25 mg tablet Route: Orally, on an empty stomach 1 hour before breakfast or 2 hours after first meal of the day	Usual Care: stimulant laxative (i.e. up to 8 tablets/day of senna or up to 30mg/day of bisacodyl) ± osmotic laxative (e.g., polyethylene glycol)	Daily, Days 1-14	2 weeks (14 days)
Cross-Over	Usual Care: stimulant laxative ± osmotic laxative	Single 25 mg tablet Route: Orally, on an empty stomach 1 hour before breakfast or 2 hours after first meal of the day	Daily, Days 18-31	2 weeks (14 days)
Extension (Optional)	Single 25 mg tablet Route: Orally, on an empty stomach 1 hour before breakfast or 2 hours after first meal of the day	Single 25 mg tablet Route: Orally, on an empty stomach 1 hour before breakfast or 2 hours after first meal of the day	Daily, Days 32-116	12 weeks (84 days)

Wash out: Based on an elimination half-life of 10 hours, a 3-day washout period (50 hours or 5 half lives, approximately 48 hours) will occur before crossover.

Optional 12-week extension: Patients on Arms A and B will have the option to continue on naloxegol at 25 mg daily for an additional 12-week extension phase upon completion of initial and crossover treatment phases.

On Study Days 1, 18, 32, patients will undergo physical exam with vital signs and weight, ECOG performance status, complete blood count, comprehensive metabolic panel, and will receive a new treatment supply. Pill counts and study drug accountability will also be performed.

During initial and crossover treatment periods, patients will complete daily questionnaires and diaries, including the patient study drug diary, patient bowel movement diary, patient medication use diary, BSS, and BPI-sf. Concomitant medications and adverse event data will also be collected daily. All adverse events will be graded according to NCI CTCAE v4.03. Weekly assessments will include patient completion of the PAC-SYM questionnaire. Bi-weekly assessments include patient completion of the PAC-QOL questionnaire. Pill counts will be performed weekly throughout the duration of study, and may be performed via telephone call by a member of the study team if no in-person visit has occurred with the patient during a previous week.

During the optional extension phase, patients will be asked to return to clinic every 28 days for a new supply of naloxegol, return of any unused naloxegol, review of the previous month's study drug diary, pill count and completion of PAC-SYM, PAC-QOL, and BPI-sf. Concomitant medications and adverse event data will continue to be collected daily.

Within 28 days after the patient's final dose of treatment on study, patients will undergo an end-of-study visit during which a final pill count and study drug accountability will be performed. Final PAC-SYM, PAC-QOL, and BPI-sf questionnaires will also be completed. Adverse event information will be collected until 28 days following final dose of study treatment.

4.2 Treatment Administration

Patients in Arm A will receive a single daily dose of 25mg naloxegol for the 2-week initial treatment period, followed by a 3-day washout period and 2-week crossover treatment period in which the patient will receive the treating physician's usual care for OIC using a stimulant laxative ± rescue medication.

Patients in Arm B will receive the treating physician's usual care for OIC using a stimulant laxative ± rescue medication for the 2-week initial treatment period, followed by a 3-day washout period and 2-week crossover period in which the patient will receive a single daily dose of 25mg naloxegol.

Patients on Arms A and B will have the option to continue on naloxegol at 25 mg daily for an additional 12-week extension phase upon completion of initial and crossover treatment phases.

Patients will be instructed to take naloxegol on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal. Tablets must be swallowed whole, and not crushed or chewed by the subject. Subjects will also be instructed to avoid consumption of grapefruit or grapefruit juice as this is a potent inhibitor of the CYP3A4 enzyme.

Patients will also be instructed to complete a daily study drug diary during the treatment phases when naloxegol is being administered. Patients will be asked to bring their completed study drug diary with them during each visit for review with a member of the study team.

If the patient misses their daily morning dose of naloxegol and it has been less than 2 hours since the missed dose, they will be instructed to take naloxegol as soon as it is remembered on the same day. If it has been more than 2 hours since missing a dose, the patient will be instructed to skip the dose for that day not to make up that dose. If the patient vomits after taking a dose, he/she will be instructed not to repeat the dose or attempt to make up that dose.

If a patient takes more than the assigned daily dose of naloxegol, they should be monitored closely for evidence of opioid withdrawal symptoms and reversal of central analgesic effects. In cases of known or suspected overdose, symptomatic treatment as well as monitoring of vital functions should be performed. In cases of severe intoxication, intensive care procedures are recommended. Close medical supervision and monitoring should be continued until the patient recovers.

Any adverse events or serious adverse events resulting from known or suspected overdose will be reported according to instructions in **Section 7.6** of the protocol.

Treatment with naloxegol does not require that any pre-treatment parameters be met prior to dispensing and/or administration.

4.3 Pre-Medications

There are no required pre-medications on this study.

4.4 Permitted Concomitant Therapy

Throughout the study, investigators will be encouraged to maintain a patient's baseline pain control regimen, with dose adjustments made as clinically indicated throughout participation in the study. It is anticipated that the majority of participants will be receiving a long-acting opioid for control of background pain and an immediate-release opioid as needed ("prn") for breakthrough pain, although some may be receiving only a short-acting opioid on a scheduled basis. Changes in the opioid regimen may be made to ensure appropriate pain control. Any changes to the maintenance opioid dosing regimen will be recorded. Concomitant non-opioid analgesics will be permitted, but investigators will be encouraged to maintain such drugs at stable doses on-study as possible.

It is recognized that some patients may have their pain managed by physicians who are not co-investigators on this study. In these cases, patients will be asked to notify their UCSD treating investigator or study team member of any changes in a patient's pain control regimen.

Patients may take laxatives during the screening period of the study, but must discontinue use of laxatives at least 3 days prior to Study Day 1. In addition, patients may take an opioid antagonist, mixed antagonist, a strong CYP3A4 and/or P-gp inhibitor, a moderate CYP3A4 and/or P-gp inhibitor, and/or a strong CYP3A4 inducer during the screening period of the study, but must discontinue use of these agents at least 3 days prior to Study Day 1. During the initial and cross over treatment periods, if a bowel movement has not occurred within at least 72 hours, a patient may take bisacodyl as a laxative rescue medication in addition to the dosage of Naloxegol or stimulant laxative. If after a minimum of 72 hours, the patient has not experienced a BM, he/she may take bisacodyl rescue therapy (10-15 mg dose or 2-3 tablets at a time). If the patient remains constipated, bisacodyl rescue therapy may be repeated up to two additional times, as necessary, each 10-15 mg dose separated by 12 hour intervals. It is recommended that the bisacodyl tablets be taken either at bedtime or before breakfast. Of note, both the usual care arm and rescue therapy will use standard doses of bisacodyl (5-15 mg per day). If after 3 doses of rescue therapy, the patient still has not experienced a bowel movement, the investigator may prescribe a one-time use of an enema. The timing of administration of this therapy will be noted on the patient medication use diary. If these secondary interventions fail, the patient should be discontinued from the study and referred for additional medical evaluation. The investigator should recommend initiation of any therapy deemed most appropriate.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator, and will be recorded on the patient medication use diary as well as the concomitant medications case report form.

4.5 Prohibited Concomitant Therapy

Unless there is a need for urgent intervention, additional medication for pain control or treatment of constipation (other than their maintenance opioid regimen and approved opioid medication for breakthrough pain) will not be allowed without prior approval from the principal investigator. This includes over-the-counter treatments for constipation and pain.

Unless defined as part of the usual care treatment arm, prohibited laxatives will include the

following:

- Milk of magnesia
- Magnesium citrate
- Non-absorbable phosphate
- Cascara sagrada
- Castor oil/mineral oil
- Epsom salt
- Lactulose
- Docusate
- Enemas (see Section 4.4 for exception to use)
- Tegaserod
- Lubiprostone (Amitiza®)
- Drugs blocking fat absorption with an associated laxative effect
- Prucalopride
- Prune juice
- Herbal preparations for constipation
- Bulk laxatives, such as psyllium and methylcellulose
- Any agent that is used in an off-label fashion to treat constipation (eg, colchicine, misoprostol, erythromycin, cholinesterase inhibitors such as donepezil)
- Any experimental constipation therapy

Prohibited medications include metoclopramide given its 5HT₄ agonism at the stomach causing promotility.

Opioid antagonists and mixed agonists/antagonists are also prohibited during study participation, which includes the following:

- Pentazocine
- Buprenorphine
- Nalbuphine
- Naloxone and other naloxone containing products, such as oxycodone/naloxone combinations (Targin®)
- Naltrexone and other natrexone containing products such as morphine/naltrexone combinations (Embeda®)
- MethylNaltrexone (Relistor®)
- Alvimopan (Entereg®)

Naloxegol is a sensitive substrate of CYP3A4 enzyme and a substrate of P-gp transporter, and CYP3A4 is the major CYP enzyme responsible for the metabolism of naloxegol. Concomitant use with strong CYP3A4 and/or P-gp inhibitors, moderate CYP3A4 and/or P-gp inhibitors, and/or strong CYP3A4 inducers are prohibited during study participation. Please see **Appendices B and C** for a list of these medications.

Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) may be given to patients during study participation.

4.6 Adverse Drug Reactions, Dosing Delays/Dose Modifications

From initial treatment period to end of study visit, participants will be evaluated for possible toxicities that may have occurred during the previous treatment phase or drug dispensing cycle. Any patient who receives treatment on this protocol will be evaluable for toxicity. Severity of all adverse events will be evaluated according to the NCI CTCAE v4.03. Dose adjustments will be based on the naloxegol-related toxicity experienced during a treatment phase or newly encountered at the start of each treatment phase or drug dispensing cycle. Dose adjustments should be made according to the system showing the greatest degree of adverse event severity. If a patient experiences multiple adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment

that reduces or delays the dose to the greatest degree. The participant may continue on therapy if the toxicity can be managed according to the dose modification guidelines as outlined below.

A separate 12.5 mg tablet will be available for study participants who develop more severe GI adverse events. For study drug compliance the pharmacy will indicate the date, dosage and quantity of drug dispensed. The subject will also maintain a the patient study drug diary (see sections 5.1.13.1 and section 8.1.2) that will be reviewed along with study drug counts to ensure that all missed doses or dose changes have been documented.

Patients requiring a delay of ≥ 2 weeks in initiation of study participation or requiring more than 2 dose adjustments during the course of naloxegol therapy will require authorization from the principal investigator to continue study participation.

Table 1: Dose Modifications for Naloxegol-Related Nausea and/or Vomiting

Vomiting	Management for Naloxegol
\leq Grade 1	No action required.
Grade 2	Hold until \leq Grade 1. Resume at same dose level.
Grade 3	Hold until $<$ Grade 2. Resume at reduced dose (12.5mg tablet).
Grade 4	Off protocol therapy
Recommended management: Dopamine antagonist antiemetic	

Table 2: Dose Modifications for Naloxegol-Related Diarrhea

Diarrhea	Management for Naloxegol
\leq Grade 1	No action required.
Grade 2	Hold until \leq Grade 1. Resume at same dose level.
Grade 3	Hold until $<$ Grade 2. Resume at reduced dose (12.5mg tablet).
Grade 4	Off protocol therapy
Recommended management: Loperamide antidiarrheal therapy, 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Table 3: Dose Modifications for Naloxegol-Related Abdominal Pain

Abdominal Pain	Management for Naloxegol
\leq Grade 1	No action required.
Grade 2	Hold until \leq Grade 1. Resume at same dose level.
Grade 3	Hold until $<$ Grade 2. Resume at reduced dose (12.5mg tablet).
Grade 4	Off protocol therapy

Table 4: Dose Modifications for Other Naloxegol-Related Toxicity

Grade	Management for Naloxegol
\leq Grade 1	No action required.
Grade 2	Hold until \leq Grade 1. Resume at same dose level.
Grade 3	Hold until $<$ Grade 2. Resume at reduced dose (12.5mg tablet).
Grade 4	Off protocol therapy

Dose Modifications for Renal Impairment

If a participant's renal function becomes compromised during the course of treatment with naloxegol, defined as GFR < 60 mL/min/1.73m², the naloxegol dose will be reduced to 12.5 mg tablet once daily.

Rare cases of GI perforation associated with the use of other peripheral opioid antagonists in OIC have been reported to occur shortly after initiation with drug and appear to be more commonly reported in patients with multiple co-morbidities, particularly those that might impair the local or global structural integrity of the GI tract.

Any at-risk patient who reports progressive or persistent severe abdominal pain should be evaluated immediately by their physician or referred for urgent medical assessment, especially in the presence of other symptoms such as fever, malaise or mental status changes.

4.7 Duration of Study Treatment

In the absence of treatment delays due to adverse events, treatment may continue up to a total 16 weeks (treatment periods including optional extension) or until:

- Inter-current illness or worsening of a medical condition that prevents further administration of treatment
- Unacceptable adverse event(s)
- Rescue therapy for patient's constipation fails secondary interventions and/or the investigator believes that other treatment options may be more beneficial
- The investigator believes that study treatment is jeopardizing patient safety
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.8 Duration of Follow Up

Patients will be followed for occurrence of adverse events for 28 days after removal from treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be asked to return to clinic for an end of study visit within 28 days of the final dose of study treatment.

4.9 Discontinuation from Study Participation

Patients may be removed from study participation at any time or at the discretion of the investigator for any of the following reasons:

- The patient or legal representative withdraws consent to participate;
- The patient is lost to follow-up;
- The patient dies;
- The patient is non-compliant with study procedures;
- The investigator believes that study treatment is jeopardizing patient safety.

5.0 STUDY PROCEDURES

Refer to the study **Schedule of Events** for assessments to be performed.

All patients will be closely monitored for safety and tolerability throughout treatment and at the completion of study treatment.

5.1 Definitions of Study Assessments

5.1.1 Medical history

A complete medical, surgical and oncology history as well as history of OIC are obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

5.1.2 Demographics

Demographic profile will include date of birth, sex, race, and ethnicity.

5.1.3 Review subject eligibility criteria

Review of eligibility criteria as described in Section 3 to ensure subject qualification for study entry.

5.1.4 OIC confirmation

Prior to randomization, patients will be asked to report the number of bowel movements and rate their stool quality (using BSS) they have had in the past week. In order to meet study eligibility, the patient must report ≤ 3 bowel movements, or their estimated percentage of hard and lumpy stools (BSS of 1 or 2) $\geq 25\%$ during the preceding week. OIC may be confirmed at any time during screening and prior to initial treatment period Day 1.

5.1.5 Concomitant medications

All concomitant therapy, including anticancer therapy, anesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, opioid medication use, over-the-counter analgesic medication use, rescue laxative use, and all other over-the-counter “as needed” (prn), received by patients from 3 days prior to Study Day 1 until 28 days after the last study dose will be recorded in the patient’s medical record. If a reportable adverse event deemed related to study intervention (see Section 7) occurs within 28 days after last study dose and the patient has not started a new treatment, recording of concomitant medications related to the treatment of that adverse event should continue until resolution of the adverse event.

5.1.6 Physical exam

A complete physical examination should include the evaluation of general appearance; evaluation of head, eyes, ears, nose, and throat (HEENT); and cardiovascular, pulmonary, abdominal, musculoskeletal, skin, lymph nodes, neurological, and genitourinary systems. Subsequent exams may be targeted as appropriate.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if clinically significant.

5.1.7 Vital signs and height

Vital signs should include temperature, pulse, and blood pressure and weight. Height will only be collected at screening.

5.1.8 Performance status

Performance status is evaluated by the Eastern Cooperative Oncology Group (ECOG) performance scale.

5.1.9 Adverse event assessment

Baseline assessment of subject status for determining adverse events. Adverse events will be assessed using NCI CTCAE v4.03. See Section 7 for Adverse Event monitoring and reporting.

5.1.10 Hematology

Complete blood count to include hemoglobin, platelets, total white blood cell count and differential.

5.1.11 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, total protein, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.12 Pregnancy test (females of child bearing potential)

See section 3.1 for definition.

5.1.13 Patient-Reported Measures

All patient-reported measures will be completed via paper format, with materials provided to the patient by a study team member. A study member will provide initial training to the patient on how to complete study-required questionnaires and diaries. Patients are to complete the questionnaires and diaries in a quiet area, without assistance from family, friends or study team members. Patients must be able to read and comprehend the questionnaire in the language presented, and will be translated into foreign languages as needed for patient recruitment. Patients must complete the questionnaires prior to any interventions or discussions regarding their OIC with the investigator or study team members.

5.1.13.1 Patient Study Drug Diary

Patients will complete a daily study drug diary (**Appendix D**) during the period of time that they are receiving naloxegol: initial treatment phase for patients randomized to Arm A, crossover treatment phase for those randomized to Arm B; extension phase for all patients who choose to continue receiving naloxegol for an additional 12 weeks following the crossover phase. Participants will be asked to complete this diary even on days when a naloxegol dose was missed. The study drug diary will be reviewed with the patient during each visit to clinic, and a copy will be collected by a member of the study team. This diary will be used in combination with a pill count by the study team to support drug accountability.

5.1.13.2 Patient Medication Use Diary

Patients will complete a daily medication use diary as a record of all oral and self-administered medications received during the initial and crossover treatment periods (**Appendix E**). This includes any vitamins, homeopathic/herbal remedies, nutritional supplements, opioid medication use, over-the-counter analgesic medication use, rescue laxative use, and all other over-the-counter “as needed” (prn) medications. A copy of the medication use diary will be collected from the patient by a member of the study team during each visit to clinic and entries will be recorded on the concomitant medications case report form.

5.1.13.3 Patient Bowel Movement Diary

Patients will complete a daily bowel movement diary as a record of the number of daily bowel movements during the initial and crossover treatment periods (**Appendix F**). Participants will be asked to complete this diary even on days where no daily bowel movement has occurred. A copy of the bowel movement diary will be collected from the patient by a member of the study team during each visit to clinic.

5.1.13.4 Bristol Stool Scale (BSS)

Subjects will rate stool consistency through completion of the Bristol Stool Scale (BSS) after each bowel movement. The BSS was developed by Heaton at the University of Bristol and was first published in the Scandinavian Journal of Gastroenterology in 1997 (Lewis and Heaton 1997). It is a medical aid designed to classify feces into seven categories (**Appendix G**), as follows:

- 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

Subjects will be asked to document a BSS score at the time of OIC confirmation and daily during the initial and crossover treatment periods. This score takes approximately 1 minute to complete.

5.1.13.5 PAC-SYM Questionnaire

The PAC-SYM questionnaire¹² (**Appendix H**) will be used to assess patient quality of life. The PAC-SYM questionnaire 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 7 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. The translations into local languages have been performed according to a linguistic validation process. The PAC-SYM is validated for a **7-day recall**, therefore, participants will be asked to complete this questionnaire every 7 days during the initial and crossover treatment periods, every 28 days during the optional extension phase and at the end of study visit. This questionnaire takes approximately 5 minutes to complete.

5.1.13.6 PAC-QOL Questionnaire

The PAC-QOL questionnaire¹³ (**Appendix I**) will be used to assess patient quality of life. The PAC-QOL questionnaire is a 28-item self-report instrument designed to evaluate the burden of constipation on patient's 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). 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.¹³ This questionnaire takes approximately 5 minutes to complete. 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 is validated for a **2-week recall**, therefore, participants will be asked to complete this questionnaire every 14 days during the initial and crossover treatment periods, every 28 days during the optional extension phase and at the end of study visit. This questionnaire takes approximately 5 minutes to complete.

5.1.13.7 Brief Pain Inventory-Short Form (BPI-sf)

The Brief Pain Inventory (BPI) is one of the most widely used measurement tools for assessing clinical pain. The BPI allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. The BPI is available in two formats: the BPI-Short Form (BPI-sf), which is used for clinical trials, and the BPI-Long Form, which contains additional descriptive items that may be clinically useful. For the purposes of this study, we will use the BPI-sf, a 9 item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning (**Appendix J**). The patient is asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10 point scale. The BPI-sf is validated for **24-hour recall**. Participants will be asked to complete this questionnaire daily during the initial and crossover treatment periods, every 28 days during the optional extension phase, and at the end of study visit. This questionnaire takes approximately 5 minutes to complete.

5.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 21 days prior to initiation of study treatment unless otherwise stated. The screening procedures include:

- Written informed consent
- Review of inclusion and exclusion criteria
- Complete medical/surgical/OIC history

- OIC Confirmation (see Section 5.1.4)
- Demographics
- Documentation of concomitant medications
- Complete physical examination, including vital signs, weight and height
- ECOG performance status assessment
- Complete blood count with differential and platelets
- Comprehensive metabolic panel
- Serum or urine pregnancy test (*within 72 hours of Study Day 1*) for females of child-bearing potential (see inclusion/exclusion criteria)
- PAC-SYM
- PAC-QOL
- BPI-sf
- BSS

Following confirmation of all eligibility criteria, subjects will be randomized in a 1:1 ratio to either Arm A or Arm B. Randomization will occur within 3 days of the initial treatment phase.

5.3 Procedures During Initial Treatment and Crossover Treatment Phases

During the initial and crossover treatment phases of the study, physical exam, ECOG performance status, vitals, weight, and laboratory tests will be performed on the first day of each treatment period. Thereafter, these procedures will be performed according to routine frequency for the participant's oncology care. If these procedures are performed as part of routine oncology care, results will be collected for the study.

5.3.1 Day 1, Day 18

- Documentation of concomitant medications, adverse events and serious adverse events
- ECOG performance status assessment
- Physical exam, vital signs, and weight
- Complete blood count with differential and platelets
- Comprehensive metabolic panel
- Naloxegol dispensing (*Arm A, Day 1 only; Arm B, Day 18 only*)
- Naloxegol administration (*Arm A, Day 1; Arm B, Day 18*)
- Patient study drug diary (*Arm A, Day 1; Arm B, Day 18*)
- PAC-SYM
- PAC-QOL
- BPI-sf
- BSS
- Patient medication use diary
- Patient bowel movement diary

5.3.2 Days 2-7, Days 9-14, Days 19-24 and Days 26-31

- Documentation of concomitant medications, adverse events and serious adverse events
- Naloxegol administration (*Arm A, initial period only; Arm B crossover period only*)
- Patient study drug diary (*Arm A, initial period only; Arm B crossover period only*)
- BPI-sf
- BSS

- Patient medication use diary
- Patient bowel movement diary

5.3.3 Day 8, Day 25

- Documentation of concomitant medications, adverse events and serious adverse events
- Naloxegol administration (*Arm A, initial period only; Arm B crossover period only*)
- Naloxegol pill count (*Arm A, initial period only; Arm B crossover period only, via phone if in-person visit not conducted*)
- Patient study drug pill diary (*Arm A, initial period only; Arm B crossover period only*)
- PAC-SYM
- BPI-sf
- BSS
- Patient medication use diary
- Patient bowel movement diary

5.4 Procedures During Optional Extension Phase (up to 12-weeks)

Physical exam, ECOG performance status, vitals, weight, and laboratory tests will be performed at the start of the optional extension phase, on Day 32. Thereafter, these procedures will be performed according to routine frequency for the participant's oncology care. If these procedures are performed as part of routine oncology care, results will be collected for the study.

5.4.1 Days 32-116 (Daily)

- Documentation of concomitant medications, adverse events and serious adverse events
- ECOG performance status assessment (*Day 32 only*)
- Physical exam, vital signs, weight (*Day 32 only*)
- Complete blood count with differential and platelets (*Day 32 only*)
- Comprehensive metabolic panel (*Day 32 only*)
- Naloxegol dispensing (*Day 32 only*)
- Naloxegol administration
- Patient study drug diary

5.4.2 Days 32, 39, 46, 53, 60, 67, 74, 81, 88, 95, 102, 109 (Weekly)

In addition to daily assessments listed in Section 5.5.1, the following will be performed:

- Naloxegol pill count (*via phone if in-person visit not conducted*)
- PAC-SYM (*Days 32, 60, 88 only*)
- PAC-QOL (*Days 32, 60, 88 only*)
- BPI-sf (*Days 32, 60, 88 only*)

5.5 End of Study Visit

The End of Study Visit will occur within 28 days of final day of study treatment. This visit will be scheduled at the time of a routine oncology visit. If physical exam, ECOG performance status, vitals, weight, and laboratory tests are performed at the End of Study timepoint as part of routine oncology care, results will be collected for the study.

- Documentation of adverse events and serious adverse events
- Naloxegol pill count and final study drug accountability
- PAC-SYM
- PAC-QOL
- BPI-sf
- Return of unused study materials, including study medication, patient questionnaires and diaries

5.6 Follow-up Procedures

Patients will be followed for occurrence of adverse events for 28 days after the final study treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. There are no additional follow-up requirements beyond the end of study visit, as detailed in Section 5.5

6.0 Measurement of Effect

6.1 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.03 (<http://ctep.cancer.gov/reporting/ctc.html>) for reporting of adverse events. Safety will be assessed within the first 4 weeks of study treatment.

6.2 Feasibility Assessment

The primary endpoint on this study is defined as completion of all required study drugs over the first 4 weeks of study treatment (initial and cross-over treatment phases).

6.3 Efficacy Assessment

The efficacy of treatment with naloxegol versus treatment with usual care will be evaluated by the number of bowel movements per week, as captured on the Patient Bowel Movement Diary, and the stool quality as defined by the Bristol Stool Scale. These measures will be assessed within the first 4 weeks of study treatment.

6.4 Quality of Life

Quality of Life will be assessed by the following instruments: PAC-SYM, PAC-QOL, and BPI-sf. These instruments are described further in Sections 5.1.13.5-5.1.13.7. Quality of life will be assessed within the first 4 weeks of study treatment.

7.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Progression of the cancer under study or events which are unequivocally due to disease progression should not be reported as an AE during the study (unless it is considered to be drug related by the investigator).

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during a trial. Additionally, certain AEs must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

AE monitoring begins at the time of informed consent signature and ends 28 days following the last administration of study treatment.

All patients experiencing an AE, regardless of its relationship to study drug will be monitored until:

- the event resolves or the symptoms or signs that constitute the event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Severity

All AEs will be graded according to the NCI CTCAE v4.03. The NCI CTCAE v4.03 is available at <http://ctep.cancer.gov/reporting/ctc.html>

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

7.3 Seriousness

A “serious” adverse event (SAE) is defined in regulatory terminology as any untoward medical occurrence that:

1. Results in death.
If death results from (progression of) the disease, the disease should be reported as the event itself.
2. Is life-threatening.
The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires in-patient hospitalization or prolongation of existing hospitalization.
Note: Hospitalization (including hospitalization for an elective procedure) for a pre-existing condition which has not worsened does not constitute a serious adverse event.
4. Results in persistent or significant disability or incapacity.
5. Is a congenital anomaly/birth defect
6. Is an important medical event
Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

Given that the Investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the Investigator believes that the event is serious, the event will be considered serious.

7.4 Relationship

The relationship to the IP of each AE/SAE will be evaluated by the investigator using the following levels:

- **Not related:** The temporal relationship of the clinical event to the administration of IP makes a causal relationship unlikely; and other drugs, therapeutic intervention or underlying conditions provide a sufficient explanation for the observed event.
- **Related:** The temporal relationship of the clinical event to the administration of the IP makes a causal relationship possible; and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the observed event. A clear-cut temporal association with improvement on cessation of the study drug or recurrence upon rechallenge may also be observed.

7.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An AE is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol, the Investigator Brochure, or the current Product Label.

7.6 Reporting Requirements for Adverse Events

7.6.1 Safety Reporting

A. **Principal Investigator** must be notified within 24 hours of learning of any SAE, regardless of attribution, occurring during the study or within 28 days of the last administration of the study drug.

B. The **UCSD Human Research Protections Program (HRPP) and Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior Institutional Review Board (IRB) review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

C. This study sponsor is exempted from the IND Safety Reporting by the FDA.

AstraZeneca is responsible for NDA expedited safety reporting to FDA in accordance with local regulatory requirements. Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying AstraZeneca of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to AstraZeneca within 24 hours of learning of the new information.

AstraZeneca should be notified within one (1) calendar day of initial receipt from the site for all fatal and life-threatening cases and within five (5) calendar days of initial receipt from the site for all other SAEs.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-15-11108)

The Principal Investigator 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 AstraZeneca by email to AE Mailbox Clinical Trial (TCS) <AEMailboxClinicalTrialTCS@astrazeneca.com> or by fax to 1-302-886-4114 (US Fax number). Email is the preferred method.

7.6.2 Routine Reporting Requirements

- A. The **UCSD HRPP** must be notified of any AEs that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.
- B. SAEs that do not require expedited reporting will be reported to AstraZeneca at least every month preferably using the MedDRA coding language for SAEs.

All SAEs must be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The Principal Investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

7.6.3 Pregnancy Reporting Requirements

If a patient becomes pregnant during the course of the study, naloxegol should be discontinued immediately. The **Principal Investigator** must be notified within 24 hours of any pregnancies occurring in a female patient or a female partner of a male patient. The Principal Investigator or designated site personnel will then inform AstraZeneca representatives no later than the end of the next business day of when he or she becomes aware of it.

Pregnancy itself is not regarded as an AE unless there is a suspicion that naloxegol 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 considered AEs unless they were therapeutic abortions. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented. The outcomes of any conception occurring from the date of the first dose until 12 weeks after the date of last dose will be followed up and documented. The Investigator should follow-up with the study patient or the female partner of the study patient, even if the patient was discontinued from the study.

7.6.4 Adverse Event Data Collection

The following data will be collected on an Adverse Event case report form for each adverse event experienced during the 30-day adverse event monitoring period:

- Event term
- Narrative description of event
- Start and stop date/time of event
- CTCAE grade
- Seriousness (yes/no) – *if yes, see further below*
- Relationship to protocol therapy
- Action taken with regard to protocol therapy (including therapy start and stop dates)
- Did AE cause subject's withdrawal from study (yes/no)?
- Outcome of treatment-related variable

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

- Date AE met criteria for SAE
- Date Investigator became aware of serious AE

- Criteria met for “seriousness” (see Section 7.3)
- If hospitalization or prolongation of hospitalization:
 - Date of hospitalization (if applicable)
 - Date of discharge (if applicable)
- If death:
 - Date of death (if applicable)
 - Cause of death (if applicable)
 - Autopsy performed (yes/no) (if applicable)
- Description of SAE(s)

8.0 AGENT INFORMATION

8.1 Naloxegol

Please refer to Investigator’s Brochure for more comprehensive information. IDS will be responsible for all naloxegol storage, preparation, accountability, and dispensing throughout the trial.

Other names for the drug: MOVANTIK™

Mechanism of action (or Product description): Naloxegol is an antagonist of opioid binding at the mu-opioid receptor. At recommended dose levels, naloxegol functions as a PAMORA (Peripherally Acting Mu-Opioid Receptor Antagonist) in tissues such as the bowel, thereby decreasing the constipating effects of opioids. Naloxegol is a PEGylated derivative of naloxone, and a substrate for the P-gp. The presence of the PEG moiety in naloxegol reduces its passive permeability as compared with naloxone. Due to the reduced permeability and increased efflux of naloxegol across the blood-brain barrier, related to P-gp substrate properties, the central nervous system penetration of naloxegol is negligible at recommended dose levels, limiting the potential for interference with centrally mediated opioid analgesia.

Availability: provided by AstraZeneca, free of charge

How supplied: Study drug tablets are supplied as mauve, oval, biconvex, film coated, and intagliated with “nGL” on one side and “25” on the other.

Tablets will be supplied in 25-mg dose form, in high-density polyethylene (HDPE) bottles. IDS will dispense a 14-day supply of naloxegol at the initiation of the initial treatment phase for those patients randomized to Arm A. For patients randomized to Arm B, IDS will dispense a 14-day supply of naloxegol at the initiation of the crossover treatment phase. Patients who choose to participate in the optional extension portion of the study will receive a 28-day supply every 4 weeks during the extension phase.

Naloxegol will be packaged and labeled by AstraZeneca. It will be clearly marked according to national requirements regarding use for clinical trial investigation only and will be labeled with drug name, study reference number, and storage conditions.

Storage and stability: Naloxegol will be stored and locked in a secure location within IDS, with access restricted to pharmacy personnel only. All study drug will be stored in original containers until dispensed to study subjects. Naloxegol must be stored at room temperature between 20-25C (68-77F). Excursions are permitted to 15-30C (59-86F). Storage temperature will be

monitored

Preparation: Given its oral formulation, there is no product preparation required. IDS will prepare 14-day and 28-day supplies of naloxegol for dispensing to subjects according to randomization assignment and phase of study participation.

Route of administration for this study: Naloxegol will be administered as a single 25-mg tablet, once daily. Subjects will be instructed to take naloxegol on an empty stomach 1 hour before breakfast or 2 hours after their first meal of the day.

Side effects: The most common side effects associated with naloxegol are gastrointestinal in nature: abdominal pain, diarrhea, nausea, flatulence, vomiting, headache, and excessive sweating. Patients taking naloxegol may also experience additional symptoms of opioid withdrawal, including chills, anxiety, irritability, and yawning. There is also risk of developing abdominal or intestinal wall perforation.

8.1.1 Return and Retention of Study Drug

Remaining drug is to be destroyed on-site, according to UCSD Moores Cancer Center IDS drug destruction policy.

8.1.2 Drug Accountability/Subject Compliance

Records of study medications used, dosages administered, and intervals between visits will be kept during the study. Subjects will be asked to fill out a daily study drug diary while taking naloxegol and bring with them, along with any unused study drug, when they return to clinic every 14 days during the initial and crossover treatment phases, and at each in-person visit during the optional extension phase. A review of the subject-completed study drug diary and pill count will be performed by a member of the study team at each of these visits. In addition, a study team member will contact the patient weekly via telephone to perform pill counts if no in-person visit has occurred with the patient during a previous week.

Final drug accountability will be noted at the completion of the trial. Patients will be asked to return all unused medication at the end of the study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

The proposed study is a prospective, single-center, feasibility trial. Ideally, a phase III placebo controlled trial would be completed to demonstrate the efficacy of naloxegol in cancer patients with OIC. However, placebo controlled trials are inherently difficult to accrue to in supportive oncology. Plus, the prior attempt at a phase III placebo controlled trial failed to accrue patients, and was closed early. We believe that a more feasible trial design would be a randomized phase II crossover study. The crossover design has multiple advantages including the potential for increased statistical efficiency requiring smaller sample sizes. Additionally, the crossover study design should appeal to patients more so than a classic placebo-controlled study because all patients will receive the experimental drug that has the potential to offer benefit. Additionally, patients will serve as their own controls, thus minimizing potential confounding factors. A brief washout period before crossover of 3 days based on the elimination half-life of 10 hours (5 half lives, ~50 hours) is also clinically appropriate and is not expected to impact cancer patient symptom management. Prior to embarking on a large phase III placebo controlled crossover study we propose to conduct a smaller simpler phase II crossover study to confirm feasibility of

the crossover strategy.

9.2 Sample Size and Accrual

The primary aim of this study is feasibility – specifically feasibility will be defined as completion of all study drugs over 4 weeks. For the primary aim we believe an acceptable completion rate would be at least 70%. Assuming a true completion rate of 85% (H_A), a sample size of 50 patients would have an 80% power to show that the true rate is at least 70% (H_0), using a one-sided exact test with $\alpha=0.05$. Any dropout or loss to follow up after the initiation of study treatment will be categorized as a non-completer and remain in the analytic sample. Thus we plan to recruit until 50 subjects have commenced study treatment.

The Palliative Care Service sees approximately 1,200 new inpatient consults and approximately 250 new outpatient cancer consults per year, and is integrated into the cancer care delivery model. OIC is a common symptom in patients with cancer-related pain and requires burdensome self-titration of laxatives for prophylaxis and treatment. Potential study participants will be recruited primarily from the outpatient clinic at Moores Cancer Center, where an estimated 70% of our patient population is currently being treated for OIC. We anticipate that enrollment will be completed in approximately 12 months, therefore, the expected accrual rate is approximately 5 patients per month.

Ethnic Category	Accrual Targets		
	Sex		
	Females	Males	Total
Hispanic or Latino	4	3	7
Not Hispanic or Latino	25	28	53
Ethnic Category: Total of all subjects	29	31	60
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	3	2	5
Black or African American	4	2	6
Native Hawaiian or other Pacific Islander	1	1	2
White	20	25	45
Racial Category: Total of all subjects	29	31	60

9.2.1 Evaluable Subjects and Subject Replacement

Analyses of secondary endpoints will be performed using data from patients that have both baseline and follow-up information.

We will characterize patients that drop out early by comparing baseline demographic data of the early dropouts to the patients who complete treatment. This will allow us to identify patients at risk of not completing treatment, which will provide critical information when defining eligibility criteria for future trials in this study population.

9.3 Data Analyses Plans

All analyses will be conducted using the latest version of R.

9.3.1 Primary Endpoint

The primary aim of this study is feasibility – specifically feasibility will be defined as completion

of all study procedures over the first 4 weeks of study treatment. For the primary aim we believe an acceptable completion rate would be $\geq 70\%$. We will assess this using a one-sided binomial exact test, where a p-value ≤ 0.05 will be considered statistically significant.

9.3.2 Safety Endpoint

Safety endpoints will be evaluated by monitoring AEs from clinical and laboratory reporting. Adverse events will be classified according to the NCI-CTCAE version 4.03. Trends in the distribution and severity of the AEs across the study groups will be assessed by examining the count of total AEs and count of AEs at each severity level over the course of the 2 weeks for the initial treatment and over the 2 weeks of the crossover treatment phases of the study.

9.3.3 Secondary Endpoints

Secondary outcome measures are the effect of naloxegol versus usual care on; bowel movements per week, stool quality using the BSS,² occurrence and grade of AEs using the NCI CTCAE version 4.03,³ health related quality of life utilizing the PAC-SYM⁴ & PAC-QoL,⁵ and changes in patient reported pain using the BPI-sf.⁶

For variables in the secondary aim, we plan to use generalized linear mixed effects models to determine the impact of naloxegol on each endpoint over the course of 2 weeks for the initial treatment and crossover treatment phases of the study, achieved by including treatment group as a categorical covariate, and including a categorical time effect to account for a potential period effect. Counts of bowel movements per week will be assessed using a Poisson model. Stool quality (BSS, 7 point Likert-type scale), PAC-SYM (5 point Likert-scale), and PAC-QOL (5 point Likert-scale) will be assessed using an ordinal logistic model. The two parts of the BPI-sf (Intensity of pain and inference of pain) are calculated as the mean of several questions; as such they will be assessed as a continuous outcome with possible transformation for skewness if necessary.

To control for the multiple comparisons, a Bonferroni-Holm (e.g. Stepwise Bonferroni) method will be applied to the combined secondary and exploratory analyses, using an omnibus $\alpha = 0.05$.

9.3.4 Exploratory Endpoints

Exploratory aims include laxative compliance (weekly pill counts), healthcare resource utilization (per electronic medical record evaluation of emergency room visits, hospitalizations, telephone encounters, and Mychart encounters), and patient preference (as evidenced by patient desire to continue naloxegol optional 12-week extension).

For analysis of differences in weekly pill counts between naloxegol and usual care, we plan to use a Poisson generalized linear mixed effects model to determine the impact of naloxegol on weekly pill counts, over the course of 2 weeks for the initial treatment and cross over phases of the study.

Count of healthcare utilization resource- will be the sum of total utilizations (summed separately for each of the two weeks for initial treatment and cross over phase). Differences in healthcare utilization between the arms will be determined by fitting a Poisson regression model (or negative binomial in the case of over dispersion) of treatment arm on bi-weekly utilization count. We will examine patient preference by calculating a 95% confidence interval for the proportion

of patients who wish to continue the optional 12-week extension.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

10.2 IRB Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 Registration and Randomization Procedures

All patients must be registered with the UCSD Moores Cancer Center Clinical Trials Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed and an eligibility checklist completed. Once eligibility is confirmed, patient will be given a unique sequential study number.

Patients will be randomized in a 1:1 ratio to either Arm A or Arm B by block randomization within 3 days of the initial study treatment day. Randomization will be performed by CTRI using a randomization package in the software R (blockrand)^{15,16}. The CTRI office will provide the study coordinator with prestuffed envelopes numbered 1-62. In the envelope, a paper will indicate the treatment assignment. One envelope will be assigned to each patient by the study coordinator in order of accrual. The number on the envelope will become the patient number and will be the identification number on all study documents. Individual patient randomization arm must be assigned prior to the patient being treated on study. The study coordinator will contact IDS once subject randomization arm has been confirmed.

10.4 Data Collection and Management

Records and data to be obtained from the study subjects are detailed above in the **Schedule of Events**. Subject outcome information will be documented in the electronic medical record and subject's research record. Data for this study will be entered into a password-protected set of electronic case report forms via the Velos eResearch web-based system. Velos eResearch is an integrated software system for managing clinical trials. This system supports several clinical trial functions, including electronic case report forms, tracking and scheduling of subject visits and events, and study reporting. The software links to the UCSD Health System's EPIC Electronic Medical Record System to provide improved information and integration for clinical research projects. A robust support team assists investigators in implementing protocols and calendars and building electronic case report forms. Velos provides automated data export procedures for designated users into Excel, and then transferred into R. Access to the Velos database for this study will be limited to those users required to perform study-specific functions such as data entry and monitoring. A designated study coordinator from the UCSD Moores Cancer Center Clinical Trials Office will be responsible for entering all study data.

10.5 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or IRB access to subject's medical information relevant to the study.

10.6 Data and Safety Monitoring/Auditing

In addition to AE monitoring and clinical oversight by the principal investigator and co-investigators, quality assurance of the study will be performed by a UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be dependent upon the rate of enrollment, and are anticipated to occur approximately every 3-6 months.

This study will also use the UCSD Moores Cancer Center DSMB to provide oversight in the event that this treatment approach leads to unforeseen toxicities. The DSMB will operate according to the DSMB charter. Data from this study will be reported every 6 months and will include:

- 1) the protocol title, IRB protocol number, and the activation date of the study
- 2) the number of patients enrolled to date
- 3) the dates of patient enrollment
- 4) a summary of all adverse events regardless of grade and attribution
- 5) endpoint evaluation for evaluable patients when available
- 6) a summary of any recent literature that may affect the ethics of the study

It will be left to the Investigator's clinical judgment whether or not an AE is related and of sufficient severity to require the subject's removal from treatment. Subsequent review of serious, unexpected and related AEs by the principal investigator, DSMB, UCSD HRPP, and/or AstraZeneca may also result in suspension of further trial interventions/ administration of study drug at a site. The principal investigator or AstraZeneca retains the authority to suspend additional enrollment for the entire study as applicable.

10.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators will conduct their research according to the plans reviewed and approved by the IRB.

10.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate apparent immediate hazards/risks to trial subjects without prior IRB approval. Any such emergency modification implemented must be noted and reported to the IRB along the lines of a protocol deviation or violation, depending on the nature of the modification.

10.7.2 Protocol Violations

Any unplanned variance from an IRB approved protocol is considered a violation and must be reported to the IRB in a timely fashion.

A. Major violations must be reported to the IRB within 10 working days of awareness of the violation.

Major violations include:

- Instances that have harmed or increased the risk of harm to one or more research participants.
- Instances that have damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

B. Minor violations may be reported to the IRB at the time of the continuing review. Minor violations have no substantive effect on the risks to participants or on the scientific integrity of the research plan or the value of the data collected.

10.8 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the UCSD IRB for approval prior to implementation.

10.9 Record Retention

Study documentation includes all case report forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all

reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.10 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11.0 REFERENCES

1. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology* 2016;150:1393-407. e5.
2. Lewis S, Heaton K. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997;32:920-4.
3. National Cancer Institute. Common terminology criteria for adverse events (ctcae) version 4.03.
<http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CB4QFjAA&url=http%3A%2Fwww.hrcgovtnz%2Fsites%2Fdefault%2Ffiles%2FCTCAE%2520manual%2520-%2520DMCCpdf&ei=2ptfVa-tKpGuogTbo4HoCq&usq=AFQjCNG4OnSycmuS6wqwm2C0zVI8pT4qyA&sig2=K7D0s5d5nOMk0CEi6X0rEw&bvm=bv93990622,dcGU;Accessed May 22, 2015>
4. Frank L, Kleinman L, Farup C, Taylor L, Miner P. Psychometric validation of a constipation symptom assessment questionnaire. *Scand J Gastroenterol* 1999;34:870-7.
5. Cook S, Bell T, Sweeney C, Fehnel S, Hollis K. (883): Impact on quality of life of constipation-associated gi symptoms related to opioid treatment in chronic pain patients: Pac-qol results from the opioid survey. *The Journal of Pain* 2007;8:S71.
6. Cleeland C, Ryan K. Pain assessment: Global use of the brief pain inventory. *Ann Acad Med Singapore* 1994;23:129-38.
7. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: Results of a us and european patient survey (probe 1). *Pain Med* 2009;10:35-42.
8. Lembo A, Camilleri M. Chronic constipation. *N Engl J Med* 2003;349:1360-8.
9. Bell T, Annunziata K, Leslie J. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: Findings from the national health and wellness survey. *Journal of opioid management* 2008;5:137-44.
10. Roeland E, Buckholz G. Gi palliative care issues. *Palliative care*: Springer; 2010:43-9.
11. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008;358:2332-43.
12. Wolff BG, Michelassi F, Gerkin TM, et al. Alvimopan, a novel, peripherally acting μ opioid antagonist: Results of a multicenter, randomized, double-blind, placebo-controlled, phase iii trial of major abdominal surgery and postoperative ileus. *Ann Surg* 2004;240:728.
13. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med* 2014;370:2387-96.
14. U.S. National Institutes of Health. Assessment of efficacy and safety in relieving opioid-induced constipation in patients with cancer-related pain (nct 01384292).
<https://clinicaltrials.gov/ct2/show/NCT01384292?term=01384292&rank=1>, Accessed May 22, 2105.
15. Slappendel R, Simpson K, Dubois D, Keininger DL. Validation of the pac-sym questionnaire for opioid-induced constipation in patients with chronic low back pain. *European Journal of Pain* 2006;10:209-17.

12.0 APPENDICES

Appendix A. ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead.

Appendix B. Strong and Moderate CYP3A4 and/or P-glycoprotein Inhibitors

Strong CYP3A4 inhibitors prohibited during study, include but are not limited to the following:

Boceprevir	Nefazodone
Clarithromycin	Nelfinavir
Conivaptan	Posaconazole
Grapefruit juice	Ritonavir,
Indinavir	Saquinavir
Itraconazole	Telaprevir
Ketoconazole	Telithromycin
Lopinavir/ritonavir	Voriconazole
Mibepradil	

Moderate CYP3A4 inhibitors prohibited during study, include but are not limited to the following:

Amprenavir	Erythromycin,
Aprepitant,	Fluconazole,
Atazanavir,	Fosamprenavir,
Ciprofloxacin,	Grapefruit juice,
Darunavir/ritonavir,	Imatinib,
Diltiazem,	Verapamil

P-glycoprotein inhibitors prohibited during study, include but are not limited to the following:

Cyclosporine,	Quinidine
Elacridar	Ritonavir
Erythromycin	Valspodar
Itraconazole	Verapamil,
Ketoconazole	

Please refer to the U.S. Food and Drug Administration website for additional information:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm>.

Appendix C. Strong CYP3A4 and P-glycoprotein Inducers

Strong CYP3A4 inducers and/or P-glycoprotein inducers prohibited during study, include but are not limited to the following:

- Avasimibe
- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampin
- St. John's wort

Please refer to the U.S. Food and Drug Administration website for additional information:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm>.

Appendix D. Patient Study Drug Diary

Protocol No.	Participant No.	Participant Initials	Treatment Phase
UCSD XXXXXX			

- Please complete this diary on a daily basis. Enter the time you take naloxegol in the appropriate box.
- If you forget to take your dose and it has been less than 2 hours since the missed dose, it should be taken as soon as you remember on the same day. If it has been more than 2 hours since missing a dose, put a line through the box for time taken on that day and do not make up that dose. If you vomit after taking a dose, do not repeat the dose and record that on your diary.
- If you experience any health/medical complaints, please record this information on the back of this diary.

Naloxegol Dose: _____ mg

Number of pills per day: 1

Date:	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Naloxegol	Time:						

Date:	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14
Naloxegol	Time:	Time:	Time:	Time:	Time:	Time:	Time:

Please sign at completion of the treatment period and return with pill bottle(s) to the study team.

Patient Signature: _____ Date: _____

Protocol No.	Participant No.	Participant Initials	Treatment Phase
UCSD XXXXXX			

- Please complete this diary on a daily basis. Enter the time you take naloxegol in the appropriate box.
- If you forget to take your dose and it has been less than 2 hours since the missed dose, it should be taken as soon as you remember on the same day. If it has been more than 2 hours since missing a dose, put a line through the box for time taken on that day and do not make up that dose. If you vomit after taking a dose, do not repeat the dose and record that on your diary.
- If you experience any health/medical complaints, please record this information on the back of this diary.

Naloxegol Dose: _____ mg

Number of pills per day: 1

Date:	DAY 15	DAY 16	DAY 17	DAY 18	DAY 19	DAY 20	DAY 21
Naloxegol	Time:						

Date:	DAY 22	DAY 23	DAY 24	DAY 25	DAY 26	DAY 27	DAY 28
Naloxegol	Time:						

Please sign at completion of the treatment period and return with pill bottle(s) to the study team.

Patient Signature: _____ Date: _____

Protocol No.	Participant No.	Participant Initials	Treatment Phase
UCSD XXXXXX			Extension

- Please complete this diary on a daily basis. Enter the time you take naloxegol in the appropriate box.
- If you forget to take your dose and it has been less than 2 hours since the missed dose, it should be taken as soon as you remember on the same day. If it has been more than 2 hours since missing a dose, put a line through the box for time taken on that day and do not make up that dose. If you vomit after taking a dose, do not repeat the dose and record that on your diary.
- If you experience any health/medical complaints, please record this information on the back of this diary.

Naloxegol Dose: _____ mg Number of pills per day: 1

Date:	DAY 29	DAY 30	DAY 31	DAY 32	DAY 33	DAY 34	DAY 35
Naloxegol	Time:						
Date:	DAY 36	DAY 37	DAY 38	DAY 39	DAY 40	DAY 41	DAY 42
Naloxegol	Time:						
Date:	DAY 43	DAY 44	DAY 45	DAY 46	DAY 47	DAY 48	DAY 49
Naloxegol	Time:						
Date:	DAY 50	DAY 51	DAY 52	DAY 53	DAY 54	DAY 55	DAY 56
Naloxegol	Time:						

Please sign at completion of the treatment period and return with pill bottle(s) to the study team.

Patient Signature: _____ Date: _____

Protocol No.	Participant No.	Participant Initials	Treatment Phase
UCSD XXXXXX			Extension

- Please complete this diary on a daily basis. Enter the time you take naloxegol in the appropriate box.
- If you forget to take your dose and it has been less than 2 hours since the missed dose, it should be taken as soon as you remember on the same day. If it has been more than 2 hours since missing a dose, put a line through the box for time taken on that day and do not make up that dose. If you vomit after taking a dose, do not repeat the dose and record that on your diary.
- If you experience any health/medical complaints, please record this information on the back of this diary.

Naloxegol Dose: _____ mg

Number of pills per day: 1

Date:	DAY 57	DAY 58	DAY 59	DAY 60	DAY 61	DAY 62	DAY 63
Naloxegol	Time:						
Date:	DAY 64	DAY 65	DAY 66	DAY 67	DAY 68	DAY 69	DAY 70
Naloxegol	Time:						
Date:	DAY 71	DAY 72	DAY 73	DAY 74	DAY 75	DAY 76	DAY 77
Naloxegol	Time:						
Date:	DAY 78	DAY 79	DAY 80	DAY 81	DAY 82	DAY 83	DAY 84
Naloxegol	Time:						

Please sign at completion of the treatment period and return with pill bottle(s) to the study team.

Patient Signature: _____ Date: _____

Protocol No.	Participant No.	Participant Initials	Treatment Phase
UCSD XXXXXX			Extension

- Please complete this diary on a daily basis. Enter the time you take naloxegol in the appropriate box.
- If you forget to take your dose and it has been less than 2 hours since the missed dose, it should be taken as soon as you remember on the same day. If it has been more than 2 hours since missing a dose, put a line through the box for time taken on that day and do not make up that dose. If you vomit after taking a dose, do not repeat the dose and record that on your diary.
- If you experience any health/medical complaints, please record this information on the back of this diary.

Naloxegol Dose: _____ mg

Number of pills per day: 1

Date:	DAY 85	DAY 86	DAY 87	DAY 88	DAY 89	DAY 90	DAY 91
Naloxegol	Time:						
Date:	DAY 92	DAY 93	DAY 94	DAY 95	DAY 96	DAY 97	DAY 98
Naloxegol	Time:						
Date:	DAY 99	DAY 100	DAY 101	DAY 102	DAY 103	DAY 104	DAY 105
Naloxegol	Time:						
Date:	DAY 106	DAY 107	DAY 108	DAY 109	DAY 110	DAY 111	DAY 112
Naloxegol	Time:						

Please sign at completion of the treatment period and return with pill bottle(s) to the study team.

Patient Signature: _____ Date: _____

My next scheduled visit is: _____

HEALTH/MEDICAL COMPLAINTS

Please record all health/medical complaints you have experienced below.

Please describe what you experienced	Date Started	Date Stopped

For UCSD Staff Use Only:

Signature: _____

Date: _____

Pill Count (to be completed by study team):

of capsules returned

Appendix E. Patient Medication Use Diary

Medication Use Diary

Protocol No.	Participant No.	Participant Initials	Treatment Phase
UCSD XXXXXX			

Instructions for completion:

- Please remember to complete this diary daily while participating in this study.
- Remember to record all opioid medications being used and be sure to include whether these are "immediate-release" or "extended-release" medications.
- Record each medication you are taking at home on a separate line. For each medication recorded, please list the date or dates that it was taken, how many times it is taken each day, the dose each time it is taken, and the reason why you are taking the medication.
- If there is any information that you do not know, please write "UNK" in the space provided.

Name of Medication	Date(s) Medication Taken (mm/dd/yy)	No. of times taken each day	Dose (each time it is taken)	Reason for Taking Medication

Please sign when all spaces are full and return to the study coordinator during your next clinic visit.

Patient Signature:

Date:

version dated 14DEC15

Appendix F. Patient Bowel Movement Diary

Laxation Diary

Protocol No.	Participant No.	Participant Initials	Treatment Phase/Day No.	Date Diary Completed
UCSD XXXXXX				

Instructions for completion:

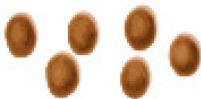
- Please remember to complete this diary daily while participating in this study.
- Record each bowel movement that you have throughout the day on a separate line. For each bowel movement recorded, please list the time and Bristol Stool Scale type (see opposite side of this diary for description of types).
- At the end of each day, please record the total number of bowel movements for that day in the space provided.
- If you did not have any bowel movement throughout the day, please leave all spaces for time and Bristol Stool Scale Type blank, and record "0" in the space for total number of bowel movements.

Time of bowel movement (hh:mm) am/pm	Bristol Stool Scale Type (Type 1-7)
Total number of bowel movements in the last 24 hours? _____	
Please sign when the diary has been completed at the end of each day and return to the study coordinator during your next clinic visit.	
Patient Signature: _____ Date: _____	

version dated 25SEP15

Appendix G. Bristol Stool Scale (BSS)²

Bristol Stool Chart

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

Appendix H. Patient Assessment of Constipation Symptoms (PAC-SYM)¹⁵

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.

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

English (USA) PAC-SYM Version 2.1-Sd (12-item, Standard version)
PAC-SYM © 1999 Mapi Research Trust, All rights reserved

Appendix I. Patient Assessment of Constipation Quality of Life (PAC-QOL)⁵

PAC-QOL ©

PATIENT ASSESSMENT OF CONSTIPATION ©

The following questions are designed to measure the impact constipation has had on your daily life **during the past 2 weeks**. For each question, please tick one box.

The following questions ask you about the <u>intensity</u> of your symptoms. To what extent, during the past 2 weeks...	Not at all 0	A little bit 1	Moderately 2	Quite a bit 3	Extremely 4
1. have you felt bloated to the point of bursting?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. have you felt heavy because of your constipation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The next few questions ask you about the <u>effects</u> of constipation on your <u>daily life</u>. How much of the time, during the past 2 weeks...	None of the time 0	A little of the time 1	Some of the time 2	Most of the time 3	All of the time 4
3. have you felt any physical discomfort?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. have you felt the need to open your bowel but not been able to?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. have you been embarrassed to be with other people?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. have you 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"/>

English (UK) PAC-QOL 2.1-Sd (28-item, Standard version)
PAC-QOL© 2005 Mapi Research Trust, All rights reserved

PAC-QOL 28 - United Kingdom/English - Mapi.
ID7520 / PAC-Qol28_AU2.1_eng-GBori.doc

The next few questions ask you about the effects of constipation on your daily life. To what extent, during the past 2 weeks...	Not at all 0	A little bit 1	Moderately 2	Quite a bit 3	Extremely 4
7. have you had to be careful about what you eat?	<input type="checkbox"/>				
8. have you had a decreased appetite?	<input type="checkbox"/>				
9. have you been worried about not being able to choose what you eat (for example, at friend's)?	<input type="checkbox"/>				
10. have you been embarrassed about staying in the toilet for so long when you were away from home?	<input type="checkbox"/>				
11. have you been embarrassed about having to go to the toilet so often when you were away from home?	<input type="checkbox"/>				
12. have you been worried about having to change your daily routine (for example, travelling, being away from home)?	<input type="checkbox"/>				

The next few questions ask you about your <u>feelings</u> . How much of the time, during the past 2 weeks...	None of the time 0	A little of the time 1	Some of the time 2	Most of the time 3	All of the time 4
13. have you felt irritable because of your condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. have you been upset by your condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. have you felt obsessed by your condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. have you felt stressed by your condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. have you been less self-confident because of your condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. have you felt in control of your situation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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The next questions ask you about your <u>feelings</u> . To what extent, during the past 2 weeks...	Not at all 0	A little bit 1	Moderately 2	Quite a bit 3	Extremely 4
19. have you been worried about not knowing when you are going to be able to open your bowels?	<input type="checkbox"/>				
20. have you been worried about not being able to open your bowels when you needed to?	<input type="checkbox"/>				
21. have you been more and more bothered by not being able to open your bowels?	<input type="checkbox"/>				

The next questions ask about <u>your life with constipation</u> . How much of the time, during the past 2 weeks...	None of the time 0	A little of the time 1	Some of the time 2	Most of the time 3	All of the time 4
22. have you been afraid that your condition will get worse?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. have you felt that your body was not working properly?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. have you had fewer bowel movements than you would like?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The next questions ask you about how <u>satisfied</u> you are. To what extent, during the past 2 weeks...	Not at all 0	A little bit 1	Moderately 2	Quite a bit 3	Extremely 4
25. have you been satisfied with how often you open your bowels?	<input type="checkbox"/>				
26. have you been satisfied with the regularity with which you open your bowels?	<input type="checkbox"/>				
27. have you been satisfied with your bowel function?	<input type="checkbox"/>				
28. have you been satisfied with your treatment?	<input type="checkbox"/>				

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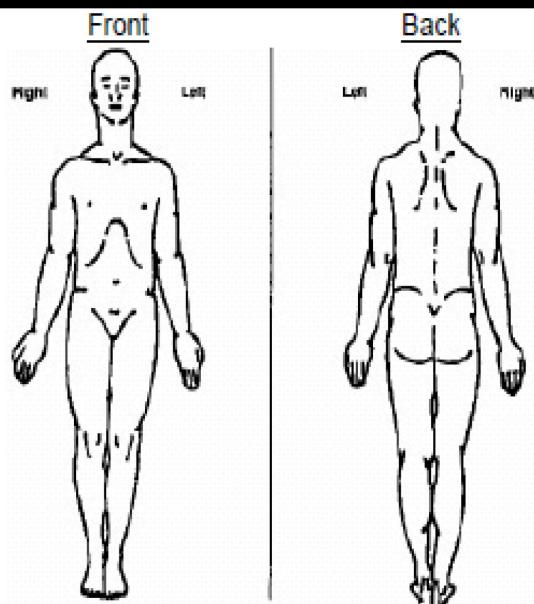
Appendix J. Brief Pain Inventory-Short Form (BPI-sf)⁶

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No
Pain
Pain As Bad As
You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10

No Pain
Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
<input type="checkbox"/>										
No Relief	Complete Relief									

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Does Not Interfere									Completely Interferes	

B. Mood

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10

Does Not Completely Interfere

D. Normal Work (includes both work outside the home and housework)

By Normal Work (includes both work outside the home and household)

0 1 2 3 4 5 6 7 8 9 10

Does Not Interfere Completely Interfere

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does Not Completely Interface Completely Interface

E. Sleep

11. Group 0 1 2 3 4 5 6 7 8 9 10 Completely Interferes

G. Enjoyment of life

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Does Not Interfere										

Appendix K. Equianalgesic Dosing Guidelines for Chronic Pain

PO / PR	IV / SC / IM
3	1

PO	APAP 325 + Codeine 30mg	APAP 500 mg + hydrocodone 5mg	APAP 325 + oxycodone 5mg
~Morphine Equivalent	3-4 mg	5-6 mg	7-8 mg

PO / PR Dose (mg)	Analgesic	IV / SC / IM Dose (mg)
150 mg	Meperidine	50 mg
150 mg	Tramadol	-
150 mg	Codeine	50 mg
15 mg	Hydrocodone	-
15 mg	Morphine	5 mg
10 mg	Oxycodone	-
3 mg	Hydromorphone	1 mg
-	Fentanyl	0.05 mg (1000 mcg = 1 mg)

PO Morphine	Transdermal Fentanyl
50mg PO in 24 hours	~25 mcg patch Q72 hours

Ferris FD, Pirrello RD: Improving Equianalgesic Dosing for Chronic Pain Management, American Association for Cancer Education Annual Meeting, oral presentation. Cincinnati, Ohio, Sept 2005.