Official Study Title: A Double-blind, Randomized, Placebo-controlled Trial of Naloxegol for Prevention of Post-operative Constipation in Spinal Surgery Patients

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A Double-blind, Randomized, Placebo-controlled Trial of Naloxegol for Prevention of Post-operative Constipation in Spinal Surgery Patients

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Sponsor: AstraZeneca

I. Background and Significance

a.) Historical background

Constipation remains one of the most common clinical conditions encountered by physicians with an estimated general population prevalence ranging from 2% to 28%[1] generating 2.5 million physician visits per year[2] with an annual direct medical cost of more than $230 million in the U.S. alone.[3] Despite the high prevalence of constipation in the population at large, comparatively little is known about secondary constipation amongst acutely-hospitalized individuals. Indeed, hospitalized patients suffer disproportionately from constipation during their stays,[4-6] with incident constipation occurring in 6.8% of admitted stroke patients,[7] approximately 70% of critically-ill ICU patients,[8,9] and in more than 70% of a geriatric hospitalized population.[5] Prior studies have primarily focused on chronic constipation in the outpatient setting, using patient-reported outcomes that can be difficult to translate to hospitalized individuals. In fact, inpatient constipation is more likely to arise as a secondary phenomenon from change in environment, emotional stressors, administration of constipating medications,[3,6] alterations in splanchnic blood flow as a result of illness,[10] dehydration,[11] and decreased activity.[3,12,13] Post-spinal surgery patients represent an ideal population for study, in that they are frequently immobile, receive constipating opioids frequently, and are otherwise healthy enough to undergo an elective surgical procedure. Despite the fact that constipation is a known complication of spinal surgery that keeps patients in the hospital longer, there is no current standard of care for constipation prophylaxis in this population—or any hospitalized population.

Naloxegol is a pegylated μ-opioid receptor antagonist that acts on μ-opioid receptors in the enteric nervous system with limited ability to cross in to the central nervous system; thus naloxegol can reverse the effects of systemic opioids in the gut without attenuating the analgesic properties of opioids on the brain. Two recent, phase 3, double-blind studies demonstrated that daily administration of 25 mg of po naloxegol resulted an improvement in bowel movement frequency and specifically a decreased time to first, post-dose spontaneous bowel movement in patients with non-cancer pain and opioid-induced constipation.[14] Importantly, there was no reduction in opioid-mediated analgesia.

b.) Previous studies supporting the proposed research

There is a paucity of studies examining the effect of constipation prophylaxis on incidence of constipation in hospitalized patients. Notably, there are only four known studies examining this question and none have examined surgical patients. The most relevant study randomized ICU patients to polyethylene glycol, lactulose, or placebo who did not have a bowel movement in the first three days of admission.[15] They measured time to first defecation (after 3 days) and found that the median time from start of the study medication to first defecation was 75.0 hrs (IQR 36.0 hrs) for the placebo group, 36.0 hrs (IQR 30.2 hrs) for the lactulose-treated patients (p = 0.001 vs. placebo), and 44.0 hrs (IQR 43.0 hrs) for the PEG-treated patients (p = .001 vs. placebo and p = .1 vs. lactulose).

Our own recently-published data demonstrates that constipation prophylaxis reduced length of stay in elderly patients hospitalized with congestive heart failure who take laxatives at home.[16] These patients received far fewer opioids than the typical spinal surgery patient.

c.) Rationale behind the proposed research

To our knowledge, there are no data addressing whether the impact of bowel prophylaxis on constipation in ICU or cancer patients translates to other populations, specifically surgical patients. We have preliminary retrospective data demonstrating a decreased incidence of constipation in hospitalized patients, but these data are observational.

Patients receiving naloxegol in the post-operative period after spinal surgery could potentially benefit from a decreased time to first spontaneous bowel movement after surgery and decreased incidence of overall inpatient constipation with its attendant complications. After surgery, this patient population is routinely maintained on a patient-controlled anesthesia (PCA) device for 18-30 hours before transitioning to oral pain medications for discharge and up to 2 week beyond. As such, patients treated post-operatively with naloxegol would potentially have improvement in comfort, decrease in delirium, and decreased time to discharge. A trial of prophylactic naloxegol in post-operative spinal surgery patients represents the logical next step in investigation, as spinal surgery patients are a microcosm for many of the aforementioned secondary drivers of constipation.

II. Specific Aims

The primary objective is to determine whether naloxegol prophylaxis decreases the median time to first spontaneous, rescue laxative-free, post-operative bowel movement in patients undergoing spinal surgery at Massachusetts General Hospital (MGH) compared to placebo. The secondary objectives are to determine whether the aforementioned constipation prophylaxis reduces length of stay, improves patient satisfaction with their bowel management, and decreases need for rescue laxatives. We also want to determine the incidence of diarrhea in each of the groups.

III. Subject Selection

The study population will include any adult patient undergoing non-urgent, elective spinal surgery (spinal fusions) at Massachusetts General Hospital who is admitted to the neurosurgery floor from the operating room are allowed to enroll within the confines of the eligibility caveats outlines below. Patients must fulfill all entry criteria to be enrolled in the study. We have selected spinal fusion patients as they tend to have longer lengths of stay with higher analgesic requirements (especially opioids). Furthermore, enhanced recovery after surgery (ERAS) protocols are not utilized in this patient population at MGH.

a.) Inclusion criteria

1. Male or female between the ages of 18 and 80 years undergoing non-urgent, elective spinal fusion at Massachusetts General Hospital who are admitted to the neurosurgery floor from the operating room
2. Patients with preexisting opioid use will not be excluded
3. Post-operative spinal surgery patients receiving opiods with preexisting constipation not meeting criteria for irritable bowel syndrome (IBS) receiving opioids will not be excluded
4. Patients with inactive non-GI cancer, or inactive GI cancer will not be excluded.

b.) Exclusion criteria

1. Patients who are taken to the operating room from another inpatient floor or service (already hospitalized prior to surgery)
2. Patients with evidence of bowel obstruction (a contraindication to laxatives)
3. Patients unable to take oral medications by mouth or by enteric feeding tube (gastrostomy or jejunostomy)
4. Patients with a documented or potential allergy or adverse reaction to the study medication from outpatient use
5. Patients currently taking naloxegol in the outpatient setting
6. Patients with a preoperative diagnosis of irritable bowel syndrome (IBS) obtained via Rome III questionnaire on screening
7. Patients with disruptions to the blood-brain barrier (eg, multiple sclerosis, recent brain injury, Alzheimer's disease, and uncontrolled epilepsy)
8. Patients with active GI cancer involving the GI lumen (stomach cancer, small bowel cancer, or colorectal cancer) who could be at risk for bowel obstruction due to residual disease.
9. Patients with history of disruption in the blood brain barrier, including those where the disruption is known to occur during the spinal fusion procedure
10. Patients concomitantly using strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole), strong CYP3A4 inducers and other opioid antagonists.
11. Patients with severe hepatic impairment.
12. Patients with a previous history of or risk of bowel perforation.
13. Patients with a post-op regional anesthetic technique employed like a continuous epidural or spinal.

c.) Source of subjects and recruitment process

Subjects will be recruited from the MGH outpatient neurosurgery clinics after the scheduling of their spinal fusion surgery. Subjects typically have two appointments before their surgery: an evaluation with a Neurosurgeon, and a pre-operative visit. A Neurosurgeon on the protocol will introduce the trial to the subject at the initial visit, and provide them with the contact information of the study staff. If the subject is interested in the trial and they contact study staff, study staff can follow-up by sending trial information and review the Inclusion/ Exclusion criteria to ensure the subject qualifies for the study. Subjects who qualify will be consented by a licensed Physician Investigator on the protocol at their pre-operative visit. In this way, patients are not asked on the day of their procedure, when there is significant peri-procedural anxiety.

IV. Subject Enrollment

a.) Methods of enrollment

1. Patients scheduled for spinal fusion surgery may learn about the study from their Neurosurgeon at their initial visit prior to their surgery and asked if they would like to hear more about the trial
2. Any patients agreeing to hear more about the trial would learn more before beginning the informed consent process should they agree to participate
3. A Neurosurgeon on the protocol will introduce the trial to the patient at the initial visit, and provide them with the contact information of the study staff.

4. If the patient is interested in the trial and they contact study staff, study staff can follow-up by phone or email with trial information, as well as determining whether they meet all of the inclusion criteria
5. Subjects who qualify will be consented by a licensed Physician Investigator on the protocol at their pre-operative visit

b.) Procedures for obtaining informed consent

1. Patients agreeing to participate would complete an informed consent with one of the licensed Physician Investigators listed on the protocol during their pre-operative visit.

c.) Treatment assignment and randomization

1. Patients who have been enrolled and consented in the trial will be randomized to the placebo or naloxegol arms
2. A total of approximately 166 unique patients will be randomly assigned in a 1:1 ratio to receive either naloxegol 25 mg daily (as is consistent with FDA guidelines) or a matching placebo control
3. There will be no stratification
4. The study personnel and patients will be blinded to treatment allocation
5. Patients who fulfill study admission criteria and have a signed consent form will be assigned a 3-digit sequential patient number. The number will be used throughout the study.
6. Randomization will be conducted using the MGH research pharmacy's internal randomization system. The research pharmacist will use an application on randomization.com to randomly decide the assignment (treatment vs. placebo) of the first participant. All subsequent participants will be randomized in a 1:1 ratio**.** Based on the randomized treatment assignment, an unblended pharmacist at MGH will prepare the study drug in a manner that ensures maintenance of the blind utilizing study-specific labels and completing details pertinent to the individual participant.
7. This is a double blind study. The individual treatment assignment will not be revealed to patients or their representatives, study staff (except for the unblinded pharmacist), or the sponsor of the sponsor's representatives, until all patients complete the study and the database is locked. The unblinded pharmacist will maintain the treatment assignment for each patient.

V. Study Procedures

a.) Study visits and parameters to be measured

1. After informed consent, the initial study visit will occur with the research coordinator and will include completion of the Bowel Function Index,[17] a short, validated questionnaire for the detection of opioid-induced constipation as well as collection of self-reported laxative and opioid use in the preceding 2 weeks, and the Rome III questionnaire to identify IBS.
2. After confirming continued eligibility, the patient will return home prior to their scheduled surgery.

3. Schedule of Events:

	Study Period					
	Enrollment	Allocation	Operation	Hospitalization	1st Bowel Movement	Hospital Discharge
Time Point	$-t_2$	$-t_1$	0	t_1 (variable)	t_x	t_y
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Treatment group			←	→	→	
Control group			←	→	→	
Baseline laxative use	X					
Baseline opioid use	X					
Rome III questionnaire	X					
1° outcome variable (time to first BM)					X	
2° outcome variables				X	X	
Bowel Function Index	X			X	X	X
Bowel satisfaction question						X
Adverse events				X	X	X
Cumulative opioid dose measurement						X

4. After confirming that inclusion and exclusion criteria continue to be satisfied on the day of surgery, the patient will be randomized using the MGH research pharmacy's internal randomization system (randomization output must only be seen by unblinded pharmacist).
    a. Patients will receive their first dose of study drug in the Post-Anesthesia Care Unit (PACU) approximately two hours postoperatively
    b. Patients will undergo their scheduled operation without modification of the individual surgeon's or hospital protocol
5. Post-operative patients will be moved to the Post-Anesthesia Care Unit (PACU) per protocol for recovery before transfer to the inpatient floor
6. On arrival to the neurosurgery floor, patients will be admitted as per hospital protocol
7. Patients will receive the study medication daily as close to the initial administration time as possible pending nursing demands
8. There will be no routine monitoring of labs or imaging for the purposes of the study outside of usual care on the floor
9. Patients enrolled in the study will be allowed to be given Colace (Docusate) and Senna (Senokot) as standing laxative medications for prophylactic purposes. Other laxatives will not be allowed to be given for prophylactic purposes, but "prn" rescue medications will be allowed.

b.) Drugs to be used

1. The study drug and placebo will be supplied by the Sponsor and stored in the MGH inpatient pharmacy

2. Naloxegol is supplied in 25 mg tablets
3. Matching placebo consists of an inert mixture supplied by the Sponsor in identical-appearing tablets
4. Dosage and administration
    a. Subjects will be administered naloxegol 25 mg (as is consistent with FDA guidelines) or placebo once daily until their discharge from the hospital (variable timing), after two weeks, until they are off oral opioid pain medications, or until transfer to an acute care unit (i.e. intensive care unit) whichever comes first. The 25 mg tablets are not scored.
    b. Subjects with renal impairment (creatine clearance rate of less than 60 mL/min) will receive a 12.5 mg dose of naloxegol or placebo in place of the 25 mg dose as advised by FDA guidelines
    c. The Sponsor will supply both 25mg and 12.5 mg naloxegol tablets as well as matching placebo.
    d. Naloxegol will be administered as label indicated (1 hr pre first meal or 2 hr post meal)
    e. Inpatient neurosurgery nursing will be instructed to administer the medication orally once daily at a time corresponding to the initial preoperative dosing
    f. Subjects may receive naloxegol via a feeding tube as necessary. The naloxegol or placebo tablets can be crushed and mixed in water for patients who are unable to swallow.
    g. Subjects will not receive study drug if they are transferred to another unit of the hospital due to postoperative complications or if their length of stay is more than 2 weeks.
5. Treatment compliance
    a. Study drug will be administered on the MGH inpatient neurosurgery unit by nursing staff
    b. If a subject misses a dose, the missed dose will be recorded in the hospital's inpatient electronic medication administration record (eMAR) as well as a reason for the missed dose as per hospital protocol
    c. Adverse Events. On the basis of clinical studies, the following adverse events may occur in subjects receiving naloxegol:
        i. >10%: abdominal pain (12-21%)
        ii. 1-10%: headache (4%), hyperhidrosis (≤3%), diarrhea (6-9%), flatulence (3-6%), vomiting (5%)
        iii. <1% (limited to important or life-threatening): anxiety, arthritis, back pain, chills, gastrointestinal perforation, irritability, joint pain, yawning
    d. While the structure of naloxegol has been shown to prevent influx of the drug across the blood-brain barrier it is possible that interruption of the blood-brain barrier in patients with spinal surgery while taking naloxegol could result in decreased effectiveness of post-operative opioids. Patients will be withdrawn from the study if surgery results in tearing or breach of the dura matter as this could result in decreased effectiveness of post-operative opioids. Any observed decreased in effectiveness in post-operative opioids will be recorded as described in section V.c.3.f.
6. Rescue medications
    a. If a subject experiences inadequate prevention of constipation while on the study drug or placebo, the patient may be administered a rescue medication (laxative) at

the discretion of the patient's nurse consistent with "prn" orders or new orders from the medical team. Drugs that are available to treat constipation include: Colace (Docusate), Polyethylene glycol (Miralax), Senna (Senokot), magnesium citrate, and lactulose. The current standard protocol for laxative use in post-op settings is a course of Colace (Docusate) and Senna (Senokot). Because constipation is not a side effect of the medication, all patients will be able to receive laxative doses as needed at their request throughout the study consistent with hospital policies or at their nurse's or physician's discretion without restriction.

7. Home opioid use
    a. All home opioids will be stopped on admission and patients placed on their surgeon's standard pain control regimen, which includes an initial patient-controlled anesthesia (PCA) pump followed by a transition to oral opioids.

c.) Data to be collected and timeline for collection

1. Initial data collection
    a. On study enrollment in the MGH Neurosurgery clinic, patients will complete the Rome III constipation module, Bowel Function Index, and a standardized assessment of laxative and opioid medications, doses, and frequency
2. Procedure
    a. We will retrospectively use the medical record to determine procedure duration, attending physician, and immediate adverse events that occur during the planned procedure
3. Hospital Day
    a. Patients will complete a Bowel Function Index questionnaire at the beginning of each hospital day
    b. <u>PRIMARY OUTCOME</u>: The primary endpoint of this study will be time to first post-operative bowel movement, as defined by the first spontaneous bowel movement reported by nursing staff without use of a rescue laxative after transfer from the operating room to the hospital ward. A bowel movement will be defined as a spontaneous passage of1 tablespoon or more of liquid or solid stool (excluding flatus), which can be measured and verified by nursing staff and was not the result of a rescue laxative. Time will be measured in hour increments on standardized report forms, with bowel movement times occurring between hours rounded up or down to the nearest hour. This will account for variations in nursing contact time with the patient, who would be expected to check in on their patients' status at least once every hour.
    c. Any new rescue medications for constipations (laxatives) or use of "prn" orders will be retrospectively determined through the Electronic Medication Administration Record after discharge
    d. Feeding and IV fluid I/O will be determined through the Electronic Medication Administration Record after discharge
    e. Opioid type (generally via PCA pump) and cumulative dosage
    f. Adverse events: adverse events will be collected daily from the operative period through discharge and recorded on the CRF
        i. Definition of adverse events
            1. An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether

or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

ii. Treatment emergent adverse events (TEAE)
    1. Treatment emergent adverse events are defined as AEs that occur after the treatment start date and prior to the completion of the drug "washout" period. All adverse events for individual participants will be categorized as TEAEs or non-TEAEs in the CRF following completion of the study.

iii. Definition of serious adverse event
    1. A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:
        a. Results in death
        b. Is immediately life threatening
        c. Requires in-patient hospitalization or prolongation of existing hospitalization
        d. Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
        e. Is a congenital abnormality or birth defect
        f. Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

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

iv. Recording of adverse events
    1. Time period for collecting adverse events
        a. Adverse events will be collected daily from the operative period through discharge
        b. To allow for collection of any adverse events that may occur following discharge, daily post-discharge phone calls will be made to all patients for 3 days if they had a bowel movement during their hospitalization or until they have a bowel movement post-discharge. Adverse events will be recorded as described in section V.b.8.c.e.
        c. Any unresolved adverse events will be tracked via daily phone call to the patient by the study staff until they are resolved. Adverse events will be recorded as described in section V.b.8.c.e.
        d. Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in

accordance with PHRC unanticipated problems reporting guidelines

2. All adverse events will be recorded directly on the CRF. The following variables will be collected for each AE:
    i. AE (verbatim)
    ii. The date <<and time>> when the AE started and stopped
    iii. Whether the AE is serious or not
    iv. Information relevant in determining causality
    v. Action taken for study drug
    vi. Outcome
    b. In addition, the following variables will be collected for SAEs
        i. Date AE met criteria for serious AE
        ii. Date Investigator became aware of serious AE
        iii. AE is serious due to
        iv. Date of hospitalization
        v. Date of discharge
        vi. Probable cause of death
        vii. Date of death
        viii. Autopsy performed
        ix. Causality assessment in relation to Study procedure(s)
        x. Causality assessment in relation to Other medication
        xi. Description of AE.
        It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section V.c.3.eii. Reporting of serious adverse events
3. Causality Assessment
    a. The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug therapy using clinical judgment and the following considerations
        i. **No**: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
        ii. **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.
    b. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting. The relationship to study procedures (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

i. **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
ii. **Yes:** The adverse event occurred as a result of protocol procedures, (e.g., venipuncture)

c. A summary of any causality assessment will be recorded in the CRF.

4. Reporting of serious adverse events
   a. A copy of the MedWatch/AdEERs report of any serious, unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32 must be emailed or faxed to AstraZeneca at the time the event is reported to the FDA AT . It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

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

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

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

      Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-302-886-4114 or by email to AE Mailbox Clinical Trial (TCS) <AEMailboxClinicalTrialTCS@astrazeneca.com>. Email is the preferred method.

      Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. These events will be reported on a weekly basis.

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

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

4. Day of Discharge
    a. On the day of discharge from the hospital, the patient will complete an additional bowel satisfaction question: "How satisfied are you with the management of your bowels in the hospital?" which will be asked via standardized form at the time of discharge using a 5-point Likert scale consistent with previous work.[4]
    b. Length of stay will be determined from retrospective review of the medical record. We will specifically record the date/time of the discharge order.
5. We will determine the incidence of diarrhea in each group via examination of the electronic medication record, which also includes mandatory reporting (with reason) for any held doses of the study medication.
6. Unblinding procedure
    a. Unblinding may be necessary in order to make clinical decisions in the case of an adverse event. The need to unblind a participant will be determined by the PI in consultation with the clinical team.
    b. In order to unblind a participant, a member of the study staff will contact the site pharmacy and provide the patient's identifying information. The site pharmacy may then inform the study staff of the patient's medication status. Unblinding will recorded in the CRF.
7. Withdrawal from study
    a. Withdrawal from the study may be necessary if:
        i. The subject violates the exclusion criteria or no longer meets the inclusion criteria.
        ii. The PI determines that termination is clinically necessary following an AE.
        iii. Spinal surgery results in tearing or breach of the dura matter
        iv. Non-compliance with study procedures
        v. The subject no longer wishes to participate in the study
    b. The reason for withdrawal will be recorded in the CRF.
    c. Administration of the study drug will cease immediately upon withdrawal.

VI. Biostatistical Analysis

1. Specific data variables to be collected
    a. Prospective
        i. Bowel Function Index
        ii. Home opioid use
        iii. Home laxative use
        iv. Bowel satisfaction
        v. Time to first bowel movement (primary outcome)
        vi. Adverse events
        vii. Pain VAS measurement
        viii. Safety (defined as occurrence of TEAEs segregated into serious and minor events)
    b. Chart review

i. Length of stay
ii. In-hospital opioid use
iii. In-hospital rescue laxative use

2. Study endpoints – As above
3. Statistical methods
    a. Analysis populations
        i. Intent-to-treat (ITT) population: all patients who are randomized will be included in the ITT population. This will be the primary population for all analyses of demographics, patient characteristics and disposition, and efficacy data.
        ii. Safety population: All patients who are randomized and receive any study treatment will be included in the safety population. This will be the primary population for all analyses of safety data
        iii. Per-Protocol (PP) population: All patients who are randomized and receive the study medication on each day of their hospitalization. Major protocol violations include the following:
            1. Prohibited concomitant medication usage (specifically standing laxatives during hospitalization)

        The PP population may be used for supplementary analysis of selected efficacy and safety data, as appropriate.
    b. Endpoint analyses
        i. Primary endpoint: The primary endpoint of this study will be time to first post-operative bowel movement, as defined by the first spontaneous bowel movement reported by nursing staff without use of a rescue laxative after transfer from the operating room to the hospital ward. A bowel movement will be defined as a spontaneous passage of 1 tablespoon or more of liquid or solid stool (excluding flatus), which can be measured and verified by nursing staff and was not the result of a rescue laxative. Time will be measured in hour increments on standardized report forms, with bowel movement times occurring between hours rounded up or down to the nearest hour. This will account for variations in nursing contact time with the patient, who would be expected to check in on their patients' status at least once every hour.

            We will analyze the data using a time-to-event methodology and our primary endpoint, time to first bowel movement, will be compared between arms using median time to bowel movement as a group measure. A log-rank test with Kaplan-Meier estimations will compare the unadjusted medians between groups. We will also calculate hazard ratios using Cox Proportional Hazards methods to control for known and putative risk factors for inpatient constipation—most importantly use of opioids during hospitalization. In this case, a hazard ratio greater than 1 would correspond to a decreased time to first bowel movement. The Cox model assumes that the risks are proportional. A survival-type analysis is most appropriate as we are looking at time to event—a bowel movement—with potential censoring in the form of missed bowel movements and from those who receive a rescue laxative. We feel that competing risks are unlikely to be a major factor in this study, as the majority of these surgeries are elective and

thus, we would be enrolling relatively-healthy subjects. We will also perform various post-hoc subgroup analyses including separate statistical analysis for opioid naive versus chronic opioid users and for patients with different spinal fusion types such as cervical vs lumbar vs thoracic etc.

ii. Secondary endpoints:
    1. Length of stay, which will be defined from as the elapsed time (in hours) from admission to discharge.
    2. Need for rescue medications, which will be defined as administration of any laxative other than Colace (Docusate) and Senna (Senokot) after admission as determined from the hospital's electronic medication administration record (which provides date, time, and type of medication). Rescue medications may be given after passage of 72 hours without a bowel movement.
    3. Patient's satisfaction with their bowels by use of the Bowel Function Index pre-operatively and post-operatively, a validated instrument for opioid-induced constipation.
    4. Patients will answer a single question: "How satisfied are you with the management of your bowels in the hospital?" which will be asked via standardized form at the time of discharge using a 5-point Likert scale.
    5. Incidence of diarrhea in each group via examination of the electronic medication record

d. Power analysis
    i. This is a randomized, double-blind, single-center clinical trial comparing prophylaxis with naloxegol to placebo for prevention of constipation in hospitalized, post-operative patients undergoing neurosurgical spinal fusion surgery at Massachusetts General Hospital. The primary objective is to compare the median time to first post-operative bowel movement between the prophylaxis and the placebo groups. We hypothesize that the median time to first bowel movement will be sooner in patients randomized to the prophylaxis group compared to the placebo group.
    ii. We have calculated that we will need a sample size of 186 subjects (including a 20% buffer for study dropout) to power this trial. Using the limited available data from a previous trial, we assumed a control effect size of 75.0 hours and a treatment effect size of 36.0 hours as time to first bowel movement. Although the van der Spoel trial[15] saw a more pronounced effect with an alternative prophylaxis regimen (treatment effect of 36.0 hours), we felt that the more conservative effect size would be appropriate given that the aforementioned trial evaluated critically-ill patients—likely subject to even more gastrointestinal motility effects of critical illness and more prolonged hospitalization. Our subjects are generally healthy enough to undergo mostly elective spinal surgery and the effect of prophylaxis is likely to be less pronounced, so we chose a more conservative effect estimate. Because our guidance study was based on an hours-to-first-bowel movement outcome, we specified a 1 subject per hour recruitment rate as the lowest possible value in the software program given we expect at best (assuming all patients enrolled) 10 patients per day to be enrolled. The follow-up period is limited to the length of hospitalization, which has a

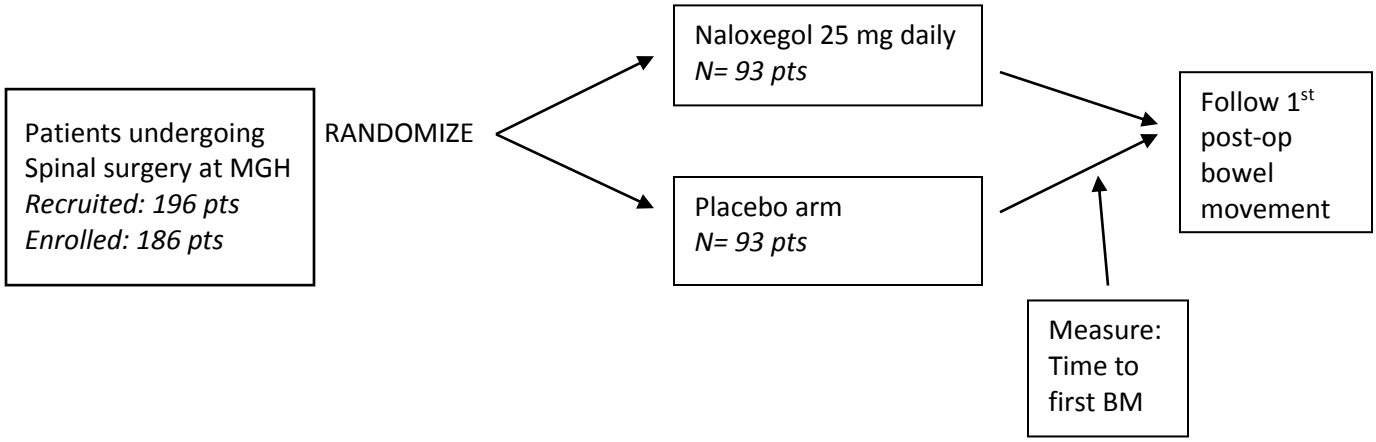
median value of 4 days in this population. No interim analyses are planned. A total of 186 patients, approximately 93 in each arm, will be needed to detect a difference between 44 hours and 75 hours in median time to first bowel movement with a power of 80% using a two-sided p=0.05 level test allowing for a 20% censoring effect/study dropout.

	Power=0.80	Power=0.90
Effect Size 39 hours (75h vs 36h)	90 subjects	112 subjects
Effect Size 31 hours (75h vs 44h)	149 subjects	188 subjects
Effect Size 23 hours (75h vs 52h)	279 subjects	359 subjects

iii. We chose to evaluate sensitivity at effect sizes with median time to bowel movement 8 hours sooner than our selected effect (representing the other effect group in the ICU study) and 8 hours later than our selected effect. We also varied the power between 0.80 and 0.90 with the unsurprising consequence of a large increase in sample size, which would be difficult in a single-center trial looking at a specific surgery type.

iv. A sample size of 186 patients will allow the study to stay within the confines of the one site that has already signed on to the trial. Assuming 10 spinal surgeries per day, it would be reasonable to assume a generous enrollment of 5 patients per day. Thus, enrolment could conceivably last 37 surgical days—translating to 7 weeks given that spinal surgeries primarily occur on weekdays. Follow-up will be limited to the length of hospitalization for each patient, with no intention to follow patients after discharge from the hospital.

Schema:



VII. Risks and discomforts

1. Drug side effects and adverse events
    a. On the basis of clinical studies, the following adverse events may occur in subjects receiving naloxegol:
        i. >10%: abdominal pain (12-21%)
        ii. 1-10%: headache (4%), hyperhidrosis (≤3%), diarrhea (6-9%), flatulence (3-6%), vomiting (5%)
        iii. <1% (limited to important or life-threatening): anxiety, arthritis, back pain, chills, gastrointestinal perforation, irritability, joint pain, yawning
2. Psychosocial risks: none

VIII. Potential benefits

1. Potential benefits to participating individuals: Equipoise exists in the proposed trial because spinal surgery patients currently receive either no prophylaxis (the placebo/control group) or prophylaxis depending on the admitting provider without evidence as to the benefit of one treatment over lack of treatment.
    a. Decreased risk of opioid-induced constipation while in the hospital
    b. Less abdominal discomfort secondary to constipation
    c. Shorter length of hospital stay due to decreased constipation
    d. Decreased complications of constipation:
        i. Poor po intake
        ii. Nausea/vomiting
        iii. Potential decreased risk of infection
2. Potential benefits to society
    a. More standardization of post-operative bowel regimens on patients receiving opioids
    b. Increased awareness of the occurrence of constipation in the post-operative patient receiving opioids
    c. Cost savings to the healthcare system from potentially decreased length of stay and decreased complications from post-operative constipation

IX. Monitoring and Quality Assurance

1. Good clinical practice
    a. The investigator will ensure that this study is conducted in accordance with the principles of "Good Clinical Practice", as outlined in Title 21 of Code of Federal Regulations (CFR), Part 312, subpart D, "Responsibilities of Sponsors and Investigators"; 21 CFR, part 50, "Protection of Human Subjects"; 21 CFR, part 54, "Financial Disclosure by Clinical Investigators"; 21 CFR, part 56, "Institutional Review Boards"; and 21 CFR, Part 11,"Electronic Records, Electronic Signature", are adhered to.
2. Institutional review board (IRB) approval
    a. The protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to the MGH IRB. Approval from the IRB must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted approval. Any modifications made to the protocol after receipt of IRB approval must also be submitted to the IRB for approval before implementation.
3. Informed consent
    a. Written informed consent, in accordance with 21 CFR Part 50, must be obtained prior to participation in the study. Within the context of the inclusion criteria, a proportion of eligible patients may be exhibiting significant cognitive impairment and the lack of capacity to provide consent. As such, all patients will require surrogate consent by a legally authorized representative. The investigator or staff will determine the appropriate family member-person to contact regarding the study, based on the standard operating procedures of MGH and local and state laws. The signed consent form must remain in the patient's medical chart and must be available for verification at any time.
4. Liability and insurance
    a. The civil liability of the investigator, the persons instructed by the investigator and the hospital, practice, or institute in which they are employed, and the liability of the financial loss due to personal injury and other damage which may arise as a result of the carrying out of this study are governed by the terms and conditions set forth in the Clinical Trial Agreement and applicable law.
5. Documentation of study findings
    a. Required information will be entered into the appropriate CRFs. All CRFs are to be completed accurately and promptly, and should be updated as needed so they reflect the latest information on the patient's file. All records are to be kept in conformance with applicable guidelines and SOPs. When the study is completed, the investigator must retain the essential documents for as long as needed to comply with regulatory authority, local regulations and sponsor requirements further detailed in Section 10.2.5. The investigator shall notify the sponsor prior to moving or destroying any of the study documents.
6. Study monitoring
    a. The sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities, and

upon request, inspecting the various records of the trial. The sponsor's clinical monitors are responsible for inspecting the CRFs throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of data; and adherence to GCPs. The monitors should have access to patient medical records and other study-related records needed to verify entries on the CRFs. In accordance ICH Good Clinical Practice (ICH/GCP) guidelines, the sponsor's clinical monitors must have direct access to the investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

b. The monitor is responsible for routine review of the eCRFs at regular interval throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. This study may be selected for audit by representatives of the sponsor's Clinical Quality Assurance department or designee. Inspection of the site facilities (i.e., participant areas, drug storage areas, record storage areas, etc.) and review of study-related records may occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.
c. An independent Data and Safety Monitoring Board (DSMB) external to the sponsor and investigators will monitor data integrity and safety of participants throughout the life of the study. A DSMB is a formal committee that is established specifically to monitor data throughout the life of a study to determine if it is appropriate, from both the scientific and ethical standpoint, to continue the study as planned. The DSMB procedures are described in detail on the DSMB charter, which is attached separately.

7. Access to Information for Auditing or Inspections
    a. Representatives of regulatory authorities, IRB, or of the Sponsor may conduct inspections or audits of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Sponsor immediately. The investigator agrees to provide to representatives of a regulatory agency, IRB or IEC, or Sponsor access to source documents/records, facilities, and personnel for the effective conduct of any inspection or audit.
8. Data quality assurance
    a. Data will be entered into a secure and validated database using eCRF's. Data entered may be checked at the point of entry and through external validation checks for accuracy. After resolution of any discrepancies and automated data-review procedures, the final data sets will be subject to a quality assurance audit. When the database is declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made by written notice. The investigator will be responsible for ensuring the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRFs, which are derived from source documents, should be consistent with source documents or the discrepancies should be explained. To ensure the quality of the clinical data across all participants and sites, a clinical data management review will be performed on all patient data. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to protocol and GCPs. To resolve any questions arising from the clinical data-review process, data queries will be sent for the site to complete. The principal investigator will electronically sign and date the indicated places on the CRF. This signature will indicate

that the principal investigator inspected or reviewed the data on the CRF and the data queries, and that the investigator agreed with the content.

9. Study Files and Retention of Records
    a. The investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data is subsequently verified. These documents should be classified into two separate categories: (1) investigator's study file, and (2) patient clinical source documents. The investigator's study file will contain the protocol/amendments, printed (or electronically archived) copies of the patient CRFs, IRB, and governmental approval with correspondence, informed consent, drug accountability (receipt/dispensing) records, staff curriculum vitae and authorization forms, information regarding monitoring activities, sponsor/investigator correspondence, and other appropriate documents and correspondence.
    b. Patient clinical source documents for this study would include, but are not limited to, the following:
        i. Patient identification (name, date of birth, gender)
        ii. Documentation that patient meets eligibility criteria, i.e., relevant medical history, physical examination, and confirmation of diagnosis
        iii. Dated notes of the day of entry into the study including study number, patient identification number, verification that the trial was discussed and written informed consent was obtained
        iv. Dated notes for each protocol assessment and documentation that protocol specific procedures were performed
        v. Study drug accountability (investigator must keep blinded records of volume of study drug given and timing of each daily dose based on the hospital chart; this will not entail review of the unblinded pharmacy records for the sake of maintaining the blind)
        vi. Documentation of all adverse events, including any action taken with regard to study drug and outcome
        vii. Concomitant medications (including start and end date, dose if relevant)
        viii. Date of trial completion and reason for early discontinuation, if applicable
10. Confidentiality
    a. The investigator must ensure that all participants' confidentiality will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names and addresses for all patients screened and for all patients enrolled in the trial. On CRFs or other documents that are submitted to the sponsor, participants should be identified by an identification code and not by their names.
    b. The investigator agrees that all information received from the Sponsor, including but not limited to the Investigator Brochure, this protocol, eCRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11. Publication
    a. After the completion of the study and the analysis of all data, the Sponsor will support efforts by all Study Investigators to jointly publish the primary study results.
12. Protocol and Protocol Amendments
    a. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. No amendments will be permitted to this protocol or to the conduct of the study without approval from the Sponsor and if applicable, the IRB. These communications will be documented in writing.
    b. All protocol amendments must be submitted to the IRB in accordance with local requirements. Approval must be obtained before changes are implemented.

X. References

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